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Plenary Lectures

Society for Endocrinology Medal Lecture

PL1

Understanding estrogen receptor gene regulation in breast cancer

Jason Carroll
University of Cambridge, Cambridge, UK.

Estrogen Receptor (ER) is the defining feature of luminal breast cancers, where is functions as a transcription factor. ER requires associated proteins to interact with the DNA, including the pioneer factors FoxA1 and GATA3, both of which mediate where in the genome ER resides. In the absence of FoxA1, ER binding and transcriptional activity is diminished, even in endocrine resistant contexts. We have utilized ChIP-seq in primary tumor material, coupled with functional analysis, to identify mechanisms that govern FoxA1-ER DNA interactions and the variables that alter binding capacity. Based on these findings, we have screened chemical libraries to identify specific inhibitors of FoxA1, with the goal of blocking ER function via inhibition of its associated pioneer factor. In addition, we have sought to discover novel ER associated proteins that are involved in endocrine resistance and to achieve this, we have established a method for rapid unbiased discovery of protein interacting complexes, which we have applied to discover ER and FoxA1 associated proteins. We find an unexpected interaction between ER and progesterone receptor (PR) in ER+ breast cancer. We show that PR is a negative regulator of the ER complex, where it is important for modulating cellular growth. Our findings suggest that there is substantial cross-talk between parallel hormonal pathways and that we can use this information to repurpose existing steroid receptor ligands for therapeutic use.

DOI: 10.1530/endoabs.44.PL1

Society for Endocrinology International Medal Lecture

PL2

From genetic and genomic to the patient

Mercedes Robledo[1,2]
[1]Spanish National Cancer Research Center, Madrid/Madrid, Spain;
[2]ISCIII Center for Biomedical Research on Rare Diseases (CIBERER), Madrid/Madrid, Spain.

During the last two decades the Scientific Community has assisted to an exponential increase of knowledge of genetic factors related to cancer susceptibility, as well as of key molecular mechanisms involved in tumour progression. In part, this has been the result of using high-throughput platforms able to interrogate any part of the genome following a hypothesis-free strategy. Without a doubt, the success achieved in recent years has to do not only with the improvement in the efficiency of applied OMIC techniques, but also in an exquisite clinical stratification of patients of interest.

One of the best examples of the usefulness of this type of approach can be found in Pheochromocytomas (PCC) and Paragangliomas (PGL), altogether PPGL research. PPGL are rare neuroendocrine tumours with the highest heritability of all human neoplasms. These tumours hide a complex genetic scenario related so far to 31 major and minor genes. New genes are incorporated each year into this long list, and their contribution has still to be addressed. It is worthy to note that while many of these tumors are morphologically indistinguishable, their genomic profiles show a close relationship with the specific driver gene involved in the disease. Comprehensive analyses of OMIC results have lead to the identification of specific altered pathways according to the genetic status in each particular case. In fact, we are closer to recognize the weaknesses of these tumors, and we could take advantage of this feature as the start point of an individualized clinical management of patients.

DOI: 10.1530/endoabs.44.PL2

Society for Endocrinology Starling Medal Lecture

PL3

Breaking NAD+: Vitamin B3 salvage and metabolism in metabolic health

Gareth Lavery
University of Birmingham, Birmingham, UK.

NAD+, as well as its phosphorylated form NADP+, are best known as electron carriers and co-substrates of various redox reactions essential to the cellular processes of energy metabolism and biosynthesis. Dynamic changes in NAD+ availability can trigger sensors, such as the protein deacetylase sirtuin enzymes, to adjust cellular and tissue physiology in response to changes in nutrient availability and energy demand. These signalling processes consume NAD+ and release nicotinamide (Nam), necessitating constant replenishment via enzyme mediated recycling of Nam to NAD+. Importantly Vitamin B3, comprising a family of preformed NAD+ precursors, can be salvaged by cells to also augment intracellular NAD+ availability. The combined pathways contributing to dynamic changes in NAD+ homeostasis can also be regulated by multiple systems such as circadian clock, hormones and nutritional status. Given that NAD+ homeostasis is vulnerable to ageing and metabolic disease, we are aiming to delineate the pathways that determine tissue-specific regulation of NAD+ availability. To this end we are identifying how NAD+ metabolism can impact steroid metabolism and muscle energy sensing, and are revealing the role of the nicotinamide riboside kinases in modulating the ability of various Vitamin B3 molecules to augment NAD+ availability, and rewire cellular energy metabolism. Our human clinical studies are investigating how replenishment or augmentation of cellular and tissue NAD+, using Vitamin B3 supplementation, impact systemic and muscle-specific energy metabolism and mitochondrial function. These studies will be help to understand possible ameliorative effects Vitamin B3 may have on ageing or disease phenotypes. Thus, uncovering the range of tissue-specific pathways of NAD+ metabolism could provide key biomarkers and parameters for assessing and modulating organism health.

DOI: 10.1530/endoabs.44.PL3

Society for Endocrinology Dale Medal Lecture

PL4

The ever changing facets of Cushing's syndrome

Paul Stewart
University of Leeds, Leeds, UK.

100 years have passed since Harvey Cushing linked a basophilic pituitary adenoma to bilateral adrenal hyperplasia, and in doing so elegantly depicted the clinical phenotype of "Cushing's syndrome. Today we are uncovering the molecular basis for these tumours and pioneering novel surgical and medical therapies to improve clinical outcome, but fortunately they remain rare. Conversely iatrogenic Cushing's with concomitant adrenal suppression is seen in the 1% of the population (3% over 70 years) treated with corticosteroids and represents a major management dilemma. More subtle abnormalities may occur in patients on glucocorticoid replacement therapy and those with adrenal incidentalomas.

Our expertise has focussed on aberrant cortisol metabolism causing "tissue-specific" cushings in the face of normal circulating cortisol concentrations. 11b-hydroxysteroid dehydrogenases type 1 and 2 (11b-HSD1,2) interconvert active cortisol to inactive cortisone (and prednisolone to prednisone). Apparent mineralocorticoid excess (caused by mutations in the gene encoding 11b-HSD2) result in Cushings disease of the kidney and florid cortisol-induced hypertension. 11b-HSD1 is expressed in liver and fat, muscle and skin where it augments cortisol induced hepatic glucose output, central adiposity, sarcopenia and dermal atrophy. Mice lacking 11b-HSD1 have favourable metabolic traits and are protected from the phenotype of exogenous Cushing's syndrome. In collaboration with major Pharma, selective 11b-HSD1 inhibitors have shown therapeutic benefit in patients with Metabolic syndrome and hepatic steatosis but probably not of a magnitude that will see further clinical development. Reversal of poor wound healing and skin thinning and their use as steroid sparing agents preventing the side effects of therapeutic prednisolone are likely to be more fruitful translational outcomes.

DOI: 10.1530/endoabs.44.PL4

Society for Endocrinology Jubilee Medal Lecture

PL5

Gut and money, customer shrunk

Stephen Bloom
Imperial College, London, UK.

The endocrine cells of the gastrointestinal system are scattered amongst the mucosal cells and respond to luminal influences via projecting microvilli. They also respond to a rich neural supply through the submucous plexus. These two influences, luminal nutriments and local innervation, compete with control by circulating hormones and also nutriment concentrations. The gut endocrine cells are widely scattered down the mucosa (diffuse endocrine system) and their response is proportional to the length of gut stimulated. The same peptides are also present as neurotransmitters in the central nervous system, which led to study

of their central actions. CNS GLP1 was found to inhibit gastric emptying through dorsal vagal complex in the brain stem. All the gut hormones also block appetite through various central mechanisms.
The world pandemic of obesity shortens life through many mechanisms and is also socially unhelpful. Eat less food, take more exercise, advice only works for some of us. Medication is also mostly ineffective and not free of side effects. Bariatric bypass surgery works. Although designed to produce malabsorption it actually doesn't and acts by dramatically reducing long term appetite. Bypass halves cancer rates and causes remission in the majority of type 2 diabetics, through weight loss. Thinner you actually live longer. However, the procedure is risky, expensive and cannot be adjusted easily.
We identified the most important mechanism involved in gastric bypass was an increased release of the satiety inducing gut hormones, and embarked on a long journey to create a "medical bypass". Thus, we developed analogues of the three main gut satiety hormones so they can be given weekly. In animals they produce massive weight loss and diabetes remission. We are now involved in phase 1 human trials of these agents. This programme has required considerable time and resources but could save a lot of life.

DOI: 10.1530/endoabs.44.PL5

Society for Endocrinology European Medal Lecture
PL6

Toward metabolic precision medicines for obesity and type 2 diabetes

Matthias Tschöp
Munich, Germany.

After decades of research unraveling complex metabolic control networks, medicines capable of a safe reversal of morbid human obesity and type 2 diabetes are still not available. Historically, complex diseases have repeatedly proven to be defiant to the best mono-therapeutic approaches. Several examples of combination therapies have largely overcome such challenges, notably for the treatment of severe hypertension and tuberculosis. Obesity and its consequences, such as type 2 diabetes, have proven to be equally resistant to therapeutic approaches based on single medicines. Appropriate management of type 2 diabetes often requires adjunctive medications, and the recent registration of a few compound mixtures has set the precedent for combinatorial treatment of obesity. On the other hand, double or triple therapeutic combinations are more difficult to advance to regulatory approval. Following an improved understanding of the molecular basis for metabolic benefits following bariatric surgery interventions, several classes of novel unimolecular or independent combination therapeutics were discovered. These new classes of drug candidates are based on gastrointestinal hormones, offer efficacy superior to currently prescribed options and seem to have potential to fully reverse human obesity and type 2 diabetes. Moreover, gut peptide-based cell-specific targeted delivery of small molecules offer additional potential for novel metabolic precision medicines and reduced systemic side effects. In this presentation the discovery, pre-clinical validation and first clinical test of peptide hormone poly-agonist drug candidates as well as of combinatorial single molecule therapeutic candidates will be summarized, including previously unpublished observations.

DOI: 10.1530/endoabs.44.PL6

Society for Endocrinology Transatlantic Medal Lecture
PL7

Abstract unavailable.

British Thyroid Association Pitt-Rivers Lecture
PL8

Thyroid hormone: far reaching consequences of local actions

Graham Williams
London.

Thyroid hormone action in individual target tissues is a complex and tightly regulated process. Thyroid hormones (thyroxine, T_4 and triiodothyronine, T_3) enter target cells via active transport mediated by specific transporter proteins. T_4 is a biologically inactive pro-hormone that is converted to the active hormone T_3 by removal of a critical iodine atom. Two iodothyronine deiodinase enzymes (Dio2 and Dio3) are expressed in peripheral tissues; Dio2 is an activating enzyme that converts T_4 to T_3 whereas Dio3 inactivates both T_4 and T_3 by generating inactive metabolites. The relative activities of Dio2 and Dio3 thus regulate the intracellular availability of T_3. T_3 enters the nucleus and binds with high affinity to nuclear thyroid hormone receptors (TRs) that activate hormone-dependent target gene expression. Thyroid hormone action in individual target cells may be adjusted locally by tissue-specific regulation of thyroid hormone transporter, deiodinase and receptor expression. In studies focusing on the skeleton as an archetypal and physiologically important T_3 target tissue, we show that thyroid hormones exert diverse responses *in vivo* that are restricted in time and space during development and in adulthood, and which also interact with other endocrine signalling pathways.

DOI: 10.1530/endoabs.44.PL8

Clinical Endocrinology Trust Visiting Professor Lecture
PL9

Genomics and Steroidobolomics in Cushing's syndrome: the perspective of a clinician scientist

Martin Reincke
Munich, Germany.

Cushing's disease results from uncontrolled ACTH secretion by corticotroph adenomas of the pituitary, resulting in excess cortisol secretion. Numerous previous studies attempted to gain insight into the molecular mechanisms underlying the development of Cushing's disease, but only few rare mutations have been reported. Recently, an exhaustive exome-wide screening has led us to identify somatic mutations in the ubiquitin-specific protease 8 (USP8) in 36% of adenomas. This gene codes for a protein with deubiquitinase (DUB) activity that inhibits the lysosomal degradation of EGFR. USP8 is tightly regulated by 14-3-3 proteins. Mutated USP8 overrides 14-3-3 control and displays higher DUB activity than the wild-type, therefore increasing EGFR stability and enhancing EGFR-induced POMC transcription and ACTH secretion. Meanwhile, we have generated additional data regarding patients with Nelson s tumor and the ectopic Cushing's syndrome. In a second approach we are aiming to classify patients with suspected Cushing's syndrome using urine and plasma steroid finger prints. These studies are performed in collaboration with the University of Birmingham (W. Arlt) and University of Dresden (G. Eisenhofer). My presentation will show preliminary data of those studies and will close with an outlook of future research outcome, based on the hypothesis, that translational medicine will change diagnosis and therapy of Cushing's syndrome within the next 5 years.

DOI: 10.1530/endoabs.44.PL9

Clinical Endocrinology Trust Lecture
PL10

Endocrine development is for life: looking beyond paediatrics

John Achermann
UCL GOS Institute of Child Health, London, UK.

It is well established that certain endocrine disorders can progress over time, such as autoimmune endocrinopathies or the multiple pituitary hormone insufficiency following cranial irradiation. Although most developmental endocrine disorders are widely considered to be paediatric conditions, milder "non-classic" variants may first present to adult endocrinologists or long-term monitoring may be needed of established conditions as additional endocrine features may only become apparent in later life.

Here, I will highlight three key areas we have been working on in recent years, which have potential implications for long-term endocrine practice. First, I will describe the wide spectrum of phenotypes associated with variations in the transcription factor, steroidogenic factor-1 (SF-1, NR5A1). Although SF-1 is widely regarded as a "master-regulator" of adrenal and gonad development and function, most pathogenic variants in humans cause a reproductive phenotype, ranging from complete gonadal dysgenesis to male factor infertility and primary ovarian insufficiency. The natural life-course of these conditions is still not well understood, and long-term follow up of individuals at risk of developing additional endocrine features is needed. Secondly, I will describe how milder or non-classic conditions can occur due to disruption of key enzymes and transcription factors such as steroidogenic acute regulatory protein (STAR), CYP11A1 and DAX-1 (NR0B1). Patients with these changes may present with adrenal insufficiency but develop reproductive dysfunction with time. Finally, a fascinating new multisystem growth disorder associated with gain-of-function of the growth repressor SAMD9 will be described. In this condition, somatic genomic changes can occur that modify the disease phenotype in different tissues. Given the long-term and dynamic nature of these disorders, close liaison between paediatric and adult endocrinologists is needed to better understand the life-course of these conditions and to monitor and manage subsequent endocrine events.

DOI: 10.1530/endoabs.44.PL10

Society for Endocinology Journal Awards

Society for Endocrinology Journal Award – *Journal of Molecular Endocrinology*

JA1

Gene expression changes in subcutaneous adipose tissue due to Cushing's disease

Irit Hochberg, Innocence Harvey, Quynh T Tran, Erin J Stephenson, Ariel L Barkan, Alan R Saltiel, William F Chandler & Dave Bridges

J Mol Endocrinol October 1, 2015 **55** 81–94. **DOI: 10.1530/JME-15-0119**

DOI: 10.1530/endoabs.44.JA1

Society for Endocrinology Journal Award – *Journal of Endocrinology*

JA2

Hippocampal spine changes across the sleep-wake cycle: corticosterone and kinases

Muneki Ikeda, Yasushi Hojo, Yoshimasa Komatsuzaki, Masahiro Okamoto, Asami Kato, Taishi Takeda & Suguru Kawato

J Endocrinol August 1, 2015 **226** M13–M27. **DOI: 10.1530/JOE-15-0078**

DOI: 10.1530/endoabs.44.JA2

Society for Endocrinology Journal Award – *Endocrine-Related Cancer*

JA3

Pituitary tumors contain a side population with tumor stem cell-associated characteristics

Freya Mertens, Lies Gremeaux, Jianghai Chen, Qiuli Fu, Christophe Williems, Heleen Roose, Olivier Govaere, Tania Roskams, Carolina Cristina, Damasia Becú-Villalobos, Mark Jorissen, Vincent Vander Poorten, Marie Bex, Johannes van Loon & Hugo Vankelecom

Endocr Relat Cancer August 1, 2015 **22** 481–504. **DOI: 10.1530/ERC-14-0546**

DOI: 10.1530/endoabs.44.JA3

Society for Endocrinology Journal Award – *Endocrine Connections*

JA4

Treatment of subclinical hyperthyroidism: effect on left ventricular mass and function of the heart using MRI technique

Peter D Mark, Mikkel Andreassen, Claus L Petersen, Andreas Kjaer & Jens Faber

Endocr Connect 2015 vol. 4 no. 1 37–42. **DOI: 10.1530/EC-14-0137**

DOI: 10.1530/endoabs.44.JA4

Society for Endocrinology Journal Award – *Clinical Endocrinology*

JA5

Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy

Gudmundur Johannsson, Alberto Falorni, Stanko Skrtic, Hans Lennernas, Marcus Quinkler, John P Monson & Paul M Stewart

Volume 82, Issue 1, January 2015, Pages 2–11. **DOI: 10.1111/cen.12603**

DOI: 10.1530/endoabs.44.JA5

Symposia

Challenges in pituitary disease

S1.1

How to manage patients with acromegaly and discordant GH and IGF-I results

Peter Trainer
Manchester.

Serum GH and IGF-I levels are closely correlated but discordance between GH and IGF-I levels can occur in patients with acromegaly either as a consequence of biological factors or as an artefact of the means of assessment or definitions of normality.

Pegvisomant as a GH receptor antagonist lowers serum IGF-I but, due to negative feedback, increases GH levels. Raloxifene has been shown to lower IGF-I in men and women with acromegaly and oestrogen has been described as the 'poor woman's pegvisomant' because it induces a state of relative GH resistance. In our studies in women with untreated acromegaly, serum IGF-I was 82 ng/ml lower than men, with the difference being 130 ng/ml in women on oral oestrogens. Mean IGF-I was 14 ng/ml lower in men with acromegaly on testosterone therapy, presumably a consequence of aromatisation. Increasing age was associated with a fall in IGF-I, for a given GH level.

Pituitary radiotherapy results in apparent discordance between GH & IGF-I levels as the former declines faster than the latter. Pulsatility studies indicate that circulating IGF-I values correlate most closely with trough, rather than mean or peak, GH values. As $>70\%$ of circulating IGF-I is hepatic in origin, liver disease can result in impaired IGF-I generation.

A plethora of consensus statements and guidelines on the management of acromegaly have been published in the last 15 years resulting in regular revisions of the biochemical criteria of the goals of therapy. However vigilance is required when applying international criteria to local practice, as bias in assay performance can be significant, a problem compounded by quality assurance concerns with some commercial kits. Furthermore, the commendable trend to use several thousand samples to define reference ranges has resulted in a significant lowering of the upper limit of reference ranges for IGF-I, such that a patient regarded as controlled by IGF-I criteria a decade ago may no longer be so.

When GH & IGF-I levels are grossly elevated the factors described above are of little clinical relevance. The true challenge of discordant results is in the patient with nearly ideal control and who may benefit from additional treatment. In an era of ever-greater technology, seeking symptoms from patients remains critical to management and good outcomes.

DOI: 10.1530/endoabs.44.S1.1

S1.2

Abstract unavailable.

S1.3

Quality of life in patients with pituitary disease

Niki Karavitaki[1,2]
[1]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK; [2]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK.

Pituitary disease covers a wide spectrum of conditions associated with considerable physical, psychological and cognitive manifestations, a number of which persist even after successful treatment of the pituitary gland disorder.

Quality of life (QoL) is defined as 'the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient''. In the last years, the area of QoL in patients with pituitary disease has received significant attention and the relevant literature has expanded confirming the negative impact of hypothalamo-pituitary pathology on this aspect. These findings have been revealed by generic, as well as disease-specific questionnaires. Notably, impaired QoL (as compared with controls) has been reported even in patients with functioning pituitary adenomas which have achieved remission after treatment. The factors contributing to the impaired QoL have not been established and proposed predictors include age, gender, tumour recurrence, non-replaced hypogonadism or growth hormone, visual field defects, previous radiotherapy and delays in diagnosis. Further parameters requiring exploration include negative illness perceptions, negative beliefs about medications or needs not covered by the packet of care offered.

The development of more comprehensive and disease-specific questionnaires, as well as adequately powered studies involving patients affected by all pituitary disorders will provide further insight in this field, will allow identification of factors predisposing to compromised QoL and will lead to measures aiming to minimize the disease burden for the individual, his/her family and social environment and for the health care system.

DOI: 10.1530/endoabs.44.S1.3

Grappling with the future of anti-inflammatory steroids

S2.1

Designer drugs: uncoupling the beneficial and harmful effects of glucocorticoids

Karolien De Bosscher[1,2]
[1]UGent-VIB, Ghent, Belgium; [2]Receptor Research Laboratories, Nuclear Receptor Lab, Ghent, Belgium.

Glucocorticoid receptor (GR) agonists are amongst the most effective anti-inflammatory drugs available. These drugs are used in the treatment of a wide range of inflammatory and autoimmune diseases, and for the clinical management of cancer and organ/tissue transplantation. Unfortunately, the full clinical potential of these drugs has not been achieved, especially upon chronic use, due to the occurrence of side effects and/or resistance. The past years, most attention has focused on the development of novel compounds favoring the protein-protein interaction dependent, so-called transrepressing, actions of the glucocorticoid receptor, explaining its anti-inflammatory profile. This strategy was adopted since the DNA-dependent transactivating actions were assumed to predominantly underpin undesirable actions. Compounds with this specific profile are classified as SEGRAMs, including selective glucocorticoid receptor agonists (SEGRAs) or selective glucocorticoid receptor modulators (SEGRMs). The latter class rather modulates the activity of a GR agonist and/or may not classically bind the glucocorticoid receptor ligand-binding pocket. Although nowadays it is realized the transrepression vs transactivation concept is a too simplistic and far from watertight approach, currently developed SEGRAMs have nevertheless been helpful in elucidating various molecular actions of the glucocorticoid receptor. As could be expected, their preclinical use also provoked many novel questions.Corticosteroids currently in the clinic are used with a "one-fits-all" rationale for the treatment/management of inflammatory diseases and cancer. Glucocorticoid receptor (GR) regulation and responses are far more complex than previously recognized. GR is not a "one-fits-all" type of target, but requires a tailored approach when it comes to drug discovery to meet the new insight that GR is a receptor demonstrating a high degree of plasticity. Multiple GR conformations must exist, likely resulting in different anti-inflammatory (AI) profiles. Trying to achieve a selective GR-mediated activation of particular AI profiles may offer the potential for the development of safer and disease-tailored GR-targeting medicines.

DOI: 10.1530/endoabs.44.S2.1

S2.2

Combination therapies that lighten the glucocorticoid load

Robert Newton
University of Calgary, Alberta, Canada.

We ask that you provide an abstract of your lecture by using the online submission system. Please click here to create an account and, when asked, please submit your abstract under the INVITED SPEAKER category. Abstracts should be submitted in order for it to be included in the *Journal Endocrine Abstracts*. Any talks which do not have an abstract submitted will appear in Endocrine Abstracts with the phrase "abstract unavailable". Abstracts should be no longer than 300 words which includes words in tables.

Glucocorticoids act on the glucocorticoid receptor (GR) and as inhaled corticosteroids (ICSs) effectively control mild to moderate asthma. However, during exacerbations, or more severe disease, ICS monotherapies are less effective and international guidelines recommend adding-on a long-acting β_2-adrenoceptor agonist (LABA). ICS/LABA combination therapies provide superior asthma control and reduce exacerbation rates compared to increasing the ICS dose. This suggests a biological interaction between these drug classes.

Indeed, LABAs synergistically enhance glucocorticoid-dependent transcription from a simple 2× glucocorticoid response element (GRE)-driven luciferase reporter. This effect occurs via a classical cAMP-protein kinase A (PKA)-dependent pathway and can be observed in human bronchial epithelial and airway smooth muscle cells. The effect is recapitulated using agonists of other Gs-coupled receptors, including PGE2, prostacyclin analogs and agonists at the adenosine A2 receptor. Similarly, phosphodiesterase (PDE) 4 inhibitors enhance GR-dependent transcription and sensitise to cAMP-elevating agents. Such approaches may be used to enhance GR action in systems whether the β2-adrenoreceptor coupling or expression is low.
Not only do LABAs enhance glucocorticoid-dependent transcription, but glucocorticoids enhance LABA-induced gene expression. Both these effects may contribute to the enhanced therapeutic efficacy of ICS/LABA combination therapies. Thus regulator of G-protein signalling 2 (RGS2), a GTPase-activating protein that reduces signalling from Gq-coupled receptors that are central to the pathogenesis of asthma, is induced by LABAs. This effect is enhanced by glucocorticoids to promote responses consistent with bronchoprotection. Conversely, TNFα inducible protein 3 (TNFAIP3), also known as A20, is an inhibitor of NF-κB and is induced by a glucocorticoid and this is further enhanced by a LABA. Glucocorticoid/LABA combination leads to enhanced TNFAIP3 expression to plays a role in the inhibition of NF-κB-dependent transcription. Mechanisms are therefore shown by which glucocorticoid/LABA combinations may promote enhanced bronchoprotective and anti-inflammatory effects that could help explain the clinical efficacy of ICS/LABA combination therapies.
DOI: 10.1530/endoabs.44.S2.2

S2.3

Effective delivery of anti-inflammatory glucocorticoids is a matter of timing
Julie Gibbs, Andrew Loudon & David Ray
University of Manchester, Manchester, UK.

The circadian clock is a key regulator of immune responses. Both circulating and resident immune cells possess intrinsic timers, which act to impart time-of-day variation in their function. It is now becoming evident that the circadian clock is also critically involved in regulating the function of endogenous anti-inflammatory glucocorticoid hormones. Consequently, we see variation in an animal's inflammatory responses dependent on the time the stimulus was delivered. This can vary to such an extent, it can affect survival outcome.
We have demonstrated that the time of day at which a 20 min burst of aerosolized lipopolysaccharide is applied strongly influences the amplitude of the resultant pulmonary neutrophilic response. Exposing mice at the start of the day (lights on) causes significantly greater transcription of the cytokine *cxcl5*, resulting in significantly increased recruitment of neutrophils to the lung. Ablation of the circadian clock in Club cells (bronchiolar epithelial cells critical for maintaining pulmonary timing and the major source of CXCL5) not only abolishes this time-of-day gating in response amplitude, but causes a dramatic increase in CXCL5 production and thus neutrophil recruitment. This is a consequence of reduced binding of the glucocorticoid receptor (GR) to the glucocorticoid response element on the *cxcl5* promoter. We conclude from this that the intrinsic clock within cells regulates the anti-inflammatory action of endogenous glucocorticoid signals via the GR.
This interaction between the circadian clock and GR has significant consequences on the action of applied therapeutic glucocorticoids. Indeed, the repressive action of applied glucocorticoids to pulmonary inflammation varies dependent on time-of-day. With subsets of inflammatory cytokines being responsive to dexamethasone repression only at certain phases of the clock. These findings have implications in the use of therapeutic glucocorticoids, and suggest that effective delivery of anti-inflammatory glucocorticoids is a matter of timing.
DOI: 10.1530/endoabs.44.S2.3

Osteoporosis: translating the new bone biology (*Suported by Journal of Endocrinology*)

S3.1

Abstract unavailable.

S3.2

Abstract unavailable.

S3.3

Abstract unavailable.

Advances in the genetic understanding of endocrine disease

S4.1

Abstract unavailable.

S4.2

Applying new developments in the genetic understanding of inherited pituitary adenoma
Albert Beckers
Centre Hospitalier Universitaire de Liege, University of Liege, Liege, Belgium.

There are a number of established and recently identified inherited or congenital forms of growth hormone (GH) secreting pituitary tumors. These may be caused by an abnormality in the genetic sequence of responsible genes including *MEN1*, *AIP*, *CDKN1B*, and *PRKAR1A*. Copy number variation for these and other genes may also contribute to pituitary tumorigenesis, such as duplication of the gene *GPR101* in X-linked acrogigantism (X-LAG) syndrome. Mosaicism for mutations or copy number variations an also play a causative role in the pathogenesis of pituitary adenomas, including those causing acromegaly and gigantism. Genetic forms of GH secreting pituitary adenomas tend to have more aggressive features than those without a known genetic cause, including a younger age of onset and resistance to medical therapy. Familial isolated pituitary adenomas (FIPA) and MEN1 represent the most frequent causes of genetically related or inherited pituitary adenomas; however to date a genetic component has only been discovered in about 5% of pituitary adenomas overall. In the absence of testing guidelines for all of the various isolated and syndromic forms of pituitary adenomas, clinical characteristics of the patient or kindred are important for guiding the choice of genetic testing.
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S4.3

Somatic mutations and adrenal remodelling in hyperaldosteronism
Morris Brown
Queen Mary University of London, London, UK.

Primary Aldosteronism (PA), due to a unilateral aldosterone-producing adenoma of the adrenal (APA), is the commonest curable cause of Hypertension, but the prospects for cure fall with age. APAs rarely increase in size, suggesting an origin

much earlier than the development of resistant hypertension. Most APAs have gain-of-function somatic mutations which result in increased Ca^{2+} entry, and constitutive activation of aldosterone production. Women with larger APAs, and cells resembling zona fasciculata (ZF) cells, are likely to have *KCNJ5* mutation, whilst smaller APAs in men, with resemblance to zona glomerulosa (ZG) cells, are more likely to have mutations of *ATP1A1, ATP2B3, CTNNB1* or *CACNA1D*.[1,2] The number of different gain-of-function mutations within one gene (19 in CACNA1D), and overall frequency of APAs, suggest a common driver, which we believe may, paradoxically, be salt. A striking difference between ZG of human adrenals and other species is the sparseness of aldosterone synthase expression, and an irregular, even atrophic, ZG. A microarray of ZG cells found several genes which are many-fold upregulated in human ZG (vs ZF) that do not feature in similar analysis of rat adrenals.[3] Functional analysis of some of these genes (e.g. LGR5, DACH1) showed that they inhibit aldosterone production. Since the CYP11B2$^{-/-}$ mouse, and monkeys treated with a selective aldosterone synthase inhibitor, have apoptotic ZG cells, we hypothesize that aldosterone protects against apoptosis, and that the prevailing salt-induced suppression of aldosterone in human ZG selects for ZG cells with mutations causing constitutive aldosterone production. The selective advantage comes not from proliferation, but from synthesis of aldosterone. Indeed, on ^{11}C-metomidate PET CT, ZG-like APAs are often detected as small, bright hot spots within adrenals previously reported as 'normal', and immunohistochemistry shows an inverse correlation between size and CYP11B2 density.

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New frontiers for Vitamin D

S5.1

'Free vitamin D': another twist in the vitamin D story?

Martin Hewison
University of Birmingham, Birmingham, UK.

Research carried out over the last 10 years has supported a wider role for vitamin D in human health, with proposed beneficial effects for cancer, inflammation and infection and cardiovascular disease. A key component of this new perspective on vitamin D is the increased risk of common human diseases associated with decreased circulating levels of 25-hydroxyvitamin D (25D), more commonly referred to as vitamin D-deficiency. Although 25D is the major serum form of vitamin D, it is an inactive precursor of hormonal 1,25-dihydroxyvitamin D (1,25D). There is therefore a broad assumption that 25D is converted to 1,25D in a tissue-specific manner via localised expression of the enzyme 25-hydroxyvitamin D-1α-hydroxylase (*CYP27B1*). Expression of *CYP27B1* has been described for many tissues, but this intracrine model is nevertheless dependent on another key facet of vitamin D physiology, namely the delivery of substrate 25D to the appropriate cells. In serum 25D circulates predominantly by binding to vitamin D binding protein (DBP), which has a higher affinity for 25D than 1,25D. DBP is therefore a key factor in mediating many of the actions of vitamin D, but it is still unclear whether DBP plays an active role in the delivery of 25D to *CYP27B1*-expressing cells. The membrane receptor for DBP, megalin, is widely expressed but is not detectable in many key target cells for vitamin D, notably cells from the immune system. Thus in some settings, it appears that unbound or 'free' 25D is the form of vitamin D that is able to access cells, even though this fraction of circulating vitamin D is very small. The aim of this presentation is to explore the importance of bound versus free 25D in defining the different actions of vitamin D, and the implications this may have for the analysis and clinical application of vitamin D.

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S5.2

Vitamin D and brain development

Darryl Eyles[1,2]
[1]QBI University of Qld, Brisbane, Qld, Australia; [2]QCMHR University of Qld, Brisbane, Qld, Australia.

I have established that low levels of vitamin D at birth increase the risk of schizophrenia in later life in two independent large Danish case/control studies. I have also shown such exposures are associated with increased rates of autism in a large Dutch general population cohort. I have developed an animal model of Developmental Vitamin D (DVD) deficiency which produces phenotypes that mimic many of the symptoms of schizophrenia. In our latest study we have shown the hormonally active form of vitamin D abolishes all phenotypes in a leading inflammatory animal model of relevance to autism.
In this talk I will discuss our extensive data that indicates optimal vitamin D status is required for normal healthy brain development. The evidence obtained from our epidemiological studies is convergent with data obtained from our preclinical and cellular models indicating vitamin D is a powerful developmental neurosteroid. In the absence of this steroid, brain ontogeny is irreversibly affected leading to permanent molecular, cellular and functional brain abnormalities.

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S5.3

Prevention and management of nutritional rickets; a 21st century approach

Wolfgang Hogler[1,2]
[1]Department of Endocrinology and Diabetes, Birmingham Children's Hospital, Birmingham, UK; [2]Institute of Metabolism and systems Research, University of Birmingham, Birmingham, UK.

Calcium and phosphorus represent the main building material for bone stiffness. The supplier of these bone minerals is the hormone calcitriol, which originates from vitamin D, itself made by sunshine in human skin. Requirement for bone mineral supply is highest during phases of rapid growth, such as in the foetus, infant and pubertal child, making them particularly vulnerable.
Deprivation of calcium, whether through low dietary calcium intake and/or low vitamin D, leads to serious health consequences throughout life, such as hypocalcaemic seizures, dilated cardiomyopathy, skeletal myopathy, congenital and infantile rickets, and osteomalacia. These 5 conditions, often summarised as 'symptomatic vitamin D deficiency', are fully reversible but also fully preventable.
However, in the 21st century, calcium deprivation has reached epidemic proportions, not only in the third world, but also in high-income countries - specifically amongst dark-skinned and other at-risk ethnic populations. The increasing prevalence of rickets and osteomalacia, and the deaths from hypocalcaemic cardiomyopathy, demand action from global health care providers. Clarification of medical and parental responsibilities is a prerequisite to deliver successful prevention programmes, and the UK lags behind most other European countries.
The quality of a nation's public health can be derived from how it treats and invests in its children and other vulnerable risk groups. The foetus and infant have the human right to be protected against harm. Prevention programs, including vitamin D supplementation and food fortification, should have the same public health priority as vaccinations. The global consensus for the prevention of management of rickets has provided evidence-based guidance on how such programs can be delivered, and recommend vitamin D supplementation for pregnant women, infants, and risk groups.

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Why endocrinologists should pay attention to gut feelings (Supported by *Endocrine Connections*)

S6.1

Abstract unavailable.

S6.2

Where the gut meets the brain

Diego Bohorquez
Duke University, Durham, NC, USA.

Body surfaces, like the skin or the gut lumen, are protected from the outer world by a layer of epithelial cells. Almost all epithelial sensory cells communicate stimuli from the outer world to neurons via direct neurotransmission, but in the gut, the epithelial sensory cells, the enteroendocrine cell, is thought to communicate indirectly via the release of hormones.
However, enteroendocrine cells have striking features of epithelial cell transducers: they are electrically excitable, possess voltage-gated channels, express synaptic proteins; and recently, we reported that nerves innervate them. The source and function of these connections remains to be documented. Here, we discovered that enteroendocrine cells transduce nutrient signals to cranial nerves. First, we adapted a neurotracing vector, based on the neurotropic rabies virus, and used it to define a physical innervation of enteroendocrine cells by cranial nerves. Second, we developed a co-culture system in which enteroendocrine cells and neurons connect. And third, using electrophysiology, we found that a glucose stimulus applied to the enteroendocrine cell induces excitatory post-synaptic potentials and action potential spikes in the connected neuron. Notably, glucose does not activate a neuron by itself.
The functional innervation of enteroendocrine cells by cranial nerves represents a novel neural circuit for the brain to receive and respond to sensory stimuli from the gut lumen.

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S6.3

Abstract unavailable.

Hormones through the ages

S7.1

Abstract unavailable.

S7.2

Thyroid and ageing

Diana van Heemst
Leiden University Medical Center, Leiden, The Netherlands.

Several differences have been observed in thyroid function parameters between older and younger individuals. Notably, circulating thyroid stimulating hormone (TSH) levels gradually increase with age, a shift shown to extend to extremely high ages. While clinically abnormal thyroid function parameters have been consistently associated with ill health, the mechanisms underlying mild age-related variations in circulating levels of TSH and thyroid hormones and their health consequences remain poorly understood, especially at advances ages.
Although ageing is universally driven by deterioration of biological integrity over time, it manifests itself in different individuals at a different pace and by different (tissue-specific) pathologies. The heterogeneity and complexity of the ageing process impose specific challenges for studies on age-related hormonal changes. Theoretically, mild age-related differences in thyroid function parameters might be indicative of (i) subclinical thyroid disease, (ii) adaptive hormonal responses to underlying disease(s), or (iii) selective survival of individuals genetically predisposed to higher TSH levels.
In order to identify determinants of human longevity, the Leiden Longevity Study (LLS) included 421 families with at least two long-lived Caucasian siblings fulfilling the age criteria (men $\geq$89 years and women $\geq$91 years) without selection on health or demographics. We also included the offspring of these long-lived siblings and partners thereof, serving as a control group. In a subsample of offspring and controls, blood was frequently sampled over 24 hours, from which circulating TSH levels were measured every 10 minutes and levels of thyroid hormones every hour. Previously, we found higher TSH secretion and a stronger TSH-fT3 temporal relationship in the offspring compared to controls. Our current research which is performed in the THYRAGE (Resetting the THYRoid axis for prevention of AGE-related diseases and co-morbidities) consortium is devoted at disentangling what mechanism(s) underlie the observed differences in thyroid function parameters and how these might favour longevity.

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S7.3

Glucocorticoids and the Ageing Brain

Joyce Yau
University of Edinburgh, Edinburgh, UK.

Chronic stress or excess glucocorticoids may promote brain ageing and cognitive decline. Elevated blood cortisol levels or increased sensitivity to cortisol's action in brain cells play a crucial role in the development of age-dependent memory deficits. It is now recognized that the concentration of glucocorticoids within specific tissues including brain are derived not just from blood hormone levels but also from the local regeneration of active glucocorticoids by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Our studies highlight the important contribution of brain 11β-HSD1 generated glucocorticoids in age-associated memory decline. Thus life-long deficiency of 11β-HSD1 or short-term 11β-HSD1 inhibition protects against spatial memory impairments in aged mice, despite elevated plasma glucocorticoid levels. We recently investigated whether brain 11β-HSD1 generated glucocorticoids also play a prominent role in stress-induced memory impairments. Here we present data that show chronic stress in mid-aged wild type mice leads to impaired spatial memory, an effect that persisted for at least 6 months after the period of stress thus accelerating cognitive ageing. Importantly, 11β-HSD1 deficient mice resisted both the immediate and persisting effects of chronic stress on impairment of spatial memory. 11β-HSD1 is therefore a promising novel target for the treatment of age and stress related cognitive impairments in humans.

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Thyroid hormone: the journey from cell surface to action (Supported by *Journal of Molecular Endocrinology*)

S8.1

Thyroid hormone transport into target tissues

Jiesi Chen[1], Steffen Mayerl[2] & Heike Heuer[1,2]
[1]Leibniz Research Institute f. environmental Medicine, Düsseldorf, Germany; [2]Leibniz Institute on Aging, Jena, Germany.

Thyroid hormone (TH) actions and metabolism are intracellular events that require the transport of TH across the plasma membrane. This process is facilitated by TH transporters of which the monocarboxylate transporter 8 (MCT8), encoded by the Slc16a2 gene, has been most intensively analyzed. In humans, inactivating mutations in the X-linked *MCT8* gene are associated with a severe form of psychomotor retardation in combination with abnormal serum TH parameters. The clinical picture (also known as Allan-Herndon-Dudley syndrome) clearly underscores the significance of MCT8 for proper brain development as well as normal TH metabolism and signaling. In mice, however, Mct8 deficiency does not grossly affect brain development whereas the endocrine abnormalities of the patients are fully replicated.
Our studies revealed that in the mouse CNS, another TH transporter is present that can partially compensate for the absence of Mct8. Whereas Mct8 plays a prominent role in facilitating the uptake of the active hormone T3 into the brain, the organic anion transporting peptide Oatp1c1 (Slco1c1) mediates the transport of T4 across the blood-brain barrier. Consequently, mice deficient in both transporters (Mct8/Oatp1c1 dko mice) exhibit a pronounced hypothyroid situation in the CNS whereas peripheral organs are in a thyrotoxic state.
A first phenotypic description of Mct8/Oatp1c1 dko mice revealed distinct deficits in neuronal differentiation as well as pronounced locomotor deficiencies. The latter phenotype may be explained by a reduced myelination, a retarded cerebellar development and cortical as well as striatal abnormalities. Interestingly, application of the TH analog Triac during early postnatal periods was sufficient

to normalize brain abnormalities and significantly improved locomotor functions of Mct8/Oatp1c1 dko mice. These data underscore the potential of Triac as a therapeutic option for patients with AHDS.

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S8.2

Thyroid hormone metabolism in target tissues

Monica Dentice
Napoli, Italy.

Thyroid hormone (TH) is a major determinant of muscle physiology, and thyroid dysfunctions are leading causes of many myopathies. Precise control of thyroid hormone-dependent transcription is required by multiple cell system, including muscle stem cells, but how this is achieved is still largely unknown. Intracellular TH concentration is determined by a metabolic balance between the activating and inactivating deiodinase enzymes, D2 and D3. In functional combinations, these regulatory enzymes provide the ability to fine tune TH action at cellular level.
We demonstrated that D2-induced T_3 production is essential for normal myogenesis and muscle regeneration and that mice lacking D2 fail in their regeneration process. D3 − the TH inactivating enzyme − is an oncofetal protein frequently re−expressed during the adult life in proliferating tissues. In addition to D3's expression in embryonic tissues and tumors, D3 can also be reactivated in response to diverse tissue injuries, which include myocardial infarction and hypertrophic cardiac failure, inflammation liver regeneration and neural injury. We recently demonstrated a novel role of the TH inactivation by D3 in muscle stem cells (satellite cells) and in muscle regeneration. Our data demonstrate that in response to proliferative stimuli such as skeletal muscle acute injury, D3 is specifically induced in satellite cells where it reduces intracellular thyroid signaling. Satellite-specific genetic ablation of D3 impairs skeletal muscle regeneration. This impairment is due to massive satellite cell apoptosis, caused by aberrant exposure of activated satellite cells to the physiological, but spatio-temporally excessive, TH concentrations in the circulation. In conclusion, our results indicate that the D2 and D3 enzymes are dynamically exploited *in vivo* to adapt TH-signaling and simultaneously orchestrate distinct gene activation and repression programs required for the satellite cell lineage progression and survival. These studies suggest that the selective modulation of thyroid hormone concentration could be used to enhance rate-limiting steps in the muscle regeneration process, modulating stem cells expansion and/or differentiation, this might contribute to optimizing

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S8.3

Abstract unavailable.

Exposing the sins of our fathers (and mothers)

S9.1

Maternal nutrition around conception and its influence on fetal development and adult health

Tom Fleming
University of Southampton, Southampton, UK.

The early embryo before implantation, in addition to undergoing the intrinsic steps of morphogenesis, demonstrates external 'awareness' of environmental conditions in particular maternal nutritional quality. These nutritional cues are used to optimise the developmental programme for long-term survival, a form of developmental plasticity. Thus, maternal protein restriction exclusively during mouse preimplantation development with normal nutrition thereafter and postnatally, is sufficient to induce adult-onset cardiometabolic and behavioural disease risk. Related human models show a similar legacy for periconceptional maternal nutrition on long-term health. We have shown changes in maternal metabolites induced by diet are detected by embryos within the uterine environment via signalling mechanisms. These programme a series of compensatory responses within the embryo affecting differentially the embryonic and extra-embryonic cell lineages. Collectively, these changes alter the fetal growth trajectory via epigenetic, cellular and physiological mechanisms, leading ultimately to postnatal disease risk. The mechanisms and consequences for periconceptional maternal nutritional programming on intergenerational health will be discussed. Funding: BBSRC, MRC, NICHD, EU-FP7, Rosetrees Trust, Kerkut Trust.

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S9.2

Epigenetic mechanisms in the transgenerational transmission of disease risk – myth or reality?

Amanda Drake
University of Edinburgh, Edinburgh, UK.

Although development is a highly organised and tightly regulated process, the developing embryo is sensitive to environmental influences, resulting in pathophysiological changes which may increase the risk of later cardio-metabolic, neurobehavioural and reproductive disorders. We have shown that prenatal overexposure to the synthetic glucocorticoid dexamethasone (Dex) in rats reduces birthweight in the first generation (F1) and leads to hypertension and insulin resistance in the offspring. Since we originally reported that these 'programmed' phenotypes could be transmitted to a second generation (F2), particularly through the male line, a growing number of studies have shown that the effects of early life exposure to environmental influences are not limited to the F1 generation, but may be transmitted to a second or further generations through non-genomic mechanisms. In this talk I will review the evidence for the transmission of programmed effects across generations and discuss potential mechanisms, including whether induced changes in DNA methylation, histone modifications or non-coding RNA may be transmissible through the gametes.

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S9.3

Abstract unavailable.

Clinical thyroidology update

S10.1

Thyroid incidentalomas, US, CT, MR and PET

Petros Perros
Department of Endocrinology, Royal Victortia Infirmary, Newcastle upon Tyne, UK.

Over the past two decades, the developed world has witnessed an epidemic of incidental thyroid nodules diagnosed through imaging of the neck for other indications. This has created new challenges for patients and clinicians. Several guidelines have been published in the past 2 years on this topic, which are broadly concordant and only differ in detail. Optimal management is based on the following principles:

1. Avoidance of imaging unless there is a clear indication
2. Clinical risk stratification based on individual patient's characteristics
3. Ultrasound-based risk stratification

4. Progress to cytological evaluation if indicated
5. Clear communication between responsible clinician, patient and other relevant parties at all stages of the diagnostic process

09:45 – 11:15

I am not a radiologist and I don't perform US of the thyroid. Got as far as attending an ETA workshop on thyroid US about 8 years ago and decided it was not for me, based on the fact that the environment in which I worked offered high quality thyroid US and US guided FNA that was easily accessible, which I would never match. It perplexes me that colleagues (mainly in Europe) who have been trained in thyroid US, are total converts and will use it in their clinic, not just in patients with nodules but any thyroid patient. "My clinical assessment of any patient with thyroid disease seems incomplete without the US probe".

As for my personal experience with CT, MR and PET it is confined to what comes my way form referrals and our MDT.

Speaking of our MDT, since I was asked to produce this talk, I started to collect some data on incidentalomas and here they are.

So, I will approach this topic from the "jobbing" endocrinologist

Themes

1. Definition
2. Extent of the problem
3. Trends over time
4. What do the guidelines tell us
5. What the guidelines do not tell us (clinical vignettes)
6. Glimpse into the future

christosandrakakos@yahoo.co.uk

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S10.2

Thyroiditis: Post-partum, subacute and new drugs

Mark Vanderpump
Physicians' Clinic, London, UK.

Destructive thyroiditis is characterised by hyperthyroidism due to release of preformed hormones. The increased concentration of thyroid hormone suppresses serum TSH. Radioactive iodine uptake is close to nil in all cases when hyperthyroidism is present. The duration of hyperthyroidism is generally 2–3 months and limited by the amount of thyroid hormone present. The ratio of serum T3:T4 is lower in destructive thyroiditis than in Graves' disease. Hypothyroidism is common after the hyperthyroid phase. In some patients, only the hyperthyroid or hypothyroid phase is noted. Permanent hypothyroidism can complicate some forms of destructive thyroiditis more than others. In most cases specific therapy is not necessary during the hyperthyroid phase although beta-blockers can be helpful. Glucocorticoids may decrease the duration of the clinical syndrome but are rarely necessary in painful or painless subacute thyroiditis. The most common variant of painless subacute thyroiditis is post-partum thyroiditis occurring in approximately 5% of all post-partum women in iodine sufficient areas. The presence of pain in patients with destructive thyroiditis is generally considered the important diagnostic point. Painful thyroiditis is thought to be post-viral, self-limited with a granulomatous histology. Painless thyroiditis is usually considered to be autoimmune and to require long-term surveillance. A destructive thyroiditis has been observed in a significant number of patients treated with immune checkpoint inhibitors which have substantially improved the prognosis for patients with advanced melanoma and a number of other malignancies.

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S10.3

Sick Euthyroid Syndrome

Anita Boelen
Academic Medical Center, Amsterdam, The Netherlands.

The "sick euthyroid syndrome" or "non-thyroidal illness syndrome" (NTIS) occurs in a large proportion of hospitalized patients and comprises a variety of alterations in the hypothalamus-pituitary-thyroid (HPT) axis that are observed during illness. One of the hallmarks of NTIS is decreased plasma triiodothyronine (T3) levels, in severe illness accompanied by low plasma thyroxine (T4) and increased plasma reverse T3 (rT3) concentrations. Downregulation of hypophysiotropic thyrotropin releasing hormone (TRH) neurons in the paraventricular nucleus (PVN) of the hypothalamus and of thyrotropin (TSH) production in the pituitary gland points to altered feedback regulation during illness. The extent of the NTIS correlates with prognosis, but at this stage there is no proof for causality of this association. The changes in thyroid hormone (TH) metabolism are organ-specific, occur in a time-dependent manner and depend on the severity of illness. Acute alterations in plasma TH concentrations are a reflection of altered TH binding, uptake and metabolism by deiodinating enzymes, as well as by concomitant macronutrient restriction. Acute NTIS appears to be adaptive and probably beneficial, and may be considered part of the acute phase response to systemic illnesses. However, the pathogenesis of NTIS is different in prolonged critical illness when patients continue to depend on intensive medical care. In this prolonged critical illness, hypothalamic thyrotropin releasing hormone (TRH) expression is suppressed, explaining persistently reduced TSH secretion and TH release in spite of low plasma TH. At present there is no evidence-based consensus or guideline advocating thyroid hormone treatment of NTIS in the critically ill patients. Adequately powered RCTs should be performed to define whether active management of NTIS, e.g. using hypothalamic neuropeptides including TRH, may yield clinical benefit in terms of outcome.

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Diabetes mellitus – it's all about the beta cell, stupid! (Supported by *Journal of Endocrinology*)

S11.1

Genetic causes of impaired insulin secretion in type 2 diabetes

Sof Andrikopoulos
University of Melbourne, Melbourne Victoria, Australia.

Hyperglycaemia in type 2 diabetes is caused by insufficient insulin being secreted by the islet β-cell. In addition, the progressive nature of diabetes is due to the continuing decline of islet β-cell function with time. Currently we do not know what causes islet β-cell dysfunction in diabetes and we do not have effective drugs that specifically target the defect in insulin secretion. Clinical studies show that existing therapies have variable glucose-lowering effects, and a significant proportion of patients with T2D (perhaps up to 50%) have a poor response and therapeutic failure. These responses are likely to have a genetic basis, but currently there is limited information available to predict outcomes. Clearly to provide effective and durable treatment for T2D we first need to identify the genes causing islet β-cell dysfunction and to then understand how drugs can interact with the patient's genetic constitution. We have been using a powerful genetic resource called the Gene Mine to identify causative genes of type 2 diabetes. We have demonstrated the power, speed and accuracy of our world-leading gene mapping resource in discovery of clinically relevant diabetes genes. By identifying the genes underlying the insulin secretory response and efficacy associated with targeting the incretin response, our findings will assist in identifying and testing new gene targets

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S11.2

Beta-cell adaptation and failure during progression of type 2 diabetes

Ross Laybutt
Garvan Institute of Medical Research, Sydney, Australia.

The critical contribution of deficient insulin secretion to the pathogenesis of type 2 diabetes is beyond doubt. The normal beta-cell response to obesity-associated insulin resistance is hypersecretion of insulin that maintains blood glucose levels within the normal range. This is associated with both expansion of beta-cell mass and enhanced beta-cell function. Type 2 diabetes only develops in subjects that are unable to sustain the beta-cell compensatory response. This is associated with a progressive deterioration of beta-cell function, particularly impairment of glucose stimulated insulin secretion (GSIS), and a loss of beta-cell mass through an increased rate of apoptosis. Thus, type 2 diabetes arises in subjects with islets that are susceptible to dysfunction and apoptosis under conditions of high demand. Stress within the endoplasmic reticulum (ER) organelle of the cell has been proposed as a mechanism for beta-cell dysfunction and death in type 2 diabetes. ER stress activates a signalling cascade known as the unfolded protein response (UPR) – the role of which is both to alleviate the ER stress through the upregulation of protein folding enzymes and chaperones and,

paradoxically, to activate apoptosis via deleterious UPR signalling if the stress is too severe or prolonged. Recent findings suggest that upregulation of the adaptive UPR is linked with beta-cell compensation and protection against obesity-associated diabetes. Conversely, in genetically susceptible islets, suppression of ER adaptation and loss of beta-cell differentiation underlies beta-cell failure and progression to diabetes. Factors leading to failure of ER adaptation include chronic hyperglycaemia, inflammation and hypoxia. This knowledge is critically important to understanding the mechanisms responsible for the switch from beta-cell compensation to failure in type 2 diabetes.

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S11.3

The role of mitochondrial metabolism in the control of insulin secretion

Hindrik Mulder
Lund, Sweden.

Mitochondria are essential for the fuel-stimulated processes in beta-cells that control insulin secretion. Indeed, mutations in mitochondrial DNA underlie rare forms of maternally-inherited diabetes, where insulin secretion is impaired. Studies in human islets have identified several perturbations of mitochondrial function but whether they are causal or not has not been determined. Mining data from genome-wide association studies led us to the discovery of a variant of *TFB1M*, which encodes a protein that controls translation of mitochondrial proteins. Risk variant carriers exhibit elevated plasma glucose levels, reduced insulin secretion, lower TFB1M protein levels and impaired mitochondrial function, as well as increased risk of type 2 diabetes. Mice with a heterozygous general knock out or beta-cell-specific knock out of *Tfb1m* become glucose intolerant and ultimately hyperglycemic. Functional studies of islets from such mice or clonal beta-cells, where *Tfb1m* has been silenced, revealed abrogated fuel-stimulated insulin secretion, loss of mitochondrial proteins, impaired respiration and reduced ATP generation. Beta-cell-specific homozygous and heterozygous knock out of *Tfb2m*, a paralogue of *Tfb1m* and a *bona fide* transcription factor, exhibited an even more pronounced phenotype, with rapidly evolving diabetes and mitochondrial dysfunction. These studies demonstrate, on a functional and molecular level, the critical role of mitochondria in control of beta-cell function and insulin secretion. Human genetics lends support to the notion that mitochondrial dysfunction plays a contributing, but causal, role in the deterioration of beta-cell function in type 2 diabetes.

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Novel approaches to endocrine neoplasia (Supported by *Endocrine-Related Cancer*)

S12.1

Identification of New Therapeutic Targets in MEN1

Paul Newey
University of Dundee, Dundee, UK.

Multiple Endocrine Neoplasia type 1 (MEN1) is a highly penetrant autosomal dominant disorder characterized by the combined occurrence of parathyroid, anterior pituitary and pancreatic islet tumours. Affected individuals are also at risk from a wider spectrum of tumours, which includes thymic and bronchial carcinoids, and adrenal cortical tumours. MEN1 results from germline mutation of the *MEN1* gene, which encodes the tumour suppressor protein Menin. The absence of a genotype-phenotype correlation results in the recommendation for lifelong screening, although despite this, MEN1-associated tumours continue to be associated with significant morbidity and premature mortality. In addition, the unpredictable course of disease results in considerable uncertainty for affected individuals and their families. The treatment strategies for MEN1-associated tumours are typically based on those employed for their sporadic counterparts, namely that of intervention once observable disease has occurred. Key differences in disease natural history, including a frequent early age of onset, tumour multi-focality, and an increased risk of further tumour development, indicates that improved approaches are required. However, the development of MEN1-specific treatments requires an improved understanding of disease pathogenesis, as well as the availability of relevant model systems in which to evaluate their use. Addressing this challenge, several recent studies have provided an improved understanding of the mechanisms responsible for MEN1-associated tumourigenesis as well as fundamental insights into Menin protein function. Together, these studies indicate that Menin is implicated in widespread epigenetic regulation, whilst influencing several key cellular signaling pathways in a cell context dependent fashion. Similarly, murine models of MEN1 have enabled proof-of-concept studies to evaluate novel therapeutic approaches.
This talk will review recent progress in defining the natural history of MEN1 as well as highlighting advances in both clinical and molecular aspects of the disease with a particular focus on current and future therapeutic prospects.

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S12.2

Novel techniques for nuclide imaging in pituitary and adrenal tumours

Olympia Koulouri
University of Cambridge, Cambridge, UK.

Functional imaging in endocrine disease is now being increasingly used as an aid in the management of challenging cases, where conventional imaging techniques are inadequate/inconclusive. This talk will provide an overview of available nuclide imaging techniques and specifically focus on the use of ^{11}C-Methionine PET in pituitary and ^{11}C-Metomidate PET in adrenal tumours.

^{11}C-Methionine PET in pituitary disease

Although MRI is very useful in pituitary imaging, it can not detect all microadenomas and does not always reliably distinguish between post-operative remodelling and residual tumour. Methionine, as the first amino acid incorporated into all peptides, is an ideal substrate for ^{11}C-labelling to allow identification of sites of increased peptide/protein synthesis. In contrast to ^{18}F-FDG, it is preferentially taken up by the normal pituitary gland compared to surrounding brain. Its potential utility has been explored in the identification of pituitary microadenomas, but also in the detection of residual functioning pituitary adenomas following primary intervention (surgery, radiotherapy).

^{11}C-Metomidate PET in adrenal disease

As primary aldosteronism (PA) is increasingly recognized to be the cause of hypertension in a significant proportion of hypertensive patients, prompt detection and resection of the offending adrenal lesion is crucial. Although adrenal vein sampling remains the gold-standard diagnostic technique in PA, it is technically demanding and not always feasible. Metomidate, a potent inhibitor of CYP11B1 and CYP11B2, can be C^{11}H$_3$-labelled as a PET tracer and has been shown to be taken up avidly by aldosterone producing adenomas (APAs). ^{11}C-metomidate PET-CT has thus been used in a proportion of patients as an alternative to AVS for localising unilateral APAs.

DOI: 10.1530/endoabs.44.S12.2

S12.3

Abstract unavailable.

Special Workshops and Sessions

Applied Physiology Workshop: Endocrinology on safari: using comparative biology to unravel the complexities of endocrine physiology

APW1.1

Unravelling endocrine autoimmunity in companion animals

Lorna Kennedy
Manchester.

Auto-immune diseases are complex diseases, that occur as a result of the influence and interaction of multiple genes, (at least 20, could be more than 100). However, the critical feature of these diseases is that they only occur after exposure to an environmental trigger. As yet, most environmental triggers have not been identified. Most human autoimmune diseases have been shown to have an association with genes in the Major Histocompatibility Complex (MHC). However, since man is essentially outbred, thousands of cases and controls are required for Genome wide association studies (GWAS) in order to have the power to detect less strongly linked markers.
Many canine autoimmune diseases have been shown to have associations with the canine MHC. Dogs spontaneously develop these diseases and most dogs also share their environment with humans. These factors, plus the similar aetiologies of the canine and human diseases, suggest that the dog could be a good model for human disease.
Each dog breed represents a genetically inbred population, thus it is possible to study the same disease in different genetic backgrounds. Significant disease associations have been identified in canine GWAS, using only 100 cases and 100 controls.
We have used this approach to study canine diabetes, hypothyroid disease and Addison's disease.
One key question is: "Could there be a genetic test for complex diseases?"

DOI: 10.1530/endoabs.44.APW1.1

APW1.2

Abstract unavailable.

APW1.3

Employing zebrafish and mice to study neuroendocrine programming

Deborah Kurrasch
Calgary, Canada

The neuroendocrine hypothalamus is located at the base of our brain and is important for controlling various physiologies, such as hunger, thirst, thermoregulation, and reproduction. Despite considerable knowledge about the hormones that regulate these physiologies and the circuits responsible for transmitting their cues, very little known about the developmental programs that govern hypothalamic formation the first place. Indeed, questions still remain about how individual hypothalamic neurons acquire a particular cell fate and then migrate to an exact location to enable proper circuit formation. For the past several years, our lab has been using mice and zebrafish as complementary model systems to understand neuroendocrine developmental programs.
In this talk, I will outline some of our work exploring the role of the homeodomain transcription factor *Rax* on conferring a hypothalamic neuronal fate in both mice and zebrafish. I will also share our results of the requirements of the proneural genes *Neurog2* and *Ascl1* in establishing final positioning of neurons within a nuclear structure in mice. And finally, I will end showing some evidence that endocrine disrupting chemicals, such as bisphenol A, are interfering with these normal developmental programs and leading to lasting changes in the neuroendocrine hypothalamus in zebrafish. Combined, I hope to demonstrate the utility of using mice and zebrafish to study the development of neuroendocrine centers.

DOI: 10.1530/endoabs.44.APW1.3

Early Career Symposium: Launching your career whatever it may be

EC1.1

Abstract unavailable.

EC1.2

A career in professions allied to science and medicine

Victoria Cabrera-Sharp
University of Oxford, Oxford, UK.

It's crowded at the top of the academic pyramid. A large percentage of doctoral graduates and research staff will not gain tenure in academic research positions. Universities now provide career advice for graduate students and post-doctoral researchers, usually regarding careers outside of academia, be that in research or otherwise. What, then, for those of us that are still passionate about science and working within academia? A career in science administration may not be as dull as it sounds; it can be a great way to keep you at the forefront of cutting edge science, but it relies heavily on networking to get into and succeed. Simply playing an active role within this Society can help you here. There is a growing field within universities offering opportunities to work both in administration (research funding, clinical trials, project management, contracts and technology transfer, for example) or in research facilitation, directly with academic researchers (administering grant applications, providing advice to potential applicants, organising peer review of grants applications and so on). Research experience is usually a requirement, especially for roles which involve developing and maintaining contacts within the research community, for instance, university departments, funding bodies and Government departments. As medical schools are aligned to NHS partners, opportunities arise to work directly for the NHS whilst supporting honorary lecturers within the University setting. The work involves many of the skills that will have been honed during your years as a PhD student or post-doc and, with the right coaching, it is relatively easy to turn you and your CV into a credible candidate for one of these positions. Don't think that research stops once you've left the lab. In the right position, you can forge opportunities to undertake research projects to drive science policy within your institutions or in collaboration with funding bodies.

DOI: 10.1530/endoabs.44.EC1.2

EC1.3

Abstract unavailable.

EC1.4

The route to floristry via medicine – forging a clinical academic career as a trainee

Anna L Mitchell
Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK.

In recent years, the integrated clinical academic pathway has made a previously seemingly chaotic career pathway far more organised. This is now a well-trodden path; for those interested in research, there are opportunities to join this pathway at every stage, from academic foundation programmes through to fellowships

aimed at those post-CCT. Combining clinical training in endocrinology (and not forgetting diabetes and general internal medicine too) with research, whether basic or clinical, is a real challenge, but also offers unique opportunities. There are highs (landing your first grant, getting your research published, presenting at a sunny international conference) and there are lows (writing a point-by-point rebuttal to a pedantic peer-reviewer's 67 comments on your resubmitted manuscript, the day you receive your first funding rejection and then have to spend hours cheering yourself up by planning your escape into your alternative "dream career"). This talk will detail the speaker's adventures through the clinical academic career pathway to date, and highlight opportunities to get involved in research, even for those who intend to finish their training without ever stepping foot on the integrated clinical academic pathway.

DOI: 10.1530/endoabs.44.EC1.4

EC1.5

Rejection from Tesco: Making your PhD work

Samantha Mirczuk
Royal Veterinary College, London, UK.

We all work incredibly hard to produce a thesis that will allow us to sail through our vivas and get that piece of paper, which says we have a doctorate. The next step is to grab hold of an exciting post-doc position, where we can press the "start" button on a rather traditional career path to independence. During the course of two post-docs, the golden numbers of research articles will be written, submitted, peer-reviewed and published, allowing for a fellowship application to be submitted, awarded, and independence achieved. But what happens if your career path is not as straightforward as this? Perhaps, your project takes longer to establish, resulting in a delay in publications. You may get rejected for a fellowship and have to take on another post-doc position. You may even take a career break as you start a family. Does a career path that is a little more indirect than expected mean that we should give up on the idea of becoming an independent scientist and apply for a position in Tesco? The short answer is, No. Teaching is a skill that is often overlooked by PhD students and post-docs in their quest for independence. Teaching can help complement a CV, to show a diversity of skills other than writing research papers. Teaching could involve; presenting lectures, developing direct learning activities, running tutorials, writing exam questions, working with the widening participation department or simply supervising students in the laboratory. There are also teaching courses available to enhance your understanding of the methods used to teach students. Teaching is a fun and rewarding way of developing skills that will show you to be a well-rounded individual, capable of not only being an independent researcher by getting project grants, but also a successful lecturer.

DOI: 10.1530/endoabs.44.EC1.5

Nurse session 1: Preparing for endocrine pregnancies

N1.1

Abstract unavailable.

N1.2

Nurse session: Preparing for Endocrine Pregnancies: Thyroid

Kristien Boelaert
Birmingham.

Thyroid hormones play crucial roles in foetal growth and neurodevelopment which are dependent on adequate supply of maternal thyroid hormones from early gestation onwards. During pregnancy there are important physiological changes resulting in altered reference ranges and complicating the interpretation of thyroid function tests. Thyroid dysfunction is common in pregnancy and the prevention of adverse obstetric and foetal outcomes relies upon careful monitoring and treatment before and during pregnancy.

Overt and subclinical hypothyroidism are usually managed through increased doses of levothyroxine replacement, although there is ongoing debate regarding the optimal target ranges as well as the need for universal screening. Further controversies surround the management of isolated hypothyroxinaemia and TPO antibody positivity before and during pregnancy and particularly in the setting of infertility.

Hyperthyroidism in women of childbearing age is usually due to Graves' disease. In the early stages of pregnancy the differential diagnosis from transient gestational thyrotoxicosis may be difficult. Uncontrolled thyrotoxicosis in pregnancy is associated with poor outcomes and optimisation of thyroid function prior to conception as well as careful management of treatment during pregnancy are crucial for mother and foetus.

Thyroid nodules are common in the general population and may occur in women of childbearing age. Their management is similar to that outside the setting of pregnancy. When thyroid cancer is diagnosed during pregnancy, often a conservative approach is adopted for low risk tumours. In patients who are on suppressive treatment with levothyroxine following treatment of thyroid cancer, careful monitoring of thyroid function is required.

This lecture will give an overview of the diagnosis and management of thyroid diseases before, during and after pregnancy with reference to the most up to date national and international guidelines.

DOI: 10.1530/endoabs.44.N1.2

N1.3

Preparing for endocrine pregnancies: prolactinoma

Aled Rees
Cardiff University, Cardiff, UK.

Endocrinologists are faced with three main issues when managing a woman with a prolactinoma contemplating pregnancy: restoration of fertility, consideration of the effects of dopamine agonists on the developing foetus, and the effects of the high oestrogen environment of pregnancy on prolactinoma expansion. Untreated hyperprolactinaemia leads to anovulatory menstrual cycles with resultant amenorrhoea and infertility in most patients. Therefore, treatment is usually required in order to achieve pregnancy. Dopamine agonists are very effective in restoring ovulatory cycles ($>90\%$) and fertility, and are generally used in preference to transsphenoidal surgery. Cabergoline is better tolerated than bromocriptine and has better efficacy in restoring ovulatory cycles, hence is usually preferred. Dopamine agonists can cross the placenta. Treatment should thus be discontinued as soon as pregnancy is confirmed in order to limit drug exposure to the developing foetus. Neither drug appears to increase the risk of foetal malformations although experience with cabergoline in pregnancy is more limited. However, the data for quinagolide are currently less reassuring. Clinically relevant tumour growth occurs in approximately 2% of microprolactinomas but up to 20% of macroprolactinomas. This risk is significantly lower in patients who have previously undergone transsphenoidal surgery or radiotherapy. Prolactin rises normally during pregnancy, hence routine measurement is not helpful. Surveillance in pregnancy is thus reliant on clinical assessment, including regular formal assessment of visual fields in women with macroprolactinomas. Dopamine agonists may be recommenced to good effect in patients who develop significant tumour expansion, and transsphenoidal surgery is rarely required. There are no special requirements for delivery, other than the need for increased glucocorticoid cover in macroprolactinomas with associated hypopituitarism. Breast feeding should be encouraged in the standard manner as there is no evidence that this results in clinically important tumour expansion. However, dopamine agonists cannot be used until breast feeding is complete.

DOI: 10.1530/endoabs.44.N1.3

Nurse session 2: Male fertility

N2.1

Male puberty and spermatic development

Kate Davies
London, UK.

This session will focus on spermatogenesis and pubertal development in boys, emphasizing the use of the Tanner staging system in clinical practice. Implications of early and delayed puberty will be discussed, plus normal pubertal development, and its relevance in sperm banking for children undergoing cancer treatment.

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N2.2

Abstract unavailable.

N2.3

Secondary Infertility

Andrew Dwyer[1,2]
[1]University of Lausanne, Institute of Higher Education & Research in Healthcare, Lausanne, Switzerland; [2]Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.

Primary forms of infertility result from gonadal causes and have limited treatment options. In contrast, secondary infertility is of neuroendocrine origin and is amenable to several therapeutic approaches. Reproductive capacity depends on critical developmental windows of hormonal activity during neonatal life and during puberty. Thus, a developmental perspective can provide insight for predicting fertility potential as well as for guiding the selection of treatment to maximize outcome. This presentation will provide an overview of male reproductive physiology and the respective targets for fertility-inducing treatment. The evidence base for different fertility-inducing treatment will be reviewed as well as a brief summary of emerging therapeutics and their pros and cons. Particular attention will be given to predictors of outcome and the importance of tailoring the treatment approach. This nursing-focused presentation will provide a foundation for understanding treatments for the patient with secondary infertility and will highlight the importance of patient education and shared decision-making.

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Senior Endocrinologists' Session

SE1.1

Abstract unavailable.

SE1.2

Conservation endocrinology: What, are there more than two species to consider?

Alan McNeilly
University of Edinburgh, Edinburgh, UK.

Conservation is a tricky subject to discuss when people actually are asked to consider the present situation, and the virtual world that many live in today. Many of the losses of species are due to human intervention, through killing for pleasure, food, or profit (greed), or through habitat destruction. The species are innocent. Zoos provide a sanctuary for maintaining some numbers of species on a limited scale, but can only ever be a stop-gap to maintain the species, although with a reduced gene pool. Feral animal control on the other hand is difficult, and attempts to introduce robust methods that do not involve killing the animal to avoid upsetting the general public and/or politicians, e.g. immuno-contraception, have met with limited success. For breeding success to be maximized requires an in depth knowledge of the endocrine control of egg production and maintenance of pregnancy through to birth of a viable offspring. Most studies use urine as blood sampling usually requires anaesthesia, and this limits the endocrine profiling that can be achieved. Nevertheless reasonable data bases are being developed for a few species. Further success will require more comparative studies, given the different strategies utilized by different species to establish a pregnancy once an egg is fertilized. This may involve delayed implantation but determining the signals that control implantation is difficult to study. Drawing on our previous studies on meerkats, elephants, deer, wallabies, squirrels, badgers, and currently pandas, we will review potential problems in saving species through controlled breeding programs, and emphasize that studying only e.g. human and mice, or a few cell types often in isolation, will never advance knowledge. This is particularly the case given the inadequate career track for many scientists on year by year funding crises, and inadequate development and assessment of reagents supplied commercially.

DOI: 10.1530/endoabs.44.SE1.2

SE1.3

Gut Dysbiosis and Hypertension – new or resurrected

John Honour
University College London, London, UK.

New research claims, for the first time, that gut microbiota affect hypertension in rats but authors were unaware of historical research indicating this link. The urine steroid metabolome by gas chromatography of a patient with congenital adrenal hyperplasia from 17-hydroxylase (CYP17) deficiency was reported in 1978. Many of the steroids were 21-deoxy products of corticosterone and could be hypertensinogenic or glycerrhitinic acid like factors. Further studies in CYP17 deficient patients supported an enterohepatic circulation of corticosterone. 21-dehydroxylation of corticosterone by bacteria was characterised in 1969 by Sjovall and Gustafsson from comparisons of normal and germ free rats. In studies in 1982-1985 hypertension was induced by corticosterone or adrenocorticotrophin administration to Sprague Dawley rats. The increase in blood pressure was attenuated by antibiotic treatment. The normal development of high blood pressure in spontaneously hypertensive rats (SHR) was also attenuated by antibiotic administration. Full characterisation of the gut microbiome was difficult then, especially for the anaerobes. The gut microbiota is now much easier to study using bacterial 16S ribosomal RNA analysis. An imbalance of gut microbiota is called dysbiosis. Experiments involving the transplantation of caecal contents between rat strains support the link of gut dysbiosis with hypertension. Elevated blood pressure is associated with a decrease in bacteria involved in acetate (Holdemania and Coprobacillus) and butyrate production (Clostridia). An increase in lactate production (Lactobacilli) is also seen. Short chain fatty acids activate G-protein coupled receptors and affect vaso-reactivity and renin secretion. The microbiota of human hypertensive patients has a dysbiotic pattern similar to the SHR. The maintenance of blood pressure is a complex process. The kidney and caecum are important sites of salt absorption under steroid control. Further analysis of the gut microbiome in hypertension is needed. In the future, dietary intervention to adjust gut bacteria could be an innovative strategy for treating hypertension.

DOI: 10.1530/endoabs.44.SE1.3

SE1.4

On gonads and gadflies: the oestrus angle

Stephen G Hillier
MRC Centre for Reproductive Health, The Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, UK.

"In the Lucanian woods among the oaks ‖ Of green Alburnus' slopes there swarms a fly ‖ (By us called gad-fly, *oestrus* by the Greeks). ‖ It's fierce and buzzes monstrously: whole herds ‖ In terror of it scatter through the woods, ‖ Until the sky rings with their bellowing…" *Virgil, Georgics, Book III [K.R. Mackenzie's translation]*.

Virgil's description of demented cattle shrouded in clouds of stinging gadfly provides a striking metaphor for hormone-induced sexual arousal and unwittingly links steroid signalling in mammals and insects. The Victorian reproductive biologist Walter Heape seized upon Virgil's verse to bring forward the concept of the 'oestrous' cycle, in which the female's period of heightened sexual receptivity to the male is called *oestrus* (derived from Greek οἶστρος 'gadfly, breeze, sting, mad impulse' https://en.wikipedia.org/wiki/Estrous_cycle). Crystallisation of an oestrus-inducing steroid – oestrone – from the urine of pregnant women in 1929 founded the sex hormone era and launched reproductive medicine. A quarter of a century later a co-discoverer of oestrone, Adolph Butenandt, had a major hand in purifying ecdysone, the steroid hormone that induces moulting (ecdysis) in insects – including gadflies. Beyond their role in insect moulting, ecdysteroids are found at high concentrations in various plants including commonly consumed vegetables such as spinach. Their roles in plant physiology are uncertain but as nutraceuticals they have anabolic effects similar to androgenic steroids, apparently mediated via oestrogen receptor beta signalling. As such, ecdysteroids are putatively subject to misuse as performance enhancing substances in athletics [Parr MK et al. *Biol. Sport* 2015;32:169–173]. This talk explores the fascinating historical and chemical connections between oestrone and ecdysone and celebrates the ubiquity of steroid physiology and pharmacology.

DOI: 10.1530/endoabs.44.SE1.4

Clinical Management Workshops

Workshop 1: Endocrinology at the edge of the reference range (Supported by *Endocrinology, Diabetes & Metabolism Case Reports*)

CMW1.1

Normocalcaemic hyperparathyroidism – treat or discharge

Graham Leese
University of Dundee.

Primary hyperparathyroidism (PHPT) has become more prevalent as routine screening for serum calcium became more widespread. The current prevalence of PHPT is about 0.5–1% and possibly higher. The majority of patients are asymptomatic or have relatively subtle symptoms. NIH criteria for surgery are mainly based on patient symptoms and/or signs of end-organ damage, and the majority of patients do not fulfil these criteria. However it has become apparent that patients not fulfilling the surgical criteria may have increased rates of cardiovascular disease and other adverse endpoints. As assays for plasma PTH and vitamin D assays have become more widely used, the condition of "normo-calcaemic primary hyperparathyroidism" (NCPHPT) has emerged. Patients with NCPHPT have a normal serum calcium but raised PTH concentration in the absence of vitamin D deficiency, chronic kidney disease or the use of thiazide diuretics or lithium. It is thought that NCPHPT may be a stage in the natural history before PHPT develops, although it may also reflect inappropriate reference ranges for older and obese individuals. Most studies of 1–17 years follow up show low levels of progression but in one study 19% progressed to PHPT at 3% years. Patients who progressed were older, and had higher baseline serum and urinary calcium concentrations. A small number of patients with NCPHPT have undergone parathyroidectomy, and histology has almost universally demonstrated an adenoma or hyperplasia. It is unclear whether NCPHPT is related to increased morbidity as most studies are observational have been done in selected patients, with small numbers of patients and with limited duration of follow up. The condition of normo-calcaemic hypoparathyroidism has also been described and investigated.

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CMW1.2

Low testosterone and normal gonadotrophins: Who, when and how to treat?

Richard Quinton[1,2]
[1]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; [2]Endocrine Unit, Newcastle-upon-Tyne Hospitals Foundation NHS Trust, Newcastle upon Tyne, UK.

Hypogonadotrophic hypogonadism (HH) in males is defined both biochemically – low serum testosterone (T) level with LH+FSH levels in or below the lower half of the reference range – and clinically. *ie.* the person is actually hypogonadal. This clinical criterion is crucial for an accurate diagnosis adult-onset HH in men, because biochemical features are common to other scenarios for which T treatment is presently not indicated. These include afternoon-, or non-fasted-venepuncture, intercurrent or chronic non-gonadal illness of any description, sleep-deprivation, reversed sleep-wake cycles from night shifts, recent abuse of non-prescription opiates or androgens, and hyperinsulinaemic diabetes/prediabetes (where hepatic SHBG secretion is suppressed, leading reduced total T with preserved free T).

A notable feature of the male hypothalamo-pituitary-gonadal (HPG) axis is that, though far less vulnerable to bioenergetic deficit–highly-associated with hypothalamic amenorrhoea in women – it is uniquely vulnerable to obesity. By contrast, obesity *per se* doesn't result in women developing HH. Despite interesting preliminary data that should prompt definitive clinical trials of T therapy for men with "diabesity", there are insufficient safety and outcome data to support off-label prescribing.

For men presenting as adult with this biochemical picture, the diagnosis of HH requiring T therapy may be obvious through absence of secondary sexual characteristics, a history of pituitary surgery, irradiation, or trauma, otherwise unexplained anaemia or osteoporosis, or indefinite high-dose prescribed opiates. By contrast there may be evident signs of systemic illness, such as sleep apnoea, for which therapy should instead be directed at the underlying disease.

However, in the absence of such features, a fasted 8–9 am screen comprising Hb/Hct/ferritin, anterior pituitary function (including calculated free T) and lipid/metabolic profile usually separates men with organic HPG disease (who will likely need MRI pituitary as well as T therapy) from those with physiologically low LH/FSH/T (who require neither, particularly if desiring fertility).

DOI: 10.1530/endoabs.44.CMW1.2

CMW1.3

Mild glucocorticoid autonomy and the adrenal nodule: medical or surgical management?

John Newell-Price
[1]University of Sheffield, S Yorks, UK; [2]Sheffield Teaching Hospitals NHS Foundation Trust, S Yorks, UK.

Adrenal incidentalomas (AI) found on axial imaging are common. In ages <20 y the prevalence is $<1\%$, but this increases around 10% of the population aged 70 y. Depending on definitions anything between 10–40% of these tumours exhibit low-grade cortisol excess, but patients are without the classic features of Cushing's syndrome. This equates to 1–4% of the ageing population.

Independent studies from our own group and others have demonstrated excess mortality and cardiovascular risk in these patients with AI and low-grade cortisol secretion. Numerous cross sectional studies demonstrate increased rates of glucose intolerance, diabetes and osteoporosis. The key question is whether intervening in these patients is associated with patient benefit. Numerous uncontrolled surgical series have shown improvements in co-morbidities in patients who have undergone adrenal surgery in this context, but this is not a uniform finding. Selecting such patients remains an art, with no objective stratification tool available.

In light of this we have used the GR antagonist mifepristone for short durations in such patients to ask whether offsetting the action of cortisol improves parameters that may be cortisol-dependent. We have found that insulin resistance may be improved in some but not all, potentially providing a means to stratify patients to intervention. In 24-hour sampling studies we have established that the cortisol rhythm in AI patients with low grade cortisol secretion differs in the early to late evening and that it is possible to 're-set' this by timed cortisol-lowering medical intervention, resulting in an immediate improvement in key cortisol-dependent parameters, and a rationale for medical therapy or a stratification step. What is needed are large scale intervention studies to formally assess the impact of such medical approaches as these may be of significant relevance to a large number of the ageing population.

DOI: 10.1530/endoabs.44.CMW1.3

Workshop 2: Adrenal insufficiency and CAH

CMW2.1

Dynamic control of tissue glucocorticoids and its implications for replacement therapy

Brian Walker
University of Edinburgh, Edinburgh, UK.

Although Endocrinologists have focused for decades on circulating concentrations of cortisol, arguably the important concentrations are those within tissues which are available at corticosteroid receptors. Tissue concentrations are influenced by plasma proteins binding cortisol, by physicochemical characteristics of the steroid, by active transport across cell membranes, and by steroid metabolism within target tissues. Many of these factors vary between individuals, and within individuals according to nutritional and inflammatory status. For example, common variants at the locus encoding corticosteroid binding globulin (CBG) make a genetic contribution to variations in plasma cortisol, affecting CBG stability and affinity for cortisol and thereby potentially altering the tissue delivery of cortisol. Moreover, cortisol metabolism within tissues varies substantially after feeding and during acute illness. These variations reinforce the unmet need for monitoring of glucocorticoid effects which extends beyond measurement of blood steroid concentrations.

Recently, we discovered differences between tissue-specific control of cortisol and corticosterone, the other endogenous glucocorticoid in humans. Using stable isotope tracers we found rapid exchange between free and bound cortisol pools in plasma, and between plasma and brain or liver cortisol pools, but very slow exchange between plasma and adipose tissue, consistent with substantial buffering of ultradian and circadian cortisol rhythms within adipose. We attributed this to tissue-specific expression of ABCB1, an ATP-binding cassette transporter, which exports cortisol from brain but not adipose tissue. However, in adipose we showed that an alternative transporter, ABCC1, exports corticosterone and not cortisol. Consistent with these findings, in Addison's disease we showed that ACTH suppression is relatively resistant to cortisol while adipose tissue transcript induction is relatively resistant to corticosterone. Development of corticosterone as a novel replacement therapy may therefore allow adequate suppression of ACTH, for example in congenital adrenal hyperplasia, without adverse effects that are mediated in adipose tissue such as obesity and metabolic dysfunction.

DOI: 10.1530/endoabs.44.CMW2.1

CMW2.2

Abstract unavailable.

CMW2.3

Outcome in CAH around the globe

Miguel Debono
Sheffield Teaching Hospitals, NHS Foundation Trust, Sheffield, UK.

The management of congenital adrenal hyperplasia is challenging. Patients suffer from multiple morbidities related to excess androgens or glucocorticoid over-replacement. Multiple studies in Europe and the US have shown a high rate of metabolic complications in patients suffering from CAH including obesity, hypercholesterolaemia, insulin resistance, high blood pressure and low bone mineral density. Some studies have shown that patients with CAH have a poor quality of life and impaired fertility and the condition has also been associated with an excess mortality due to adrenal crises. It has been suggested that non-physiological glucocorticoid replacement in these patients could be one of the prime factors resulting in these complications. Different groups are developing novel strategies for treatment to mirror the physiological cortisol rhythm and provide more effective treatment resulting in less adverse effects; these include oral formulations of modified release hydrocortisone or subcutaneous hydrocortisone infusions. Other upcoming treatments added to a regime including glucocorticoids and mineralocorticoids, acting to directly suppress androgens, include CRF1 receptor antagonists and CYP17A1 inhibitors. Endocrinologists all over the world continue to play a central role in the management of patients with CAH and together with other members of the multidisciplinary team it is our duty to persist with improving health outcomes.

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Workshop 3: How do I …

CMW3.1

How I approach Drug-Induced Hyperprolactinaemia

Paul Newey
University of Dundee, Dundee, UK.

Drug-induced hyperprolactinaemia is a frequently encountered clinical entity due to the large number of commonly prescribed medications that may influence prolactin secretion. Anti-psychotics, anti-depressants and anti-emetics are most frequently culpable, predominantly due to inhibitory effects on hypothalamic-pituitary dopamine signalling. The onset and severity of hyperprolactinaemia may be highly variable, and individuals may harbour typical symptoms (e.g. galactorrhoea, amenorrhoea, erectile dysfunction) or remain asymptomatic. Initial clinical assessment typically involves the exclusion of other causes of hyperprolactinaemia, whilst the short-term discontinuation of implicated medications frequently allows the diagnosis to be confirmed. When cessation of medication is not possible, or other aetiologies suspected, pituitary imaging is frequently employed. Once a diagnosis of drug-induced hyperprolactinaemia is established, the decision to treat depends on the presence or absence of symptoms and/or evidence of clinical sequelae resulting from associated hypogonadism. Where possible, switching to an alternative medication may resolve the problem, whilst for those individuals in whom alternate agents are not suitable, treatment of hypogonadism with oestrogen or testosterone may be appropriate. The use of dopamine-agonists remains controversial in this setting and is typically avoided due to concerns over the potential to exacerbate underlying psychiatric diagnoses. This presentation will highlight the potential challenges of managing drug-induced hyperprolactinaemia, and will have a particular focus on areas of clinical uncertainty

DOI: 10.1530/endoabs.44.CMW3.1

CMW3.2

Abstract unavailable.

CMW3.3

Abstract unavailable.

CMW3.4

How do I manage refractory hypercalcaemia?

Jeremy Turner
Norfolk and Norwich University hospital, Norwich, UK.

Hypercalcaemia is a moderately common condition accounting for approximately 1% of all acute general medical presentations. Guidance on emergency management of the hypercalcaemic patient, aimed primarily at the generalist and at guiding initial stages of management has recently been developed by the society (https://www.endocrinology.org/policy/docs/13-02_Emergency-Guidance-AcuteHypercalcaemia.pdf). Indeed, management of hypercalcaemia is often relatively straight forward and based on adequate rehydration, identification of the cause and appropriate onward management depending on the underlying diagnosis. However, for a variety of reasons management can sometimes become extremely challenging. In this presentation I will briefly summarise the potential causes of a case of hypercalcaemia becoming refractory and outline a structured approach to the management of such cases of hypercalcaemia. I will discuss the role of less common but sometimes essential interventions such as emergency parathyroidectomy, dialysis, use of Denosumab as a hypocalcaemic agent and others. I will also share some "tricks of the trade" and give advice on when and when not to use these as well as outlining pitfalls that may sometimes cause problems. My aim is that by the end of this session you will have a better understanding of the causes of refractory hypercalcaemia, a structured approach to dealing with a case of refractory hypercalcaemia and more confidence in your approach to these cases.

DOI: 10.1530/endoabs.44.CMW3.4

CMW3.5

How do I prepare a patient for phaeo surgery?

Amir Sam
London.

All patients with phaeochromocytoma should undergo surgical resection by an experienced surgeon. Surgery should only be carried out after adequate medical preparation to minimize catecholamine-related adverse events. Pre-operative pharmacologic treatment is aimed at controlling hypertension and tachycardia, and volume expansion. This session will summarise the current practice in the medical management of patients with phaeochromocytoma at Hammersmith Hospital.

DOI: 10.1530/endoabs.44.CMW3.5

CMW3.6

How do I determine Cortisol deficiency in the critically ill patient?
Jeremy Tomlinson
University of Oxford, Oxford, UK.

Critical illness is associated with significant morbidity and mortality. The changes in the hypothalamo-pituitary-adrenal (HPA) axis that occur during critical illness are complex and whilst early studies had suggested improved outcome in patients with septic shock treated with parenteral glucocorticoids, this was not endorsed in subsequent studies and it remains a highly controversial area.
In patients with underlying pituitary or adrenal disease where compromise of HPA axis function is documented prior to the onset of critical illness, stress dose hydrocortisone replacement is essential, although there is still debate as to the precise dose and mode of administration.
In the absence of established endocrine disease, diagnosing adrenal insufficiency during critical illness (often termed relative adrenal insufficiency or critical illness related corticosteroid insufficiency) remains contentious and challenging. There are few robust data upon which to base absolute cut-offs and differences between cortisol assays add a further layer of complexity. Studies using both 250 μg and 1 μg short Synacthen tests have been used and incremental cut-offs have been proposed and these will be discussed. However, the most recent guidance available for the management of septic shock advises against the use of dynamic testing of the HPA axis. Furthermore, recent insights into the dynamics of cortisol metabolism have suggested that many of the abnormalities that are observed during critical illness may relate to decreased cortisol clearance. This has implications both for the interpretation of the assessments that are made as well as the doses of hydrocortisone treatment that may be used.
DOI: 10.1530/endoabs.44.CMW3.6

Workshop 4: How do I manage… (Supported by *Endocrinology, Diabetes & Metabolism Case Reports*)

CMW4.1

How should I counsel a young woman with PCOS about fertility?
Stephen Franks
Imperial College London, London, UK.

Fertility problems in women with PCOS are by no means inevitable. Indeed women who have symptoms of PCOS have at least one child just as often as those who do not have PCOS. But there is no doubt that women with PCOS who have oligo- or amenorrhoea are likely to require induction of ovulation and, in these circumstances, the sooner they seek the appropriate treatment for induction of ovulation, the better the chances of a timely pregnancy.
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CMW4.2

Abstract unavailable.

CMW4.3

How long should I treat prolactinoma?
James Ahlquist
Southend Hospital, Westcliff on Sea, UK.

Many patients taking medical therapy for a prolactinoma may assume that they need treatment for life. In reality it is often possible to stop treatment after a while. In considering whether to stop treatment of a prolactinoma, it is helpful first to review the diagnosis and clarify whether the patient has a prolactinoma. Hyperprolactinaemia has many causes, and some patients are treated without a secure diagnosis of prolactinoma.
For a woman with a microprolactinoma, the usual aim is to allow normal ovarian function and so maintain a healthy degree of oestrogenisation. It follows that, after the menopause, there may be no benefit in treatment of hyperprolactinaemia. For a patient with a macroprolactinoma, in whom treatment is reducing the size of the tumour and protecting vision, life-long treatment may be necessary. However, in some cases it is possible to reduce or stop treatment without a new threat to vision, for example after an episode of pituitary apoplexy causing infarction of the prolactinoma.
In considering whether to stop treatment of a prolactinoma it is helpful to take into account the size of the prolactinoma before treatment and the response to treatment, as these factors help predict the likely outcome of stopping treatment. In principle patients should be treated for a prolactinoma for as long as they are deriving a clinical benefit from treatment. Where this may no longer be the case consideration should be given to stopping treatment. After stopping treatment a period of follow-up is important to determine whether it is appropriate for the patient to continue without treatment.
DOI: 10.1530/endoabs.44.CMW4.3

CMW4.4

Abstract unavailable.

CMW4.5

How do I manage hypothalamic amenorrhoea?
Anna Crown
Brighton and Sussex University Hospitals NHS Trust, Brighton, UK.

'Functional' hypothalamic amenorrhoea (FHA) is a common cause of secondary amenorrhoea. A focused history should include a full menstrual history (including hormonal contraception); diet, weight and exercise (including any eating disorder); any significant stressors; the woman's current situation in relation to contraception and fertility plans; a personal or family history of a lack of sense of smell (suggesting Kallmann syndrome); and any family history of delayed menarche, menstrual or fertility problems. Symptoms of acne or hirsutism, hot flushes or galactorrhoea suggest other diagnoses. The clinical examination should include height, weight and visual fields. Typical laboratory results supporting a diagnosis of FHA include a low/normal LH, normal FSH, normal prolactin, normal/low TSH, normal/low FT4, and low oestradiol. It may also be helpful to check a 9 am cortisol, coeliac screen and vitamin D. A 'Provera test' can be used to assess oestrogen status. Usually there is no need for a pituitary MRI scan or a transvaginal ultrasound scan. A DEXA scan is unlikely to change management. Clear explanations are vital, including the cause of FHA, from a physiological and evolutionary perspective, research evidence about the interactions between genetic and environmental causes, reassurance about ovarian function, discussion about future fertility options, and why oestrogen is important for bone health. Initial approaches to treatment are psychological and dietary. Resumption of natural menses is best for bone health, together with vitamin D3 treatment if required and adequate dietary calcium, but not bisphosphonates. If menses do not resume, oestradiol treatment with a cyclical progestogen is recommended. Transdermal oestradiol has the best evidence for improving bone mass, but a variety of other factors may influence patient choice, including social acceptability, stigma and prescription charges. Oestrogen treatment should be paused for a few months at appropriate intervals to reassess the endogenous menstrual cycle.
DOI: 10.1530/endoabs.44.CMW4.5

CMW4.6

Abstract unavailable.

Meet the Expert Sessions

Extracellular vesicles in health and disease
MTE1

Extracellular vesicles in health and disease
Chris Gardiner
Uviversity College London, London, UK.

Extracellular vesicles (EVs) are membrane-bound vesicles which are release by most, if not all, cell types into the extracellular space. They may be divided into two types: microvesicles which are shed directly from the plasma membrane; and exosomes which are released via multivesicular bodies. Although initially thought to be cellular junk, EVs represent an important mode of intercellular communication and are highly conserved across species. This is achieved through the transfer of nucleic acids, proteins and lipids which effect changes in physiological and pathological processes in recipient and parent cells. The removal of unwanted cellular components via EV release is important in maintaining cellular homeostasis, while plasma EVs play an important role in maintaining vascular integrity by contributing to haemostasis. EVs are also important in innate and adaptive immune responses. However, it is the role of EVs in cancer that has been most widely studied and best understood. The transfer of oncogenic receptors and nucleic acids from tumour cells to normal cells can result in oncogenic transformation. EVs also play an important role in metastasis and angiogenesis. As the composition of EVs reflect the phenotype and function of their parent cell, their analysis as biomarkers of disease has generated a great deal of attention and circulating EVs are increasingly being used as "liquid biopsies" in a variety of pathological conditions. This work has been hampered by the small size of EVs and the unpredictable expression of marker present on the parent cell. Consequently, there has been an explosion in techniques for the isolation and characterisation of EVs which poses challenges for standardisation. Finally, the potential of EVs for drug delivery or therapeutic agents in their own right is starting to be realised, with the first clinical trials being developed over the last few years.

DOI: 10.1530/endoabs.44.MTE1

Society for Endocrinology guidance on the late endocrine effects of cancer treatment
MTE2

Abstract unavailable.

Sport – how to support endocrine patients in sport from recreation to Olympics
MTE3

Abstract unavailable.

Real-time metabolomics in clinical settings
MTE4

Abstract unavailable.

Nutritional support post bariatric surgery
MTE5

Nutritional support post-bariatric surgery
Barbara McGowan
Guy's & St Thomas NHS Trust, London, UK.

Bariatric surgery is a well established treatment for obesity and its associated co-morbidities. Many obese patients undergoing bariatric surgery have pre-existing micronutrient deficiencies which can potentially worsen post-bariatric surgery. Pre- and post- surgical nutritional monitoring and follow-up of these patients is imperative as part of long term bariatric care. This lecture will review common nutritional deficiencies post-bariatric surgery, and current guidelines for monitoring and replacement of vitamins and minerals prior to, and following bariatric surgery. Case studies will be used to highlight clinical presentations of micronutrient deficiencies and the importance of early intervention to prevent long term adverse events.

DOI: 10.1530/endoabs.44.MTE5

Endocrine disruptors – fact or fiction?
MTE6

Abstract unavailable.

A Year in Thyroid
MTE7

Abstract unavailable.

The adolescent with DSD
MTE8

The Adolescent With DSD
S. Faisal Ahmed
University of Glasgow, Glasgow, UK.

It is paramount that any adolescent with a suspected disorder of sex development (DSD) is assessed by an experienced clinician with adequate knowledge about the range of conditions associated with DSD. If there is any doubt, the case should be discussed with the regional team. In most cases, a named endocrinologist within the regional DSD team acts as the first point of contact. The underlying pathophysiology of DSD and the strengths and weaknesses of the tests that can be performed should be discussed with the affected young person and parents and tests undertaken in a timely fashion. This clinician should be part of a multidisciplinary team experienced in management of DSD and should ensure that the affected person and parents are as fully informed as possible and have access to specialist psychological support. Finally, in the field of rare conditions, it is imperative that the clinician shares the experience with others through national and international clinical and research collaboration.

DOI: 10.1530/endoabs.44.MTE8

Illuminating the islets

MTE9

Using photo-pharmacology to reveal the importance of the islet beta cell network

David Hodson
University of Birmingham, Birmingham, UK.

Type 2 diabetes mellitus (T2DM) is one of the foremost health challenges presently facing developed society, affecting almost 10% of the UK adult population. This disease state can be best described as a failure of the insulin-secreting pancreatic beta cell mass to compensate for peripheral resistance. The resulting increases in blood glucose concentration lead to a range of co-morbidities including renal and heart disease, as well as blindness and nerve problems. Mounting evidence suggests that, by focusing on individual isolated beta cells, we may be missing key elements in the tissue-level regulation of insulin release, as well as how this is impaired during T2DM. By harnessing the spatiotemporal precision of light to finely control electrical activity, optogenetics and photopharmacology have opened up the possibility to study the behaviour of beta cells directly within the islet context. This presentation will describe how these techniques are being combined with *in situ* imaging approaches to investigate the role of beta cell-beta cell communication in insulin secretion, thus re-defining our view of the mechanisms underlying T2DM.

DOI: 10.1530/endoabs.44.MTE9

Futures

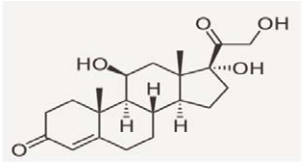
Futures 1: My future career in endocrinology?

FUT1.1

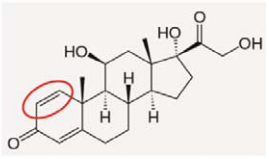
This house believes that prednisolone should be the first line for glucocorticoid replacement in adrenal insufficiency: The case FOR…

Karim Meeran
Imperial College, London, UK.

Natural hormones are continuously secreted and metabolised and thus have a short half-life. When administered exogenously, either the natural hormone needs to be administered often, or analogues with longer half-lives are given. For insulin, slow release (zinc suspensions) have been used, and more recently, the molecule has been extensively modified to give longer lasting insulins. Similarly, hydrocortisone can be given as a slow release or modified release preparation, or the molecule can be modified to lengthen its half-life. Prednisolone by virtue of a single double bond binds more than twice as avidly to the Glucocorticoid Receptor and has a longer half-life than hydrocortisone.



Hydrocortisone



Prednisolone

The combination of the increased binding and longer half-life renders prednisolone six times more potent than hydrocortisone. Thus 3 mg prednisolone taken once daily is similar to 20 mg hydrocortisone in divided doses. Levels of prednisolone can now be used to monitor replacement, and an 8-hour level of between 10 and 20 mcg/l is adequate replacement.
Traditionally replacement has been with higher doses such as 20 mg + 10 mg hydrocortisone, or 5 mg prednisolone as it was believed that an excess of steroid reduced the risk of an Addisonian crisis without harm, but even a slight excess is now thought to be harmful. Audits of patients reveal that patients on excessive doses have more osteoporosis than expected. Because prednisolone is widely used in larger doses for autoimmune diseases, the rate of side effects in those on prednisolone is artificially elevated compared to hydrocortisone. However a once daily replacement dose of between 3 mg and 4 mg daily avoids the high afternoon and evening levels that occur with hydrocortisone, especially when patients take a dose late. Once daily prednisolone mimics the normal endogenous circadian rhythm better than other glucocorticoids.

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FUT1.2

My future career in endocrinology? Endocrine careers: a trainee's view

Christine May
Worcestershire Royal Hospital, Worcestershire, UK.

As a specialist trainee nearing the end of training in endocrinology and diabetes I will share my experience and thoughts about specialty training and a career in endocrinology.
If you are wondering why to choose endocrinology and diabetes as a specialty, what the specialty has to offer you, what you will experience as a specialty trainee and how to make the most out of your training program, then this presentation is designed with you in mind.
The UK training for endocrinology and diabetes is based on a 5-year training program with dual certification in general internal medicine. The specialty covers both common long-term conditions, such as thyroid dysfunction and diabetes, but also a wide range of other conditions including the rare and unusual. The complexity of cases and inter-specialty working are two of the many factors that have drawn me to the specialty as well as the ability to forge relationships with patients whom you may care for over their entire lifetime. With new therapies on the horizon and genomics starting to influence practice, the specialty is constantly progressing, providing new challenges and areas to specialise in. Furthermore, training and pursuing a career in endocrinology presents ample opportunities for research and the satisfaction derived from providing tangible benefits for patients.

DOI: 10.1530/endoabs.44.FUT1.2

FUT1.3

"Why, where and when to do Endocrinology Research"

Stephen O'Rahilly
University of Cambridge, Cambridge, UK.

Endocrinology is a discipline that has always attracted doctors with inquisitive minds. There is much that is still to be learned about the causes of endocrine diseases and how to best prevent and treat them. Whether your principal goal is to be a basic scientist, a clinical scientist and educator or a practitioner, there are numerous ways that you can contribute to the advancement of your discipline through leading or participating in research. In this talk I will discuss the current UK landscape, mainly from the point of view of what opportunities are possible for medical graduates to become involved in research.

DOI: 10.1530/endoabs.44.FUT1.3

Futures 2: Mapping your route through the Research Funding maze

FUT2.1

Starter grants and building your pilot data

Roland Stimson
University of Edinburgh, Edinburgh, UK.

Obtaining research independence and running your own research group can seem very far away at the end of your PhD and during your early postdoctoral career. However, starter grants are an invaluable resource to help you down this path, allowing you to develop and strengthen your research career, pursue independent strands of research, improve your ability to write grants and make you more competitive to obtain more substantial funding.
Starter grants are available from a number of schemes for both clinical and non-clinical researchers, from local and national funding bodies. These grants are primarily designed to allow you to generate pilot data for further fellowship applications but these grants also provide invaluable experience of planning projects, managing budgets and staff and delivering to deadlines. Starter grants generally provide modest budgets, as such projects should be designed appropriately to best acquire the key data required to make your future applications more competitive and prove that you are developing an independent niche from your current or previous supervisors.
Applications for starter grants should not be overly ambitious as the work should be deliverable over a relatively short time frame to allow incorporation into future grant applications. Outputs from the research performed under these grants are not expected to be high impact papers but more show the potential for high impact publications once more substantial funding is obtained. In addition, pilot data is vital to prove to reviewers that your proposal is feasible and that you are the right person in the ideal environment to be a success.
Those who obtain starter grants are more likely to be successful at obtaining fellowships and some schemes provide additional support such as mentoring and networking events which can be invaluable for your development.

DOI: 10.1530/endoabs.44.FUT2.1

FUT2.2

Abstract unavailable.

FUT2.3

Abstract unavailable.

Oral Communications

Early Career Oral Communications

OC1.1

Mutations in *SGPL1*, encoding sphingosine-1-phosphate lyase, cause a novel form of primary adrenal insufficiency with steroid resistant nephrotic syndrome

Rathi Prasad[1], Avinaash Maharaj[1], Eirini Meimaridou[1], Paul VanVeldhoven[2], Federica Buonocore[3], Ignacio Bergadá[4], Eliana Barbagelata[5], Hamilton Cassinelli[4], Urmi Das[6], Ruth Krone[7], Moin Saleem[8], Bulent Hacihamdioglu[9], Erkan Sari[10], Helen Storr[1], John Achermann[3], Leonardo Guasti[1], Debora Braslavsky[4], Tulay Guran[11], Nanik Ram[12] & Lou Metherell[1]
[1]Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, London, UK; [2]KULeuven, LIPIT, Leuven, Belgium; [3]UCL Institute of Child Health, London, UK; [4]Centro de Investigaciones, CONICET – FEI – División de Endocrinología Endocrinológicas "Dr. César Bergadá" (CEDIE), Hospital de Niños R. Gutierrez, Buenos Aires, Argentina; [5]Unidad de Nefrología, Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina; [6]Department of Paediatric Endocrinology, Alder Hey Children's Hospital, Liverpool, UK; [7]Department of Paediatric Endocrinology, Birmingham Children's Hospital, Birmingham, UK; [8]Bristol Children's Renal Unit, Bristol Royal Hospital for Children, Bristol, UK; [9]Department of Pediatric Endocrinology and Diabetes, Health Sciences University, Suleymaniye Maternity and Children's Training and Research Hospital, Istanbul, Turkey; [10]Department of Pediatric Endocrinology and Diabetes, Gulhane Military Medical School, Ankara, Turkey; [11]Department of Pediatric Endocrinology and Diabetes, Marmara University, Pendik Education and Research Hospital, Istanbul, Turkey; [12]Section for Endocrinology, Aga Khan University, Karachi, Pakistan.

Background
Primary adrenal insufficiency (PAI) is most commonly congenital in children. PAI is genetically heterogeneous with some gene defects causing syndromic disease. A third of patients have no genetic diagnosis rendering their prognosis uncertain. We investigated families with a novel combination of PAI and steroid resistant nephrotic syndrome.
Objective and hypotheses
To discover the genetic defect underlying this syndrome.
Method
Whole exome sequencing (WES) was performed in two families with Sanger sequencing of SGPL1 to confirm segregation and screen further families.
Results
By WES and Sanger sequencing three different mutations in SGPL1 were identified in four families. All mutations were homozygous in affected individuals and heterozygous in their asymptomatic parents. Kindred 1, three patients had a novel missense mutation (c.665G>A; p.R222Q), the index case presented with PAI (8 m), developed focal segmental glomerulosclerosis (FSGS) at 2.5 y, requiring a kidney transplant aged 5 y. A younger sibling with similar clinical history (not sequenced) died (4 y) whilst an older sibling (8 y) and cousin (3 y) have only PAI. Kindred 2, a child presenting with PAI had the p.R222Q mutation and has no renal phenotype at 3.7 y. Kindred 3, a female baby presenting with PAI (6 m) had a novel in-frame deletion, (c.1633_1635delTTC; p.F545del) and developed FSGS (5 y) on follow-up, additional features included ichthyosis and neurological symptoms. Kindred 4, two affected siblings manifesting PAI and nephrotic syndrome (<1 yr) had a canonical splice site change, (c.261+1G>A; p.?), the male sibling additionally has micropenis, unilateral cryptorchidism, ichthyosis and neurological symptoms.
Conclusion
We have identified a novel, potentially progressive, disorder incorporating PAI and nephrotic syndrome amongst other features. This novel syndrome highlights the importance of the sphingolipid metabolic pathway in adrenal function. A genetic diagnosis for patients with this form of PAI is important for correct treatment, genetic counselling and screening for co-morbidities.

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OC1.2

11β-HSD1 deficiency modulates brain energy homeostasis during acute systemic inflammation

Manu Verma[1], Tiina Kipari[2], Tak Yung Man[1], Thorsten Forster[3], Natalie Homer[1,4], Jonathan Seckl[1], Megan Holmes[1] & Karen Chapman[1]
[1]University/BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK; [2]MRC Centre For Inflammation Research, University of Edinburgh, Edinburgh, UK; [3]Division of Infection and Pathway Medicine, University of Edinburgh, Edinburgh, UK; [4]Edinburgh Clinical Research Facility Mass Spectrometry, University of Edinburgh, Edinburgh, UK.

Chronically elevated glucocorticoid (GC) level impairs cognition. In rodents, elevated plasma GC levels, prior to an inflammatory challenge, potentiates neuroinflammation that is abolished by GR but not MR antagonism. 11β-hydroxysteroid dehydrogenase type-1 (11β-HSD1) increases intracellular GC levels by regenerating active GCs from inert forms. Inhibition/deficiency of 11β-HSD1 is protective against age-related cognitive decline presumably by lifelong reduced brain exposure to GC, especially during stress/aging. We hypothesised that 11β-HSD1 deficiency will attenuate the brain response to inflammation and will be associated with an attenuated switch to aerobic glycolysis. C57BL/6 and *Hsd11b1*$^{-/-}$ mice were injected (i.p.) with 100 μg/kg LPS or 0.9% saline and culled 3, 6 or 9 h later. Sickness behaviour was assayed 2 h prior to cull. Pro-inflammatory responses and energy metabolising pathways in the brain were investigated. Compared to controls, *Hsd11b1*$^{-/-}$ mice showed a quicker recovery from sickness behaviour, post-LPS ($P<0.01$; $n=7$–8). Post-LPS, circulating neutrophil and Ly6C^{+} monocyte numbers were reduced ($P<0.05$; $n=4$–10) and plasma corticosterone levels were increased ($P<0.05$; $n=6$–9) equally in both genotypes, suggesting similar peripheral inflammatory responses. However, 11-dehydrocorticosterone (11β-HSD1 substrate) levels were higher in *Hsd11b1*$^{-/-}$ mice, compared to controls ($P<0.01$; $n=6$–9;). Post-LPS, the increase in hippocampal *Tnfa*, *Il-1b* and *Il-6* mRNAs were attenuated in *Hsd11b1*$^{-/-}$ mice ($P<0.001$; $n=7$–8;), compared to controls, suggesting reduced inflammation. Principle component analysis of hippocampal level of mRNAs encoding metabolic transporters and enzymes revealed a distinct response in *Hsd11b1*$^{-/-}$ mice, compared to controls, post-LPS (cumulative variance=54%). Further analysis, revealed an attenuated switch to aerobic glycolysis in *Hsd11b1*$^{-/-}$ mice, compared to controls ($P<0.05$; $n=6$–8). Hippocampal metabolites showed correspondence with mRNA results with an increased fumrate/succinate ratio in *Hsd11b1*$^{-/-}$ mice, compared to controls ($P<0.05$; $n=7$–10) suggesting reduced inflammation and an enhanced hypoxia response. These data suggests an attenuated hippocampal pro-inflammatory response and better metabolic support for neuronal function could, at least in part, underlie the neuroprotection associated with 11β-HSD1 inhibition/deficiency during stress/aging.

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OC1.3

Investigating the interaction between KNDy peptides on gonadotrophin release in humans – novel findings with therapeutic importance

Shakunthala Narayanaswamy[1], Julia K Prague[1], Channa N Jayasena[1], Deborah A Papadopoulou[1], Maria Mizamtsidi[1], Amar J Shah[1], Paul Bassett[2], Alexander N Comninos[1], Ali Abbara[1], Stephen R Bloom[1], Johannes D Veldhuis[3] & Waljit S Dhillo[1]
[1]Imperial College, London, UK; [2]Statsconsultancy Ltd, Amersham, Buckinghamshire, UK; [3]Mayo Clinic, Rochester, Minnesota, USA.

Background
Hypothalamic KNDy neurons have recently been identified as key regulators of reproductive function by releasing three neuropeptides namely kisspeptin, neurokinin B (NKB) and dynorphin. Animal studies show they interact to control pulsatile GnRH release, which is vital for fertility. In animals, kisspeptin stimulates, NKB modulates and the opioid dynorphin inhibits GnRH pulsatility. However, the interaction of these peptides has never been studied in humans. To investigate the importance of KNDy neuropeptides for the first time in humans, we assessed the effects of co-administration of kisspeptin-54, NKB and an opioid antagonist naltrexone on LH pulsatility (a surrogate marker of GnRH pulsatility) and gonadotrophin release.
Methods
We conducted an ethically approved prospective, single-blinded placebo-controlled study. Healthy male volunteers ($n=5$/group) attended our research facility for 8 study visits and received a different treatment intervention at each visit: oral 50 mg naltrexone (NAL), 8 h intravenous infusions of vehicle, 2.56 nmol/kg per h NKB (NKB) or 0.1 nmol/kg per h kissspeptin-54 (KP) alone and in combination. The treatment intervention was started after 1 h of baseline blood sampling. Frequent blood sampling to measure serum gonadotrophins and sex steroids was conducted for 8 h. LH pulsatility was determined using blinded deconvolution analysis.
Results
All kisspeptin and naltrexone containing groups potently increased serum LH and LH pulsatility ($P<0.001$ vs vehicle). NKB alone did not affect serum gonadotrophin levels. NKB+KP had significantly smaller increases in

gonadotrophin levels when compared with kisspeptin alone ($P<0.01$). NAL+ KP was the only combination to significantly increase LH pulse amplitude ($P<0.001$ vs vehicle).
Conclusions
Our results show for the first time in humans significant interactions between the KNDy neuropeptides on LH pulsatility and gonadotrophin release in humans. This data has important implications for improving our understanding of GnRH pulse generation and therapeutic implications for treating patients with reproductive failure and infertility.

DOI: 10.1530/endoabs.44.OC1.3

OC1.4

The urinary steroid metabolome as a non-invasive tool to stage non-alcoholic fatty liver disease

Ahmad Moolla[1], Amin Amin[2], Bev Hughes[2], Wiebke Arlt[2], Zaki Hassan-Smith[2], Matt Armstrong[3], Philip Newsome[3], Tahir Shah[3], Luc Van Gaal[4], An Verrijken[4], Sven Francque[4], Michael Biehl[5] & Jeremy Tomlinson[1]
[1]Oxford Centre for Diabetes, Endocrinology & Metabolism, University of Oxford, Oxford, UK; [2]Centre for Endocrinology, Diabetes & Metabolism, University of Birmingham, Birmingham, UK; [3]Centre for Liver Research, University of Birmingham, Birmingham, UK; [4]University of Antwerp, Antwerp, Belgium; [5]University of Groningen, Groningen, The Netherlands.

Introduction
Dysregulation of glucocorticoid (GC) metabolism is implicated in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). The only available treatment for NAFLD is weight loss and the gold standard diagnostic test is liver biopsy, which is invasive and resource intensive. NAFLD ranges from simple steatosis, to inflammation (steatohepatitis/NASH), fibrosis and cirrhosis. It may be regarded as the hepatic manifestation of the metabolic syndrome and is strongly associated with increased cardiovascular mortality. Changes to GC metabolism, thus far described in small numbers of patients, relate to the metabolism of cortisol. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates cortisol (F) from inactive cortisone (E), whilst A-ring reductases 5α and 5β reductase (5αR/5βR) inactivate cortisol to tetrahydrocortisol metabolites (THF/5αTHF).
Methods
Using gas chromatography / mass spectrometry, we analysed steroid metabolites in spot urine samples (corrected for creatinine) in a large cohort of patients with biopsy proven NASH ($n=39$) alongside patients with cirrhosis ($n=44$), and compared them to healthy controls without liver disease ($n=58$).
Results
Total cortisol metabolites differed significantly across all 3 groups allowing discrete separation ($P<0.0001$) with the highest levels seen in patients with NASH. Interestingly, 11β-HSD1 activity (THF+5αTHF/THE ratio) was significantly increased in patients with cirrhosis in comparison to NASH or healthy controls ($P<0.0001$). A-ring reductase activity (THF/5αTHF ratio) was not significantly different between the 3 groups. Furthermore, machine learning-based analysis by generalised matrix learning vector quantisation (GMLVQ) achieved complete separation of control and cirrhosis groups (AUC ROC: 0.99).
Conclusion
Our work has identified steroid metabolic pathways that appear differentially regulated across the spectrum of NAFLD and has the potential to lead to the identification of as yet unidentified treatment targets. Additionally, through the adoption of an unbiased computational (GMLVQ) approach, we have raised the potential to use this technique as a novel, non-invasive assessment to stage the severity of NAFLD.

DOI: 10.1530/endoabs.44.OC1.4

OC1.5

A missense mutation in the islet-enriched transcription factor *MAFA* leads to familial insulinomatosis and diabetes

Donato Iacovazzo[1,*], Sarah E. Flanagan[2,*], Emily Walker[3,*], Richard Caswell[2], Michael Brändle[4], Matthew Johnson[2], Matthew Wakeling[2], Min Guo[3], Mary N. Dang[1], Plamena Gabrovska[1], Bruno Niederle[5], Emanuel Christ[6], Stefan Jenni[6], Bence Sipos[7], Maike Nieser[7], Andrea Frilling[8], Ketan Dhatariya[9], Philippe Chanson[10], Wouter de Herder[11], Björn Konukiewitz[12], Günter Klöppel[12,*], Roland Stein[3,*], Sian Ellard[2,*] & Márta Korbonits[1,*]
[1]Centre for Endocrinology, Barts and The London School of Medicine, London, UK; [2]Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK; [3]Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee, USA; [4]Division of Endocrinology and Diabetes, Department of Internal Medicine, Kantonsspital St. Gallen, St. Gallen, Switzerland; [5]Section of Endocrine Surgery, Division of General Surgery, Department of Surgery, University of Vienna, Vienna, Austria; [6]Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital of Bern, Inselspital, Bern, Switzerland; [7]Department of Pathology, University of Tübingen, Tübingen, Germany; [8]Department of Surgery and Cancer, Imperial College London, London, UK; [9]Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK; [10]Service d'Endocrinologie et des Maladies de la Reproduction, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France; [11]Department of Internal Medicine, Sector of Endocrinology, ENETS Centre of Excellence for Neuroendocrine Tumors, Erasmus MC, Rotterdam, The Netherlands; [12]Department of Pathology, Consultation Center for Pancreatic and Endocrine Tumors, Technical University, Munich, Germany;
*equally contributing to the work.

Introduction
Insulinomatosis is a rare disorder characterised by persistent hyperinsulinaemic hypoglycaemia (PHH) due to the occurrence of multifocal pancreatic insulinomas. This condition, whose pathogenesis is unknown, can occur in a familial setting. Paradoxically, while some family members develop PHH, others develop diabetes mellitus.
Methods
We have identified a family with autosomal dominant familial insulinomatosis and diabetes. Exome sequencing was employed to identify the disease causing mutation. Functional *in vitro* studies were undertaken to characterise the effects of the identified mutation.
Results
A novel missense heterozygous mutation was identified in the transactivation domain of the islet-enriched transcription factor *MAFA*, and was found to segregate with both the insulinomatosis and diabetes phenotype. MAFA regulates the expression of several genes involved in glucose-stimulated insulin secretion, and its levels and activity are acutely induced in the presence of high glucose concentrations. Phosphorylation within the transactivation domain drives the proteosomal degradation of MAFA. MAFA has oncogenic transformation potential, and rearrangements leading to the overexpression of large MAF proteins play a pathogenic role in haematological malignancies.
In vitro, the mutation was found to impair phosphorylation within the transactivation domain of MAFA. No significant effect was observed in the transactivation activity, while the stability of mutant MAFA was profoundly increased in HEK293 cells. Notably, in the EndoC-βH1 human beta cell line, mutant MAFA was extremely stable, even at low glucose concentrations, when wild type MAFA is normally undetectable.
Conclusion
We report, for the first time, that a mutation in the transcription factor *MAFA* leads to familial insulinomatosis and diabetes. We hypothesise that dysregulation of MAFA turnover impairs glucose-stimulated insulin secretion, causing beta cell dysfunction and diabetes. At the same time, increased levels of MAFA are expected to induce cell transformation, leading to the development of insulinomatosis.

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OC1.6

A time controlled β-cell specific mouse model *Men1$^{L/L}$/RIP2-CreER* for pancreatic neuroendocrine tumours (NETs)

Roeland P Vas Nunes, Morten Frost, Mark Stevenson, Kate E Lines & Rajesh V Thakker
Academic Endocrine Unit, OCDEM, University of Oxford, Oxford, UK.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterised by occurrence of parathyroid tumours and neuroendocrine tumours (NETs) of the pancreas and pituitary, which is caused by mutations of the *MEN1* gene, encoding menin. Mouse models are important in elucidating mechanisms of *MEN1* tumourigenesis and treatments, but the current models have limitations. Thus, in conventional heterozygous *MEN1* knockout models, tumour development is unpredictable as spontaneous loss of heterozygosity in tumours may arise in different tissues at different times. Conditional models with homozygous *Men1* knockout restricted to specific tissue types, using a Cre-LoxP system and a targeted promoter (e.g. *UBC9*-whole pancreas or *RIP2*-pancreatic β-cells),

overcome this unpredictability, but are of limited use in elucidating early tumourigenic events as in MEN1 one allele is lost from conception. To study early events, conditional models with gene expression under temporal control can be generated by fusing an oestrogen receptor to Cre constructs, to selectively delete both *Men1* alleles, by tamoxifen administration, as shown by the development of islet hyperplasia and increased β-cell proliferation in *Men1$^{L/L}$/UBC9-ERt-Cre* mice within 1 month after tamoxifen administration. We therefore used *Men1$^{L/L}$/RIP2-CreER* mice to establish a pancreatic β-cell-specific NET model under temporal control. *Men1$^{L/L}$/RIP2-CreER* mice (12 males and 14 females) aged 12–14 weeks were given tamoxifen in the diet for 5 days, and pancreata harvested 8–10, 12–14, and 25–29 weeks later. Control mice (7 males and 10 females) did not express *Cre* and did not receive tamoxifen. Immunostaining of pancreata from *Men1$^{L/L}$/RIP2-CreER* mice 8–10 weeks after tamoxifen administration showed: loss of menin in all islets; increased islet area ($>$4.2-fold, $P<0.05$); and increased β-cell proliferation ($>$2.5-fold, $P<0.013$). There were no gender and α-cell proliferation differences. Thus, *Men1$^{L/L}$/RIP2-CreER* mice develop insulin-expressing NETs and provide a model to study early events in development of pancreatic β-cell NETs.

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Neuroendocrinology and Reproduction

OC2.1

Kisspeptin: A Novel Neuroendocrine Modulator of Sexual and Emotional Processing in Men

Alexander Comninos[1], Matthew Wall[2], Lysia Demetriou[2], Amar Shah[1], Sophie Clarke[1], Shakunthala Narayanaswamy[1], Alexander Nesbitt[1], Chioma Izzi-Engbeaya[1], Julia Prague[1], Ali Abbara[1], Risheka Ratnasabapathy[1], Victoria Salem[1], Gurjinder Nijher[1], Channa Jayasena[1], Mark Tanner[2], Paul Bassett[3], Amrish Mehta[4], Eugenii Rabiner[2], Christoph Honigsperger[5] & Waljit Dhillo[1]
[1]Imperial College, London, UK; [2]Imanova Centre for Imaging Sciences, London, UK; [3]Statsconsultancy Ltd, Bucks, UK; [4]Imperial College Healthcare NHS Trust, London, UK; [5]University of Oslo, Oslo, Norway; [6]University of Sao Paulo, Sao Paulo, Brazil.

Kisspeptin is a crucial activator of reproductive function, playing a critical role in the hypothalamus to activate GnRH neurons and downstream reproductive hormones. However, kisspeptin and its receptor are also expressed in other brain areas, yet little is known about their function here. The limbic system plays a key role in sexual and emotional behaviours and has a high expression of kisspeptin receptors. We therefore hypothesised that kisspeptin administration may modulate limbic brain activity in humans.

We mapped brain activity using fMRI in 29 heterosexual men (age 25.0 ± 0.9 y) using a randomised blinded two-way placebo-controlled protocol. We used validated sexual/couple-bonding/negative/neutral themed images to stimulate limbic brain activity and determined if kisspeptin administration altered this response. Reproductive hormone measurements and psychometric assessments were performed throughout.

Kisspeptin administration increased circulating kisspeptin ($P<0.001$) and LH ($P<0.001$) but not testosterone ($P=0.23$) for the duration of the scans, as expected. Region of Interest analysis of the fMRI data revealed that kisspeptin (vs. vehicle) significantly enhanced activation in key limbic and para-limbic structures on viewing sexual images including the amygdala and cingulate. Viewing non-sexual couple-bonding images resulted in increased activity in similar structures with the addition of the thalamus and globus pallidus, important reward regions. Kisspeptin did not affect limbic brain activity on viewing negative images, but did enhance activity in the medial frontal gyrus. Consistent with this, psychometric analysis demonstrated that kisspeptin reduced negative mood ($P=0.031$).

Collectively, these data provide the first evidence that kisspeptin modulates limbic brain activity in response to sexual and emotional stimuli, and influences mood in healthy men. This is the first report of a novel role for kisspeptin in the integration of sexual and emotional processing in humans. Therefore, these data have important implications for our understanding of reproductive biology, as well as the development of kisspeptin as a potential therapeutic.

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OC2.2

MLE4901, a neurokinin 3 receptor antagonist, shows reproductive tract effects and sustained pharmacodynamic activity consistent with HPG suppression after 13 weeks of oral administration in dogs

Michelle Coulson[1] & Stephen Hunt III[2]
[1]AstraZeneca, Melbourne, Herts SG8 6EE, UK; [2]Millendo Therapeutics, Inc., Ann Arbor, Michigan 48104, USA.

MLE4901 (previously AZD4901) is a potent and selective neurokinin 3 receptor (NK3R) antagonist being developed for the treatment of polycystic ovary syndrome (PCOS). Clinical studies indicate the compound negatively regulates the hypothalamus-pituitary-gonadotropin (HPG) axis to reduce pituitary luteinizing hormone and gonadal sex steroids. To understand the longer-term *in vivo* effects of MLE4901, a 13-week safety study was carried out. Groups of 3 male and female dogs received vehicle or MLE4901 at 5, 140, and 1000 mg/kg by gavage dosed once daily. Additionally, 3 dogs from each sex from the vehicle and high dose groups were maintained for a 3 month recovery period. MLE4901 was rapidly absorbed and plasma exposure increased with dose; exposures were similar at Week 4 and Week 13. MLE4901 effects were largely confined to reproductive organs. In females, reduced ovary and uterine weights as well as an increased incidence of anestrus were observed. In males, MLE4901 administration resulted in reduced testes, epididymides, and prostate weights which were associated with atrophic microscopic changes. MLE4901 effects showed evidence of reversibility following the 3 month recovery period. At doses of 140 mg/kg/day and above, MLE4901 completely suppressed the secretion of testosterone in male dogs as measured on Day 92. Some recovery of serum testosterone levels became apparent within 48 hours of the end of the dosing period. The pharmacodynamic response of MLE4901 was intact after 91 consecutive days of administration, as demonstrated by the acute reduction in plasma testosterone and its subsequent recovery to pre-dose concentrations at 24 hours in the 5 mg/kg/day dose group. These findings, which are believed to result from suppression of the HPG axis and reflect the primary pharmacology of MLE4901 as a NK3R antagonist, provide support for the development of MLE4901 as a treatment for PCOS and related endocrine diseases.

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OC2.3

Associations between karyotype and long term health outcomes in adults with Turner Syndrome; The Turner Syndrome Life Course Project

Antoinette Cameron- Pimblett, Clementina La Rosa, Thomas King, Lih-Mei Lioa, Melanie C Davies & Gerard S Conway
University College London Hospital, London, UK.

Background

Turner syndrome (TS) comprises a group of sex chromosome anomalies affecting approximately 15,000 in the UK. TS affects every organ system in the body through haploinsufficiency of genes that are normally expressed by both X chromosomes. Common features include short stature, congenital heart diease and gonadal dysgenesis requiring long-term oestrogen replacement but the adult phenotype extends to excess risk of diabetes, hypertension and hepatosteatosis. UCLH has the longest standing adult TS surveillance clinic and has provided care to 750 women over 20 years resulting in approximately 7,500 clinic visits.

Methods

A retrospective analysis of health surveillance parameters in 583 women with TS and a confirmed karyotype. The most common karyotype groups were compared: monosomy X; mosaic 45,X/46,XX; isochromosome X; mosaic 45,X/46,XY and ring chromosome X. Other karyotype variants were not included. Continuous variables were divided by upper quartiles and karyotype subgroups compared. The resulting binary variables were tested using chi- squared analysis with correction for multiple testing.

Results

Ring chromosome group had an increased prevalence of elevated HbAc1 ($P=0.03$), GGT ($P=0.02$) and diastolic blood pressure ($P=<0.01$), and excess risk of treated depression ($P=0.04$). Ring chromosome groups showed reduced risk of bicuspid valve and dilated aortic root diameter ($P=0.02$ and 0.01) compared to monosomy X. 45,X/46,XY had a decreased prevalence of hearing loss and metabolic syndrome.

Conclusions

We have shown novel health risk stratification for adults with TS. The ring chromosome is associated with excess risk for diabetes and hepatic dysfunction with bicuspid aortic disease protection. Y chromosome subtypes were protected from thyroid autoimmunity, hearing loss and had a decreased prevalence of metabolic syndrome. We confirmed the mild phenotype associated with 45,X

mosaicism but failed to identify excess risk associated with isochromosome X such as autoimmunity.

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OC2.4

Heteromers of luteinising hormone and follicle stimulating hormone receptor positively and selectively modulates the LH-induced calcium signalling response

Kim Jonas[1,2], Stanford Chen[1], Ilpo Huhtaniemi[1,3] & Aylin Hanyaloglu[1]
[1]Imperial College London, London, UK; [2]St George's, University of London, London, UK; [3]University of Turku, Turku, Finland.

The gonadotrophin receptors, luteinising hormone receptor (LHR) and follicle-stimulating hormone receptor (FSHR) are G-protein coupled receptors, vital in regulating reproductive functions. Whilst FSHR and LHR are known to form homomers, and have been recently shown to heterodimerise/oligomerise, the functional and physiological significance of LHR/FSHR heteromerisation remains elusive. This study aimed to explore the functional significance of LHR/FSHR crosstalk, exploring mechanistic detail in HEK293 cells, and translating findings into primary human ovarian granulosa cells. Using HEK293 stably expressing LHR +/− transient-transfection of FSHR, the pattern of LH-induced increase in intracellular calcium signalling, measured via Fluo-4direct indicator dye and confocal imaging, was significantly altered in the presence of FSHR, from an acute and rapid signal to a sustained calcium response. To ascertain the molecular mechanisms governing this change, pharmacological inhibitors were employed. Inhibition of Gαq/11 with UBO-QIC and Gαi with pertussis toxin showed the full calcium signal and profile was Gαq/11 dependent and Gαi independent. Interestingly, the sustained LH-dependent calcium profile was nifedipine-sensitive, indicating that crosstalk between LHR and FSHR enabled LH-dependent activation of L-type calcium channels. Moreover, inhibition of βγ subunits and PI3Kinase activation with gallein and wortmannin respectively, resulted in a sustained calcium signalling profile in cells expressing LHR alone, but had no further effect on LHR/FSHR calcium profile, suggesting FSHR alters the ability of an LHR-Gβγ-PI3Kinase pathway to inhibit L-type calcium channel activity. Translation of this work to primary human granulosa lutein cells, that co-express the LHR and FSHR, revealed an intact LH-dependent calcium response that was nifedipine-sensitive, indicating that LH-dependent activation of L-type calcium channels is an integral pathway with potential physiological significance *in vivo*. Together these data suggest that crosstalk between LHR/FSHR may represent a key mechanism for generating sustained LH-mediated signal responses in the ovary, responding to the changing physiological requirements of LHR signalling.

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OC2.5

Ipilimumab Hypophysitis – single centre experience of an emerging endocrine diagnosis

Lai Zhuangming Marc[1], Lavinia Spain[2], Martin Gore[2], James Larkin[2] & Daniel Morganstein[1,2]
[1]Chelsea and Westminster Hospital, London, UK; [2]Royal Marsden Hopsital, London, UK.

Background
Ipilimumab is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor that improves survival in advanced melanoma. However, ipilimumab induces immune-related adverse events including hypophysitis and hypopituitarism. We describe one of the largest single centre series of ipilimumab induced hypophysitis.
Methods
We retrospectively analysed all patients ($n=301$) treated with ipilimumab either as a monotherapy or in combination with nivolumab for advanced melanoma at the Royal Marsden Hospital from 2010 to 2016. We reviewed clinical presentations, MRI reports and endocrine test results. Data on last contact and date of death was also collected.
Results
The overall incidence of IH was 6.9%, with an incidence of 3.3% before 2013 and 10.8% since 2013 suggesting increased awareness and recognition. There were no significant differences in age, gender or number of treatment cycles (median = 3) received between the hypophysitis cohort ($n=21$) and no hypophysitis cohort ($n=280$). In the hypophysitis cohort, 17 patients reported fatigue and 18 reported headaches of which 9 had enlarged pituitary glands on MRI. Headache developed a mean of 60 days after starting treatment. Secondary adrenal insufficiency ($n=21$) was the most common pituitary dysfunction followed by secondary hypothyroidism ($n=14$) and secondary hypogonadism ($n=13$).
Mean TSH fell prior to cycle 3 and 4 in those who developed hypophysitis, but not in those who did not, but this did not reach significance levels, with considerable overlap of TSH levels.
The hypophysitis cohort had a significantly better overall survival compared to the no hypohysitis cohort even after accounting for patients who only received 1–2 treatment cycles.
Conclusion
IH occurred at a rate comparable to the published trials, with an increased rate in more recent years, reflecting difficulties in diagnosis. Multiple hormone deficiencies were common, requiring replacement. Patients with hypophsyitis had improved overall survival compared to those without hypophysitis, perhaps reflecting activation of the immune system.

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OC2.6

Dysregulation of the steroidogenic gene network in granulosa cells from women with PCOS

A Lerner[1], M Coates[1], J Velupillai[1], G Christopoulos[2], M Liyanage[2], R Islam[2], S Lavery[2], V Tsui[1], K Hardy[1] & S Franks[1]
[1]Imperial College London, London, UK; [2]Imperial College Healthcare NHS Trust, London, UK.

Polycystic ovary syndrome (PCOS) is a common endocrinopathy that is associated with anovulatory infertility, menstrual disturbances as well as an adverse metabolic profile. Although the pathophysiology of PCOS remains unclear, dysregulation of gene expression has been previously shown in theca and granulosa cells (GC). However, there has been no comprehensive analysis of steroidogenic gene expression in GCs from women with PCOS. In this study, we performed a comprehensive gene expression analysis of the steroidogenic network in human GCs. GCs were retrieved during egg collection for *in-vitro* fertilisation from women with (1) normal ovaries and regular cycles (2) PCO with regular, ovulatory cycles (ovPCO) and (3) anovulatory PCOS (anovPCO). Quantitative PCR was used to analyse changes in gene expression. Cultured GCs were used to investigate direct effects of the androgen dihydrotestosterone (DHT) on steroidogenic gene expression. Finally, using Mapper2 software we searched for putative androgen response elements (AREs) in the promoters of genes involved in steroid synthesis and metabolism. We found that CYP11a1 was significant decreased (3-fold, $P<0.01$) in GCs of both ovPCO and anovPCO. However, the biggest change was seen in estrogen sulfotransferase (SULT1e1) expression that was strongly upregulated (7-fold, $P<0.001$) in both ovPCO and anovPCO. In the light of this, genes encoding ERα and ERβ were investigated, the expression of which was also shown to be significantly increased (3-fold, $P<0.05$). Interestingly, we identified several putative AREs in the promotors of CYP11a1, SULT1e1, ERα and ERβ supporting the notation of direct regulation by androgen receptor binding. Furthermore, preliminary *in-vitro* studies showed that SULT1e1 expression is directly upregulated by DHT treatment. In summary we show differential expression between GCs from women with and without PCO, of genes implicated in estrogen action and metabolism and suggest that these may be, at least in part, a function of androgen action.

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Thyroid and Neoplasia

OC3.1

Frequent Occurrence of DUOX2 and DUOXA2 Mutations in Cases with Borderline Bloodspot Screening TSH who Develop 'True' Congenital Hypothyroidism

Catherine Peters[1], Adeline K Nicholas[2], Greta Lyons[2], Shirley Langham[1], Eva Serra[3], Erik Schoenmakers[2], Marina Muzza[4], Laura Fugazzola[4] & Nadia Schoenmakers[2]
[1]Department of Endocrinology, Great Ormond Street Hospital, London, UK; [2]University of Cambridge Metabolic Research Laboratories, Wellcome Trust-Medical Research Council Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK; [3]Department of Human Genetics, The Wellcome Trust Sanger Institute, Hinxton, UK; [4]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

The UK newborn screening programme for congenital hypothyroidism (CH) facilitates prevention of neurodevelopmental delay in CH by enabling prompt

diagnosis and treatment. Although the UK Newborn Screening Programme Centre (UKNSPC) defines a borderline bloodspot screening TSH (bsTSH) concentration as 10–20 mU/l, the lower cutoff used at Great Ormond Street Hospital (6 mU/l), enables diagnosis of true and transient CH in cases missed using UKNSPC criteria. We hypothesised that mutations in DUOX2 and its accessory protein DUOXA2 may be common in borderline CH cases and have broader management implications.

We screened 40 term babies with eutopic gland-in-situ, including 21 with Asian/Chinese ethnicity (53%). Biochemical recruitment criteria comprised a 1st bsTSH measuring 6–20 mU/l, and confirmatory venous TSH (vTSH) >25 mU/l. DUOX2 was sequenced initially, followed by DUOXA2 in mutation negative cases. Mutations were classified as pathogenic based on in silico predictions including molecular modeling for DUOX2 mutations affecting the peroxidase-like domain.

Nineteen cases (47.5%) harboured likely disease-causing mutations in either DUOX2 ($n=13$, 32.5%) or DUOXA2 ($n=6$,15%) and confirmatory venous thyroid hormone levels in mutation-positive cases demonstrated subnormal mean free T4 9.1 ± 0.8 (NR 12.5–24.6 pmol/l). Initial or repeat bsTSH was below the UKNSPC cutoff (10 mU/l) in 42% of mutation-positive cases. We detected 7 rare novel DUOX2 mutations and 6 novel DUOXA2 mutations; two DUOX2 mutations (p.Q570L, p.F966Sfs$\times$29) were recurrent and occurred more frequently (MAF ≤0.01). Significant enrichment of DUOXA2 variants in our cohort compared with healthy populations (15% vs 1%, $P=1.70\times10^{-5}$) supported an aetiological contribution of both monoallelic ($n=5$) and biallelic mutations ($n=1$).

Recommended TSH screening cut offs fail to detect individuals with true dyshormonogenesis who develop at least moderate CH, despite borderline bsTSH concentrations. Targetted sequencing of DUOXA2 and DUOX2 in such cases will have a high diagnostic yield, especially in Asian/Chinese populations, and genetic ascertainment will facilitate prompt diagnosis in familial cases.

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OC3.2

Pharmacological enhancement of radioiodine uptake through Src kinase inhibition

Vikki Poole, Alice Fletcher, Bhavika Modasia, Neil Sharma, Rebecca Thompson, Hannah Nieto, Waraporn Imruetaicharoenchoke, Martin Read, Kristien Boelaert, Christopher McCabe & Vicki Smith
University of Birmingham, Birmingham, UK.

In thyroid cancer, a reduction in sodium iodide symporter (NIS) expression at the basolateral plasma membrane (PM) of thyrocytes decreases the efficacy of radioiodine imaging, ablative therapy and treatment of metastases. NIS overexpression in breast cancer has resulted in radioiodine being widely proposed as a novel therapeutic strategy. However, uptake is insufficient for tumour destruction. Augmenting NIS PM localisation represents an important therapeutic strategy for increasing radioiodine delivery in both tumour types. We previously described a mechanism by which NIS is internalised by pituitary tumor-transforming gene-binding factor (PBF) in thyroid cells, significantly reducing radioiodine uptake. PBF phosphorylation at Y174 by Src kinase mediates NIS repression, which can be rescued by the Src family kinase (SFK) inhibitor PP1. We have now replicated these findings in breast cancer cells, further elucidated the mechanism of repression and identified a more potent inhibitor of PBF-pY174. In MCF-7 and MDA-MB-231 breast cancer cells PBF significantly repressed radioiodine uptake and this was reversible with PP1 treatment. Mutation of a predicted Src consensus sequence (EEN170-172AAA) abrogated pY174 and radioiodine uptake repression. PBF-pY174 was most potently inhibited by the SFK inhibitor dasatinib, which restored PBF-mediated radioiodine uptake. In the presence of dasatinib-resistant Src (T341I), dasatinib no longer rescued PBF repression of NIS, indicating that Src specifically mediates PBF phosphorylation. A post-translational modification of Src, myristoylation, inhibits Src plasma membrane localisation. Utilising a new high affinity inhibitor of myristoylation, N-myristoyltransferase inhibitor 3 (NMTi3), radioiodine uptake in MDA-MB-231 cells lentivirally expressing NIS was significantly increased. Interestingly, combined dasatinib and NMTi3 treatment synergistically induced endogenous radioiodine uptake in MCF-7 cells ($P<0.01$; $N=3$). Taken together, these data suggest that Src inhibition can effectively enhance radioiodine uptake in multiple tumour types, with implications for improving outcomes in thyroid cancer and making radioiodine a potentially viable new strategy for breast cancer treatment.

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OC3.3

Post-Radioiodine Graves' Management: The Pragma-Study

Petros Perros[1], Colin Dayan[2], Bijay Vaidya[3], Graham Williams[4], John H Lazarus[2], Janis Hickey[5], Debbie Willis[6], Natasha Archer[6], Jayne Franklyn[7] & Ansu Basu[8]
[1]Royal Victroria Infirmary, Newcastle upon Tyne, UK; [2]Cardiff University, Cardiff, UK; [3]University of Exeter, Exeter, UK; [4]Imperial College, London, UK; [5]British Thyroid Foundation, Harrogate, UK; [6]Society for Endocrinology, Bristol, UK; [7]University of Birmingham, Birmingham, UK; [8]Sandwell and West Birmingahm Hospitals, NHS Trust, Birmingham, UK.

Introduction

Radioiodine (RI) is a safe and effective treatment for Graves' disease. In the months following RI different strategies are used to gain control of thyroid status, although there is no evidence base as to the optimal approach.

Objectives

To compare the incidence of dysthyroidism post-RI between three principal management strategies employed by clinicians.

Study design and methods

Retrospective, observational, multi-centre, UK based study.

Results

About 812 patients were studied from 31 centres. Mean age was 49.7 years (SD 14.2); 75.7% were female. After RI, 46.2% of patients were commenced on anti-thyroid drugs (ATD) alone (Group A), 21.5% on ATDs and levothyroxine (Group B), and 32.3% on levothyroxine when judged appropriate (Group C). Hypothyroidism developed in 67.2% and hyperthyroidism in 36% of patients during the first year post-RI. At 9-12 months post-RI 14.5% of patients had hyperthyroid and 11.4% hypothyroid biochemistry. Graves' orbitopathy (GO) was present in 18.2% of patients before RI. New onset or exacerbation of pre-existing GO developed in 5.7% of patients. Weight gain occurred in 67.0% of patients in Group A, 59.5% in Group B and 64.7% in Group C (Group B vs C, $P=0.002$). Patients in Group B were least likely to experience hypothyroidism ($P<0.0001$).

Conclusions

In this UK based study, dysthyroidism occurred with high frequency in the first 12 months post-RI and was still present in 25.9% of patients at 9–12 months. The use of the block and replace regimen after RI was associated with a lower probability of hypothyroidism and less weight gain. New onset, or exacerbation of GO after RI was uncommon. Achieving and maintaining euthyroidism post-RI is challenging in clinical practice in the UK. Although the block and replace strategy is associated with better outcomes, additional interventions need to be identified and implemented in order to improve outcomes.

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OC3.4

Identification of novel sodium iodide symporter (NIS) interactors which modulate iodide uptake

Alice Fletcher, Vikki Poole, Bhavika Modasia, Waraporn Imruetaicharoenchoke, Rebecca Thompson, Neil Sharma, Hannah Nieto, Martin Read, Andrew Turnell, Kristien Boelaert, Vicki Smith & Christopher McCabe
University of Birmingham, Birmingham, UK.

By exploiting the canonical function of the sodium iodide symporter (NIS) ablative radioiodine therapy is an effective treatment for thyroid cancer. However, a subset of patients are unable to accumulate sufficient radioiodine for effective treatment due to the dysregulation of NIS, which can occur through decreased expression and/or reduced plasma membrane localisation. Although NIS localisation at the plasma membrane is critical for radioiodine uptake the mechanism of NIS trafficking remains ill-defined. The importance of understanding protein interactomes for cellular trafficking is well-documented. We previously identified the first proven modulator of NIS localisation, pituitary tumor-transforming gene (PTTG) binding factor (PBF). In order to expand the NIS interactome, and subsequently unravel the mechanism of NIS trafficking, we have now used mass spectrometry to identify proteins that bind to NIS specifically at the plasma membrane. Using plasma membrane extracts from a cell line stably-expressing NIS, we have identified a number of novel NIS-interactors. To examine the biological impact on NIS-mediated radioiodine uptake, siRNA knockdown of the six highest ranked NIS-interactors was followed by functional screening. NIS activity was significantly altered by three proteins; ADP-ribosylation factor 4 (ARF4), Rab18 and valosin containing protein (VCP). Each of these proteins have roles in protein trafficking and/or endocytosis. siRNA knockdown of ARF4 decreased NIS-mediated radioiodine uptake by 31%, whereas Rab18 and VCP downregulation increased NIS-mediated radioiodine

uptake by 58% and 68% respectively ($P<0.01$). Critically, through co-immunoprecipitation we have confirmed that both ARF4 and VCP bind NIS *in vitro* ($n=3$). Taken together these data highlight a number of novel NIS-interactors that alter NIS-mediated radioiodine uptake. Our studies may thus aid the understanding of NIS plasma membrane localisation, and also provide therapeutic targets which could be manipulated to increase radioiodine uptake in those patients who are radioiodine-refractory.

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OC3.5

Identification of murine neuroendocrine tumour (NET) cell binding peptides identified through phage display

Mark Stevenson, Mahsa Javid, Kate Lines & Rajesh Thakker
Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology & Metabolism, University of Oxford, Oxford, UK.

Neuroendocrine tumours (NETs) may occur in multiple sites including, the pancreas, gastrointestinal tract, lung, thymus, adrenals and pituitary, and as part of the multiple endocrine neoplasia type 1 (MEN1) syndrome. Current treatments for advanced NETs, rarely achieve a cure due to metastases at presentation and therefore additional treatments are required. Identification of cell surface receptors or binding sites that are unique to NETs could lead to novel targeted drugs, radio-isotope or gene therapy treatments. To identify such receptors we used a phage display selection technique in which a library of peptides is expressed on the outside of phage virions encoded by the genetic material inside. Using 20 month old *Men1*$^{+/-}$ mice, which develop pancreatic NETs (PNETs), three rounds of phage display screening using a 12-mer library (New England Biolabs) were performed with mice that had been previously intravenously administered with clodronate liposomes, to deplete resident macrophages in the liver and spleen, prior to intravenous administration of 1.65×10^{11} plaque forming units of phage. PNETs were harvested after 3 hours and binding phage identified. From two independent experiments seven peptides emerged after the third round of screening that were recovered on at least three clones, and designated mouse PNETs peptides (MPP) 1–7 which represented 65%, 24%, 11%, 13%, 3%, 3%, and 3% of clones, respectively. MPP1, when compared with vehicle only or scrambled peptide control, was found to increase murine insulinoma (MIN-6) cell proliferation, assessed by trypan blue exclusion assay, at day 6 by 1.43-fold and 1.43-fold ($p<0.05$), respectively. Basic Local Alignment Search Tool (BLAST) analysis suggested that MPP1 has homology to the Niemann-Pick C1-like protein 1 precursor which plays a role in cholesterol homeostasis and is known to be expressed in human pancreas. Thus, our studies have identified a peptide that may play a role in targeting NET cells.

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OC3.6

Oestrogens Stimulate Proliferation in Colorectal Cancer via GPER and the Hippo signalling pathway

Anastasia Arvaniti, Lorna Gilligan, Habibur Rahman, Ali Gondal & Paul Foster
University of Birmingham, Birmingham, West Midlands, UK.

Circulating oestrogen concentrations affect the incidence of and outcomes for patients with colorectal cancer (CRC). We have previously shown that steroid sulphatase (STS), the fundamental enzyme that liberates conjugated oestrogens into their active forms, is significantly elevated in human CRC tissue. Here we demonstrate that elevated STS activity correlates to increased CRC proliferation, and that these effects are mediated through G-protein coupled oestrogen receptor (GPER) signalling via connective tissue growth factor (CTGF), yes-associated protein 1 (YAP1), and the Hippo-signalling pathway.

We developed a novel *in vivo* CRC mouse model using HCT116 xenografts stably over-expressing STS cDNA ($HCT116_{STS}$), with vector-only over-expressing xenografts ($HCT116_{VO}$) acting as controls. Animals were treated orally with the specific STS inhibitor, STX64 (20 mg/kg per thrice weekly), or vehicle control. At the end of the experiment, tumour wet weight and STS activity was measured. To investigate GPER effects in CRC, we determined how oestrogens and G1, a GPER agonist, and G15, a GPER antagonist, impacted proliferation in CRC cell lines. Using immunoblotting in CRC cell lines and human CRC samples we further examined whether GPER signalling increases CTGF and activates YAP1 and its transcriptional co-activator TAZ, key effectors of the Hippo pathway.

After 21 days, $HCT116_{STS}$ xenografts *in vivo* exhibited significantly ($P<0.01$) greater proliferation (426 ± 81 mm^3) compared to controls (273 ± 42 mm^3). This increased growth was significantly ($P<0.001$) inhibited by STX64. G1 and oestrogen treatment increased CRC proliferation in a dose-dependent manner. GPER-stimulation increased CTGF expression and deactivated the Hippo pathway with these effects inhibited by G15. Furthermore, GPER and CTGF expression significantly correlates ($P<0.001$) in human CRC tissue with expression elevated in malignancy compared to tissue matched controls.

These results define a new oestrogen-driven pro-proliferative GPER-stimulated pathway through Hippo signalling in CRC.

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Adrenal and Steroids

OC4.1

Novel brain biomarkers of cognitive abnormalities identified in patients with congenital adrenal hyperplasia

Emma A Webb[1,2], Lucy Elliott[1], Dominic Carlin[1], Kirsty Hall[1], Timothy Barrett[1,2], Vijay Salwani[3], Wiebke Arlt[1,3], Nils Krone[4], Andrew Peet[1,2] & Amanda Wood[1]
[1]University of Birmingham, Birmingham, UK; [2]Birmingham Children's Hospital, Birmingham, UK; [3]University Hospital Birmingham, Birmingham, UK; [4]Sheffield Children's Hospital, Sheffield, UK.

Background

Management of patients with CAH remains challenging. There is increasing evidence to suggest that failure to optimize treatment during childhood not only affects final height but also leads to psychological and psychiatric problems. Previous qualitative structural T2-weighted MRI studies have identified white matter hyper-intensities in up to 46% of CAH patients. The nature and functional relevance of these abnormalities remains unknown.

Objective and hypotheses

We aimed to identify novel MRI brain biomarkers of CAH using quantitative imaging and to examine their association with cognitive abnormalities.

Method

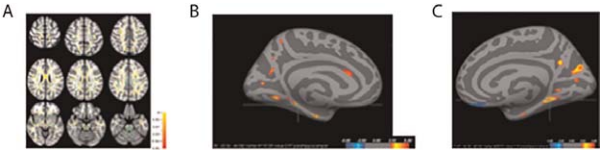
All participants completed IQ assessment and underwent brain volumetric, magnetic resonance spectroscopy and diffusion tensor imaging. Freesurfer (neural volumes and cortical thickness), TARQUIN (metabolites) and Tract Based Spatial Statistics (fractional anisotropy) were used for neuroimaging data analyses. ANCOVA were performed to compare groups, adjusted for multiple comparisons. Partial correlations were performed to assess the relationship between MRI markers and neuropsychological measures controlled for age and socioeconomic status.

Results

Seventeen females with 21-hydroxylase deficiency and eighteen age-matched healthy females were recruited (32.7 and 32.8 years, $P=0.95$). Patients with CAH had significantly lower processing speed ($P=0.05$), verbal fluency ($P=0.01$) episodic memory, learning and spatial working memory ($P=0.001$) scores. Patients with CAH had significant reductions in total brain volume ($P=0.02$), corpus callosum volume ($P=0.03$), hippocampal N-Acetyl Aspartate ($P=0.03$) and choline ($P=0.002$), brain fractional anisotropy (Figure A, $P=0.01$) and parahippocampal cortical thickness (B, left, C, right, $P=0.05$). There were significant relationships between; corpus callosum volume and spatial working memory ($P=0.001$), parahippocampal thickness, episodic and working memory ($P=0.05$), hippocampal choline and rapid visual information processing ($P=0.02$).

Conclusion

We have identified novel central nervous system imaging biomarkers of clinically significant cognitive abnormalities in patients with CAH. Further studies are required to determine the age of onset of these abnormalities and to develop preventative strategies.



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OC4.2

Nicotinamide riboside and cellular NAD+ redox state influence 11β-HSD1 mediated glucocorticoid regeneration in skeletal muscle cells

Yasir Elhassan[1,2], Rachel Fletcher[1,2], Lucy Oldacre-Bartley[1,2], Craig Doig[1,2] & Gareth Lavery[1,2]
[1]Institute of Metabolism and Systems Research, Birmingham, UK; [2]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK.

11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an NADPH-dependant oxo-reductase located in the sarcoplasmic reticulum (SR) lumen of skeletal muscle. Here it generates active glucocorticoids to regulate permissive and adaptive metabolism, and can mediate the pathological effects of glucocorticoid excess. Hexose-6-phosphate dehydrogenase (H6PD) in the SR interacts with 11β-HSD1 to generate an appropriate NADPH/NADP+ ratio to support activity. H6PD depletion impairs SR NADPH generation causing 11β-HSD1 to assume glucocorticoid inactivating dehydrogenase activity. We tested whether modulating cellular nicotinamide adenine dinucleotide (NAD+) availability (as the parent molecule of NAD(P)(H)) influenced 11β-HSD1 activity in the SR. We used FK866 to inhibit nicotinamide phospho-ribosyltransferase (NAMPT, rate-limiting enzyme in NAD+ biosynthesis) to deplete NAD(P)(H) in mouse C2C12 myotubes. 48 h FK866 treatment impaired cellular energetic status, reducing NAD+(>90%), NADP+(>50%) and ATP (>30%) levels without inducing apoptosis or affecting cell viability. 11β-HSD1 reductase activity was 30% that of untreated cells (152±18 vs. 512±44 pmol steroid/mg protein/h respectively, $P<0.005$). Despite impaired reductase activity, FK866 treatment did not induce 11β-HSD1 dehydrogenase activity, likely reflecting an intact SR 11β-HSD1-H6PD system. To examine the mechanisms of FK866 mediated suppression of 11β-HSD1 activity, cells were co-treated with the NAD+ precursor nicotinamide riboside (NR, 0.5 mM) to bypass NAMPT inhibition. NR supplemented to 48 h FK866 treated myotubes for the last 24 h fully restored NAD+ levels and fully rescued 11β-HSD1 activity. We next ascertained the time course of the NR rescue effect. Intriguingly, 11β-HSD1 activity normalised in proportion to the duration of NR supplementation, with as little as 30 min inducing a significant increase in 11β-HSD1 activity (202±22 pmol steroid/mg protein/h, $P<0.05$). These data suggest a novel level of regulated glucocorticoid metabolism in skeletal muscle whereby 11β-HSD1 activity can be influenced by cellular redox status and NAD+ levels beyond the SR.

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OC4.3

Genome wide ChIP-Seq analysis of Glucocorticoid Receptor and RNA Polymerase 2 binding in rat liver during physiological and non-physiological corticosterone replacement

Benjamin P. Flynn[1], Matthew T. Birnie[1], Yvonne M. Kershaw[1], Songjoon Baek[2], Sohyoung Kim[2], Diana A. Stavreva[2], Gordon L. Hager[2], Stafford L. Lightman[1] & Becky L. Conway-Campbell[1]
[1]University of Bristol, Bristol, UK; [2]National Institute of Health, Maryland, USA.

Ultradian glucocorticoid (GC) secretion is highly conserved, having been detected in all species studied. The GC corticosterone (CORT) is a ligand for the glucocorticoid receptor (GR), inducing GR recruitment to glucocorticoid responsive elements (GREs) to modulate transcription of GC-target genes. We have previously demonstrated that pulsatile GR recruitment to GREs upstream of the *Period1* gene is associated with its pulsatile transcription in rat liver. Similarly the gene pulsing phenomenon was demonstrated in cell lines, where constant GC treatment was found to induce prolonged GR activity and overexpression of GC-target genes. However the effects of GC pattern dysregulation on GR transcriptional dynamics at more physiologically relevant metabolic targets *in vivo* are less well understood.

Adrenalectomized male Sprague Dawley rats were administered with physiological CORT replacement over 3 hr, as hourly 20 min pulses or matched constant infusion. Vehicle-infused rats served as controls. Liver samples were collected at 2 hr 20 min and 3 hr (times corresponding to pulse peak and trough respectively). Samples were ChIP'd with GR and RNA Polymerase (Pol2) antibodies and sequenced. GR binding at a large range of genomic sites was found to faithfully track the pulsatile peak and trough, whereas constant CORT generally induced sustained GR recruitment.

Pol2 activity was found to be highly dynamic and differentially regulated in a gene-specific manner. Notably Pol2 activity at metabolic targets involved in gluconeogenesis and lipolysis, such as Tyrosine aminotransferase, Lpin1 and Angptl4, was markedly increased with constant infusion relative to both pulsatile CORT and vehicle-infused controls. Interestingly pulsatile infusion resulted in pulsatile Pol2 activity along entire GC-regulated gene bodies in many cases, and actually reduced Pol2 activity relative to both constant and vehicle-infusion in some cases such as for Angptl4.

Therefore, we have demonstrated that disrupting the ultradian GC rhythm causes complex genome-wide dysregulation of metabolic targets potentially resulting in development of adverse metabolic phenotypes.

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OC4.4

A Single Nucleotide Polymorphism in the BACH2 Gene Contributes to Susceptibility to Autoimmune Addison's Disease in UK and Norwegian cohorts

Agnieszka Pazderska[1], Bergithe Oftedal[2], Catherine Napier[1], Holly Ainsworth[1], Eystein Husebye[2,3], Heather Cordell[1], Simon Pearce[1] & Anna Mitchell[1]
[1]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; [2]Department of Clinical Science, University of Bergen, 5021 Bergen, Norway; [3]Department of Medicine, Haukeland University Hospital, 5021 Bergen, Norway.

Background

Autoimmune Addison disease (AAD) is a rare but highly heritable endocrinopathy. The BACH2 protein plays a crucial role in T lymphocyte maturation, and in particular in regulatory T cell formation, and allelic variation in its gene has been associated with autoimmune conditions such as type 1 diabetes, autoimmune thyroid disease and vitiligo. Its role in susceptibility to autoimmune Addison's disease (AAD) has not been investigated.

Aim

To investigate whether the intronic SNP *rs3757247* in the *BACH2* gene is associated with AAD.

Methodology

A case-control association study was performed. The *rs3757247* SNP was genotyped in 357 UK AAD patients using Taqman chemistry (Life Technologies) and results compared to genotype data from 5097 healthy individuals available from the Wellcome Trust (WTCCC2). The SNP was then genotyped in a validation cohort comprising of 330 Norwegian AAD subjects and 384 local controls. Statistical association analysis was performed using PLINK.

Results

The minor T allele frequency was significantly higher in UK AAD subjects compared to the controls (58% vs 48%; $p=1.4\times10^{-6}$; OR 1.44 [95% CI 1.23–1.69]). This finding was replicated in the Norwegian validation cohort ($p=0.0015$; OR 1.41 [95% CI 1.14–1.75]). Subgroup analysis showed that this association is true for both isolated AAD (iAAD; OR 1.53 [95% CI 1.22–1.92]) and autoimmune polyglandular syndrome type 2 (APS2; OR 1.37 [95% CI 1.12–1.69]) in the UK cohort, and for APS2 in the Norwegian cohort (OR 1.58 [95% CI 1.22–2.06].

Interpretation and conclusion

This is the first report of a *BACH2* variant being associated with susceptibility to AAD. The association of *BACH2* SNPs with multiple autoimmune endocrinopathies supports existing evidence that the BACH2 protein is a crucial regulator of immune function and dysfunction.

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OC4.5

ARID1a is required for regulation of a subset of glucocorticoid target genes involved in cell-cycle and p53 pathway regulation

Felicity E. Stubbs[1], Matthew T. Birnie[1], Hai Fang[2], Simon C. Biddie[1], Stafford L. Lightman[1] & Becky L. Conway-Campbell[1]
[1]The University of Bristol, Bristol, UK; [2]University of Oxford, Oxford, UK.

Clinically, glucocorticoids are widely used as a treatment mainly due to their potent anti-inflammatory abilities, however these are associated with several side effects and furthermore some patients go on to develop glucocorticoid resistance. ARID1a mutations have been linked to glucocorticoid resistance and are frequently identified across numerous cancers; therefore it is important to determine the functional role of ARID1a to GR signalling. The ATPase driven SWItch/Sucrose NonFermentable (SWI/SNF) chromatin-remodelling complex interacts with GR through ARID1a. Chromatin-remodelling by the SWI/SNF complex is a vital component of genomic GR signalling, with chromatin being dynamically opened and closed at GR binding sites in target genes to regulate transcription. We therefore hypothesize ARID1a is key in facilitating this GR

mediated transcriptional regulation. In this study expression profiling using next-generation RNA sequencing enables the assessment of GR regulated gene transcription in the absence of the full-length ARID1a and chromatin immunoprecipitation (ChIP) is used to assess GR and RNA Polymerase II binding. Here we assess ARID1a knock-down and the functional interference of the endogenous ARID1a by the overexpression of the ARID1a C-terminal in HeLa cells. Surprisingly, our genome-wide data shows that loss or functional interference of ARID1a does not impact upon the majority of robustly regulated GR responsive genes. In addition, our ChIP studies reveal no affect of ARID1a knock-down on GR or RNA Polymerase II binding at the Per1 gene, consisting of a chromatin-remodelling dependent GR binding site. Instead, we demonstrate the importance of GR regulation on cell-cycle progression through ARID1a and that disruption of this interaction impacts upon P53 pathways. We also reveal a novel role of GR in the regulation of histone gene expression. Understanding this role of GR is important for understanding the potential of GR as a therapeutic target in diseases associated with loss of ARID1a and those with cell-cycle dysregulation.

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OC4.6

Demographics of adrenal incidentaloma – results from an international prospective multi-centre study in 2190 patients

Irina Bancos[1,2], Vasileios Chortis[2,11], Katharina Lang[2,11], Massimo Terzolo[3], Martin Fassnacht[5], Marcus Quinkler[8], Darko Kastelan[9], Dimitra Vassiliadi[7], Felix Beuschlein[6], Urszula Ambroziak[4], Jonathan Deeks[2,10] & Wiebke Arlt[2,11]
[1]Mayo Clinic, Rochester, MN, USA; [2]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK; [3]University of Turin, Turin, Italy; [4]Warszawski Uniwersytet Medyczny, Warszawa, Poland; [5]Universitätsklinikum Würzburg, Würzburg, Germany; [6]Klinikum der Ludwig-Maximilian-Universität München, München, Germany; [7]Attiko University Hospital, Athens, Greece; [8]Charité Universitätsmedizin Berlin, Berlin, Germany; [9]University Hospital Zagreb, Zagreb, Croatia; [10]Institute of Applied Health Research, University of Birmingham, Birmingham, UK; [11]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK.

Background
Adrenal masses are discovered in 5% of cross-sectional abdominal imaging scans. Work-up aims at exclusion of malignancy and hormone excess. However, estimates of these risks presently derive from retrospective studies only, mostly small and with significant selection bias.
Methods
Prospective multi-centre study (2011–2016) in 21 centres (17 countries) of the European Network for the Study of Adrenal Tumours (ENSAT) with consecutive enrolment of patients with newly diagnosed adrenal mass. Extra-adrenal malignancy and biochemically proven phaeochromocytoma were exclusion criteria. Diagnosis was confirmed by histology or imaging follow-up.
Results
We enrolled 2190 patients with an adrenal mass (median size 3 cm). Overall, 1933 (88%) had an adrenocortical adenoma (ACA) and 73 (3%) were diagnosed with other benign masses (adrenomyelolipoma, ganglioneuroma, schwannoma, cyst). In addition, 155 patients (7.1%) were diagnosed with adrenocortical carcinoma (ACC) and 29 (1.3%) with other malignant masses (metastases, primary adrenal lymphoma, sarcoma). Risk of ACC was highest in young patients (<40 yrs 22%; 40–60 yrs 9%; >60 yrs 5%). In adrenal masses <4 cm diameter, ACC was diagnosed in only 0.2% (3/1666) whereas an incidence of 29% (152/524) was found in masses >4 cm.
CT imaging with quantification of tumour density in Hounsfield units (HU) was available for 1252 ACA patients; of those, only 67% had HU <10 indicative of benign disease (10–20 HU 14%; >20HU 19%). Similarly, 24% of 233 ACA patients characterised by MRI showed no drop in signal intensity in chemical shift analysis, wrongly suggestive of malignant disease. Incidence of subclinical Cushing syndrome was 33% (517/1555) in patients with dexamethasone overnight suppression test results. Adrenalectomy was performed in 18.6% (379/2035) of patients with benign tumours.
Conclusion
Risk of ACC needs to be seriously considered in patients with adrenal incidentaloma. On the other hand, benign masses are frequently misclassified as malignant by routine imaging, resulting in a high rate of unnecessary adrenalectomies.

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Diabetes Mellitus and Metabolism

OC5.1

Does type of diabetes, and treatment prescribed prior to admission influence quality of treatment of inpatient hypoglycaemia?

Christopher Sainsbury, Jansher Khan & Greg Jones
Department of Diabetes, Gartnavel General Hospital, Glasgow, UK.

Inpatient hypoglycaemia is common and associated with adverse outcome during admission and post discharge. We investigated management of hypoglycaemia using the time to repeat (TTR) capillary blood glucose (CBG) measurement as a surrogate for engagement with clinical guidelines.
Methods
Inpatient CBG data from 8 hospitals over a 7 y period were analysed. Primary care prescribing information was available, and admissions were associated with insulin or SU therapies if a prescription was identified during the 4 months prior to admission. During an admission, the time interval between each CBG measurement was calculated, and analysed per initial (index) CBG value. For each index CBG, the TTR for those individuals with T2DM – insulin or SU treated – was compared with the TTR for those individuals with T1DM, using a t test performed on log(TTR) to test significance.
Results
T1DM: 4304 individuals with 406490 CBG values. T2DM/insulin therapy: 5163 IDs with 484067 CBGs. T2DM/SU therapy: 13015 IDs with 589778 CBGs.
Hypoglycaemic (<4 mmol/l) CBGs – T1DM: 26664. T2DM/insulin: 23591. T2DM/SU: 30344
Median (IQR) TTR for index CBGs in the range 1–3.9 mmol/l: T1DM 53 (26–112) mins; T2DM/insulin 64 (30–147) mins; T2DM/SU 97 (40–292) mins.
The TTR in the T2DM/SU was significantly greater than T1DM where the index CBG is $>=2.3$ (except index CBG 2.6). For the T2DM/insulin significance exists for index CBGs of $>=3.2$.
Conclusions
Guidelines suggest identical action for hypoglycaemic index CBGs regardless of clinical context. This analysis suggests that quality of care varies according to the underlying diagnosis and prescribed drugs. TTR decreases as the index CBG decreases as clinically expected. The group with the highest TTR (T2DM SU treated) are possibly the clinical group in whom the risks associated with hypoglycaemia are greatest. These data therefore suggest a need for education and raising awareness within ward staff.ain

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OC5.2

Transcriptomic analysis of the onset of pancreas and liver differentiation in human embryos

Rachel Jennings[1,2], Andrew Berry[1], Karen Piper Hanley[1] & Neil Hanley[1,2]
[1]Institute of Human Development, University of Manchester, Manchester, UK; [2]Endocrinology Department, Central Manchester University NHS Foundation Trust, Manchester, UK; [3]Section of Endocrinology Research, University of Copehagen, Copehagen, Denmark.

The incretin hormone glucagon-like peptide-1 (GLP-1) has been proposed to increase beta cell mass, via effects on proliferation, apoptosis and neogenesis. However, the role of GLP-1 during normal human development is unclear. We have addressed this in human fetuses by quantifying GLP-1 secretion during fetal development and determining how GLP-1 signalling impacts on early human fetal pancreas in explant culture.
GLP-1 is first secreted by the stomach, duodenum, terminal ileum and rectum at 8 weeks post conception (wpc). Levels of GLP-1 increased considerably during fetal development, most notably within the terminal ileum ($\sim 60\times$) and rectum ($\sim 200\times$). Active GLP-1 was secreted by the fetal pancreas, with a significant increase in secretion from 12 wpc ($\sim 150\times$). By immunohistochemistry, GLP-1 co-localised with prohormone convertase 1/3, detected at low levels in fetal pancreatic alpha-cells as well as in enteroendocrine cells. Interestingly, the GLP-1 receptor (GLP-1R) was detected on PDX1-positive cells but absent on NEUROG3-positive cells and fetal beta cells. Culturing fetal pancreatic explants with long-acting GLP-1 analogue (Liraglutide) significantly increased the number of insulin-positive cells whilst decreasing proliferation of progenitors. No effect was observed on beta cell apoptosis.
Taken together, these studies identify for the first time active GLP-1 production from multiple sites within the developing human fetus including the pancreas, with the potential to impact on human pancreas development and beta cell differentiation.

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OC5.3

Depot specific transcriptional signatures of adipose tissue in sheep and humans during early life

Hernan Fainberg[1], Shalini Ojha[1], Ahmad Alhaddad[1], Reham Alagal[1], Mark Birtwistle[1], Graeme Davies[1], Marcos Castellanos[2], Sean May[2], Giussepe Pelella[3], Attilio Lotto[3], Harold Sacks[4], Helen Budge[1] & Michael Symonds[1]
[1]Division of Child Health, Obstetrics & Gynaecology, School of Medicine, Queen's Medical Centre, University Hospital, The University of Nottingham, Nottingham, UK; [2]Nottingham Arabidopsis Stock Centre, School of Biosciences, The University of Nottingham, Sutton Bonington, UK; [3]University Hospitals NHS Trust, Leicester, UK; [4]4VA Endocrinology and Diabetes Division, VA Greater Los Angeles Healthcare System, and Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, USA.

The identification and characterisation of unique gene profiles expressed in specific adipose tissue depots around the body could provide novel insights on fat development.
We report a comprehensive analysis of transcriptome from the five major (epicardial, pericardial, perirenal, sternal and omental) adipose depots from one week old sheep. This study also provides an integrated view of the preservation and differences between mitochondrial gene co-expression networks found in each adipose depot in relation to paediatric human epicardial adipose tissue (EAT). Based on microarray analysis, we identified novel adipose depot-specific gene expression patterns for a significant portion of transcripts ($\sim$10%). By weighted gene co-expression network analysis, we observed that each depot can be delineated concisely by a small number of functional modules of co-expressed genes. This result indicates a consistent transcriptional change in each depot in pathways indicative of different cellular origin, metabolism and thermogenic functionality. Cross-species comparisons of mitochondrial genes with human paediatric EAT revealed that the modules encapsulating mitochondrial functional and structural composition were preserved in 3 out of 5 ovine adipose depots. However, the majority of DNA and RNA transcriptional regulation, as well as the reactive oxygen cell defence module, differed between humans and sheep. Furthermore, we identified that the key module confining mitochondrial thermogenic activity showed negative correlation with the child's weight and height. Together, the results provide unique information of regulatory mechanisms underlying the adaptable morphology of adipose tissue over time and location.

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OC5.4

Two contrasting cases of spontaneous severe hypoglycaemia secondary to anti-insulin antibodies (Insulin Autoimmune Syndrome / Hirata disease)

Myuri Moorthy[1], Bernard Freudenthal[3], David Church[2], Judith Kisalu[1], Emma Woolman[1], Amy Hale[1], Huw Beynon[1], Efthimia Karra[1], Mark Cohen[3] & Bernard Khoo[1]
[1]Department of Endocrinology & Diabetes, Royal Free Hospital London NHS Foundation Trust, London, UK; [2]Department of Clinical Biochemistry, University of Cambridge, Cambridge, UK; [3]Department of Endocrinology and Diabetes, Barnett Hospital, London, UK.

IAS is a very rare condition in which anti-insulin antibodies carry high concentrations of insulin in suspension in circulation. Hypoglycaemia occurs when insulin is released from the antibodies during fasting or post-prandially.
We present two cases. Patient-A is a 52-year old Thai obese female, with acanthosis nigricans and a strong family history of T2DM. Patient-B is a 28 year-old normal- BMI Caucasian female with an unremarkable history. None of the patients received any regular medication or had history of autoimmunity. Both presented with symptomatic hypoglycaemia. Whipple's triad was noted at 10 hr of a supervised fast for patient-A. Nadir laboratory glucose was 1.8 mmol/l, and coupled with hyperinsulinaemia and a non-physiological ratio of insulin-to-C-peptide (insulin = 9809 mIU, C-peptide = 3690 pmol/l, insulin:C-peptide = 18.5). Patient-B developed hypoglycaemia at 4 hr during a supervised fast, with hyperinsulinaemia and a high ratio of insulin-to- C-peptide (plasma glucose = 2.2 mmol/l, insulin = 17800 pmol/l, C-peptide = 409 pmol/l, insulin:C-peptide-ratio = 43.5 [normal insulin:C-peptide ratio $\leq$1]). Hook-effect phenomena were excluded with insulin/C-peptide recovery post-serial dilutions. Insulin was lower post-PEG precipitation. SU screen was negative and CT CAP, MRI & Ga68-DOTATATE unremarkable. Anti-insulin-receptor Abs were negative, whereas anti-insulin IgG were positive. Chromatography demonstrated insulin-sequestration by Ab, identifying monomeric and Ab-bound insulin. Pending diagnosis, both patients received diazoxide with no efficacy. In light of positive insulin Ab, prednisolone 30 mg and add-on mycophenolate (MMF) treatment were initiated in patient-A; with later euglycaemia maintained on MMF monotherapy. In patient-B prednisolone 60 mg and add-on MMF only induced partial response, thus, CD20 depletion by Rituximab steroid adjuvant treatment strategy was adopted with efficacy.
We discuss the diagnostic challenges in IAS, the diverse phenotype and treatment responses in our two cases.

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OC5.5

5β-reductase (AKR1D1) is a potent regulator of carbohydrate and lipid metabolism in human and rodent liver

Nikolaos Nikolaou, Laura Gathercole, Charlotte Green, Catriona McNeil, Leanne Hodson & Jeremy Tomlinson
University of Oxford, Oxford, UK.

Non-alcoholic fatty liver disease is the hepatic manifestation of metabolic disease. 5β-reductase (AKR1D1) is highly expressed in human and rodent liver where it inactivates steroid hormones and catalyzes a fundamental step in bile acid synthesis. Steroid hormones, including glucocorticoids, as well as bile acids are established regulators of metabolic phenotype. We have hypothesized that AKR1D1 plays a crucial regulatory role in hepatic metabolic homeostasis.
Genetic manipulation of AKR1D1 (over-expression, siRNA knockdown) was performed in human liver HepG2 cells alongside the metabolic phenotyping of AKR1D1 KO mice. Gene expression changes in HepG2 cells were confirmed by real-time PCR. Functional activity, assessed using gas chromatography mass spectrometry to measure cortisone clearance and tetrahydrocortisone generation was paralleled by the anticipated changes in glucocorticoid receptor activation measured by luciferase reporter assays.
AKR1D1 knockdown increased glucose transporter mRNA expression (GLUT1: 0.47 ± 0.08 vs. 1.07 ± 0.15, $P<0.01$; GLUT9: 0.56 ± 0.08 vs. 0.85 ± 0.15, $P<0.05$). Extracellular glucose concentrations in the culture media decreased (15.3 ± 1.5 vs. 12.1 ± 0.9 umol/mg, $P<0.05$) as did intracellular glycogen (14.0 ± 0.1 vs. 10.5 ± 1.7 ug/ml, $P<0.05$). Endorsing our cellular observations, fed blood glucose levels in AKR1D1 KO mice were lower than wild type (WT) controls (15.1 ± 0.5 (WT) vs. 12.8 ± 0.6 mmol/L (KO), $P<0.05$). In addition, hepatic glycogen content was lower in KO mice (6.7 ± 0.3 (WT) vs. 5.1 ± 0.5 ug/gram of liver (KO), $P<0.05$).
AKR1D1 knockdown in HepG2 cells increased Acetyl CoA Carboxylase 1 expression, the rate-limiting step in *de novo* lipogenesis, DNL) (0.52 ± 0.06 vs. 0.89 ± 0.04, $P<0.01$), and increased intracellular triglyceride (54.3 ± 12.7 vs. 73.3 ± 11.0 nmol/mg, $P<0.01$). Furthermore, 3-hydroxybutyrate levels in the cell media were reduced, indicative of decreased fatty acid oxidation (18.7 ± 2.3 vs. 11.4 ± 2.7 nmol/mg, $P<0.01$). Mass spectrometry analysis of lipid composition demonstrated increased palmitic and palmitoleic acid production consistent with increased DNL and fatty acid saturation.
In conclusion, we have demonstrated that AKR1D1 activity limits steroid hormone availability and is potently able to regulate hepatic carbohydrate and lipid metabolism.

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OC5.6

IRX3 regulates Adipocyte Browning via Mitochondrial Gene Clusters

Samantha Laber[1,2], Thomas Agnew[1] & Roger Cox[1]
[1]MRC Harwell, Oxford, UK; [2]University of Oxford, Oxford, UK.

Genome-wide association studies have repeatedly shown that the strongest association with human BMI is arising from variants in the first intron of Fto. It has recently been demonstrated that intronic Fto variants are within an adipocyte-specific enhancer and that risk allele carriers have altered Irx3 and Irx5 expression in early adipogenesis (Claussnitzer et al. NEJM 2015). The aim of our study is to investigate the functional role of Irx3 in adipocytes. We show that silencing of Irx3 in mouse pre-adipocytes causes increased mRNA expression of mitochondrial electron transport chain and biogenesis genes (e.g. Pgc1a, Cox7a, Cox8b, Elovl, Dio2) at day 8 of adipogenic stimulation. A mitochondrial stress test using the Seahorse Bioflux analyser of these differentiated adipocytes shows that siIrx3 increases basal respiration, proton leak, ATP production and maximal respiration compared to control adipocytes, indicative of increased mitochondrial respiration in brown-like adipocytes. To identify the targets of the transcription factor IRX3, we performed ChIP-Seq in early differentiating mouse primary

pre-adipocytes of both visceral and subcutaneous white adipocyte depots. In gonadal-derived pre-adipocytes, we identified 2259 peaks in proximal promoter regions ($\leq$ 1 kb) and mitochondrial genes were significantly overrepresented in this data set ($P=2.2E-11$; PANTHER Overrepresentation Test). The identified mitochondrial genes could be clustered into three groups: mitochondrial ribosomal machinery, mitochondrial complex I assembly/units and mitochondrial membrane transporters. Interestingly, gene ontology of genes identified to be regulated by IRX3 in subcutaneous pre-adipocytes showed a slightly different profile, suggesting a differential role of IRX3 in white adipocytes from different depots. Finally, using publicly available chromatin maps, we found that enhancer marks in human adipocytes are conserved in mouse pre-adipocytes, opening opportunities for novel gene manipulation strategies *in vivo* in order to mechanistically dissect the Fto regulatory circuitry in mouse. In summary, our findings provide new insight into how alteration of IRX3 affects early adipocyte differentiation.

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Pregnancy and Reproductive Health

OC6.1

Two doses of kisspeptin improve oocyte maturation and implantation rates compared to a single kisspeptin injection during IVF treatment

Ali Abbara[1], Sophie Clarke[1], Rumana Islam[2], Julia Prague[1], Alexander Comninos[1], Shakunthala Narayanaswamy[1], Deborah Papadopolou[1], Rachel Roberts[1], Alexander Nesbitt[1], Chioma Izzi-Engbeaya[1], Sunitha Vimalesvaran[1], Risheka Ratnasabapathy[1], Rehan Salim[2], Stuart Lavery[2], Stephen Bloom[1], Geoffrey Trew[2] & Waljit Dhillo[1]
[1]Imperial College London, London, UK; [2]Imperial College Healthcare NHS Trust, London, UK.

Background
In vitro fertilisation is an effective therapy for infertility, but can result in the potentially life-threatening complication, Ovarian Hyper-Stimulation Syndrome (OHSS). We have previously reported that a single injection of kisspeptin results in an LH surge of ~12–14 hrs duration, sufficient to safely induce oocyte maturation, but eliminate OHSS. However, the physiological LH surge in a normal menstrual cycle has a plateaux lasting 24–28 hrs. Thus, we hypothesised that by administering a second dose of kisspeptin to women with infertility during IVF treatment, the duration of LH-exposure will more closely mimic the physiological LH-surge and hence optimise oocyte yield and pregnancy rates.
Methods
We conducted a phase2 single-blinded randomised placebo-controlled trial of 58 women at high risk of OHSS at Hammersmith IVF unit. Following a standard recombinant FSH/GnRH-antagonist IVF protocol, all patients received a subcutaneous injection of kisspeptin at 9.6 nmol/kg 36 hrs prior to egg retrieval. Patients were then randomised 1:1 to receive either a second dose of kisspeptin 10 hrs later (D; Double), or saline placebo (S; Single). IVF physicians, embryologists and participants were blinded to the randomisation. Retrieved eggs were assessed for maturation, fertilised by ICSI, with subsequent transfer of 1–2 embryos.
Outcome Measures
1. Serum LH levels
2. Oocyte Yield (%mature eggs retrieved from follicles $\geqq$14 mm).
3. Implantation rates
4. OHSS occurrence
Results
A double dose of kisspeptin resulted in:
1. Further rise in LH-secretion (mean change in LH at 4 hrs post-second injection (S: $-$12.1 iU/L, D: $+$4.0 iU/L; $P<0.0001$).
2. Optimal oocyte yield ($\geq$60%) in more patients (S:45%, D:72%).
3. Improved implantation rate (S:25%, D:38%).
4. No moderate or severe OHSS.
Conclusion
Two doses of kisspeptin administered to women with infertility during IVF treatment induces a more physiological LH-surge, improves oocyte yield and implantation rates, without OHSS. These findings identify kisspeptin as a safe and highly effective trigger for oocyte maturation in young women suffering with infertility undergoing IVF treatment.

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OC6.2

The thyroidal response to hCG stimulation is impaired in women with subclinical hypothyroidism and is influenced by BMI, fetal sex and parity

Tim Korevaar[1,2], Layal Chaker[1,2], Theo Visser[1,2] & Robin Peeters[1,2]
[1]Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Rotterdam Thyroid Center, Rotterdam, The Netherlands.

Introduction
Although hCG is an important determinant of gestational thyroid function, it is unknown to what extent hCG is a risk factor for thyroid disease and we also lack knowledge on which characteristics influence the thyroidal response to hCG stimulation.
Methods
hCG, TSH, FT4 and TPOAbs were measured in 5435 pregnant women ($<$18 weeks) in a prospective cohort. Subclinical disease entities were defined according to P2.5-P97.5 in TPOAb negative women. We investigated the association of hCG with the risk of thyroid disease, and the association of subject characteristics with thyroidal hCG response by using multivariable logistic and linear regression models adjusting for age, smoking, BMI, parity, ethnicity, education and fetal sex.
Results
hCG was not associated with subclinical hypothyroidism ($P=0.29$). As compared to euthyroid women, the association of hCG with FT4 was strongly attenuated in women with subclinical hypothyroidism ($P=0.047$). Higher hCG was associated with a lower risk of hypothyroxinemia ($P<0.0001$) and a higher risk of subclinical as well as overt hyperthyroidism (both $P<0.0001$). As compared to euthyroid women, the association of hCG with TSH was similar in women with hypothyroxinemia, and the association of hCG with FT4 was similar in women with subclinical hyperthyroidism ($P=0.72$ and $P=0.22$, respectively). In the whole population, higher BMI was associated with a lower thyroidal response to hCG stimulation in a dose-dependent manner ($P=0.068$ for FT4 and 0.003 for TSH). Also, male fetal sex and high maternal parity (>2) were associated with a lower thyroidal response to hCG stimulation ($P=0.0006$ & 0.0064; and $P=0.036$ & 0.019 for FT4 and TSH, respectively). Iodine status, smoking and maternal age were not associated with differences in the thyroidal response to hCG stimulation. All results remained similar after exclusion of TPOAb positive women.
Conclusion
Women with subclinical hypothyroidism exhibit a thyroidal hCG response that fits with a decreased thyroid functional capacity. In contrast to subclinical hypothyroidism, hCG was an important determinants of other disease entities. In the whole population, BMI, male fetal sex and a high parity are associated with a lower thyroidal response to hCG stimulation.

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OC6.3

Controlled Antenatal Thyroid Screening Study; Obstetric Outcomes

Peter Taylor[1], Arron Lacey[2], Daniel Thayer[2], Mohd Draman[1], Arshiya Tabasum[1,3], Ilaria Muller[1], Luke Marsh[1], Arwel Poacher[1], Aled Roberts[3], Marian Ludgate[1], Alex Rees[3], Kristien Boelaert[4], Aled Rees[1], Shiao Chan[4,5], John Lazarus[1], Scott Nelson[6], Bijay Vaidya[7] & Onyebuchi Okosieme[1]
[1]Cardiff University, Cardiff, UK; [2]Swansea University, Swansea, UK; [3]Cardiff and Vale Health Board, Cardiff, UK; [4]University of Birmingham, Birmingham, UK; [5]National University of Singapore, Singapore, Singapore; [6]Glasgow University, Glasgow, UK; [7]University of Exeter, Exeter, UK.

Context
Suboptimal thyroid function in pregnancy is associated with adverse obstetric outcomes but it is unclear whether levothyroxine treatment, initiated during pregnancy is beneficial.
Design & Participants
Retrospective analysis of the Controlled Antenatal Thyroid Screening (CATS) study with obstetric outcomes obtained through data-linkage in the Secure Anonymised Information Linkage (SAIL) databank. We studied 13,224 pregnant women; 12,608 had normal thyroid function, 340 had subclinical hypothyroidism (SCH), 305 had isolated hypothyroxinemia (IH). 518 women with abnormal thyroid function were randomized to receive levothyroxine ($N=263$) or no treatment ($N=255$) at the end of the first trimester.
Main Outcome Measures
Composite measure (primary outcome) of stillbirth, neonatal death, preterm delivery $<$34 weeks, APGAR score at 5 minutes $<$7, length of hospital stay $>$5 days. Secondary analyses included early gestational age ($<$37 weeks), early caesarean sections ($<$37 weeks).

Results
In individuals with abnormal thyroid function randomized to treatment or control, treatment had no discernible effect on the composite outcome. 29 events occurred in the untreated group vs 22 in the treated. OR (treated) = 0.75 95%CI (0.40, 1.40). Untreated women with SCH had increased odds of stillbirth compared to women with normal thyroid function OR = 4.37 (95%CI 1.04, 18.3). No stillbirths occurred in women on levothyroxine. Untreated women with IH had increased odds of an early gestational age at delivery (< 37 weeks) than women with normal thyroid function OR = 1.58 (95%CI 1.04, 2.50). Women with IH randomized to receive treatment with levothyroxine had reduced odds of early gestational age at delivery OR = 0.37 (95%CI 0.14, 0.99) and early caesarean sections (0% vs 4%) $p = 0.04$ than untreated women.
Conclusion
Both SCH and IH were associated with key adverse obstetric outcomes. Although there was no difference in composite outcome there were some benefits observed with levothyroxine therapy. Larger studies are required to confirm the benefits of screening and treatment in pregnancy.

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OC6.4

Iodine nutritional status among pregnant women and their offspring in Northern Ireland (NI)

Paul McMullan[1,2], Lesley Hamill[2], David McCance[1], Jayne Woodside[2] & Karen Mullan[1]
[1]Regional Centre for Endocrinology, Royal Vicotoria Hospital, Belfast, UK; [2]Centre for Public Health, Queens University, Belfast, UK.

Background
A re-emergence of mild iodine deficiency in the United Kingdom (UK) has been reported. A recent UK study suggested a dose dependent relationship between mild maternal deficiency and a number of childhood cognitive scores. The World Health Organisation defines sufficiency in a population as a median urinary iodine concentration (UIC) of ≥100 μg/l in non-pregnant women and infants and ≥150 μg/l during pregnancy. It also recommends a daily intake of ≥250 μg/day during pregnancy. Thyroglobulin (Tg) has been suggested as an alternative indicator of iodine status. No cut off value is available in adults but a study in children defined sufficiency as a median Tg value ≤13 μg/l and/or <3% of samples ≥40 μg/l.
Methods
Participants ($n = 241$) were recruited at their booking visit and followed up at each trimester and into the postpartum period. Dietary intake was collected with four day food diaries and iodine specific food frequency questionnaires. Urinary samples were obtained from 80 offspring for UIC. A separate cohort ($n = 183$) was recruited to evaluate nutrition knowledge during pregnancy.
Results
The maternal median UIC was 72 μg/l, 94 μg/l and 116 μg/l for 1st, 2nd and 3rd trimesters respectively. In the post-natal period, median UIC was 90 μg/l in women and 148 μg/l in infants. Mean iodine intake was 133 μg/day in the first trimester. First trimester median serum Tg was 19 μg/l with 18% of samples >40 μg/l. Only 30%, 15% and 9% were aware that seafood, eggs or dairy were good sources of iodine respectively. Only 5% felt they had sufficient knowledge about iodine compared to 90% when asked about folate.
Conclusion
Our study suggests that pregnant women living in NI are iodine deficient but offspring have adequate status. Currently there is no food iodine fortification program in the UK. Pregnant women are not advised how to optimise intake and public health initiatives are required.

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OC6.5

Human placental and fetal liver molecular transporters are affected by maternal smoking

Natasha Walker[1], Panagiotis Filis[1], Ugo Soffientini[2], Michelle Bellingham[2], Peter O'Shaughnessy[2] & Paul Fowler[1]
[1]University of Aberdeen, Aberdeen, UK; [2]University of Glasgow, Glasgow, UK.

Introduction
The placenta interchanges nutrients, oxygen and waste between mother and fetus, acts as a gate-keeper to protect the fetus and creates an optimal endocrine environment to maintain the pregnancy. Placental insufficiency underpins common pregnancy complications (e.g. intrauterine growth restriction, preterm birth). Perturbed expression of molecular transporter proteins in the placental syncytiotrophoblast will affect fetal exposure to harmful drugs/xenobiotics such as those in cigarette smoke. We therefore aimed to investigate the effect of maternal smoking on molecular transporters involved in trans-placental and fetal hepatic transport.
Methods
Placenta and fetal liver (same pregnancies) were extracted and sexed (8–18 weeks of gestation, MRC/Wellcome Trust Human Developmental Biology Resource [www.hdbr.org]) from electively-terminated normal pregnancies. About 49 transporter transcripts and mitochondrial DNA markers were quantified by real-time qPCR using a stable combination of house-keeping genes. Linear regression models were used to determine (1) sex and/or age-specific changes to transporter expression and (2) whether maternal smoking (confirmed using the nicotine metabolite, cotinine), perturbed these patterns.
Results & Conclusions
About 28/49 transporter transcript levels changed with gestational age in the liver and/or placenta (e.g. thyroid hormone transporter). Key transporters were effected by smoking (11, e.g. folate transporter) and/or fetal sex (9, e.g. drug resistance transporter). The fetal liver was more sexually dimorphic and more perturbed by smoke exposure (9 transcripts affected compared to 2 in the placenta). SLC22A2, a cationic drug eliminator, increased with age in placentas of smoke-exposed fetuses. SLC22A18, a candidate tumour suppressor (substrate unknown), was decreased in smoke-exposed female placenta suggesting sex-specific responses to stress. However, mitochondrial DNA content in both organs was unaffected by smoking suggesting that disruption of transporter ontogeny was preceding wider damage. A better understanding of these expression profiles is vital to recognise periods of increased placental and fetal hepatic permeability to maternally-derived chemicals, such as medications, pollutants or cigarette smoke.

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OC6.6

Defining the metabolic phenotype of peritoneal mesothelial cells from women with endometriosis

Syed F Ahmad[1], Roderick N Carter[3], Frances Collins[2], Erin Greaves[1], Nicholas M Morton[3], Philippa TK Saunders[2] & Andrew W Horne[1]
[1]MRC Centre for Reproductive Health, Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, EH16 4TJ, UK; [2]MRC Centre for Inflammation Research, Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, EH16 4TJ, UK; [3]Centre for Cardiovascular Science, Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, EH16 4TJ, UK.

Endometriosis is a chronic oestrogen-dependent incurable inflammatory disorder, defined by the presence of endometrial-like tissue outside the uterine cavity that affects 6–10% of women of reproductive age. It is associated with debilitating pelvic pain and subfertility with a significant impact on quality of life and estimated annual costs to the UK of £11.7 billion. Recent findings from our laboratory have shown that there is a shift in cell metabolism from mitochondrial oxidative phosphorylation to aerobic glycolysis in the peritoneal microenvironment of women with endometriosis compared to women without disease, a phenomenon known as the 'Warburg effect'. Similar changes in metabolism in tumour cells have been shown to promote cell invasion, angiogenesis and immune suppression, all of which are important steps in the development of endometriosis. The objective of this current work is to gain a better understanding of the bio-energetic phenotype of the peritoneal mesothelial cells from the women with endometriosis. Human peritoneal mesothelial cells (HPMC) were collected with informed consent by peritoneal brushing from women with and without endometriosis (n = 6). The Seahorse XF glycolytic stress assay was used to define the metabolic phenotypes of endometriosis-associated peritoneal mesothelial cells by simultaneously measuring glycolysis (Extra Cellular Acidification Rates) and mitochondrial respiration (Oxygen Consumption Rates) providing quantifiable metabolic data. HPMCs from women with endometriosis show higher levels of glycolysis and lower mitochondrial respiration compared to women without disease. Specifically, HPMCs from women with endometriosis show a significant increase in glycolysis ($p < 0.01$) and glycolytic capacity ($p < 0.01$) and a significant reduction in ATP production due to mitochondrial respiration ($p < 0.001$). These data indicate that HPMCs from women with endometriosis primarily utilize aerobic glycolysis, which in turn results in increased lactate to support the growth and establishment of endometriosis. Targeting lactate metabolism may offer potential as novel therapeutics for endometriosis.

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Poster Presentations

Adrenal and Steroids

P1

Audit of short Synacthen test, was the patient selection appropriate

Ursula Laverty & Naila Satti
Antrim Hospital, Belfast, UK.

Short Synacthen test (SST) is performed to exclude adrenal insufficiency; it's frequently used for investigations of hyponatremia to rule out adrenal insufficiency as a possible cause. However the cost of Synacthen® (tetracosactide) 250 µg in 1 ml has increased from £14.63 to £228.55 for box of 5 A. (15-fold rise in price). This price hike needs to be taken into considerations when ordering SST. The objective of this retrospective audit was to see if patient selection was appropriate for SST. We audited inpatient SST tests performed at two hospital sites in our Trust during the first quarter of year 2015 in medical wards. Fifty-seven charts were audited to see if clinical features suggested cortisol deficiency and SST was justified. Twenty-three (40%) patient's had sign and symptoms suggestive of possible adrenal insufficiency and out of these only three patients had positive SST and sodium was normal in all three patients. Twenty-seven patients had SST test performed for investigation of hyponatremia (of these only 12% had signs and symptoms suggestive of possible adrenal insufficiency), SST was normal in all 27 patients. We conclude 55% of SST performed were inappropriate as clinical features did not suggest adrenal insufficiency. Hyponatremia is a common finding and SST is not appropriate test unless history is suggestive of adrenal insufficiency. Given the new cost we now use random cortisol levels as screening test for suspected insufficiency in inpatient setting and if levels are 500 nmol/l or more we do not recommend SST unless there is high suspicion of primary or secondary cortisol deficiency.

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P2

Dynamic changes in nephrine levels with acclimatisation reflect acquisition of heat tolerance

Mike Stacey[1,2], Sophie Britland[3], Simon Delves[3], Anne Burnett[6], Joanne Fallowfield[3], Stephen Brett[2,5], Adrian Allsopp[3] & David Woods[1,4]
[1]Royal Centre for Defence Medicine, Birmingham, UK; [2]Imperial College, London, UK; [3]Institute of Naval Medicine, Alverstoke, UK; [4]Leeds Beckett University, Leeds, UK; [5]Hammersmith Hospital, London, UK; [6]Royal Victoria Infirmary, Newcastle, UK.

Background
Heat acclimatisation (HA) describes phenotypic changes (decreased heart rate, HR; lower core body temperature, Tc) resulting from exposure to a hot environment. Heat tolerance with HA may reflect altered adrenocortical and autonomic nervous responses to heat stress, though evidence for sympathetic downregulation is lacking. Methodological limitations to further investigation (e.g. with direct catecholamine measurement) could be overcome by assaying the catecholamine metabolites, normetanephrine and metanephrine.
Aim
To assess whether nephrine concentrations reflect changes in physiological strain with HA using serial Heat Tolerance Assessment (HTA).
Methods
Military volunteers ($n=24$) were assessed at baseline in the UK and on Day 2, 6, 9 and 23 of HA in Cyprus. HTA consisted of 60 min relative-intensity stepping exercise in a temperature/humidity-controlled chamber. During exercise, HR and Tc were recorded every 5 min. A validated Physiological Strain Index (PSI) integrated Tc and HR responses on a scale of 0 to 10 (0=resting strain, 10=maximal strain). Resting blood samples were taken before and after HTA, for assay of plasma free nephrines and serum cortisol.
Results
From UK to Day 23 in Cyprus, PSI fell from 6.7 ± 1.3 to 4.8 ± 1.4 ($F=18.2$, $P<0.0001$). Main effects of HA on each biochemical analyte ($P<0.0001$) were evident over the same period, with significant reductions in post-HTA values (normetanephrine: 948 ± 328 vs 461 ± 132 pmol/l; metanephrine: 302 ± 103 vs 230 ± 91 pmol/l; cortisol 577 ± 203 vs 314 ± 120 nmol/l). Combined data from HTAs showed significant correlations ($P<0.0001$) between ΔPSI and Δnormetanephrine ($r=0.68$), Δmetanephrine ($r=0.34$) and Δcortisol ($r=0.62$).
Conclusions
The progressive reduction in nephrine concentrations post-HTA and strong association between Δnormetanephrine and PSI provide evidence for reduced sympathetic activation with HA. Like cortisol, nephrine responses could contribute to characterising occupational heat exposure and assessing heat tolerance in future clinical and research settings.

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P3

In denial? Patient perspectives on adrenal crisis management

Alice Hacker[1], Anna Crown[1,2] & Sue Jackson[3]
[1]Brighton and Sussex Medical School, Brighton, UK; [2]Brighton and Sussex University Hospital NHS Trust, Brighton, UK; [3]University of the West of England, Bristol, UK.

Background
Understanding hypoadrenal patients' perceptions of adrenal crisis is vital in the prevention of this endocrine emergency. This study explored the experiences, knowledge and attitudes of hypoadrenal patients to adrenal crises and their prevention.
Method
A cross-sectional qualitative study using structured interviews with patients with primary and secondary adrenal insufficiency. Data were analysed using thematic content analysis.
Results
Twenty-four participants were recruited; 15 with primary adrenal insufficiency, 9 with secondary adrenal insufficiency. Eighteen (75%) had experienced an adrenal crisis; a third ($n=6$) with a sudden onset. Half ($n=9$) relied on family or friends to respond. Fifty-eight per cent described negative feelings towards the risk of adrenal crisis (feeling scared, vulnerable, insecure, resentful, annoyed, superstitious, depressed or anxious). Twenty-nine per cent tried to ignore the risk of adrenal crisis, and half focused on negative aspects of risk. About a third described a lack of trust in others to act appropriately, including health care professionals, and were fearful that an adrenal crisis could be fatal. More than half had had a negative experience involving health care professionals in the context of an adrenal crisis, and almost a third recalled experiences where they felt ignored or not listened to. Seventeen (71%) owned a MedicAlert bracelet, but 6 did not like wearing one or did not want one, 4 described unappealing aesthetics of the bracelets, and 8 felt they were impractical to wear. Fifty-four per cent were members of a patient support group, but 42% felt that experiences shared in support groups could be unhelpful if negative, or frightening.
Conclusion
There are some potential barriers to adrenal crisis prevention, including negative perceptions of adrenal crisis, healthcare professionals, patient support groups and MedicAlert bracelets. Patients in adrenal crisis often relied on family, friends and their GP; this should be taken into consideration when educating and supporting hypoadrenal patients.

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P4

Generation of human urine-derived steroidogenic cells through lineage conversion: A new technology to study the adrenal gland

Gerard Ruiz-Babot[1], Irene Hadjidemetriou[1], Sharon Jane Ajodha[1], Lea Ghataore[2], David Taylor[2], Norman Taylor[2], Mariya Balyura[3], Stefan R Bornstein[3] & Leonardo Guasti[1]
[1]Queen Mary University of London, London, UK; [2]King's College Hospital, London, UK; [3]Technische Universität Dresden, London, Germany.

Cellular reprogramming describes the process where a fully differentiated, specialized cell type is induced to transform into a different cell. Cell reprogramming techniques can become powerful tools for modelling diseases, drug testing and for personalized cellular therapy. The adrenal cortex is the primary site of steroid synthesis. Adrenal insufficiency, which can be life threatening, is caused by a number of adrenal disorders, and lifelong management of these patients with exogenous steroids can be challenging. Our long-term goal is to develop novel personalized and curative treatments that use stem cells and cellular reprogramming to treat the many progressive and debilitating conditions affecting the adrenal cortex. Steroidogenic Factor-1 (SF1) is a transcription factor essential for both adrenal and gonadal development. SF1 positively regulates steroidogenic genes transcription and can be considered a true effector of cell fate as it starts a genetic program driving embryonic mesenchymal cells towards a steroidogenic phenotype/lineage. We have discovered that cells derived from urine (urine-derived stem cells, USCs) can be reprogrammed to a steroidogenic phenotype with a highly reproducible phenotype as assessed by changes in cell morphology, gene expression, activation of adrenal-specific signalling pathways and hormonal output. Urine is the perfect cell source reservoir as its harvest is the least invasive. *In vivo* transplantation experiments in nude mice using alginate-embedded reprogrammed human urine-derived steroidogenic cells are currently being performed to test the functionality of these cells in a more physiological environment. Moreover, USCs derived from patients with familial glucocorticoid deficiency (FGD) and congenital adrenal hyperplasia (CAH) are being isolated, amplified and banked and we are aiming to use the new genome editing tool

CRISPR-Cas9 to repair the monogenic mutations occurring in these conditions. These will allow us to *in vitro* assess the hormonal profiles of affected versus CRISPR-Cas9 gene corrected cells, serving as a proof-of-concept of our technology.

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P5

Outcomes of annual surveillance imaging in an adult and paediatric cohort of succinate dehydrogenase B mutation carriers

Nicola Tufton[1], Lucy Shapiro[1], Umasuthan Srirangalingam[1], Polly Richards[1], Anju Sahdev[1], V K Ajith Kumar[2], Shern L Chew[1], William M Drake[1], Helen Storr[1] & Scott A Akker[1]
[1]St Bartholomew's Hospital, London, UK; [2]Great Ormond Street Hospital, London, UK.

Introduction
Germline mutations in succinate dehydrogenase subunit B (*SDHB*) are one of the commonest findings in familial paraganglioma (PGL) syndromes and account for one quarter of PGLs associated with germline mutations. Although the penetrance is low, the malignancy conversion is high; up to 30%. With the increasing availability of genetic testing and the identification of 'asymptomatic carriers' of the *SDHB* gene mutation, it is therefore important to establish appropriate surveillance protocols. There is currently no consensus as to the appropriate modality or frequency of imaging for these patients.
Objective
We present the experience of a single centre surveillance programme using non-ionising imaging and have combined this with carefully documented clinical outcomes.
Method
Ninety-two patients were identified with an *SDHB* gene mutation. 27 index patients (6 children) presented with symptoms and 65 patients (17 children) were identified as asymptomatic carriers. All underwent annual clinical review, urine/plasma metanephrines and MRI of the abdomen, with alternate year MRI of the neck, thorax and pelvis.
Results
Fifty-one tumours occurred in the index patients (1975–2015). A further 19 *SDHB*-related tumours were identified on surveillance in 17 asymptomatic patients aged 16–83 years (15 PGLs, 3 renal cell carcinomas, 1 GIST). Eleven of these tumours were identified on the first surveillance imaging and eight on subsequent imaging; 2–9 years after the initial negative scan. In total 14 patients had malignant disease, including eight with disseminated metastases.
Conclusions
As there is no single clinical or biochemical test that identifies *SDHB*-related disease, imaging needs to play a key role in surveillance. We demonstrate that MRI based imaging could be the mainstay of surveillance thereby minimising radiation exposure with annual surveillance such that tumours are identified at stages before they become biochemically active. *SDHB*-related tumours have been picked up as early as 2 years after first surveillance scan.

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P6

Role of computed tomography scan in adrenal tumors

Dia Eddine Boudiaf, Said Azzoug & Farida Chentli
Department of Endocrinology and Metabolic Diseases, Bab El Oued Teaching Hospital, Algiers, Algeria.

Introduction
Computed tomography (CT) scan is the first imaging method used to characterize adrenal lesions in order to select patients for surgical treatment. Our aim was to specify the performance of this tool in the work up of adrenal masses (AM) recruited in a department of Endocrinology.
Material and methods
This retrospective study included 100 patients hospitalized in our department between 2008 and 2014 for adrenal tumors. After a systematic exclusion of pheochromocytomas, the criteria used to define adrenal benign lesions were either histology ($n=24/52$) or lack of volume increase after two years follow-up ($n=30$). CT scan features were evaluated for tumor size, spontaneous density (SD), and absolute wash out (AWO). When there is a discrepancy, a blind proofreading was done by an independent radiologist.
Results
Among 100 cases: 54 were considered as adenomas, 22 as carcinomas, 4 as adrenal metastases and 20 as benign tumors. Positive predictive value (PPV) and negative predictive value (PNV) were respectively 96 and 75% for a tumor size $\leq$40 mm, 100 and 75% for a SD $\leq$ 10 UH, and 100% and 88.8% for an AWA $>$ 60%.
Discussion and conclusion
The abdominal CT scan is a fundamental tool which can differentiate benign from malignant adrenal tumors as it offers specific features characterizing adenomas. Actually, a tumor size less than 40 mm with a SD less than 10HU and an AWO $>$ 60% plead for the diagnosis of a benign process with a PPV of 100%.

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P7

Screening for Cushings syndrome: A comparison of available tests

Edward McKeever, David R McCance, Steven J Hunter, Hamish Courtney, Karen R Mullan & Una M Graham
Royal Victoria Hospital, Belfast, UK.

Nocturnal salivary cortisol (NSC), urinary free cortisol (UFC) and overnight dexamethasone suppression testing (ODS) are recommended screening tests for Cushing's syndrome (CS). Individual centers differ in their screening approach; UFC being the test of choice in Northern Ireland with ODS in patients with adrenal incidentalomas. NSC, which measures free cortisol, is not routinely used. The aims of this study were to 1. Evaluate the utility of NSC in the diagnosis of CS; and 2. Determine a NSC diagnostic threshold for CS. A retrospective study of all patients undergoing low dose dexamethasone suppression testing (LDDST) from 2010 to 2014 was performed. Patients were classified as 'Cushing's' or 'non-Cushing's' based on consultant clinical suspicion, biochemical results (UFC, ODS and LDDST) and clinical follow up. NSC samples, collected and stored over this time, were analysed using the ELISA technique. Diagnostic thresholds and test performance were determined using ROC curve analysis. Data was collected on 54 patients; 47 included in the study (20 Cushing's; 27 non-Cushing's). Seven patients were excluded (5 subclinical Cushing's, 1 cyclical Cushing's, 1 unclear diagnosis). NSC was the most effective diagnostic test for CS (AUC 0.928; $P<0.001$) with a threshold of 10 nmol/l having a sensitivity of 94.4%, specificity 88.5% and diagnostic accuracy of 90.9%. This was comparable to the LDDST (diagnostic accuracy 88.6%). UFC, and ODS ($n=14$; cut-off 50 nmol/l) were less effective with diagnostic accuracies of 72.3 and 42.9% respectively. In conclusion, NSC is an effective, easily performed screening test for CS, comparable to the LDDST and outperforming 24 h urinary collections.

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P8

Full characterisation of adrenal steroidogenesis by liquid-chromatography–mass spectrometry (LC–MS/MS) in metyrapone and/or ketoconazole-treated pituitary/adrenal Cushing's

David R Taylor[1], Christine H M Leong[2], Aagna E Bhatt[1], Lea Ghataore[1], Simon Aylwin[2], Ben Whitelaw[2] & Royce P Vincent[1]
[1]Department of Clinical Biochemistry, Viapath Analytics, King's College Hospital, London, UK; [2]Department of Endocrinology, King's College Hospital, London, UK.

Introduction
Pituitary and adrenal Cushing's may be managed by pharmacological-inhibition of adrenal steroidogenesis, using metyrapone and/or ketoconazole. Assessment of biochemical control is challenging owing to cross-reactivity in immunoassays (e.g. cortisol and 11-deoxycortisol) leading to over/under-treatment. Off-target effects can also result, e.g. hyperandrogenism/mineralocorticoid hypertension (increased 11-deoxycorticosterone/DOC). LC-MS/MS analysis is free from cross-reactivity and allows quantification of multiple steroids.
Aim
Evaluate the utility of an LC-MS/MS method quantifying 13 steroids in medically-managed Cushing's.
Methods
Eighty-one day curves (24 cases) were evaluated by LC-MS/MS and Centaur XP cortisol immunoassay. Thirteen had pituitary-disease (metyrapone $\pm$ ketoconazole treatment) and 11 had adrenal-disease (metyrapone-only).
Results
In the metyrapone-only groups, pituitary-disease received a larger dose than adrenal-disease (1500 vs 750 mg/d, $P=0.0004$). Steroid concentrations were similar between pituitary/adrenal groups, except 11-deoxycortisol (80.6 vs 41.1 nmol/l, $P=0.04$), androstenedione (16.4 vs 6.6 nmol/l, $P=0.001$) and DHEAS (4.7 vs 0.6 μmol/l, $P\leq0.0001$). In pituitary-disease, metyrapone dose

positively correlated with 11-deoxycortisol (rs = 0.53, $P = 0.01$). In adrenal-disease, dose positively correlated with 11-deoxycortisol (rs = 0.77), DOC (rs = 0.59), 17-hydroxyprogesterone (rs = 0.56) and androstenedione (rs = 0.42, all $P \leq 0.005$) and negatively with cortisol (rs = −0.45, $P = 0.02$). Cortisol method agreement differed: pituitary-disease *LC-MS/MS = 0.28 immunoassay + 101.1 nmol/l* and adrenal-disease *LC-MS/MS = 0.82 immunoassay ± 8.7 nmol/l*. Pituitary-disease treated with metyrapone and ketoconazole had higher 11-deoxycortisol ($P = 0.0003$), 17-hydroxyprogesterone ($P = 0.0006$) and DOC ($P = < 0.0001$) than those treated with metyrapone-only. LC-MS/MS cortisol was lower in the dual therapy group (128 vs 205 nmol/l, $P = 0.01$) but relatively higher by immunoassay (350 vs 232 nmol/l, NS). Cortisol method agreement in the metyrapone ± ketoconazole group: *LC-MS/MS = 0.62 immunoassay ± 32.1 nmol/l*. Seven/fourteen females demonstrated biochemical hyperandrogenism [increased testosterone/androstenedione ($n = 5$), androstenedione-only ($n = 2$)]. Across all day curves, those with highest DOC had relatively lower potassium concentration.

Conclusions

Marked differences in steroidogenesis were observed in pituitary vs adrenal Cushing's. Unpredictable cross-reactivity in cortisol immunoassays mandates LC-MS/MS use in monitoring. Additionally, LC-MS/MS offers quantification of off-target steroidogenesis effects which may be clinically relevant.

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P9

Assesment of Performance of 30 vs 60 min cortisol during SST

Dinesh Nagi, Ravikumar Bachuwar, Simon Holmes, Ruth Scoffins, Ryan D'Costa & Olivia Pereira
Pinderfield Hospital, Mid yorkshire NHS Trust, Wakefield, UK.

Aim

Short Synacthen test has been widely used screening test for assessment of hypothalamo-pituitary-adrenal axis (HPA). The most widely used is 30 min plasma cortisol Post synacthen. We have compared 30 min cortisol with 60 min for assessment of the HPA axis of patients with known endocrine disorders and on long term steroid, opiate use and obesity (non endocrine disorder).

Method

Cortisol Response to 30 and 60 min post synacthen were measured in random sample of 50 patients who have undergone testing. We divided them into Endocrine, Non endocrine and miscellaneous groups. A normal response was defined as a peak concentration of ≥ 550 nmol/l.

Result

i) Twenty patients were in non endocrine group. Fifteen (75%) patients out of this group failed 30 min response and four patients (25%) out of this sub group who failed 30 min had a normal 60 min response.
ii) Twenty patients were in endocrine group. Ten (50%) patients out of this group failed 30 min response and six (60%) patients out of this sub group who failed 30 min had a normal 60 min response.
iii) Ten patients did not have 60 min cortisol measured as it was clinically not indicated.
iv) All Patients who had normal 30 min response had also normal 60 min response

Conclusion

Our observations reveal that 10 out of 50(20%) patients with abnormal 30 min SST would have been categorised as false positive result indicating that 60 min SST is more reliable to avoid over diagnosing adrenal insufficiency. Interestingly in our endocrine disorder sub group who failed initially 60% had normal 60 min response which opens up the debate for need to measure 30 and 60 min cortisol or only 60 min cortisol.

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P10

11β-Hydroxysteroid Dehydrogenase Type 1 within Muscle Protects Against the Adverse Effects of Local Inflammation and Muscle Wasting

Rowan Hardy[1,2], Zahrah Hussain[2], Andrew Filer[1], Christopher Buckley[1], Gareth Lavery[2], Mark Cooper[3] & Karim Raza[1]
[1]Institute of Inflammation and Aging, University of Birmingham, Birmingham, West Midlands, UK; [2]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, West Midlands, UK; [3]ANZAC Research Institute, University of Sydney, Sydney, NSW, Australia.

Muscle wasting is a common feature of inflammatory myopathies. Glucocorticoids (GCs), whilst effective at suppressing inflammation and inflammatory muscle loss, also cause myopathy with prolonged administration. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is a bidirectional GC activating enzyme, potently up-regulated by inflammation within mesenchymal derived tissues. We assessed the regulation of this enzyme with inflammation in muscle and examined its functional impact on muscle. The expression of 11β-HSD1 in response to pro-inflammatory stimuli was determined in a transgenic murine model of chronic inflammation (TNF-Tg) driven by overexpression of TNFα within tissues including muscle. The inflammatory regulation and functional consequences of 11β-HSD1 expression were examined in primary cultures of human and murine myotubes and *ex vivo* human and murine muscle biopsies. The contribution of 11β-HSD1 to muscle inflammation and wasting were assessed *in vivo* using the TNF-Tg mouse on an 11β-HSD1 null background. 11β-HSD1 was significantly upregulated within tibialis anterior and quadriceps muscle from TNF-Tg mice. In human and murine primary myotubes, 11β-HSD1 expression and activity were significantly increased in response to the pro-inflammatory cytokine TNFα (mRNA; 7.6-fold, $P < 0.005$, activity 4.1-fold, $P < 0.005$). Physiologically relevant levels of endogenous GCs activated by 11β-HSD1 suppressed pro-inflammatory cytokine output (IL-6, TNFα, and IFNγ), but had little impact on markers of muscle wasting in human myotube cultures. TNF-Tg mice on an 11β-HSD1KO background developed greater muscle wasting than TNF-Tg counterparts (27.4% less; $P < 0.005$), with smaller compacted muscle fibres and increased pro-inflammatory gene expression relative to TNF-Tg with normal 11β-HSD1 activity. This study demonstrates that inflammatory stimuli upregulate 11β-HSD1 expression and GC activation within muscle. Whilst concerns have been raised that excess levels of GCs may be detrimental to muscle, in this inflammatory TNFα driven model, local endogenous GC activation appears to be an important anti-inflammatory response that protects against inflammatory muscle wasting *in vivo*.

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P11

Safe withdrawal of corticosteroids after prolonged use: A management protocol

Jeyanthy Rajkanna, Satyanarayana Sagi & Samson O Oyibo
Peterborough City Hospital, Peterborough, UK.

Introduction

Prolonged therapy (≥ 3 months) with high-dose corticosteroids (≥ 7.5 mg Prednisolone or 1–1.5 mg Dexamethasone daily) can result in adrenal atrophy and secondary adrenal failure. Abrupt withdrawal of corticosteroids after prolonged use can lead to adrenal insufficiency, corticosteroid withdrawal symptoms or a relapse of the initial disease. A safe flexible management plan is required for each patient. We illustrate with two cases.

Case 1

A 68 year old lady presents with a 2 month history of tiredness and generalised body aches. She had been on high-dose (20–40 mg) Prednisolone for polymyalgia rheumatic for over 2 years. Her Prednisolone dose had been rapidly tailed down to 5 mg daily while she remained asymptomatic, and then by 1 mg monthly until she settled on 2 mg daily. She was referred to the endocrine department and a short Synacthen test revealed adrenal insufficiency. She is now asymptomatic after her Prednisolone dose was increased to 5 mg daily.

Case 2

A 63 year old man was referred for assessment of adrenal function. He had been on high-dose (20 mg) Prednisolone along with Etoricoxib and Hydroxychloroquine for polymyalgia rheumatica and seropositive rheumatoid arthritis for over 3 years. The Prednisolone dose was tailed down fairly quickly to 7.5 mg daily then gradually by 0.5 mg monthly until he settled on 3 mg daily. After a weekend conversion to Hydrocortisone 5 mg twice a day, a short Synacthen test revealed adequate adrenal function. He continued tailing down the Prednisolone dose until stopping it, but because of ongoing rheumatology symptoms Methotrexate was added to his treatment and he remains well.

Conclusion

Our protocol ensures patients are informed of the problems that may be encountered during corticosteroid withdrawal after prolonged use, a safe and flexible corticosteroid withdrawal regimen, and that regular adrenal function assessment is carried out during and after successful corticosteroid withdrawal.

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P12

Characterization of adrenal-specific effects of ATR-101, a selective ACAT1 antagonist, in dogs

Stephen Hunt III[1], Krista Greenwood[2], Jessica Reed[1], Joseph Heward[3] & Marc Bailie[2]
[1]Millendo Therapeutics, Inc., Ann Arbor, Michigan 48104, USA; [2]Integrated Nonclinical Development Solutions, Inc., Ann Arbor, Michigan 48103, USA; [3]MPI Research, Mattawan, Michigan 49071, USA.

ATR-101 is a selective Acyl-CoA: cholesterol acyltransferase 1 (ACAT1) inhibitor in development for the treatment of diseases of the adrenal cortex including rare endocrine diseases, such as congenital adrenal hyperplasia (CAH) and Cushing's syndrome (CS), and in adrenocortical carcinoma (ACC). ATR-101 has been shown to inhibit adrenal steroidogenesis at low doses and cause apoptosis at high doses. To better understand the adrenal-specific effects of ATR-101, *in vivo*, a 13-week toxicity study was carried out in dogs. Groups of four male and four female beagle dogs received vehicle or ATR-101 at 3, 10 or 30 mg/kg by gavage dosed twice daily (BID) for 91 days (total daily doses of 6, 20 and 60 mg/kg per day). Additionally, two dogs from the vehicle and high dose cohorts were observed in a 28 day recovery period. Due to clinical signs indicative of adrenal insufficiency beginning on Day 20, the 30 and 10 mg/kg BID groups were reduced to 20 mg/kg BID and 7.5 mg/kg BID, respectively, and received replacement glucocorticoid and mineralocorticoid therapy with marked clinical improvement. Twice daily oral administration of ATR-101 for 91 days at doses of 3, 10/7.5, and 30/20 mg/kg/BID to dogs did not result in any early deaths. Systemic exposure to ATR-101 was similar between males and females, and increased with increasing dose in a greater than dose proportional manner. Clinical signs and clinical chemistry changes were predominantly secondary to adrenal insufficiency as sequelae of the intended pharmacology of ATR-101. Increases in endogenous ACTH levels and decreases in post ACTH-stimulation serum cortisol levels, and adrenal weight and the cortical atrophy were consistent with the expected pharmacological effects. The NOAEL, excluding effects secondary to the intended pharmacology, was 10/7.5 mg/kg BID. These results support the development of ATR-101 for treatment of endocrine disorders caused by adrenocortical hormone dysregulation.

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P13

Characterization of clinical, biochemical and adrenal hormonal effects of ATR-101, a selective ACAT1 antagonist, in dogs with naturally-occurring Cushing's syndrome

Stephen Hunt III[1], Michele Fritz[2], William Schall[2], N. Bari Olivier[2], Rebecca Smedley[2], Paul Pearson[3], Marc Bailey[4] & Daniel Langlois[2]
[1]Millendo Therapeutics, Inc., Ann Arbor, Michigan 48104, USA; [2]Michigan State University College of Veterinary Medicine, East Lansing, Michigan 48824, USA; [3]Pearson Pharma Partners, Westlake Village California 91362, USA; [4]Integrated Nonclinical Development Solutions, Inc., Ann Arbor, Michigan 48103, USA.

Cushing's syndrome (CS) in humans shares many similarities with its counterpart in dogs in terms of etiology (pituitary versus adrenal causes), clinical signs, and pathophysiologic sequelae. ATR-101 is a novel small molecule therapeutic currently in clinical development for the treatment of congenital adrenal hyperplasia and adrenocortical carcinoma in humans. ATR-101 is an adrenal-selective inhibitor of ACAT1 (acyl coenzyme A:cholesterol acyltransferase 1). ACAT1 catalyzes cholesterol ester formation from cholesterol and long-chain fatty acyl-CoA and, in the adrenal cortex, is particularly important in creating a reservoir of substrate for steroid biosynthesis. Previous studies in healthy dogs have shown that ATR-101 decreases adrenal steroidogenesis at low doses and induces apoptosis at high doses. Treatment led to rapid, dose-dependent decreases in adrenocorticotropic hormone (ACTH) stimulated cortisol levels consistent with ATR-101-mediated inhibition of ACAT1. In this veterinary clinical study, we characterized the pharmacokinetics and investigated the clinical, biochemical and adrenal hormonal effects of ATR-101 in dogs with naturally-occurring CS after oral administration over a 2–4 week treatment period. In addition, adrenal gland histology and tissue drug concentrations were evaluated in dogs with adrenal-dependent disease. Companion dogs with naturally-occurring CS resulting from either pituitary ($n=7$) or adrenal ($n=3$) etiology were dosed orally over 2–4 weeks with each subject receiving two dose levels. Orally administered ATR-101 is well-tolerated, achieves exposures in a dose-dependent manner, distributes to the adrenal glands, and lowers post-ACTH stimulated cortisol levels regardless of underlying etiology in dogs with naturally-occurring CS. These results support the ongoing development of ATR-101 as a novel agent for treatment of endocrine disorders associated with adrenal steroid dysregulation.

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P14

Lowered replacement glucocorticoid doses are associated with a rise in frequency of adrenal crisis

Katherine White & Alick Mackay
Addison's Disease Self-Help Group, Guildford, UK.

Good clinical practice encourages patients to minimise long-term glucocorticoid overexposure to preserve bone density and prevent the development of glucose intolerance or hyperlipidaemia. However, the absence of a protective "cushion" of excess cortisol implies an increased risk of adrenal crisis. (White & Arlt 2010) This assumption has been challenged by a leading adrenal specialist, who suggested instead that chronic over-replacement may increase the susceptibility to infection (Allolio 2014). To investigate this, we analysed self-reported frequency of adrenal crises for steroid-dependent patients belonging to support groups within the UK in two surveys, conducted in 2003 ($N=483$) and 2013 ($N=1044$), and compared to results. The two surveys capture near-identical aggregate patient 'backpacker years' of post-diagnosis experience; 12.8 years for the 2003 survey and 12.2 years in 2013. Yet respondents in 2013 reported markedly higher rates of post-diagnosis crisis. In 2003, 54% of respondents said they had never experienced an adrenal crisis post-diagnosis, compared to 35% in 2013 ($P \ll 0.0001$). Only 12.6% had experienced 4 or more post-diagnosis crises in 2003, compared to 25% in 2013 ($P \ll 0.0001$). Daily hydrocortisone doses reduced markedly over this time. In 2003, the mean dose for those who detailed their drug regime ($N=440$) was 26 mg; 43% of respondents took 30 mg or more daily. In 2013, the mean dose reported ($N=888$) was 21.5 mg and just 15% took 30 mg+ ($P \ll 0.0001$). The proportion taking hydrocortisone increased from 89 to 93%, largely due to the withdrawal of cortisone acetate from the UK market in 2011. The proportion taking prednisolone remained consistent: 3.9% in 2013, 3.6% in 2003. In 2003 only 47% had an emergency injection kit; by 2013, 82% did so. The steroid education offered by support groups means this proportion is likely to be higher than in the wider patient population. These findings emphasize that it is crucial for all endocrine departments to ensure their steroid-dependent patients are educated and equipped to self-manage during episodes of infection or injury, and that they are trained to self-inject when absorption of oral steroids is compromised by vomiting or diarrhoea.

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P15

Adrenal vein sampling for subtype classification of primary aldosteronism in British Columbia: insights and challenges

Pol Darras & Daniel Holmes
University Of British Columbia, Vancouver, British Columbia, Canada.

Background
Primary aldosteronism is identified in approximately 10% of hypertensive all-comers. Adrenal vein sampling (AVS) allows localization of aldosterone production, identifying cases where unilateral adrenalectomy can be curative. Unfortunately, AVS is technically challenging.
Methods
Data from AVS procedures performed in BC were extracted from the SunQuest laboratory information system in Vancouver Coastal Health. Cortisol and aldosterone levels from adrenal vein (AV) and inferior vena cava (IVC) samples, as previously measured by tandem mass spectrometry, were analyzed using established cutoffs for selectivity and lateralization.
Results
From 9 March 2011 to 28 January 2016, 216 AVS procedures were identified. Successful bilateral cannulation was confirmed in 174 cases (81%). Failure of right, left, and bilateral AV cannulation occurred in 27, 4, and 11 cases, respectively. Of successful procedures, secretion was right-lateralized in 30%, left-lateralized in 34%, bilateral in 32%, and equivocal in 4%. Analysis of

unilateral AV results could predict lateralization. Suppression of aldosterone, defined as post-stimulation $(aldosterone/cortisol)_{AV}/(aldosterone/cortisol)_{IVC} < 1.2$, predicted contralateral autonomous aldosterone secretion with sensitivity of 84.8%, specificity of 95.3%, and accuracy of 92.0%. Excessive aldosterone production, defined as pre-stimulation $(aldosterone/cortisol)_{AV} > 20$, predicted ipsilateral autonomous aldosterone secretion with sensitivity of 54.1%, specificity of 94.9%, and accuracy of 81.9%.

Conclusion

AVS results from a single AV can predict lateralization with a high degree of specificity and accuracy. In the right clinical context, this may limit the need for repeat AVS in cases of unilateral failed cannulation.

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P16

Comparison of insulin tolerance test performance with other dynamic tests of cortisol reserve

Payal Haria, Tricia Tan & Emma Hatfield
Imperial College London, London, UK.

Introduction

Misdiagnosis of secondary hypocortisolaemia can have profound consequences on a patient's life. Due to contraindications the gold standard dynamic diagnostic test of cortisol reserve – the insulin tolerance test (ITT) – may not always be suitable. Here we examine the diagnostic accuracy of the second line dynamic tests: the overnight metyrapone test (OMT), short synacthen test (SST) and glucagon stimulation test (GST).

Patients and methods

Retrospective collection of records of dynamic testing of cortisol in patients with suspected ACTH deficiency from two tertiary care centres for pituitary disease. The ITT was used as the reference method for comparison using a cortisol threshold value of 450 nmol/l. 119 patient records were collected, 83 being investigated for pituitary disease, 29 post-TBI and seven classified as other. Comparison of the ITT with the OMT, SST and GST was possible in 45, 37 and 26 individuals respectively.

Results

47% showed a suboptimal cortisol response on ITT. The SST demonstrated the greatest concordance with the ITT (64%) followed by the OMT (63%) and GST (36%). ROC analysis revealed an optimum cut-off of 550 nmol/l for the SST with a sensitivity of 75% and specificity of 63%, and 200 nmol/l 11-deoxycortisol for the OMT with a sensitivity of 58% and specificity of 73%.

Conclusion

The SST offers the best assessment of cortisol reserve against the ITT, but given the associated high false negative rate, the threshold value may need to be adjusted to a higher value of 550 nmol/l before the SST surpasses the OMT as the preferred second line test behind the ITT.

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P17

The effect of time of day and utility of 30 and 60 min values in 250 μg ACTH stimulation test

Vicki Munro[1], Manal Elnenaei[1], Steve Doucette[2], Stephanie Kaiser[1] & Syed Ali Imran[1]
[1]Dalhousie University, Halifax, Canada; [2]Nova Scotia Health Authority, Halifax, Canada.

Background

Despite the widespread use of the 250-μg Cosyntropin test (ACTH test) for the diagnosis of adrenal insufficiency (AI), the effect of timing of the test on 30- vs. 60-min serum cortisol values remains unclear. Also, there is limited evidence comparing the value of performing both 30- and 60-min cortisol levels.

Methods

We conducted a retrospective cohort study of all ACTH tests conducted at the Halifax Neuropituitary Program, Nova Scotia, Canada, from January 2006 to April 2016. Data were collected on serum cortisol levels at 0, 30 and 60 min after ACTH administration, time of testing, age, gender, and indication for testing.

Results

There were 345 tests performed and divided by time of day (8:00–10:00 AM, 10:01 AM–12:00 PM, and after 12:00 PM). There were no significant differences in age, gender, or indication for testing between groups. The baseline 0-min mean (nmol/l) cortisol levels were lower later in the day (269, 239, 213, respectively; $P=0.002$), but there were no differences in mean (nmol/l) cortisol levels at 30 (565.5, 553, 529.5, respectively; $P=0.38$) and 60 min (635, 620, 616, respectively; $P=0.79$) between groups. When comparing 30 vs. 60-min values while using a cut-off of >500 nmol/l, 48 patients (13.9%) failed to reach the cut-off at 30 min but met the cut-off at 60 min. Conversely, only two patients (0.6%) who met the cut-off at 30 min failed to reach it at 60 min.

Conclusion

Our data suggest that the outcome of the ACTH test is not affected by time of day. Furthermore, if using a 30-min cortisol level in isolation, more than one in seven patients would have a false positive diagnosis of AI. Additionally, our data suggest that a 60-min value alone may be sufficient to diagnose AI in >99% of cases.

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P18

Primary adrenal insufficiency – establishing aetiology and screening for associated autoimmune diseases in a tertiary clinic

Pui San Yap, Maria Gemma Rodriguez Carnero, Asha Hesarghatta, Alison Milne, Alex Graveling, Sam Philip & Prakash Abraham
NHS Grampian, Aberdeen, UK.

Aims

Recent Endocrine Society Guidelines (2016) suggest establishing the aetiology of primary adrenal insufficiency (PAI) and screening for other autoimmune conditions. The aim of our audit was to compare current practice against these recommendations.

Methods

We identified patients seen in clinic over 18 months between January 2015 and May 2016. The data was collected by reviewing electronic and paper records.

Results

Eighty-three patients (65% females and 35% males) with PAI were identified. The prevalence of PAI (143 per million inhabitants) was similar to other European cohorts. The median age is 52 (19–95 years). The most common co-existing autoimmune disease is hypothyroidism (29%), Type 1 diabetes (16%), vitamin B12 deficiency (8.4%) Grave's disease and premature ovarian failure (7.2%) and coeliac disease (1.2%). In terms of adrenal antibody testing, there are 60 patients (72%) with positive adrenal antibodies, 13 (15.6%) negative, 4 (4.8%) with unknown antibody status and 6 (7.2%) never tested. Of these 13 patients with negative antibodies, five were females and only one of them had ultrasound. Only one of eight males with negative antibodies was screened for adrenoleukodystrophy which came back negative. Three patients with negative antibodies had CT adrenals. Over the past 5 years all patients had thyroid functions tested, 94% had glucose testing, 98% full blood count, 53% vitamin B12 and 54% screened for coeliac disease.

Conclusions

Our audit showed that only a small proportion (~30%) of antibody negative patients with PAI had secondary workup as per current guidelines. Most patients had relevant screening for associated autoimmune conditions apart from coeliac disease and pernicious anaemia. We have implemented an annual check of full blood count, thyroid functions, glucose along with an enquiry regarding menstrual cycle. Coeliac serology and B12 testing would be done every 5 years.

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P19

Adrenal crisis – an important endocrine emergency needing ongoing education

Maria Gemma Rodriguez Carnero, Pui San Yap, Asha Hesarghatta, Alison Milne, Alex Graveling, Sam Philip & Prakash Abraham
NHS Grampian, Aberdeen, UK.

Aims

Adrenal crisis (AC) is a life- threatening condition with an incidence of 6–10 adrenal crises per 100 patient year in European populations. The aim of our study is to identify the prevalence of adrenal crisis in our clinic population and assess the preventative measures in use.

Methods

Data was obtained from electronic records and paper records were reviewed in adrenal crisis patients.

Results

There were 230 patients with adrenal insufficiency identified from January 2015 to May 2016 from our clinic. These include 36% Addison's disease (PAI), 10% primary adrenal insufficiency without Addison's disease (PAI -woAD) and 54%

secondary adrenal insufficiency (SAI). We had 42 admissions with AC in 230 patients since 2010. Thirty-nine in PAI, 1 PAI –woAD and 2 SAI. In PAI group, 18 patients had AC; nine patients had two or more episodes. The common causes were gastroenteritis (54%), respiratory tract infections (15%) and acute kidney injury (5%). The prevalence of AC per 100 patient year was 11 in PAI, 0.4 SAI and 0.9 PAI-woAD. 150 (65%) had documented information regarding steroid identifiers (bracelet, necklace or steroid card), with 9 (4%) carrying no identifiers. There was inadequate information for the remaining 71 (31%). In terms of steroid education, formal teaching (FT) was provided by specialist nurses and informal teaching (IT) consists of verbal information during annual review. Eighty one (98%) patients with PAI received IT. FT was delivered in 30 (36%) of PAI, 3 (13%) of PAI-woAD, 26 (21%) in SAI.

Conclusion

Patients with PAI have more frequent AC compared to the other groups and received correspondingly more FT and IT. Structured education for all patients with adrenal insufficiency with additional emphasis on PAI patients must be delivered on a rolling basis.

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P20

A quality improvement project to refine diagnostic testing for adrenal insufficiency

Grace Pink, Rakhi Kakad & Matthew Bowden
Warwick Hospital, South Warwickshire NHS Foundation Trust, Warwickshire, UK.

Current trust protocol for the Short Synacthen Test (SST) is to perform cortisol levels at 0, 30 min and 60 min; there is a variation in this policy in different trusts. This quality improvement project determined if the 60 min test was significant and, if so, in what proportion of patients. A further aspect of the audit was in regards to determining if the number of SSTs in the trust could be reduced. We investigated every adult having a SST run through the SWFT laboratory during the period 05/12/14 to 05/12/15; giving us a sample of 121 tests. There was a strong positive correlation between baseline cortisol and 30 min cortisol. 95 tests classed as passed at 30 min. Of these, 30 had a baseline cortisol level >550 nmol/l. Eight tests did not reach 550 nmol/l at 30 min, but did at 60 min; the majority of patients in this group had known hypothalamic- pituitary- adrenal disease and the remainder were elderly patients who had been admitted acutely unwell. We reviewed the literature and discussed the lack of consensus on timing of cortisol levels. We advised that removal of the 60 min test would be associated with a risk of falsely labelling 7% of the tests as adrenally insufficient and that those with known HPA axis disease should be considered for 30 and 60 min cortisol levels. We reviewed the literature regarding early morning cortisol levels as measure to predict adrenal sufficiency. We calculated that setting a threshold for early morning cortisol at 425 nmol/l would have a sensitivity of 100% and a specificity of 56.25% for identifying those with adrenal insufficiency from our sample. If this threshold was used then 54 (45%) SSTs could have been avoided, with a potential cost saving of £2700 annually.

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P21

Diagnosis of adrenal sufficiency using a highly specific cortisol immunoassay: Major implications for clinicians

Gregory Kline[1], Joshua Buse[2] & Richard Krause[1,2]
[1]University of Calgary, Calgary, Alberta, Canada; [2]Calgary Lab Services, Calgary, Alberta, Canada.

Context

Recent guidelines recommend a diagnosis of adrenal insufficiency when stimulated peak cortisol level falls below 500 nmol/l. This may not be valid when using a highly specific cortisol immunoassay or cortisol measured by liquid chromatography-mass spectroscopy.

Objective

Determine the diagnostic threshold for adrenal insufficiency using a highly specific cortisol assay.

Design

For 4 months, all subjects having a dynamic test of adrenal reserve had results measured using the historical cortisol assay (Roche Cortisol) and the newer assay (Roche Cortisol II).

Setting

Tertiary level endocrine testing unit.

Interventions

Cosyntropin stimulation tests (1 and 250 μg), insulin hypoglycaemic tests and glucagon stimulation tests.

Main outcome measures

Subjects were categorized according to the results from the traditional assay (normal considered >500 nmol/l) along with clinical case adjudication where necessary. Results from the Cortisol II assay were reported in both normals and those deemed to have adrenal insufficiency. Passing-Bablock and Bland Altman plots described the difference between the two assays; ROC curve analysis was performed to generate new diagnostic thresholds.

Results

The Roche Cortisol II compared very closely with measures by LCMS-MS and generated cortisol levels $\approx 30\%$ lower than the older immunoassay. Many normal subjects had peak cortisols as low as 300 nmol/l with the new assay. The optimized new diagnostic threshold for adrenal insufficiency was 350 nmol/l with a sensitivity of 91% and specificity 97%.

Conclusions

Transition to a more specific cortisol assay requires re-calibration of diagnostic thresholds for dynamic tests of adrenal insufficiency. With the Roche Cortisol II assay, a cut-off of 350 nmol/l would appear to best replace the traditional 500 nmol/l although a number of normal subjects may also be very close to this level. Adrenal insufficiency will be significantly over-diagnosed if the effect of assay change is not considered.

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P22

What do patients understand about how to self-manage acute adrenal insufficiency?

Emma Johns, Stewart Ferguson & Vincent McAulay
University Hospital Crosshouse, Kilmarnock, East Ayrshire, UK.

Introduction

Acute adrenal insufficiency (adrenal crisis) is a life-threatening condition caused by glucocorticoid deficiency. Patient and carer education is key in the prevention, early identification and prompt management of this condition. We assessed the knowledge of adrenal insufficiency/crisis in patients with adrenal and pituitary disease to evaluate the strengths and weaknesses of local 'sick day' education processes.

Methods

We utilised a structured questionnaire to prospectively collect data at an outpatient Endocrine clinic from 16 patients (56.3% female, mean age 53.9 years) with primary ($n=7$) and secondary ($n=9$) adrenal insufficiency.

Results

Eleven patients (68.8%) understood the term 'acute adrenal insufficiency' or 'adrenal crisis', with 14 patients (87.5%) recollecting education on this subject. Education had been received through information leaflets (14 patients, 87.5%), physicians (nine patients, 51.3%) and websites (two patients, 12.5%). Fifteen patients (93.8%) could report some symptoms of acute adrenal insufficiency. All (100%) were aware to 'double dose' their oral glucocorticoid replacement during intercurrent illness. Ten patients (62.5%) were aware when intra-muscular (IM) Hydrocortisone was indicated, 8 (50%) had an in-date Hydrocortisone injection kit, of whom seven had been instructed how to administer this. Eleven patients (68.8%) reported their next of kin was aware of the risk of acute adrenal insufficiency, although only four next of kin (25%) had been taught how to administer IM Hydrocortisone. Fourteen patients (87.5%) carried a steroid treatment card and five patients (31.3%) MedicAlert jewellery. One patient (6.3%) used neither of these.

Conclusions

There is a good understanding of hydrocortisone self-management and the risk of acute adrenal insufficiency amongst patients with adrenal insufficiency at our centre. Scope exists to improve our provision of IM Hydrocortisone and education in its use and administration for both patients and their carers.

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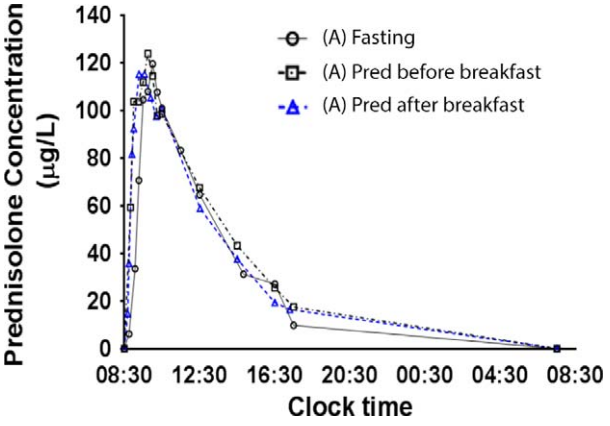
The pharmacokinetic profile of prednisolone is not affected by ingestion of food – how should patients be advised?

Sirazum M Choudhury[1,2], Emma L Williams[1], Tricia M Tan[1,2] & Karim Meeran[1,2]
[1]Imperial College Healthcare NHS Trust, London, UK; [2]Imperial College London, London, UK.

Background
Prednisolone is used for glucocorticoid replacement therapy in Adrenal Insufficiency. Package inserts indicate that prednisolone should be administered with or after food as there is a belief that prednisolone causes stomach ulcers. We have investigated the impact of various fasted and non-fasted states on its pharmacokinetic profile.
Method
A healthy volunteer provided three 4 mg prednisolone profiles. The first was a fasted reference curve. The second involved administering prednisolone 30 min before breakfast. Third, prednisolone was administered within 10 min after completing breakfast.
Prednisolone concentrations were determined at various timepoints by UPLC-MS/MS, and plotted against time to produce prednisolone day curves.
Results
Food had little effect on the absorption of prednisolone when given either before or after breakfast.
When prednisolone was taken before breakfast, the profile was comparable to that of the fasted state but with a slightly shorter T_{Max} (75 min). When prednisolone was taken after breakfast there was a similar C_{Max} (115.2 µg/l vs 119.5 µg/l) achieved with a shorter T_{Max} (64 min vs 90 min) and a shorter terminal half-life (2.52 h vs 3.16 h), compared to the fasting state.
Conclusion
To mimic the normal diurnal rhythm, one would ideally take prednisolone immediately before waking, which is not possible. Taking prednisolone after breakfast causes an unnecessary delay and does not improve absorption. We would advise taking prednisolone immediately on waking, before breakfast to produce a detectable concentrations of prednisolone as early as possible. Currently the package inserts suggest that prednisolone should be taken after breakfast. Whilst this might be appropriate for patient on anti-inflammatory doses, this may not be appropriate for individuals taking replacement therapy.



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P24

Tissue-specific regulation of recycling between cortisol and cortisone by insulin and obesity

Anna Anderson[1], Ruth Andrew[1], Natalie Homer[1], Kate Hughes[1], Fredrik Karpe[2], Roland Stimson[1] & Brian Walker[1]
[1]University of Edinburgh, Edinburgh, UK; [2]Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, UK.

Intracellular cortisol is regulated by 11βHSD1. Although the field has focused on regeneration of cortisol from inert cortisone by 11β-reductase activity of 11βHSD1, we have used stable isotope tracers and arteriovenous sampling to quantify simultaneous dehydrogenase (cortisone generation) and reductase (cortisol regeneration) in human adipose and skeletal muscle. *In vitro* studies suggest insulin regulates this balance of reductase vs dehydrogenase activity. In obesity, 11βHSD1 expression is increased in adipose. We hypothesised that the directionality of 11βHSD1 in metabolic tissues is regulated by insulin and in obesity recycling between cortisol and cortisone is accelerated.
Ten lean (BMI 23.8 ± 0.4 kg/m^2) and ten obese (32.9 ± 0.9 kg/m^2) otherwise healthy men participated in a two-phase crossover single-blinded study comparing saline infusion with a hyperinsulinaemic euglycaemic clamp. 9,11,12,12-[^{2}H]$_4$-cortisol (D4-cortisol, measuring reductase) and 1,2-[^{2}H]$_2$-cortisone (D2-cortisone, measuring dehydrogenase) were infused, samples obtained of arterialised blood and from veins draining forearm skeletal muscle and abdominal subcutaneous adipose, and blood flow measured by occlusion plethysmography and Xenon washout, respectively. Data are lean vs obese, mean ± S.E.M.
Before insulin/saline infusion, whole body 11β-reductase (Rate of appearance (Ra) D3-cortisol 22.66 ± 2.17 vs 26.17 ± 2.15 nmol/min; $P = 0.27$) and 11β-dehydrogenase (Ra cortisone 15.34 ± 3.91 vs 15.82 ± 2.67 nmol/min; $P = 0.92$) did not differ between lean and obese. However, reductase and dehydrogenase activities were only detectable across adipose tissue in obese individuals and across skeletal muscle in lean. Acute hyperinsulinaemia upregulated cortisol regeneration across adipose tissue in obese (insulin vs placebo $P = 0.006$) and tended to upregulate cortisone generation across skeletal muscle in lean (insulin vs placebo $P = 0.06$).
In conclusion, insulin has tissue-specific effects to increase net cortisol regeneration in adipose tissue but not skeletal muscle, potentially amplifying post-prandial lipid storage. Up-regulation of 11βHSD1 in adipose in obesity accelerates recycling between cortisol and cortisone, enhancing the dynamic response to insulin but not necessarily increasing basal intracellular cortisol.

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P25

Random spot urinary metanephrines compared to 24-h collection in the diagnosis and follow up of phaeochromocytomas and paragangliomas: preliminary results

Emilia Sbardella[1,2], Andrea M Isidori[2], Brian Shine[1], Bahram Jafar-Mohammadi[1] & Ashley B Grossman[1]
[1]Department of Endocrinology, OCDEM, Churchill Hospital, Oxford, UK; [2]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy.

Introduction
Phaeochromocytomas and paragangliomas (PPGLs) are rare tumours with high morbidity. The majority are benign and surgically curable, but genetic testing suggests that many are associated with germline mutations, and careful long-term follow-up of patients and their family members is important. Regular biochemical screening with plasma or urinary metanephrines (uMetanephrines) is essential, but currently 24-h collections of uMetanephrines is cumbersome and inconvenient for patients.
Objective
Our aim was to compare 24 h uMetanephrines with 'spot' samples of random urines in patients under investigation or follow-up for PPGLs.
Design, materials and methods
Prospective diagnostic study of 59 patients (mean age 51.3 ± 17.3 years, range 22–80): 18 with adrenal incidentalomas, nine with symptoms suggestive of PPGLs, four carriers of mutations associated with PPGLs, 11 follow-up of operated PPGLs, eight with surgically-verified PPGLs and nine metastatic PPGLs, evaluated at a university hospital from December 2015 to May 2016. The 24-h sample and a simultaneous urinary random spot (20 ml) were assayed for normetanephrine (NMT), metanephrine (MT) and 3-methoxytyramine (3MT) using mass spectrometry. The random samples were corrected for creatinine.
Results
We found a significant correlation between spot concentrations (µmol/mmol creatinine) and output of NMA ($r = +0.987$), MA ($r = +0.995$) and 3MT ($r = +0.865$) for all patients, especially in patients with PPGLs (new diagnosis and metastatic) (NMA $r = 0.997$; MA $r = 0.999$, 3MT $r = 0{,}998$; $P < 0.001$). We derived thresholds for 100% specificity to predict 24-h urinary results in diagnosing excessive catecholamine secretion.
Conclusion
The ratios of NMA, MA and 3MT to creatinine in spot urine samples correlate with the output of these metabolites in 24-h collection, with similar sensitivity and specificity for diagnosis of PPGLs and metastatic disease.
We propose spot random urinary threshold that could be used to diagnose excessive catecholamine secretion, simplifying patient requirements without loss of accuracy.

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P26

Could modified release prednisone hold the key to closer reproduction of the glucocorticoid circadian rhythm in Adrenal Insufficiency?

Sirazum M Choudhury[1,2], Adam Leckey[2], Emma L Williams[1], Tricia M Tan[1,2] & Karim Meeran[1,2]
[1]Imperial College Healthcare NHS Trust, London, UK; [2]Imperial College London, London, UK.

Background
The cortisol circadian rhythm has an early morning peak with an increase before awakening, and a second lunchtime peak. Using a UPLC-MS/MS technique to measure prednisolone, the active metabolite of prednisone, we investigated the suitability of modified release (MR) prednisone (Lodotra) as a replacement therapy.
Method
Blood samples were taken at fixed time points after the administration of MR-prednisone. Concentrations of the active metabolite prednisolone, were determined by UPLC-MS/MS, and were plotted against time to produce prednisolone day curves.
Results
Administration of MR-prednisone led to undetectable prednisolone levels up to 4 h. T_{Max} was achieved at approximately 5 h with an ensuing steady decline in prednisolone levels. The morphology of the curve at this point was congruent with those seen with prednisolone administration.
Conclusion
A night-time dose of MR-prednisone can be used to create an early morning peak in prednisolone levels before awakening, and can thus closely mimic the pre-awakening steroid rise that occurs in a normal diurnal rhythm.

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Structural analysis of nicotinamide nucleotide transhydrogenase (NNT) genetic variants causing adrenal disorders

Lou Metherell[1], José Afonso Guerra-Assunção[2], Michael Sternberg[3] & Alessia David[3]
[1]Centre for Endocrinology, William Harvey Research Institute, Queen Mary University of London, London, UK; [2]Centre for Molecular Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK; [3]Centre for Integrative System Biology and Bioinformatics, Imperial College London, London, UK.

Nicotinamide nucleotide transhydrogenase (NNT) is an integral protein of the inner mitochondrial membrane and plays a major role in maintaining the redox balance by catalysing the trans-hydrogenation between NADH and NADP + and proton translocation across the mitochondrial membrane.
Genetic variants in *NNT* have recently been reported in patients with familial glucocorticoid deficiency (FGD), combined mineralocorticoid and glucocorticoid deficiency and combined adrenal failure and testicular adrenal rest tumours. Moreover, knockout animal models suggest that NNT is involved in the pathogenesis of diabetes mellitus and obesity. Impaired NNT activity is also thought to be involved in the aging process and the development of neurological disorders and cancer.
In this study, we generated a 3D structural model of human NNT (H-NNT) by homology modelling using bacterial NNT as templates. We identified key structural and functional residues in H-NNT, such as those participating in NAD binding and in H-NNT homodimerization. Moreover, we mapped 14 amino acid substitutions causing adrenal disorders and 6 rare genetic variants reported in the ExAC database. This new model allowed us to demonstrate that deleterious variants affect H-NNT structure by altering its structure (p.Gly200Ser, p.Thr357Ala, p.Tyr388Ser, p.Pro437Leu, p.Ala533Val, p.Leu977Pro), its ability to dimerize (p.Phe215Ser, p.His365Pro), its ability to bind NAD (p.Ser193Asn) or NADP (p.Ala1008Pro and p.Asn1009Lys) or its ability to correctly fold within the mitochondrial inner membrane (p.Gly664Arg, p.Gly678Arg, p.Gly862Asp). Without the 3D H-NNT model, molecular mechanisms could only be identified for the two variants located in the NADP binding site.
In conclusion, availability of a 3D H-NNT model allowed us to decipher the mechanisms by which genetic variants causing adrenal disease affect NNT structure and function. Structural biology can provide valuable information on the structure-function relationship of proteins, and integration of genetic analysis with protein 3D modelling can greatly enhance prioritization and interpretation of human genetic variants.

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P28

Incidence and outcomes of hormone-secreting adrenal tumours in pregnancy: a UK 4 year prospective cohort study

Georgia Quartermaine[1], Kimberley Lambert[2], Kate Rees[1], Paul Seed[1], Mandish Dhanjal[3], Marian Knight[4], DR McCance[5] & Catherine Williamson[1]
[1]King's College London, London, UK; [2]Royal Hampshire County Hospital (RHCH), Winchester, UK; [3]Queen Charlotte's and Chelsea Hospital, London, UK; [4]Oxford University, Oxford, UK; [5]Royal Victoria Hospital, Belfast, UK.

Objective
To examine the monitoring, management and outcomes of adrenal tumours in pregnancy.
Design
A national, prospective observational, cohort study over 4 years using the UK Obstetric Surveillance System (UKOSS).
Setting
Consultant led obstetric units.
Patients
Women with hormone-secreting adrenal tumours (pheochromocytoma, primary aldosteronism or Cushing's syndrome) diagnosed before or during pregnancy. Nested case-control comparisons were performed using UKOSS controls with uncomplicated singleton ($n = 2250$) pregnancy and data from the Office of National Statistics (ONS).
Main outcome measures
Incidence, management and frequency of adverse maternal and offspring outcomes of adrenal tumours in pregnancy.
Results
Fourteen pregnant women met the inclusion criteria: nine with pheochromocytoma, three with primary aldosteronism and two with Cushing's syndrome. All of the tumours were rare with an incidence rate of $< 2/100{,}000$ pregnancies. Clinical symptoms were similar to those in non-pregnant women due to the hormones released. All women had severe hypertension in pregnancy, and in those diagnosed during pregnancy there was a more marked elevation of blood pressure than in women diagnosed prior to conception. There was a significantly increased risk of adverse pregnancy outcomes in affected women, with increased rates of stillbirth, preterm labour and operative delivery.
Conclusions
Adrenal tumours are associated with significantly increased risks for pregnant women and their babies. Data on these tumours to inform practice are limited and international collaborative efforts are likely to be needed to obtain robust data to inform guidelines for clinical management.

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P29

Oestrogen excess induces instability and loss of arterial identity in the forming vascular system

Silvia Parajes & Didier Stainier
Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany.

Disturbed oestrogen homeostasis is associated with an increased risk of cardiovascular disease. However, the impact of dysregulated oestrogen signalling on vascular development, maintenance and disease is not fully understood. Zebrafish is a well-established model in translational vascular research. In addition, oestrogen receptor expression and oestrogen-responsiveness in endothelial cells (EC) is conserved in zebrafish. Therefore, the aim of this study was to characterise the effect of oestrogen excess in the formation and maintenance of the vascular system using zebrafish as an *in vivo* model organism. The effect of oestrogen excess in the forming vasculature was investigated in transgenic *Tg(kdrl:eGFP)* embryos, which express GFP in EC, after incubation in 8 μM 17β-estradiol (E2) for 48 h. E_2 treatments from early stages of vasculogenesis (16 h post-fertilisation, hpf) induced severe vascular defects including impaired arterio-venous segregation and disconnected/missing inter-segmental vessels (ISVs). A similar ISV phenotype and a truncated circulatory loop due to a shorter functional dorsal aorta (DA) was observed when treatments were started from 24 to 26 hpf; after angiogenic sprouting has started, the DA has formed, and arterio-venous segregation has ended. qPCR analyses revealed decreased expression of *vegfr2*, *notch3*, the notch ligand gene *deltaC*, and the arterial marker gene *ephrinB2*. No overt vascular defects were observed when treatments were initiated after a functional vasculature was formed (48 hpf).

2-methoxyestradiol (2ME2) is an antiangiogenic E_2 metabolite synthesised via two enzymatic steps catalysed by CYP1A1 and catechol-ortho-methyltransferase (COMT). E_2 strongly induced *cyp1a* expression after 8 and 24 h of treatment. Treatments with 2ME2, however, only recapitulated the E_2-induced ISV phenotype, but not the shortening of the circulatory loop. Similarly, treatments with E_2 and fluoranthene, a CYP1A1 inhibitor, partially rescued the ISV but not the DA phenotype.

Herein, we show that oestrogen excess during vascular development induces severe defects in vasculogenesis, vessel destabilisation and loss of arterial identity. These vascular defects are only partly explained by the conversion of E_2 into 2ME2. Our current studies in oestrogen receptor mutants will bring new insights into the mechanisms linking oestrogen action and vascular disease. Importantly, our data suggest that increased oestrogen signalling during early development due to oestrogen excess or exposure to endocrine disruptors may predispose to vascular malformations.

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P30

Suppression of 11β-hydroxysteroid dehydrogenase type 1 target gene regulation by hypoxia

Bushra Shammout, Adewonuola Alase, Miriam Wittmann, Paul Stewart & Ana Tiganescu
University of Leeds, Leeds, UK.

Delayed wound healing (WH), characterized by ischemia, is exacerbated by glucocorticoid (GC) excess. Local GC availability is regulated by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) which generates the GC cortisol from inactive cortisone. We previously reported improved WH in 11β-HSD1-null mice but regulation of 11β-HSD1 by hypoxia in human skin remains unknown. Primary human dermal fibroblasts (HDF, biological $n=3$), were treated with vehicle, IL1β (10 ng/ml), cortisol (100 nM), IL1β + cortisol, IL1β + cortisone (200 nM) or IL1β + cortisone + 11β-HSD1 inhibitor (1 μM). Cells were incubated for 96 h in normoxia (21% O_2) or hypoxia (1% O_2). Gene expression was analysed by qPCR after normalizing to 18S rRNA. IL1β (vs vehicle) increased 11β-HSD1 mRNA by 198 ± 130 and 288 ± 125-fold (± S.E.M, $P<0.05$) in normoxia and hypoxia respectively. Hypoxia (vs normoxia) supressed 11β-HSD1 expression with IL1β + cortisol and IL1β + cortisone by 67 ± 14 ($P<0.05$) and 41 ± 28% ($P=0.07$) respectively, but not with IL1β + cortisone + 11β-HSD1 inhibitor.

MMP1 and TIMP4 differentially modulate matrix remodelling during WH. Cortisol decreased IL1β-induced MMP1 by 64 ± 12 ($P=0.07$) and 89 ± 4% ($P<0.05$) in normoxia and hypoxia respectively and upregulated TIMP4 mRNA (independently of IL1β) by 4 ± 0.5 and 2 ± 0.05 ($P<0.05$) in normoxia and hypoxia respectively. Cortisone did not significantly reproduce the effects of cortisol for these genes. COX2 is integral to inflammation and WH. IL1β (vs. vehicle) increased COX2 expression by 87 ± 28 and 183 ± 76-fold ($P<0.05$) in normoxia and hypoxia respectively. In contrast to MMP1 and TIMP4, both cortisol and cortisone supressed IL1β-induced COX2 expression by 94 ± 3 and 89 ± 5% ($P<0.05$) respectively in normoxia and the suppression by cortisone was reversed by 11β-HSD1 inhibitor co-incubation ($P<0.05$). Interestingly, cortisone did not significantly reproduce the effects of cortisol in hypoxia likely due to lower 11β-HSD1 expression.

In summary, we demonstrate a previously unreported cortisol-dependent decrease in 11β-HSD1 expression in hypoxia which may represent a protective mechanism to limit GC exposure in ischemia. Further, we report gene-specific sensitivity to 11β-HSD1-derived cortisol which may regulate responses to inflammation and hypoxia in chronic wounds.

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P31

Maternal smoking disrupts adrenal steroid production in the human fetus

Zoe Johnston[1], Michelle Bellingham[1], Denise Hough[1], Panagiotis Filis[2], Peter O'Shaughnessy[1] & Paul Fowler[2]
[1]Institute of Biodiversity, Animal Health & Comparative Medicine, University of Glasgow, Glasgow, UK; [2]Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK.

Introduction

The adrenal gland dominates in human fetal steroid endocrinology and produces large amounts of Δ5 androgens. Adrenal development in the human is poorly understood, and species differences make animal models only partially relevant. In this study we measured the steroid content of the human adrenal during fetal development and determined whether maternal smoking affects adrenal steroid concentrations or associated steroidogenic enzymes.

Methods

109 human fetal adrenals were obtained from elective terminations (REC 04/S0802/21) of second trimester fetuses between 11 and 21 weeks of gestation. Fetuses were grouped according to sex, gestational age and maternal smoking. Steroids extracted from these adrenals were quantified by LC–MS and enzyme expression analysed by RT-qPCR, Western blot and immunohistochemistry.

Results

The most abundant steroid (ng/mg of tissue) in the human fetal adrenal was pregnenolone, followed by dehydroepiandrosterone-sulphate and 17-hydroxy-progesterone (17OHP). Most steroids were unchanged during the second trimester although relative production of pregnenolone and corticosterone decreased between weeks 12 and 19 ($P=0.002$ and $P=0.06$, respectively). While steroid levels were similar between male and female fetuses, maternal smoking increased 16-hydroxyprogesterone ($P=0.04$) and deoxycorticosterone ($P=0.003$) levels in male fetuses only. Protein expression of steroidogenic enzymes CYP17A1 and CYP21A2 increased throughout the second trimester but were unaffected by sex or maternal smoking. Transient protein expression of HSD3B in the adrenal fetal zone was observed at 12–13 weeks. Maternal smoking was associated with increased mRNA of transcription factors, *SF-1* ($P=0.04$: males) and *GATA-6* ($P<0.001$: both sexes), which are involved in steroidogenesis and cell proliferation.

Conclusions

The rate of androgen and corticosteroid production is limited predominantly by expression of CYP17A1 and CYP21A1 as reflected by high levels of pregnenolone and 17OHP. Maternal smoking affects human fetal adrenal development in terms of changes in transcriptional regulation and steroid production, particularly in males, which may impact on post-natal health.

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P32

Discovery of putative aldosterone-regulating microRNAs by analysis of *in vitro* and *in vivo* microRNA profiles

Nur Izah Ab Razak, Scott MacKenzie, Stacy Robertson, Martin McBride, Marie Freel & Eleanor Davies
University of Glasgow, Glasgow, UK.

Approximately 10% of essential hypertension cases is attributed to primary aldosteronism (PA), where inappropriately high levels of aldosterone are secreted. Almost half of these PA cases result from aldosterone-producing adenoma. microRNAs are single-stranded, short non-coding RNAs that negatively regulate gene expression post-transcriptionally. In a previous study, we showed that microRNAs directly modulate *CYP11B2* (aldosterone synthase) gene expression and aldosterone levels. We also compared microRNA profiles of non-diseased adrenal tissue with those of aldosterone-producing adenoma (APA; each $n=4$). Now we have examined microRNA profiles from the widely-used adrenocortical carcinoma cell line, H295R, in both its basal state and following stimulation of aldosterone production for 24 hours with either 100 nM angiotensin II (AngII), 1 mM dibutyryl cyclic AMP (dbcAMP) or 20 mM potassium chloride (KCl; $n=3$ per cell group). The microRNA profiles of all cells and tissues were generated by microarray. CYP11B2 upregulation in stimulated H295R cells was confirmed by qRT-PCR.

We found five microRNAs to be consistently downregulated in APA relative to NA and in all stimulated H295R cells relative to basal. This is suggestive of common mechanisms underlying the abnormal secretion of aldosterone observed in APA as well as the normal physiological stimulation of aldosterone production in response to regulatory molecules. Furthermore, it implicates these microRNAs in the regulation of such mechanisms. Initial bioinformatic analysis was performed using Ingenuity Pathway Analysis (IPA) software in order to predict relevant mRNAs likely to be targeted by one or more of these 5 microRNAs. A predicted target genes of particular relevance to steroidogenesis is *HMGCR*, which encodes the rate-limiting enzyme for cholesterol biosynthesis targeted by statin treatment. As regulation of cholesterol supply is increasingly recognised as a determining factor in steroid output future study will focus on this interaction. In conclusion, we suggest that these consistently altered microRNAs are likely to be involved in aldosterone regulation and have presented relevant putative targets, which are worthy of further investigation.

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P33

What is the most appropriate cut-off for post-saline aldosterone in saline suppression test after adrenalectomy?

Ruvini Ranasinghe[1], David Taylor[1], Benjamin Whitelaw[2], Simon Aylwin[2] & Royce Vincent[1]
[1]Department of Clinical Biochemistry, King's College Hospital NHS Foundation Trust, London, UK; [2]Department of Endocrinology, King's College Hospital NHS Fondation Trust, London, UK.

Introduction
Primary aldosteronism (PA) is the most common endocrine cause of hypertension affecting up-to 10% of hypertensives. Saline suppression, a confirmatory test for PA helps avoiding patients undergoing invasive lateralisation procedures due to a false positive aldosterone-to-renin ratio (ARR). The proposed cut-off to exclude PA is post-saline aldosterone suppression to <140 pmol/l. We reviewed our biochemical work-up in order to optimise laboratory assessment.
Method
This retrospective audit reviewed adult patients who underwent saline suppression test between January 2014 and December 2015. Pathology and hospital IT systems were used to obtain relevant information (investigations, multi-disciplinary meeting (MDM) outcomes, histology and management).
Results
In total there were 54 patients (26M) aged 51 (43–59) (median (IQR)) years. Based on exclusion criteria three had post-saline aldosterone <140 pmol/l (CT scan – 2 normal and 1 adenoma) and were medically managed. MDM diagnosed PA in 37 (post-saline aldosterone >140 pmol/l) out of which 21 were managed surgically. 19, histology confirmed PA had pre and post-surgery (1–8 weeks after surgery) saline suppression. After surgery, baseline and post-saline aldosterone decreased from 831 (556–1223) to 232 (139–288) and 716 (469–1000) to 121 (89–151) pmol/l respectively (both, $P<0.0001$). Only 12 suppressed to <140 pmol/l, the other seven suppressed between 140 and 233 pmol/l. The post-surgery aldosterone suppression was 81 (range 62–96)%.
Conclusion
In our cohort the proposed post-saline aldosterone cut-off <140 pmol/l correctly identified all patients with conformed PA but, only 63% had post-saline aldosterone <140 pmol/l after surgery. However, all had >60% reduction in post-saline aldosterone. Larger studies are needed to standardise biochemical confirmation of successful surgical resection of PA.

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P34

The human fetal adrenal proteome: development, sex, and maternal smoking link in utero smoke-exposure to offspring disease

Panagiotis Filis[1], Zoe Johnston[2], Michelle Bellingham[2], Ugo Sofientini[2], Peter O' Shaughnessy[2] & Paul Fowler[1]
[1]The University of Aberdeen, Aberdeen, UK; [2]The University of Glasgow, Glasgow, UK.

Introduction
The human fetal adrenal has unique structure/function and produces hormones (DHEA, corticoids, catecholamines) that control fetal development, organ maturation and parturition. Maternal smoking during pregnancy has immediate (pre-term delivery, low birth weight) and long-term effects on the offspring (metabolic syndrome, disrupted adrenal function). We performed shotgun proteomics to characterise human fetal adrenal development and to explore adverse effects of maternal smoking.
Methods
Proteins from human fetal adrenals (12–19 weeks of gestation, divided by sex and maternal smoke exposure, $n=15$/group) from electively terminated fetuses (REC 04/S0802/21) were digested and the peptides analysed by liquid chromatography/Q-Exactive tandem Mass Spectrometry. Identified proteins were normalised using MaxQuant software and compared across groups and gestational ages using empirical moderated Bayesian statistics (limma package, R statistical software). Statistically-significant differences were filtered on a 10% False Discovery Rate and mapped using Ingenuity Pathway Analysis software.
Results and Discussion
Of 2488 human fetal adrenal proteins quantified, 423 were developmentally regulated; 39 had sex-specific expression and; 71 in females and 51 in male adrenals were dysregulated by maternal smoking. Development of the adrenal associated with reduced protein translation, increased proliferation, tissue remodelling and hypoxia signalling, as well as elevated T3 hormone, leptin and retinoid signalling. Higher levels of cholesterol and glucocorticoid biosynthesis enzymes and increased androgen receptor signalling characterised male adrenals. Maternal smoking: (i) increased cholesterol transport and proliferative pathways in females, suggesting accelerated adrenal development likely to contribute to preterm birth; (ii) increased proapoptotic factors and disrupted glucocorticoid receptor, xenobiotic metabolism, and calcium homeostasis pathways in males, suggesting alterations in the HPA axis consistent with low birth weight outcomes. Our results show that human fetal adrenals have sexually-dimorphic responses to maternal smoking and suggest that the links between in utero smoke exposure and disease involve fetal adrenal disruption. Funded by an SfE Early Career Grant (2015).

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11β-hydroxysteroid dehydrogenase type 1 mediates anti-inflammatory, pro-inflammatory and inflammation-independent effects in primary human dermal fibroblasts

Layal Abi Farraj[1], Michael Morgan[2], Adewonuola Alase[1], Ian Carr[1], Paul Stewart[1] & Ana Tiganescu[1]
[1]University of Leeds, Leeds, UK; [2]University of Oxford, Oxford, UK.

Glucocorticoids (GC) drive multiple adverse effects in skin e.g. epidermal thinning, dermal atrophy and impaired wound healing (WH). Our previous findings indicate increased expression of the GC-activating enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in primary human dermal fibroblasts (HDF), full-thickness skin from older donors and during the inflammatory phase of mouse skin WH. We also reported protection from age-induced dermal atrophy and improved WH in aged 11β-HSD1 KO mice but regulation of GC target genes by 11β-HSD1 in human skin remains unexplored. HDF treated with 10 ng/ml IL-1β induced 11β-HSD1 mRNA by 112-fold ($P<0.05$, $n=3$) and activity fourfold ($P<0.05$, $n=4$) vs vehicle-treated controls. IL-1β-induced activity was blocked by a selective 11β-HSD1 inhibitor ($P<0.05$, $n=4$). Using RNA-seq, we identified 289 genes co-regulated by IL-1β and 11β-HSD1. Of these, 204 were IL-1β-antagonizing (e.g. downregulation; BDKRB1, CCL8, CLDN1, MMP3, IL11, upregulation; ANGPTL4, GADD45B, LGR5, FSTL3 and DUSP1) and 85 were IL-1β-augmenting (e.g. downregulation; GRM1, PLCB1, AMOT, F2RL2, GPER1, upregulation; NRCAM, COL4A4, PTGDR, SERPINE1 and MT2A), indicating complex anti-inflammatory and pro-inflammatory regulation of IL-1β function by 11β-HSD1. A further 322 genes were regulated by 11β-HSD1 in an IL-1β-independent manner (e.g. down-regulation; ADCY8, PTHLH, PLA2G4A, BMP2, ITGA8, upregulation; ZBTB16, LEP, FKBP5, NKD1 and MMP7). Gene over-representation analysis indicated regulation of pathways involved in extracellular matrix organization, integrin interactions, inflammation, complement and coagulation, prostaglandin synthesis, cell cycle, TGF-β signalling, hypoxia, angiogenesis and cell signalling (AP-1, PI3K-Akt, ERK, Wnt and MAPK). Genes and pathways of interest were validated by qPCR and protein expression. Our findings demonstrate for the first time the 11β-HSD1-mediated regulation of GC target genes in HDF. We report novel pro-inflammatory functions which may contribute to skin inflammatory diseases e.g. eczema. The induction of 11β-HSD1 by inflammation and subsequent inflammation-independent regulation of GC target genes in skin may drive atrophic scarring in acne. 11β-HSD1 inhibitors may represent novel therapeutic strategies to improve skin function.

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P36

The role of 0900 h Cortisol level to predict response to Short Syancthen Test in hypoadrenalism

Najaf Haider, Pankaj Verlekar & Ma'en Al-Mrayat
University Hospital Southampton, Southampton, UK.

Aim
To define a basal Cortisol threshold that could potentially predict the outcome of short synacthen test (SST) and thus reduce the need for performing SST in patients with low clinical probability for adrenal insufficiency.
Methods
We analysed SSTs done at our hospital in non-critically ill general medical and endocrine patients, who had abnormal 0900 h Cortisol levels ($n=110$, male-45, female-65) between January 2016 to March 2016. The SST was considered pass when the 30 min Cortisol was 480 nmol/l and above as per our local laboratory protocol.

Findings
Of the 110 patients, 84 passed the SST (76%) and 23 (24%) had failed the SST. Majority of the SSTs were done between 0900 and 1100 h in the morning. All patients with a basal 0900 h Cortisol <100 nmol/l had failed the SST. Among patients with a basal 0900 h Cortisol of 350 nmol/l and above, 88.9% had passed the test. All patients with a basal 0900 h Cortisol level of 400 or above had passed the SST.
Conclusion
If the 0900 h Cortisol is less than 100 nmol/l, then there is no need to perform SST as all of them will fail. A 0900 h Cortisol level above 400 nmol/l predicts a satisfactory pass on the SST. A Cortisol level above 350 nmol/l highly predicts having a normal SST. Basal cortisol levels between 100 and 350 nmol/l should have an SST to confirm hypoadrenalism. A 0900 h baseline serum may help in avoiding unnecessary SST and provides a cost-effective approach.

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P37

Development and evaluation of the acceptability of new materials to address individualised needs to support self-management for patients with adrenal insufficiency

S Llahana[1], J Webber[3], S Chapman[2], PV Carroll[5], P McBride[4], D Phillips[3] & R Horne[2,3]
[1]University College London Hospitals, London, UK; [2]University College London, London, UK; [3]Spoonful of Sugar, London, UK; [4]The Pituitary Foundation, Bristol, UK; [5]Guy's and St Thomas' NHS Foundation Trust, London, UK.

Background
Self-management is essential for patients with adrenal insufficiency (AI) to achieve optimal outcomes of glucocorticoid (GC) replacement therapy by minimising adverse effects from over- or under-replacement and appropriately adjusting the dose in intercurrent illness to prevent adrenal crisis. Evidence suggests that many patients report deficits in self-management especially concerning 'sick day rules', prevention and management of adrenal crisis and have high concerns about adverse effects from their treatment.
Objectives
To develop and evaluate the acceptability of materials to support self-management for patients with AI aiming to identify individual needs and concerns about their condition and treatment and to improve patient-clinician communication.
Study design
The support materials were developed in collaboration with an expert faculty of endocrinologists, endocrine nurses and patients with AI from across Europe and comprise of i) a one-page patient questionnaire to help patients identify individual concerns about their AI and GC replacement therapy, ii) a patient information booklet designed to address the concerns identified in the questionnaire and iii) a short outline for healthcare professionals describing how patients can use the questionnaire in conjunction with the booklet as an aid for their endocrine clinic consultations. An on-line survey was conducted involving 100 patients recruited through patient support groups in the UK. We asked patients to read and comment on the content of the questionnaire and booklet and to respond to a number of questions designed to assess patients' acceptability of these materials as an aid to identify individual concerns about their AI and GC replacement therapy.
Outcome
Support materials that are acceptable to patients with AI and healthcare professionals and can be used to support self-management of GC replacement therapy and improve patient-clinician communication.

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P38

^{18}F-FDG PET-CT combined with ^{11}C-metomidate PET-CT for the successful characterisation of adrenal lesions; proof of utility of a novel imaging strategy in guiding management

Andrew S Powlson[1], Olympia Koulouri[1], HK Cheow[2] & Mark Gurnell[1]
[1]Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge and NIHR Cambridge Biomedical Research Centre, Cambridge, UK; [2]Department of Radiology, Addenbrooke's Hospital, Cambridge, UK.

Background/aims/method
Evaluation/management of adrenal incidentalomas (AI) is an increasingly prevalent challenge. CT/MRI characteristics may be useful in determining whether a lesion is a benign adenoma and forthcoming ESE-ENSAT guidance suggests a role for ^{18}F-FDG-PET/CT in distinguishing benign vs malignant lesions. We have previously demonstrated the utility of ^{11}C-metomidate (MTO), which binds CYP11B1/B2, in localising aldosterone-producing adenomas. A proposed European study (FAMIAN) suggests combining ^{18}F-FDG-PET/CT with 131-iodometomidate imaging to distinguish tissue of adrenocortical origin as well as malignancy. In support of this hypothesis, we have used this dual imaging approach, with ^{11}C-MTO-PET/CT in conjunction with ^{18}F-FDG-PET/CT, to investigate three patients with indeterminate adrenal pathology.
Results
(1) Double negative MTO and FDG in a benign ganglioneuroma. A 66-year-old woman presented with a non-functioning right AI (40 mm, heterogeneous features on CT, Fig. 1A), which was neither avid for FDG (1B) nor MTO (1C). She elected to have surgery; a benign ganglioneuroma (non-adrenocortical) was confirmed by histology.
(2) Double positive MTO and FDG in metastatic adrenocortical carcinoma (ACC). A 65-year-old woman with a history of right adrenalectomy (ACC) and liver lobectomy (solitary ACC metastasis) ten years previously, presented with tissue in the right adrenal bed/liver. This was avid for both FDG (suggesting malignancy, Fig. 2A) and MTO (suggesting adrenocortical origin, 2B). The diagnosis of recurrent ACC was supported.
(3) Positive FDG and negative MTO in primary adrenal lymphoma. A 66-year-old man presented with a non-functioning 30 mm right AI with indeterminate CT characteristics (baseline Hounsfield Units 40, Fig. 3A) which was FDG-avid (3B) but MTO-negative, with the adjacent normal adrenal showing physiological MTO uptake (3C). Histology demonstrated a rare primary adrenal lymphoma (non-adrenocortical).
Conclusions
Combining FDG and metomidate PET-CT can distinguish benign from malignant adrenal lesions and determine whether they are of adrenocortical origin. This novel approach may thus inform management in cases of indeterminate adrenal pathology.

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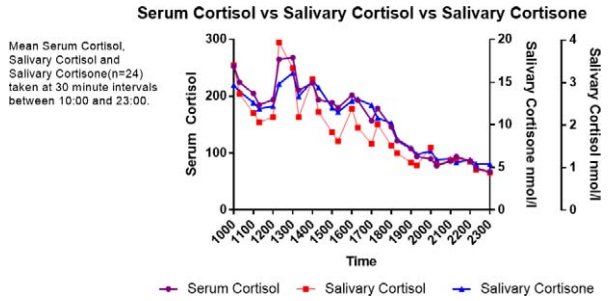
P39

Salivary cortisone is a potential surrogate for serum cortisol measurement

Safwaan Adam[1,2], Anna Minder[2], Elizabeth Cottrell[1], Alison Davies[1], Suzanne Meredith[1], Richard Preziosi[1], Brian Keevil[3], Claire Higham[2,4], Anne White[1] & Peter Trainer[2,4]
[1]Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; [2]The Christie Hospital NHS Foundation Trust, Manchester, UK; [3]University Hospital of South Manchester, Manchester, UK; [4]Manchester Academic Health Sciences Centre, University of Manchester, Manchester, UK.

Introduction
Hydrocortisone therapy in adrenal insufficiency and medical management of Cushing's syndrome requires accurate monitoring of glucocorticoid status. Currently, this necessitates admitting patients to hospital for serial measurements of serum cortisol. From previous studies in Cushing's, the goal of medical therapy is a mean (based on five samples) serum cortisol of 150–300 nmol/l, which is known to equate to a normal cortisol production rate. Salivary cortisol has the virtue of convenience and being unaffected by variation in CBG but cross-reactivity is a problem on immunoassay. Oral contamination can result in spuriously high salivary cortisol (but not cortisone) levels in patients on hydrocortisone. Cortisone, converted from cortisol, is quantitatively the predominant glucocorticoid in saliva and its measurement has the potential to overcome the limitations of salivary cortisol. We have studied the value of salivary glucocorticoids (measured by LC–MS/MS) as a patient-friendly surrogate for serum cortisol measurement.
Methods
Serum cortisol and salivary cortisol and cortisone were measured in 24 healthy volunteers (12 BMI <25; 12 BMI 25–30) every 30 min from 1000 to 2300 h. Standard meals were given at 1200, 1700 and 2100 h.
Results
Mean serum cortisol was 253 nmol/l (1000 h) and 67 nmol/l (2300 h). Pulses in serum cortisol were mimicked in salivary glucocorticoid measurements with close correlation between serum cortisol and salivary cortisol ($r=0.78$; $P<0.0001$) or salivary cortisone ($r=0.83$; $P<0.0001$). In this study, the mean of five samples (1000, 1300, 1600, 1900, 2200 h) ranged from 100–265 nmol/l for serum cortisol, 1.0–5.4 nmol/l for salivary cortisol and 6.7–18.7 nmol/l for salivary cortisone. Furthermore, the mean salivary cortisone based on five samples was representative of the mean from all 26 samples per subject ($r=0.88$; $P<0.001$).

Conclusions
Salivary cortisone accurately reflects ultradian changes in serum cortisol (better than salivary cortisol) and offers a convenient alternative to venous sampling in patients with disorders of the HPA axis.



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P40

Steroid metabolomics for diagnosis of inborn steroidogenic disorders – bridging the gap between clinician and scientist through computational approaches

Elizabeth Baranowski[1,2], Kerstin Bunte[1,3], Cedric Shackleton[1], Angela Taylor[1,2], Beverley Hughes[1], Michael Biehl[4], Peter Tino[1], Tulay Guran[5] & Wiebke Arlt[1,2]
[1]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK; [2]Centre for Endocrinology, Diabetes and Metabolism (CEDAM), Birmingham Health Partners, Birmingham, UK; [3]School of Computer Science, University of Birmingham, Birmingham, UK; [4]Johann Bernoulli Institute for Mathematics and Computer Science, Groningen, The Netherlands; [5]Department of Endocrinology and Diabetes, Marmara University, Istanbul, Turkey.

Background
The urinary steroid metabolome is considered the fingerprint of adrenal gland function. Novel methods using mass spectrometry profiling have seen the advent of a new era for metabolomics with powerful implications for both diagnostics and discovery. Its interpretation is difficult and performed by few specialists with the expertise to do so. This makes it a relatively inaccessible tool for the majority of Clinical Endocrinologists.
Objective
To create an automatous method for accurate diagnosis and differentiation of inborn steroidogenic disorders using 34 distinct measured urinary steroid metabolites, that is accurate, reproducible and suitable for high-throughput use.
Methods
Using GC/MS, 829 healthy control urines were analysed (302 neonates and infant, 149 children, 18 adolescents, 326 adults, 34 unknown age) and baseline urine from 118 newly diagnosed with inborn steroidogenic disorders (P450 oxidoreductase deficiency, 21 hydroxylase deficiency, 5a reductase deficiency, 17bHSD3 deficiency, 17 hydroxylase deficiency, 3bHSD2 deficiency, 11b hydroxylase type 1 and type 2 deficiency and cyt B5 deficiency). We custom-designed an interpretable machine learning technique, Angle Learning Vector Quantisation, designed to distinguish these conditions using the urinary steroid metabolome. We looked at all possible steroid ratios and by means of ANOVA reduced this to 165 most informative steroid ratios. Using these, the method is able to computationally determine a reduced list of the most relevant ratios to differentiate specific disorders. The method runs independent of sex and age information, method of urine collection (spot, nappy, 24 h collection), and compensates for missing measurements.
Results
Our machine learning method was able to predict an affected urine vs a healthy urine with a sensitivity of 100% and specificity of 97%. For our three most prevalent conditions (PORD, SRD5A2 and CYP21A2), the method correctly identified the specific condition in 96% of cases. Where it incorrectly identified the condition, it was mistaken for a biologically very similar one.
Conclusion
We have developed a novel machine learning which is highly sensitive and specific. With further validation, it has potential for application in routine clinical practice.

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P41

Impact of month of birth on the risk of development of autoimmune Addison's disease

Agnieszka Pazderska[1], Marta Fichna[2,3], Anna Mitchell[1], Catherine Napier[1], Earn Gan[1], Marek Ruchała[3], Mauro Santibanez-Koref[1] & Simon Pearce[1]
[1]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; [2]Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland; [3]Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland.

Background
The pathogenesis of autoimmune Addison's disease (AAD) remains incompletely understood, but it is thought to be due to interplay between genetic, immune and environmental factors. A month of birth effect, with increased risk amongst those born in autumn and winter months, have been described in autoimmune conditions such as type 1 diabetes and autoimmune thyroid disease.
Aim
To investigate month of birth effect in two independent cohorts of patients with AAD.
Methodology
The monthly distribution of birth in AAD patients was compared to that of the general population using the Cosinor test. Month- by-month variation was screened for using X^2, with odds ratios and 95% CI calculated, to compare the birth rates for each month in subjects with AAD and the control population; 415 AAD subjects from the UK cohort were compared with 8,180,180 UK births; 231 AAD subjects from the Polish cohort were compared with 2,421,385 Polish births.
Results
In the entire cohort of AAD subjects, month of birth distribution analysis showed significant periodicity with peak of births in December and trough in May ($P = 0.028$). Analysis of the odds ratio distribution based on month of birth in two cohorts of patients with AAD vs the general population revealed December peak and May trough, and January peak and July through, in the UK and Polish cohorts respectively.
Conclusions
We demonstrate that month of birth exerts an effect on the risk of developing AAD, with excess risk in individuals born in winter months and a protective effects when born in the summer. Exposure to seasonal viral infections in the per-natal period, coupled with vitamin D deficiency, could lead to dysregulation of innate immunity affecting the risk of developing AAD.

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Bone and Calcium

P42

The mechanistic role of fibroblast growth factor 21 in growth hormone resistance secondary to chronic childhood conditions

Jayna Narendra Mistry, Gerard Ruiz-Babot, Leonardo Guasti & Leo Dunkel
Department of Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

Background
Both undernutrition and chronic inflammation impair linear growth through resistance to GH. Fibroblast growth factor 21 (FGF21) is known as an important regulator of the metabolic adaptation to fasting. Elevated expression of FGF21, secondary to prolonged undernutrition has been identified to develop GH resistance and subsequent attenuation of skeletal growth and growth plate chondrogenesis in both mice and human. However, the mechanism of FGF21's actions remains largely unknown. Molecular understanding of this process may open avenues for novel therapeutic intervention to enhance linear growth of children with secondary GH resistance.
Objective and hypotheses
We envisage that elevated FGF21 exposure has a key role in GH resistance by direct action on human chondrocytes. The objective of this study is to unravel the mechanistic interplay of FGF21 in GH-receptor (GHR) signalling.
Method
Hek-293 stable lines were generated with human/mouse GHR over-expression. Time course evaluation with Cycloheximide, without/with; GH and recombinant FGF21 treatment for 1–8 h revealed GHR half-life. Hek-293 human/mouse GHR cells were treated without/with; recombinant FGF21 and GH for 0, 10 or 30 min and assessed for STAT5 and phosphorylated-STAT5 expression.

Results
Validation of stable lines confirmed the expression of FGF21 receptor complex; FGFR1 iiiC/β-Klotho and the molecular integrity of GHR signalling. We identified two interrelated mechanisms for GH resistance after exposure to FGF21. 1) FGF21 significantly reduced GHR half-life overtime. 2) GH induced the activation STAT5 phosphorylation and downstream signalling which was inhibited by FGF21 exposure. Future work will determine the role of FGF21 in GH resistance under chondrogenic differentiation.
Conclusion
Chronic FGF21 exposure increases GHR turnover and inhibits early upstream in GHR signalling, implicating a fundamental role for FGF21 in GH resistance secondary to chronic childhood conditions.

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P43

The influence of gender on the bone health of adolescent patients with hormonal deficiencies

Pauline Whittingham, Kerrie Grounds, Aftab Ahmad, Mo Didi & Pamela Corlett
Royal Liverpool University Hospital, Liverpool, UK.

Introduction
Previous audits demonstrated low bone mineral density (BMD) in adolescent patients with hormone deficiencies. We wanted to ascertain if gender had any relationship with the development of low BMD.
Method
A retrospective analysis of 42 Transitional clinic patients who underwent DEXA scanning was made using case notes and hospital systems. Follow-up data was gathered as previous audit of 25 transitional patients had shown a significant number to have low BMD.
Results
A total of 42 patient records were accessed, of these 33 patients were male. Mean age for both genders was 21. Hormonal deficiencies included: childhood growth hormone deficiency $n=22$ (17 male), hypogonadism $n=20$ (5 female), steroid deficient and on long-term replacement $n=8$ (6 male). Thirteen patients ($n=4$ female) had co-existing endocrinopathies with $n=5$ (4 male) having deficiencies of all three hormones.
Endocrinopathies were due to brain tumour/ injury, histocytosis, leukaemia, CAH, BPES syndrome, primary hypogonadism, thallasaemia, hypogonadotrophic hypogonadism.
Age range at baseline was 16–21 years for male and 17–20 years for females.
Twenty males (60.6%) and $n=7$ (77.7%) females had low BMD at baseline scans. There were 16 patients ($n=13$ male) in whom only lumbar spine was reported due to absence of age match control for femoral neck.
Of the 27 patients found to have low baseline BMD's, $n=15$ (75%) males and $n=3$ (42.8%) females were treated with combination of bisphosphonate and calcium/vit D supplements. $n=1$ female and $n=1$ male received calcium/vit D only; 8 ($n=4$ female) were untreated.
14 patients with low baseline BMD's ($n=3$ female) had follow-up scans. In the group treated with combination of bisphosphonate and calcium/vit D supplement, 9 ($n=8$ male) demonstrated improved BMD when rescanned. $n=2$ male and $n=1$ female showed no improvement and $n=2$ (1 male) showed reduction in BMD.
Three male patients had normal baseline BMD's and there was no change in the intervening 2–4 years.
Conclusion
Two thirds of the patients attending Transitional clinic were found to have low BMD's. Baseline scans would suggest that females in this age group have a higher risk of developing low BMD. In those patients who received combination of bisphosphonate and calcium/vit D; 64% male patients and 33% female patients showed improvement in BMD when rescanned.

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P44

The calcilytic SHP635 rectifies hypocalcaemia and reduced parathyroid hormone concentrations in a mouse model for autosomal dominant hypocalcaemia type 1 (ADH1)

Fadil Hannan[1,2], Valerie Babinsky[1], Caroline Gorvin[1], Tertius Hough[3], Elizabeth Joynson[3], Michelle Stewart[3], Sara Wells[3], Roger Cox[3], Edward Nemeth[4] & Rajesh Thakker[1]
[1]Radcliffe Department of Medicine, University of Oxford, Oxford, UK; [2]Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK; [3]MRC Harwell, Oxfordshire, UK; [4]MetisMedica, Toronto, Canada.

Autosomal dominant hypocalcaemia type 1 (ADH1) is a systemic disorder of calcium homeostasis caused by gain-of-function mutations of the calcium-sensing receptor (CaSR). ADH1 may lead to symptomatic hypocalcaemia, inappropriately low parathyroid hormone (PTH) concentrations and hypercalciuria. Active vitamin D metabolites are the mainstay of treatment for symptomatic ADH1 patients, however their use predisposes to nephrocalcinosis, nephrolithiasis and renal impairment. Calcilytics are selective CaSR antagonists and represent a potential targeted therapy for ADH1. We have investigated SHP635, a calcilytic compound, for the treatment of ADH1 by *in vivo* studies involving a hypocalcaemic mouse model, known as *Nuf*, which harbours a gain-of-function CaSR mutation, Leu723Gln. WT and heterozygous-affected (*Nuf*/+) mice aged 20–28 weeks were used in accordance with UK Home Office legislation and project license restrictions. A dose-ranging study was undertaken by administering a single subcutaneous bolus of SHP635 at the following doses: 0, 1, 3, 10 and 30 mg/kg to n=4–6 *Nuf*/+ mice and measuring plasma PTH responses at 30 min post-dose. At baseline, *Nuf*/+ mice had significantly reduced PTH concentrations of 17 ± 4 pmol/l compared to 68 ± 19 pmol/l for WT mice ($P<0.01$). SHP635 significantly increased plasma PTH in a dose-dependent manner with the 30 mg/kg dose leading to a maximal PTH concentration of 371 ± 30 pmol/l. To determine whether SHP635 may rectify the hypocalcaemia in *Nuf*/+ mice, a sub-maximal dose (25 mg/kg) was administered, and plasma adjusted-calcium concentrations measured at 0, 30 min, 1, 3 and 6 h post-dose. At baseline, *Nuf*/+ mice had significantly reduced adjusted-calcium concentrations of 1.87 ± 0.03 mmol/l compared to 2.49 ± 0.04 mmol/l for WT ($P<0.01$). SHP635 significantly increased plasma adjusted-calcium to a maximal concentration of 2.16 ± 0.06 mmol/l ($P<0.01$) at 1hr post-dose, with values returning to baseline by 3 h. Our findings demonstrate that SHP635 rectifies the hypocalcaemia of *Nuf* mice, and indicate that this calcilytic is a potential treatment for ADH1.

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P45

Immunomodulation by vitamin D is associated with regulation of microRNAs

Danyang Li[1,3], Louisa E. Jeffery[1,3], Karim Raza[2,3] & Martin Hewison[1,3]
[1]Institute of Metabolism and Systems Research, Birmingham, UK; [2]Institute of Inflammation and Ageing, Birmingham, UK; [3]The University of Birmingham, Birmingham, UK.

The active form of vitamin D, 1,25-dihydroxyvitamin D (1,25D), acting via the vitamin D receptor (VDR) is a potent regulator of gene expression, with effects on skeletal and extra-skeletal physiology. We have shown that actions of 1,25D on bone-forming osteoblasts also involve regulation of microRNAs (miRNAs) that play a key role in the functional development of these cells. In the current study, we have investigated miRNAs as mediators of innate and adaptive immune responses to 1,25D. Human peripheral blood mononuclear cells were used to generate models of dendritic cell (DC) maturation and function, and T cell activation and function. DCs matured in the presence of 1,25D, or treated with 1,25D following maturation, showed decreased expression of antigen-presenting marker CD86. Quantitative RT-PCR analysis of 7 candidate miRNAs associated with immune function (miR21, miR29a, miR145, miR146a, miR155, miR627 and let7i) showed miR21 was supressed significantly (0.39-fold) by 1,25D in immature DCs (5 days vehicle culture, followed by 10 nM 1,25D, 24 h), and miR155 was induced significantly (3.66-fold) in tolerogenic DCs after maturation with LPS (6 days culture with 10 nM 1,25D). For studies of adaptive immunity, T cells were activated for 24 h with anti-CD3/CD28 and cytokines (IL-2, TGFβ, IL-1β, IL-6, IL-23) to stimulate VDR expression. In these cells 1,25D (10 nM, 0–72 h) increased the cell-surface antigen CTLA4 and decreased the inflammatory cytokine IFNγ in a time-dependent fashion. This was associated with increased miR29a and miR146a (8 h), miR145 (24 h), and miR627 (48–72 h). These data indicate that miRNAs are important targets for vitamin D in both the innate (DC) and adaptive (T cell) immune systems. Future studies will aim to identify other vitamin D targeted miRNAs using unbiased screening approaches, and will explore the functional impact of these miRNAs on immune regulation by vitamin D.

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P46

Ionised calcium from blood gas measurements, often overlooked

Sushuma Kalidindi, Bonnie Dhas, Ananth Nayak & Biju Jose
Royal Stoke University Hospital, Stoke-on-Trent, UK.

Introduction
Evidence suggests that ionised calcium (iCa) and not total calcium is the physiologically relevant blood calcium component. Most blood gas (BG) analysers calculate iCa, but this is often ignored. We report our findings from a retrospective audit in medical in-patients and the potential benefit of this underused resource.
Methods
A retrospective audit of admissions to two general medical/endocrine wards during January and February 2016. Database included arterial or venous BG values, PTH, vitamin D, serum calcium, proton pump inhibitor (PPI). Clinical information was obtained from e-discharge letters.
Results
Of 270 patients admitted, 137 had one or more BG. 60 of the 137 (43.8%) had abnormal iCa; 19 (32%) had hypercalcemia (iCa > 1.27 mmolL-1) on admission, whilst 41 (68%) had hypocalcaemia (iCa < 1.15 mmolL-1). Of the 60 abnormal iCa, only 29 (48%) had laboratory calcium checked during admission. There was a significant correlation between iCa and adjusted Calcium (aCa) estimated in the lab ($R = 0.41$, $P = 0.003$). Proportion of patients with low, normal and high iCa on admission vs. discharge calcium (iCa or aCa) was 33%, 47%, 20% vs 14%, 74%, 12% ($P = 0.030$). Vitamin D/PTH estimation was undertaken in 7.3% of those with hypocalcaemia and 10% of those with hypercalcaemia. Magnesium was checked in 9 patients (22%) with hypocalcaemia. PPI use was observed in 42% of those with hypocalcaemia.
Discussion
iCa available in BG results continues to be overlooked. Three-quarters had mild hypocalcaemia; however this was acted upon or repeated in only half the cases. It is important that medical teams are encouraged to review the iCa performed on initial ABG and any follow up tests performed appropriately. Chronic PPI use can cause hypomagnesemia and consequent hypocalcaemia. Eleven patients in our study with unresolved hypocalcaemia were on PPI. We recommend all patients on PPIs with hypocalcaemia must have their magnesium checked.

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P47

Studies of an Autosomal Dominant Hypocalcemia type-1 (ADH1) associated calcium-sensing receptor (CaSR) mutation, Arg680Gly, provides insights into biased signalling

Caroline Gorvin[1], Valerie Babinsky[1], Anders Schou[2], Peter Nissen[3], Fadil Hannan[4] & Rajesh Thakker[1]
[1]University of Oxford, Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, Oxford, UK; [2]Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; [3]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark; [4]University of Liverpool, Institute of Ageing and Chronic Disease, Liverpool, UK.

The CaSR, a G-protein-coupled receptor that regulates extracellular calcium (Ca^{2+}_o), predominantly signals via G-protein-$\alpha_{q/11}$ ($G\alpha_{q/11}$), initiating IP_3-mediated intracellular calcium (Ca^{2+}_i) accumulation, and mitogen-activated protein kinase (MAPK) signalling. CaSR also activates MAPK signalling via $G\alpha_{i/o}$, or by associating with the scaffolding protein β-arrestin. CaSR gain-of-function mutations cause autosomal dominant hypocalcaemia type-1 (ADH1). Mutational analysis of *CASR* in a seven-year-old male and his father with ADH1 identified a novel heterozygous mutation (p.Arg680Gly) in both patients. The variant was functionally characterised in HEK293 cells transiently expressing WT (Arg680) or mutant Gly680 CaSRs using: a flow cytometry assay to measure Ca^{2+}_i; and a *SRE* luciferase reporter gene to assess MAPK signalling, in response to Ca^{2+}_o elevations. In contrast to reported ADH1 mutations, Gly680 had no effect on Ca^{2+}_i, but did significantly elevate MAPK responses. Measurements of the IP_3 breakdown product IP_1 showed no significant difference between WT and Gly680 expressing cells, confirming $G\alpha_{q/11}$- signalling was not responsible for elevated Gly680 MAPK responses. We hypothesized such differences could instead be due to biased signalling by $G\alpha_{i/o}$ or a G-protein-independent β-arrestin-mediated pathway. To test the former, we assessed the effect of the $G\alpha_{i/o}$-blocking agent pertussis toxin (PTx) on *SRE* reporter responses. PTx reduced *SRE* responses in both WT and Gly680 expressing cells to similar levels, indicating $G\alpha_{i/o}$ is not responsible for elevated MAPK signalling. To investigate G-protein-independent mechanisms we used a β-arrestin-1 siRNA, which had no effect on WT *SRE* reporter activity, but significantly reduced responses in Gly680 expressing cells. Structural homology modelling predicts Arg680 to form a salt bridge with CaSR transmembrane domain-7, which limits binding of β-arrestin; thus loss of this salt bridge would enhance β-arrestin binding and MAPK signalling. In conclusion, we report a CaSR mutation associated with hypocalcaemia that enhances MAPK signalling via a unique G-protein-independent mechanism involving β-arrestin-1.

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P48

Emergency management of hypercalcemia (an audit of SfE guidance in Oxford)

Haval Surchi & Paul Grant
NHS, Oxford, UK.

Background
Acute hypercalcaemia of biochemical and symptomatic nature is a relatively common emergency medical presentation. Its management has tended to vary significantly and this can affect patient's outcomes and length of hospital stay.
Aim
To assess the acute management of hypercalcaemia in relation to the new Society for Endocrinology guidance.
Method
A retrospective audit of all cases of hypercalcaemia admitted to Oxford University Hospitals emergency departments in 2015, using the SfE guidance as our audit standards.
Results
We discovered 41 patients had a coded diagnosis of hypercalcaemia. The average age ranging between 45 to 99 years old, 19 female patients and 22 male patients; 36% had a diagnosis of malignancy, 30% primary hyperparathyroidism and in 24% no cause for hypercalcaemia was identified. In terms of acute management, 90% of patients were treated with IV fluids and appropriately rehydrated, 35% received IV biphosphonates. Only 20% were reviewed by an endocrinologist; 100% had their renal function checked, but only 25% PTH and 25% vitamin D checked.
Discussion
Specific examinations in terms of assessment of fluid balance status, cognitive impairment and examination for underlying causes were sub-optimal in the majority of cases.
Conclusion
The majority of patients presenting with acute hypercalcaemia were well managed but there are obvious deficits and room for improvement in terms of adequate clinical assessment, ensuring the entire correct baseline investigations have been completed and arranging specialist Endocrinology review where appropriate. We plan to promote the SfE guidance locally in AE and AMU, update the trust guidance and medicine information leaflet through education, training and the electronic automated system (EPR).

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P49

The impact of primary hyperparathyroidism and its treatment on bone mineral density, bone mineral parameters, insulin resistance, body composition and quality of life – A prospective pilot study from India

Thomas V Paul, Shrinath Shetty, Nitin Kapoor, Sahana Shetty, M J Paul, Deepak Abraham, Pooja Ramakant, Joseph Dian & Nihal Thomas
Christian Medical College, Vellore, Tamil Nadu, India.

Aims
To study changes in bone mineral density (BMD), bone mineral parameters, metabolic profile, body composition and quality of life at base line and 6 months following parathyroidectomy, in subjects with primary hyperparathyroidism (PHPT).
Material and methods
This prospective study was conducted over 18 months with first 12 months of recruitment and next 6 months for follow-up. Sixty-eight patients with PHPT who underwent surgery were compared with 117 age, BMI and sex-matched controls. BMD, total fat mass and visceral adipose tissue (VAT) were assessed by a DXA scan at baseline and after 6 months. Other assessment included bone mineral parameters and bone turnover markers (BTMs). Thirty patients completed 6 months follow-up.

Results
Among the 68 patients (48 males, 20 females) with PHPT, the most common presentation was renal calculi (61.7%) followed by bony involvement (29.4%). There was a significant improvement in QoL and BMD on follow-up (at all sites) along with normalization of bone biochemistry and a decrease in BTMs ($P<0.05$). There was a significant increase in BMI, total fat mass and VAT ($P<0.05$). There was a non-significant increase in HOMA –IR.
Conclusion
There was a significant improvement in bone health and QoL following curative parathyroidectomy. A significant increase noted in BMI and VAT mass on follow-up needs to be further studied with regards to definite clinical outcomes like diabetes mellitus.

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P50

Impact of hepatitis B-related chronic liver disease and its therapy on bone health

Thomas V Paul, Nitin Kapoor, Kattiparambil Gangadharan Sajith, Sahana Shetty, Ashish Goel, Uday Zachariah & Chundamannil E Eapen
Christian Medical College, Vellore, Tamil Nadu, India.

Objective
To study the impact of HBV related chronic liver disease (CLD) and its treatment with Tenofovir on bone health in Indian subjects.
Methods
This cross-sectional study included men between 18 and 60 years and comprised of three groups: Group 1 was treatment naïve HBV-related CLD ($n=79$), Group 2 – those with HBV-related CLD on tenofovir for at least 1 year duration ($n=136$), Group 3 – normal age, sex and BMI-matched healthy controls ($n=58$). Bone biochemistry and bone mineral density were studied.
Results
More subjects in Group 1 and Group 2 were found to have more similar proportion of subjects with vitamin-D deficiency and a higher serum C-Terminal telopeptide but fared worse when compared to age, sex and BMI-matched controls (Group 3). A lower mean BMD and a higher prevalence of low bone mass at the spine and forearm was found in treatment naïve patients with hepatitis B related CLD (Group 1) whereas the femoral neck was most affected in tenofovir-treated patients (Group 2), these however were lower at all three sites when compared to Group 3 ($P<0.05$). Age, BMI and a high viral load ($>10,000$) emerged as significant risk factors for low bone mass at femoral neck.
Conclusion
The impact of hepatitis B related CLD and its treatment on bone health is significant. Bone health need to be periodically evaluated in these subjects especially in older men who are lean and have a higher viral load. However, long-term follow-up studies are needed to look at the impact of treatment for adverse bone health in these subjects.

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P51

An audit of the management of patients with hypoparathyroidism

Sameer Sighakoli & Trevor Wheatley
Department of Endocrinology, Brighton and Sussex University Hospitals, Brighton, UK.

Introduction
Primary Hypoparathyroidism is a rare endocrine disorder characterized by hypocalcaemia associated with an inappropriately low parathyroid hormone concentration. As currently there are no UK guidelines for the management of this condition, we performed an audit comparing our performance with published European guidelines (1). These state that

- All patients should have individualised targets for calcium and phosphate.
- Relevant biochemical variables should be monitored at least annually i.e. serum Calcium, phosphate, magnesium and vitamin D concentration, calcium phosphate product and 24 hour urine calcium excretion.
- Quality of life should be evaluated.
- Patients should be educated both to facilitate identification of hypocalcaemia and hypercalcaemia and to increase awareness of potential complications.

Methods
The notes of 18 patients aged 25–85 years with primary hypoparathyroidism for at least 1 year, managed in a single hospital by several consultants, were reviewed. Data was obtained from the clinical notes, the computerised endocrine database and the local pathology system.
Results
The most common aetiology was previous thyroidectomy. The target for calcium was stated in only 38.9% and for phosphate in only 11.1%. Serum Calcium and phosphate were measured annually in 83%. Serum Vitamin D was measured in 20% and magnesium in 28%. Annual 24 h urine calcium excretion was checked in 12.5%. In no patient was the calcium phosphate product recorded. Quality of life was informally assessed in 33%. No one had a formal assessment recorded. There was no recorded evidence of formal education.
Conclusion
It is evident that locally, the long term outpatient monitoring and recording of Primary hypoparathyroidism is inadequate. We have therefore constructed a ten point checklist of relevant variables to standardise management and facilitate further audit.

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P52

Continuous synthetic $PTH_{1\text{-}34}$ replacement therapy in the treatment of autosomal dominant hypoparathyroidism type 1

Vidhya Jahagirdar[1], Heather Stirling[2] & Sailesh Sankar[1]
[1]Department of Diabetes and Endocrinology, University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK; [2]Department of Paediatrics, University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK.

A young female with autosomal dominant hypoparathyroidism type 1 who had inherited the gene defect from her mother was under the care of paediatric endocrinologist. Since childhood she was on a large dose of calcium (elemental calcium 5 g) along with Vitamin D, potassium and magnesium replacements. Despite careful monitoring there was significant fluctuations in serum calcium levels which led to recurrent hospital admissions with hypercalcaemia and acute kidney injury or severe symptomatic hypocalcaemia. She presented frequently with hypocalcaemic seizures, one such event leading to fall, fracture of occipital bone and subdural haematoma. Ultrasound of the renal tract showed nephrocalcinosis and she had developed stable chronic kidney disease. At the age of 17 she was commenced on subcutaneous recombinant human parathyroid hormone ($rhPTH_{1\text{-}84)}$ 100 µg once daily which was switched to subcutaneous teriparatide ($rhPTH_{1\text{-}34}$) 20 µg twice daily. Despite this there was huge fluctuation in serum calcium levels. Hence she was commenced on continuous subcutaneous infusion of teriparatide via omnipod insulin pump. The daily calcium and Vitamin D requirement and the wide fluctuations in calcium were reduced and hospital admissions due to hypocalcaemic seizures were avoided. Although twice daily $rhPTH_{1\text{-}34}$ provides acceptable treatment of hypoparathyroidism in most patients, there is often nonphysiological fluctuation in serum calcium. To date, continuous subcutaneous delivery of $PTH_{1\text{-}34}$ via pump provides the closest approach to physiological replacement therapy for hypoparathyroidism.

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P53

Importance of bone mineral density care in transitional endocrine service

Karunya Yogeswaran[1] & Aftab Ahmad[2]
[1]University of Liverpool, Liverpool, UK; [2]Royal Liverpool University Hospital, Liverpool, UK.

Background
The principal cause for increased osteoporosis risk in young adults is the underlying endocrine condition that can severely compromise the prime bone building stage occurring during adolescence. As this could lead to a diminished quality of life from a relatively early stage, emphasis lies on correcting the endocrine condition with appropriately tailored management that can prevent its deterioration. Examples of treatments include replacing deficit hormones such as growth hormones or corticosteroids in hypopituitarism and HRT in hypogonadism.
Objective
The aims of this study were to assess: i) the appropriate treatment of the endocrine condition affecting the bone mineral density (BMD) and the degree of improvement in BMD since commencement of treatment, ii) the timely use of DXA scans to monitor BMD in the subject and iii) suitable follow-up times for

transitional endocrine service users in Royal Liverpool University Hospital against set standards.
Method
A retrospective study on patients seen from 1st January 2014 to 21st April 2016 was done using clinical letters available on the Trust's computer database. 66 patients were recorded, out of which 33 patients had underlying conditions affecting their BMD and required DXA scans.
Results
Out of the 33, 29 were on an appropriate treatment plan for their underlying condition. The remaining 4 patients had a justified reason for the treatment delay. Thirty (92%) out of 33 had a DXA scan done when necessary. All patient follow-ups had an average of at least once a year. Fifteen patients had normal BMD, 12 with osteopenia and 2 showing an osteoporotic range. 28% of patients undergoing treatment showed improvement in BMD and 38% showed no deterioration during the follow-ups. Ten new patients have follow-ups post study and therefore could not be assessed for BMD progression.
Conclusion
The results show that two-thirds of the patients undergoing treatment showed an improvement or no deterioration in BMD. Given this information it can be assumed that the ten new patients, if compliant with their medication should similarly show an improvement or no deterioration in their BMD. Overall this study concludes that a low BMD in young patients can be avoided given the underlying endocrine condition is appropriately treated.

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P54

Surgical management of primary hyperparathyroidism in East Sussex Healthcare NHS Trust (retrospective audit of patients had parathyroidectomy over 2 years in East Sussex NHS Trust)

Vanitha Karunakaran, Shakeel Ahmad, Simeen Ali, Rajesh Govindan, Paul Kirkland & Periasamy Sathiskumar
East Sussex Healthcare NHS Trust, Hastings, UK.

Retrospective audit of Patients had Parathyroidectomy over 2 years in East Sussex NHS trust; 73 patients had Parathyroid surgery for Primary hyperparathyroidism during this period. We have collected the data using case notes and hospital electronic records. Fifty-six patients were females and 17 were Males. Ninety-three per cent of patients were more than 50 years old. Common presenting symptoms were Lethargy (51%), bone pain (44%) and other symptoms were polyuria, polydipsia. Incidental finding in 15%. All patients had corrected calcium, parathyroid hormone levels and renal functions measured. Only 92% had tests for 24 h. urine calcium and Vitamin D levels. Cacl;crcl or fractional excretion were documented in only 12% of cases. Pre-operative localization of parathyroid adenoma was successful with ultrasound scan in 84%, SestaMIBI scan 94% and with SPECT CT 22%. All patients had both ultrasound parathyroid and sestaMIBI scan and only 75% has SPECT CT scan. Only 44% of patient had documented evidence of DEXA scan. Eighteen per cent of patients had evidence of osteoporosis. Ninety per cent of patients had preoperative localization of adenoma. Sixty-two per cent of patients had indications of permanent treatment. Successful removal of parathyroid adenoma was achieved in 95% of patients with normalization of post-operative calcium. Positive Correlation between pre-operative scans results and surgical finding were seen in 88% of patients. Six patients were persistently hypercalcemic post operatively. Three patients (4%) had evidence of vocal card paralysis. Ninety-five per cent of patients had follow up appointment once within 6 months after the surgery. Most patient had 24 h urine calcium measurement, but there is no documentation about cacl;crcl or fractional excretion of calcium measurements in the notes to exclude Familial hypocalciuric hypercalcemia. Thirty-eight per cent of patients not had international consensus guidelines criteria for permanent treatment. We have started Parathyroid multidisciplinary meeting to discuss patients before surgical treatment since.

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P55

Preoperative localisation for parathyroid surgery in primary hyperparathyroidism: a study to evaluate the clinical utility of different imaging modalities

Khyatisha Seejore[1], John Stephenson[2], Ei Mon Zin Tun[1], Dominic Martin-Hirsch[1], Khaled Al-Zwae[1] & Robert S Moisey[1]
[1]Department of Diabetes and Endocrinology, Calderdale and Huddersfield NHS Foundation Trust, West Yorkshire, UK; [2]University of Huddersfield, Huddersfield, West Yorkshire, UK.

Background
Primary hyperparathyroidism (PHPT) is caused by a solitary benign adenoma in 80–85% of cases, but may also be due to multi-gland or ectopic disease, hyperplasia, and rarely parathyroid carcinoma. Preoperative localisation studies are important to identify patients suitable for minimally invasive parathyroid surgery. The aim of this study was to evaluate the accuracy of ultrasound (US), parathyroid scintigraphy (MIBI) and computed tomography (CT) utilised in the preoperative setting in a district general hospital, with limited access to single photon-emission computed tomography (SPECT).
Methods
A retrospective study of 88 consecutive patients, who underwent parathyroidectomy for PHPT at a single unit between 2010 and 2014, was conducted. Patients were identified using discharge codes from locally held coding data. The sensitivity and specificity of each imaging modality was compared against histology as the gold standard.
Results
Eithty-two (93%) patients were first presentations of PHPT and six (7%) were relapses, requiring remedial surgery. At surgery, a solitary adenoma was identified in 72 (82%) patients, eight (9%) had parathyroid hyperplasia and one (1%) had parathyroid carcinoma. Preoperatively 100% of patients had US, 82 (93%) MIBI and 67 (59%) CT. Three (3%) had single image modality, 30 (34%) had two and 43 (49%) had three imaging modalities. 43 (53%) parathyroid adenomas were identified with US, 39 (52%) with MIBI and 31 (67%) with CT. Combined US/MIBI were carried out in 82 patients, yielding a sensitivity of 63%. Paired US/CT had a sensitivity of 75% in 52 patients. 21 patients (24%) with inconclusive imaging were referred to tertiary centres for SPECT which successfully identified ten patients. Thirteen patients (15%) underwent neck exploration due to failure of localisation studies. An overall cure rate of 92% was achieved.
Conclusion
Combined US/CT is superior for accurate preoperative localisation of solitary parathyroid adenomas over any single or combination imaging modality.

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P56

An audit of vertebral fracture assessment (VFA) selection criteria: Implications for the service and impact on clinical decision making

Aaron Dehghan, Henrietta Brain & Malgorzata Magliano
Stoke Mandeville Hospital, Buckinghamshire, UK.

Background and aims
Vertebral fractures are the most common type of osteoporotic fracture but approximately three quarters remain undiagnosed. Densitometric VFA is a recognised imaging modality for vertebral fracture identification. The International Society for Clinical Densitometry (ISCD) has published separate criteria in 2007 and 2013 to identify patients suitable for VFA. The aim of this audit is to determine the potential impact on the service of introducing VFA with each set of criteria and to analyse whether this would have any impact on clinical decision making.
Methods
One hundred consecutive patients underwent DEXA-BMD and completed detailed questionnaires regarding osteoporosis risk factors. This information was used to formulate individual management plans, based on the trust's osteoporosis guidelines. Each patient's questionnaire was then independently assessed as to whether they met the ISCD 2007 and/or 2013 criteria. From those selected, we used trust guidance to assess whether their immediate clinical management would change if a vertebral fracture was hypothetically identified.
Results
Out of the 100 patients, 69 met the 2007 criteria and 42 the 2013 criteria. The percentage that would have their immediate clinical management changed if a vertebral fracture was identified would be 40.6 and 42.9% for the 2007 and 2013 cohorts respectively.

Conclusions
A study published in 2014 suggests that approximately 25% of eligible patients undergoing VFA would have a vertebral fracture. Using this paper, we were able to estimate that from the 69 patients meeting the 2007 criteria, approximately 16 would have vertebral fractures identified and of these, six patients would have their immediate decisions changed. For the 2013 criteria, 11 out of the 42 patients would have a vertebral fracture identified and five would have their immediate decisions changed. Combining our results with supporting literature led to the recommendation that the 2013 criteria should be introduced at the trust.

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P57

Initial experience of a newly established intra-operative PTH service

Leoni Lekkakou[1], Leelavathy Kandaswamy[1], Alain Rolli[2], Claire Ford[2], Andrew Garnham[3], Catherine Spinou[4], Lenny Liew[4] & Harit Buch[1]
[1]Department of Diabetes and Endocrinology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK; [2]Blood Sciences Department, Royal Wolverhampton Hospitals NHS Trust., Wolverhampton, UK; [3]Department of Surgery, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK; [4]Department of ENT Surgery, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK.

Background
A minimally invasive approach to primary hyperparathyroidism (PHPT) is equivalent to bilateral exploration when intraoperative parathyroid hormone (iPTH) monitoring is used. We have recently established an iPTH service jointly with Surgical and Clinical Chemistry teams and the aim of the study was to evaluate our initial results with its use.
Patients and methods
We collected data from 18 operations for PHPT from October 2015, including one re-exploration. The patients had mean age 59 ± 15 years, calcium 2.96 ± 0.4 mmol/l, PTH 27.19 ± 21.48 pmol/l. All patients had ultrasound and dual-isotope 99mTc-MIBI/123I subtraction with SPECT/CT acquisition scans; six patients had discordant scans. Time-points for iPTH sampling were: before the skin incision (pre-incision S1), just before the blood supply to the gland is ligated (pre-excision S2), 20-min post-excision (post-excision S3). PTH drop of $>50\%$ in S3 from S1 or S2 was used as the criterion to suggest cure. In absence of point-of-care testing, we used Elecsys-E411 analyser (Roche) reserved for PTH-testing after a prior alert. Turnaround time was 35 min.
Results
Seventeen (94%) patients had $>50\%$ PTH drop and in all patients cure was confirmed biochemically and histologically. All 17 patients had $>50\%$ drop in both S1 and S2. One patient had $<50\%$ drop and required further exploration but this failed to identify an adenoma and biochemistry confirmed absence of cure. All six patients with discordant scans had $>50\%$ drop and were cured.
Conclusion
In our initial experience iPTH had a high success rate in predicting successful surgical outcome, including in patients with discordant scans, reducing the need for wider exploration. It correctly indicated the need for further exploration in the patient with $<50\%$ PTH drop although it did not help the surgeon to identify the culprit gland and cure was not achieved. Use of two pre-excision samples may not be necessary although a larger study is needed to confirm this.

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P58

Procollagen N-terminal propeptide in children

Mariana Costache-Outas[1,2], Camelia Procopiuc[3], Cristina Dumitrescu[3], Andra Caragheorgheopol[3], Cosmina Raluca Costache[5] & Simona Fica[1,4]
[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [2]Coltea Clinical Hospital, Bucharest, Romania; [3]"CI Parhon" National Institute of Endocrinology, Bucharest, Romania; [4]"Elias" Emergency Hospital, Bucharest, Romania; [5]Dr. Ioan Cantacuzino Clinical Hospital, Bucharest, Romania.

Aim
Somatic growth results from the generation of new support and connective tissue. Since collagen is the major protein constituent of connective tissue, its synthesis must be a prerequisite for the normal growth. The aim of the study was to determine age-related reference intervals for P3NP, a collagen – formation marker in a group of normal height prepubertal children and to compare to IGF1 levels.
Subjects
Forty-three prepubertal children, male ($n=26$) and female $n=(17)$ participated in this study. Their height and weight were recorded. All the children have normal height.
Methods
For quantitative measurement of P3NP, we used a research kit with sandwich enzyme immunoassay with a detection limit of 62.5 pg/ml. P3NP values were analyzed for normality using Shapiro–Wilk test. Tukey test was used to identify outliers. We divided the prepubertal period into three intervals for each sex: 4 to 5-year old, 6 to 7 year old, and 8 to 9 year old.
Results
Age was determinant for the standard deviation score but not for the mean of P3NP values for each age group. A *t*-test was used to compare means and SDS for each sex and age-group. There were similar values for P3NP between males and females in the group of age 4 to 5-year old and 6 to7 years old. There was a trend towards significant higher values for P3NP in the girls when compared with the male in the age group of 8 to 9-year-old. No correlation between IGF1 and P3NP was fond.
Conclusion
Higher values for P3NP in girls compared to males in the group of 8 to 9 year old can be explained by an earlier onset of puberty in girls associated with the increase during early puberty of collagen markers.

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P59

Primary hyperparathyroidism and concomitant vitamin D deficiency: Study of diagnosis and management outcomes

Uzma Khan, Ahmed Al-Sharefi, Praveen Partha, Shafie Kamaruddin, Giridhar Tarigopula & Paul Peter
County Durham and Darlington NHS Foundation Trust, Durham, UK.

Introduction
Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder; its evaluation includes biochemical investigations and imaging studies prior to surgical intervention. Imaging is advised as an aide to surgery and not for diagnostic purposes. Coexistence of PHPT and vitamin D deficiency is common; however, the exact nature of the relationship (causal vs secondary) is not clear.
Subject and methods
We conducted a retrospective review of data of 122 patients referred for sestamibi parathyroid scan over a period of 2 years. Objectives included review of the diagnosis, outcomes, associated vitamin D deficiency and appropriateness of imaging requests.
Results
Of 122 patients, 101 (82.78%) were diagnosed as PHPT. Ninety-eight (80.33%) were operated and 86 (87.76%) had good outcome with no recurrence. Out of 74 patients with PHPT who had their vitamin D levels checked prior to imaging, 26 (35.13%) had vitamin D insufficiency (<20 ng/ml or 50 nmol/l) and 20 (27.02%) were vitamin D deficient (<10 ng/ml or 25 nmol/l). Secondary causes of hyperparathyroidism were found in 17 patients; 15 were due to vitamin D deficiency and 2 were related to chronic kidney disease (CKD). Other causes of hypercalcaemia included 1 patient each with familial hypocalciuric hypercalcaemia (FHH), hypercalcaemia of malignancy and tertiary hyperparathyroidism. Nineteen patients (15.57%) were inappropriately referred for imaging studies and mostly included cases of secondary hyperparathyroidism (except 1 each of FHH and hypercalcaemia of malignancy).
Conclusion
Concomitant vitamin D deficiency or insufficiency is common in patients with PHPT and the combined prevalence was estimated as 62% in our study. To avoid unnecessary imaging in patients with PHPT, we recommend that imaging studies should be arranged only by the endocrinology team, after biochemical confirmation and once surgery is planned.

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P60

Would a 10% fracture risk threshold for direct access to dual energy densitometry (DXA) exclude patients with low bone mineral density?

Clare Wilson, Paul Loughrey, Bernie Cummings, Colette McNally & John Lindsay
Osteoporosis and Bone Metabolism Service, Musgrave Park Hospital, Belfast, UK.

The SIGN guideline group recently suggested a fracture risk threshold of 10% as an indication for DXA. Patients who do not have a 10 year fracture probability of 10% or more would therefore not meet the criteria for direct access to DXA. In order to assess whether implementing these guidelines would impact overall management, we undertook a prospective audit of our direct access DXA and health promotion service. Charts from 61 consecutive patients were reviewed (54F/7M, Mean age 60.4 years). 18 patients had a history of fragility fracture at time of referral. A range of clinical risk factors (CRFs: 0 $n=4$; 1 $n=28$; 2 $n=15$; 3 $n=8$; >3 $n=6$) were observed. Treatments at time of referral were noted and included calcium/vitamin D ($n=17$), bisphosphonate ($n=1$), or a combination of both ($n=2$). None of the 61 referrals to our service included a prospective FRAX score. Retrospective FRAX assessment showed 27/61 patients had a $<10\%$ probability of 10 year major fracture risk and would not have met SIGN criteria for DXA. However, direct access DXA identified 25 patients with osteopenia and 18 with osteoporosis. 16/61 patients with low bone mineral density (BMD) might therefore have been excluded from accessing the DXA/ health promotion service using SIGN thresholds. National Osteoporosis Guideline Group (NOGG) management recommendations for our cohort included DXA (30/61), lifestyle advice (18/61) or pharmacological therapy (10/61). This audit has shown low adherence to NICE guidelines for assessment of fracture risk in those referred for direct access DXA. Significantly, our data has highlighted that some patients with modifiable low BMD would have been excluded from scanning using proposed SIGN guidelines on fracture risk thresholds for access to DXA.

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P61

FGF23, iron and vitamin D metabolism in chronic kidney disease

Isabelle Piec[1], Allison Chipchase[2], Holly Nicholls[1], Jonathan Tang[1], Christopher Washbourne[1] & William D Fraser[1]
[1]University of East Anglia, Norwich, UK; [2]Norwich and Norfolk University Hospital, NHS Trust, Norwich, UK.

Introduction
In CKD, net effects of declining kidney function and increasing FGF23 (and PTH) concentrations on vitamin D catabolism and iron metabolism are not clear.
Objectives
Compare the Biomedica to the Immutopics' immunoassay for measurement of cFGF23. Determine the relationship between iron status; vitamin D and intact FGF23 (iFGF23) and c-terminal (cFGF23) concentrations in blood.
Method
Samples from routine care and a subset of patients with CKD (eGFR <70) were used in this study and compared to healthy controls. We used ELISA for measurements of cFGF23 (Biomedica, Vienna, Austria), cFGF23 and iFGF23 (Immutopics Inc., CA, USA). Ferritin, iron and transferrin were measured on a COBAS 6000 (Roche Diagnostics). 25(OH)D and 24,25(OH)2D3 were measured by LCMS.
Results
Biomedica cFGF23 ELISA showed a good correlation ($n=125$; $r=0.966$) to the Immutopics' assay, however, a bias became apparent in the highest range of cFGF23. In CKD, we observed a parallel increase of iFGF23 and cFGF23 concentrations as eGFR decreased. Significant negative correlations were observed between cFGF23 and both iron concentration ($r=-0.44$, $P<0.05$) and transferrin saturation ($r=-0.434$, $P<0.05$). Concentrations of 25(OH)D and 24,25(OH)2D3 decreased by 34 and 68% respectively while the ratio 24,24(OH) 2D3:25(OH)D increased by 89% between healthy and CKD4.
Conclusion
We observed a negative correlation between FGF23 and iron metabolism suggesting that metabolism and/or excretion of FGF23 in CKD patients might be an iron dependent mechanism. We observed a strong vitamin D deficiency in CKD patients associated with a decrease in 24,25(OH)2D3 metabolite concentration. The ratio of 25(OH)D: 24,25(OH)2D is markedly elevated and increases as CKD progresses suggesting a relatively lower catabolic rate of 25(OH)D towards 24,25(OH)2D metabolite as CKD progresses. This may be in an attempt to allow relatively greater synthesis of 1,25(OH)2D to maintain its biological effects.

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Clinical Biochemistry

P62

Burden of major sodium and calcium abnormalities in the non-ITU adult inpatient population of a large two-site university hospital

Philip Jones[1], Yaasir Mamoojee[2], Dermot Neely[2] & Richard Quinton[2]
[1]Newcastle University, Newcastle-upon-Tyne, Tyne and Wear, UK; [2]Royal Victoria Infirmary, Newcastle-upon-Tyne, Tyne and Wear, UK.

Background and aims
Electrolyte imbalance is common among hospital inpatients, reflecting severity of underlying illness, but also independently contributing to excess morbidity and mortality. However, studies have largely been retrospective, with incomplete data capture. We prospectively evaluated the prevalence of major Na and Ca disorders among inpatients at the Newcastle-upon-Tyne Hospitals.
Method
With approval of the Information Guardian, we used Laboratory Medicine *Cognos* software to conduct a proactive audit (28 January–28 February 2016), with data released twice-weekly, typically enabling us to complete the dataset acquisition through eRecord 'add-on requests' for stored serum. Inclusion criteria were: serum Na ≤ 120 or ≥ 160 mmol/l, serum adjusted Ca ≤ 2.00 or ≥ 2.79 mmol/l. Patients aged <18 years, on ITU, or maternity unit were excluded.
Results
114/4238 inpatients satisfied our criteria for major electrolyte imbalance. The most common abnormality was hypocalcaemia (1.3%) and the least common was hypernatremia (0.1%). 18 patients had hyponatraemia (0.4%) whilst 36 had hypercalcaemia (0.9%). Review of on-call logs over the corresponding period allowed us to estimate that $<¼$ had been discussed with Endocrinology. Twenty-two patients (19%) had persistent electrolyte disturbance at the end of the study; all Ca-related disorders. The overall mortality associated with these major electrolyte abnormalities was 18% (83% for hypernatraemia; 11% for hyponatraemia). The most common cause of hyponatremia was medication-related, whilst renal failure and malignancy accounted for the majority hypocalcaemia and hypercalcaemia, respectively. Vitamin D deficiency (pre-defined as <50 nmol/l) was coexistent in 31% of our patients with calcium disorders.
Conclusions
The incidence of major abnormalities among the general (non-ITU, non-maternity) adult inpatient population was 27/1000 inpatients per month, of which 19% were persistent. However only 21% were referred to Endocrinology. Given the high mortality of these electrolyte imbalances, the development of an eRecord alert system targeting early input from Endocrinology needs further exploration.

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P63

Pheochromocytoma and Paraganglioma audit

Ravikumar Ravindran, Thomas Dacruz & Aled Rees
University Hospital Wales, Cardiff, UK.

Aim
To assess whether using urine catecholamines as a second line investigation has affected clinical decision making in patients with suspected pheochromocytoma and paraganglioma.
The need for the audit
New society of endocrine guidelines in June 14, have recommended using urine metanephrines as the initial screening test for PPGL. Current practise at University Hospital Wales is to offer urine catecholamines as the second line test to patients with a genetic predisposition to pheochromocytoma or those with urine metanephrines above 2/3rd of the upper limit.
Data for the audit
Ten years of data of patients who had both metanephrines and catecholamines checked was obtained from the laboratory computer system. The patients were divided into two groups, one with raised urine metanephrines (55/95 patients) and the other with raised urine catecholamines (40/95 patients). The raised urine metanephrine group included five patients who had both raised metanephrines and raised catecholamines.
Results
- 13% (13/95 patients) with raised metanephrine levels had a diagnosis of PPGL. This included five patients who had both raised metanephrines and catecholamines
- **None** in the raised catecholamine group alone (40/95 patients), had a diagnosis of PPGL

The audit showed that metanephrines (urine or plasma) alone can be used for diagnosing pheochromocytoma's and paraganglioma's.

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P64

Management of hyponatraemia in acute hospital admissions: Effect on length of stay, readmission and mortality

Aditi Sharma, Parizad Avari, Jasmeet Singh, Monica Anyasodor, Julia E. Ostberg & Senan Devendra
Watford General Hospital, West Hertfordshire Hospitals NHS Trust, Watford, UK.

Objective
Hyponatraemia is the most common electrolyte disturbance encountered in patients – yet its management remains challenging and variable. We audit the management of hyponatraemia in a busy district general hospital, focusing on length of stay (LOS), readmissions and mortality.
Methodology
A retrospective analysis was carried out of 30 consecutive inpatients alerted by the hospital biochemistry department with a sodium concentration of $\leq$135 mmol/l. The results were grouped into: mild (130–135 mmol/l), moderate (125–129 mmol/l) and severe ($<$125 mmol/l), Investigations assessed included: paired serum and urine osmolalities, urine sodium, cortisol, TSH, fluid status, fluid balance and medicines review. Outcomes assessed included LOS, readmission and mortality rate.
Results
Thirty patients (12 male, 18 female) with a mean age ($\pm$SD) of 75 ($\pm$16) years were included. The majority of patients (90%) had moderate to severe hyponatraemia with an equal representation of acute versus chronic hyponatraemia. Two thirds of patients with hyponatraemia were on medications exacerbating this, with only half of these having their offending drugs withheld. The full diagnostic work-up was only carried out in 10% of patients. Out of the thirty patients, three patients (10%) were admitted to ITU and four (13%) died in hospital. The median LOS was 12 days (IQR 7.75–24.25). In comparison, the hospital median LOS for all other acute admissions (both medical and surgical) during the same period was 1 day (IQR 0–5; $P<0.001$). Similarly the mortality and readmission rates between the hyponatraemia patients and other acute hospital admissions were 13% versus 3.6% ($P=0.008$) and 26% versus 14% ($P=0.061$) respectively.
Conclusion
Hyponatraemia management remains challenging with a high variability and poor adherence to the European guidelines. In addition, we have demonstrated that hyponatraemia is associated with longer LOS and higher rates of mortality and readmission in patients. A specific hospital protocol on hyponatraemia management is being introduced to improve variability in diagnostic work-up.

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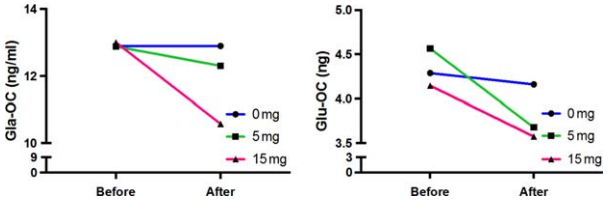
P65

Osteoporosis and low-dose prednisolone: Is there a link? Insights from bone turnover markers

Yvette Ang[1], Adam Leckey[1], Sirazum Choudhury[1], Alan Courtney[2], Tricia Tan[1] & Karim Meeran[1]
[1]Imperial College London, London, Greater London, UK; [2]Imperial College Healthcare NHS Trust, London, Greater London, UK.

Prednisolone has been reported to have greater deleterious effects on bone turnover than other glucocorticoids, although the evidence for this is confounded by the effects of higher dose prednisolone, as used in conditions such as asthma. We hypothesise that a physiological replacement dose of prednisolone will have a less dramatic effect on bone than has previously been suggested, and might be safer than hydrocortisone for replacement in adrenal insufficiency. We investigated the effect of low-dose prednisolone on bone turnover markers including carboxylated osteocalcin (Gla-OC), undercarboxylated osteocalcin (Glu-OC), procollagen type 1 N-terminal propeptides (P1NP) and N-terminal telopeptide of type 1 collagen (NTx). Participants were given an oral dose of prednisolone (0–15 mg) at 8 AM. Serum Gla-OC, Glu-OC, P1NP and urine NTx levels were measured immediately before and 24 h after the dose was taken. There was significant suppression in the Gla-OC concentrations taken immediately before the dose compared to 24 h after ($P<0.01$), with lower values 24 h after the prednisolone dose (median 10.6 ng/ml, interquartile range 10.1–11.2 ng/ml) compared to the baseline Gla-OC levels (median 12.7 ng/ml, interquartile range 10.7–12.9 ng/ml). There was also a significant suppression of Glu-OC concentrations with lower values 24 h after the prednisolone dose (median 3.6 ng/ml, interquartile range 3.5–3.8 ng/ml) compared to the baseline Glu-OC levels (median 4.3 ng/ml, interquartile range 4.1–4.5 ng/ml) ($P<0.01$). There was no significant change in NTx/creatinine ratios and P1NP concentrations after 24 h. This suggests that osteoblast production of osteocalcin is suppressed after glucocorticoid treatment. Gla-OC and Glu-OC are biomarkers that can be utilised to monitor patients' acute response to prednisolone in a larger study.



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P66

Audit of plasma catecholamines vs. plasma metanephrines: experience at a tertiary endocrine referral centre

David R Taylor[1], Alex Alexander[2], Adam Schweitzer[2], Colin Stone[1], Ben Whitelaw[3], Simon Aylwin[3] & Royce P Vincent[1]
[1]Department of Clinical Biochemistry, Viapath Analytics, King's College Hospital, London, UK; [2]CAPA Interns, King's College Hospital, London, UK; [3]Department of Endocrinology, King's College Hospital, London, UK.

Background
Phaeochromocytoma and paraganglioma (PPGLs) are rare neuroendocrine tumours arising from the adrenal medulla and paraganglia. Biochemical assessment relies on demonstrating elevated concentrations of catecholamines and their metabolites. Analytical methods for catecholamine and metanephrine measurement vary in sensitivity and specificity. We reviewed our biochemical work-up in order to optimise patient diagnosis.
Methods
This retrospective audit reviewed adult patients in whom simultaneous plasma catecholamine and metanephrine measurements were available from 2013 to 2015. Catecholamines and metanephrines were analysed by high-performance liquid-chromatography with electrochemical detection and liquid chromatography-tandem mass spectrometry, respectively. Samples (catecholamines: lithium heparin with stabilisation solution and metanephrines: EDTA) were collected using established protocols. Hospital IT systems were used to obtain relevant information (investigations, multi-disciplinary meeting (MDM) outcomes and management).
Results
In total, 110 patients with paired catecholamine/metanephrine measurements had MDM review. Of these, 28 had elevated catecholamines with normal metanephrines and one elevated metanephrines but normal catecholamines. Forty-four (17M) patients aged 60 (47–68) [median(IQR)] years had histological diagnosis (23 phaeochromocytoma, 2 paraganglioma, 8 post-op PPGLs and 11 benign/other lesions). In those without histology, MDM ruled out PPGLs in 18 with elevated catecholamines but normal metanephrines. In histologically-confirmed disease, three benign lesions, two adrenocortical carcinoma and one low-grade PPGL had elevated catecholamines but normal metanephrines, along with three PPGL under follow-up. One PPGL was biochemically silent. In three samples catecholamines couldn't be quantified due to analytical interference. PPGLs had higher catecholamines and metanephrines vs non-PPGLs: adrenaline 0.45 (0.17–1.38) vs 0.20 (0.11–0.24) [ref $<$ 0.45 nmol/l); noradrenaline 11.24 (3.46–16.42) vs 1.94 (1.68–3.46) [0.00–2.50 nmol/l]; metadrenaline 305 (113–2120) [80–510 pmol/l] vs 117(81–232) and normetadrenaline 5669 (1433–20,329) vs 277(208–378) [120–1180 pmol/l] (all $P<0.05$)]. Sensitivity, specificity, PPV and NPV for catecholamines vs. *metanephrines* were; 96/*92*, 61/*100*, 77/*100* and 92/*90,* respectively.
Conclusions
Plasma metanephrines are superior to catecholamines due to better specificity, simpler sample collection and minimal analytical interference. The MDM approach is critical in biochemical assessment of PPGLs.

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P67

Three minute run time LC-MS/MS method for separation and quantifying 25-hydroxyvitamin D from C3-epimers

Carl Jenkinson[1], James Bradbury[2], Angela Taylor[1], Shan He[2], Mark Viant[3] & Martin Hewison[1]
[1]Institution of Metabolism and Systems Research, Birmingham, UK; [2]School of Computer Science, Birmingham, UK; [3]School of Bioscience, Birmingham, UK.

Vitamin D exists as two forms; D3 (UV) and D2 (plant derived). Measuring the metabolite 25-hydroxyvitamin D (25OHD) is routinely applied in research and clinical laboratories to assess vitamin D status. The Institute of Medicine and Society for Endocrinology have previously set recommended vitamin D guidelines based on combined 25OHD3 and 25OHD2 serum concentrations. In order to achieve accurate quantitation of these metabolites, the respective C3 epimers must be separately quantified owing to varying activities between isoforms. Liquid chromatography tandem-mass spectrometry (LC-MS/MS) is considered the gold standard approach for measuring 25OHD metabolites, owing to potential interferences of the C3 epimers in other analytical techniques such as immunoassays. To account for the role of C3 epimers and accurately measure 25OHD in high throughput research and clinical analysis, we have developed an LC-MS/MS method to quantify 25OHD3 and 25OHD3 along with their C3 epimers in a total run time of three minutes. Method development and analysis was performed on a Waters AQUITY UPLC coupled to a Waters TS-MS mass spectrometer. A Phenomenex Lux cellulose-3 chiral column (100 mm, 2 mm, 3 µm) was used for separation, the mobile phase was water and methanol 0.1% formic acid. The optimised method achieved retention times of the following analytes; 25OHD3 – 1.51 min, 3-epi-25OHD3 – 1.82 min, 25OHD2 – 1.55 min, 3-epi-25OHD2 – 1.97 min. Further accuracy of 25OHD3 was achieved through separating the isobar 7αC4. Post column infusion was performed during method validation to ensure no matrix interference. Regression analysis was performed with this method comparing two previously developed LC-MS/MS methods for measuring multiple vitamin D metabolites with longer run times using a cohort of human serum samples. A strong regression was observed between methods ($R^2=0.987$ and 0.929) and no significant bias was observed between 25OHD3 measurements (0.76% [95% CI 1.888–3.403, $t=0.937$, $P=0.768$] and 1.38% [95% CI 2.864–5.614, $t=0.935$, $P=0.995$]). Application of this method could significantly enhance throughput of 25OHD measurements in research and clinical laboratories.

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P68

An audit of the acute investigation and management of hyponatraemia in a hospital population

Kate Hutchinson, Rasheeta Sivapackianatham, Susan Gelding & Ahmed Siddiqi
Barts Health NHS Trust, London, UK.

Introduction
Hyponatraemia is the commonest inpatient electrolyte abnormality and its severity correlates with inpatient mortality, length of stay and use of hospital resources. Frequently, hyponatraemia is not sufficiently acknowledged in the acute medical setting. The aim of this audit was to evaluate the investigation and management of hyponatraemia in a district general hospital.
Methods
Seventy-seven hyponatraemic patients (Na < 135 mmol/l) were identified retrospectively over six consecutive months from medical admissions take lists, where the inclusion criteria were those coded as 'hyponatraemia'. The cohort comprised 12 males and 15 females, with a mean age of 70 years. Key diagnostic investigations to determine the cause of hyponatraemia were evaluated and subsequent management was reviewed. The data were compared with the standard investigations and management of the European Society of Endocrinology guidelines.
Results
7.4% of the cohort had mild hyponatraemia (130–135 mmol/l), 18.52% had moderate hyponatraemia (125–129 mmol/l), 74.07% had severe hyponatraemia (< 125 mmol/l). Only 48.15% were assigned an aetiology, the commonest being drug-induced hyponatraemia. Urinary sodium, plasma osmolality and urinary osmolality were measured in 7 (25.93%), 12 (44.44%) and 8 (29.63%) patients, respectively. Serum cortisol and thyroid function tests were measured in 10 (37.04%) and 21 (77.78%) patients, respectively. 81.48% were discharged hyponatraemic (< 135 mmol/l), with half of these less than 130 mmol/l. None of the patients were referred to endocrinology (excluding two who were admitted under the endocrinology take). Only one patient had a follow-up blood test to re-check serum sodium post discharge.
Discussion
In a hospital population, only a minority of patients with hyponatraemia were appropriately investigated according to standard guidelines. This audit has identified hyponatraemia, a clinical entity associated with prolonged hospital stay, as poorly managed. Education of all medical staff, accompanied by practical guidelines highlighting investigation and management, are pivotal.

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P69

Evaluating the feasibility of using simulation to teach junior doctors the management of endocrine emergencies

Kate Hutchinson, Kirun Gunganah, Meera Ladwa & Susan Gelding
Barts Health NHS Trust, London, UK.

Background
Endocrine emergencies such as hyponatraemia and hypercalcaemia commonly present during unselected medical on-call. However, in our hospital a questionnaire survey of trainees revealed lack of confidence and preparedness in managing endocrine emergencies. 18 trainees responded (12 Foundation Year 1 (FY1), 1 Foundation Year 2 (FY2), 5 Core Medical trainees (CT1) reporting lack of confidence and preparedness in managing endocrine emergencies. 76.92% of FY1 doctors felt strongly underprepared and under confident. All respondents felt they would benefit from more local teaching on the management of endocrine emergencies. 96.29% listed simulation as a preferred teaching method. We therefore decided to evaluate the use of simulation as a tool to improve junior doctors' confidence, knowledge and preparedness in managing endocrine emergencies.
Methodology
Eight trainees (six FY and two CT1) participated in a three hour Simulation Training session, involving the endocrine emergencies: severe hyponatraemia, hypocalcaemia, hypercalcaemia and thyroid storm. The simulation was designed to be high fidelity, using a SimMan 3G manikin. Each scenario was followed by a debrief, facilitated by an endocrinology registrar and consultant, reflecting on both human and clinical factors. Participant feedback was collected following the session using a Likert scale.
Results
All eight trainees strongly agreed the scenarios were relevant to their training, interesting and interactive. All strongly agreed the session improved their knowledge and confidence in managing endocrine emergencies. All trainees felt that simulation training was better than traditional modes of teaching for learning the management of endocrine emergencies.
Conclusion
Simulation training was shown to be a feasible and popular method for teaching junior doctors management of endocrine emergencies. Although it is difficult to assess whether this simulation teaching will impact upon clinical outcomes, candidates reported improvements in their awareness of human factors and clinical knowledge of endocrine emergencies. This may have positive implications for future patient care.

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P70

Red blood cell folate vs serum folate: Which one to measure?

Yun Trull & Ibrahim A. Hashim
UT Southwestern Medical Center and Parkland Memorial Hospital, Dallas, Texas, USA.

This study aimed to establish the optimal cut-off decision point for Folate and B12 levels. Retrospective review of serum, RBC folate as well as B12 test results performed at our hospital for the period April 2012 up to May 2016 were analysed for concordance.
With data analysis of around serum folate and B12 20,000 results, the new cut-offs for low values are tentatively set to be 5.5 ng/ml and 178 pg/ml. The percentages of deficiencies in our patient population are calculated to be 1.6 and 1.8% for serum folate and B12 respectively, based on the new cut-offs. The new serum folate cut-off also harmonizes the percentage deficiency (5.9%) in selected patient population with both serum and RBC folate measured within 1 week ($n=51$).

While in an era of folate fortification, its deficiency in general population is expected to be very low (<1%). With the current reference cut-offs (serum folate 7.3 ng/ml, RBC folate 366 ng/ml), it is found that 5.8% of our patients' population has low serum folate, 8.3% has low RBC folate. It is also noted that there is a discrepancy between the percentages of low serum and RBC folates resulted within one week from the same patients ($n=51$): 13.7% vs 5.9%. With B12 reference range of 211–911 pg/ml, 3.7% of our patients are found to be B12 deficient.
With the low percentage deficiency in our patient population the following recommendations will be proposed: first, RBC folate testing is not warranted because serum folate testing provides the same differentiating power. Second, due to the low percentages of deficiencies in folate or B12, empirical supplementation is recommended.

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P71

Evaluation of diagnostic cut-offs for aldosterone-renin ratio using iSYS assays for aldosterone and direct renin

Charlotte Fairclough, Anna Milan & Suzannah Phillips
Liverpool Clinical Laboratories, Liverpool, UK.

Introduction
'Primary Aldosteronism Detection, Diagnosis and Treatment Guidelines' from the Endocrine Society (2008) recommend the use of the aldosterone- renin ratio (ARR) to detect primary aldosteronism (PA) in patient groups with high prevalence of PA. The guidelines suggest cut-offs specific to assay type and measurement units. The department of Clinical Chemistry and Metabolic Medicine at RLBUHT recently moved to a direct renin method (iSYS, Immunodiagnostics) and the calculated ARR and aldosterone measurement (iSYS, Immunodiagnostics) was evaluated for routine reporting in patients investigated for PA.
Method
74 patient samples were measured by direct renin assay. 43 patient samples were eligible for inclusion in the evaluation after those with non-numerical results and no concurrent aldosterone results were excluded. The concurrent aldosterone result was taken for each patient from the laboratory information management system (Telepath, iSOFT) and the ARR determined. Clinical information for each patient sample was also collected. Samples were split into categories determined by the method specific cut-off values for ARR and aldosterone (from Immunodiagnostics).
Results
32 samples were categorised as 'PA unlikely', (ARR <30 pmol/mIU). Eight samples were categorised as 'Consistent with PA (confirmatory testing suggested)', (ARR >30 pmol/mIU, aldosterone >400 pmol/l). Three samples were categorised as 'PA not excluded', (ARR >30 pmol/mIU, aldosterone 250–400 pmol/l). No samples were categorised as 'PA unlikely (aldosterone not in range associated with PA)', (ARR >30 pmol/mIU, aldosterone <250 pmol/l). Mean ARR = 29 pmol/mIU, median = 49 pmol/mIU for all samples (range = 1–279 pmol/mIU). All samples had appropriate clinical details including 'hypertension', and 'adrenal lesion'.
Conclusion
The selected cut-off values for ARR appear appropriate for use although we were unable follow up patients and thus cannot determine sensitivity/specificity. Most samples had a normal ARR of <30 pmol/mIU. Clinical information indicates that most requests are appropriate in reference to the guidelines.

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P72

Changes in serum 25-hydroxyvitamin D, 24,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D in response to three vitamin D3 supplementation regimens

Jonathan Tang[1], Holly Nicholls[1], John Dutton[1], Isabelle Piec[1], Christopher Washbourne[1], Lanja Saleh[2], A Novak[2], Graeme Close[3], Helen Macdonald[4] & William Fraser[1]
[1]University of East Anglia, Norwich, UK; [2]University Hospital of Zurich, Zurich, Switzerland; [3]Liverpool John Moores University, Liverpool, UK; [4]University of Aberdeen, Aberdeen, UK

Background
25-hydroxyvitamin D (25(OH)D) is metabolised into two forms of metabolites: 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by the actions of 1α hydroxylase, and 24,25-dihydroxyvitamin D ($24,25(OH)_2D$) by 24-hydroxylase. Studies suggest the production of $1,25(OH)_2D$ is $24,25(OH)_2D$ dependent. Genetic mutations of CYP24A1 gene resulting in reduced or total loss of 24-hydroxylase function are associated with hypercalcaemic conditions and increase renal stone formations.
Objective
To profile the changes in serum concentrations of 25(OH)D, $24,25(OH)_2D$ and $1,25(OH)_2D$ in three supplementation studies where subjects were given a single bolus, weekly or daily low dose of vitamin D_3.
Method
Samples obtained from three studies were measured for $25(OH)D_3/D_2$ and $24,25\text{-}(OH)_2D_3/D_2$ by liquid chromatography tandem mass spectrometry (LC-MS/MS) and $1,25\text{-}(OH)_2D$ by enzyme immunoassay. In the first study, healthy volunteers ($n=69$) were given either a placebo or a single 100,000 IU bolus of vitamin D_3. In the secondary study, two groups of athletes were given either 35,000 or 70,000 IU weekly dose of vitamin D_3 over 12 weeks. In the third study, three groups of postmenopausal women ($n=253$) were given either placebo, 400 or 1,000 IU daily over a 12-month period.
Results
Subjects supplemented with single bolus and weekly high doses of vitamin D_3 showed rapid increase in serum 25(OH)D and $24,25(OH)_2D$ concentrations; a significant decrease ($P>0.001$) in 25(OH)D:$24,25\text{-}(OH)_2D$ ratio and a moderate increase in $1,25(OH)_2D$ concentration. Daily low dose of vitamin D_3 showed a moderate increase in $1,25(OH)_2D$ concentration, and no significant change in 25(OH)D:24,25-d(OH)D ratio over the dosing period.
Conclusion
Increasing vitamin D_3 supplementation results in an increase but relative difference in production of metabolites. Our findings showed the metabolism favors the production of $24,25(OH)_2D$ rather than of $1,25(OH)_2D$ when high dose of vitamin D_3 is given, suggesting a mechanistic response to prevent toxicity. We advise low and regular dosing regimen may be most beneficial to the patients.

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P73

Investigations and management of hyponatraemia: experience at a district general hospital

Rahat Ali Tauni[2,3], Tahir Omer[1] & Mustafa Khan[1]
[1]Bedford Hospital NHS Trust, Bedford, UK; [2]Luton and Dunstable University Hospital NHS Foundation Trust, Luton, UK; [3]University of Bedfordshire, Luton, UK.

Background
Hyponatraemia is the most common electrolyte abnormality in hospitalised patients. It is an independent risk factor for mortality and is associated with increased length of hospital stay.
Method
The objective of audit was to review practice of investigations and management of hyponatraemia in adults at Bedford hospital in line with evidence based guidelines including European Society of Endocrinology 2014 clinical practice guidance. An observational retrospective evaluation of medical notes, laboratory results, prescription charts, and discharge letters was performed on randomly selected 50 patients admitted with serum sodium of less than 125 mmol/l from January to July 2014.
Results
There was no significant gender difference, and most cases were above 60 years of age. Volume status was documented in 50%, with postural BP in 2% only. In two thirds of the cases, no cause or diagnosis for hyponatraemia was documented, while others were attributed to hypervolaemia 14%, diuretics 12%, GI losses 4% and SIADH 4%. Diuretics were stopped where appropriate. Patients had following investigations: RFTs 100%, glucose 94%, CXR 76%, CT brain 10%, plasma osmolality 8%, urine osmolality 6%, urine sodium 4%, TFT 4% and 0900 h cortisol 2%. We extrapolate that many patients may not have received appropriate treatment due to lack of essential investigations and clear diagnosis.
Conclusion
Management of hyponatraemia in hospital settings is often below par. Training of clinical staff and timely specialist opinion are essential for correct diagnosis and treatment and may improve patient mortality and reduce the length of hospital stay. We have delivered hyponatraemia sessions in medical teachings and displayed International guidelines on intranet and as posters in AAU. Local hyponatraemia guideline is in the process of approval, and we plan to complete the audit loop 6 months after the local guideline has been disseminated.

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P74

Characterising susceptibility to heat illness by plasma copeptin measurement

Mike Stacey[1,2], Simon Delves[3], David Woods[1,4], Sophie Britland[3], Joanne Fallowfield[3], Adrian Allsopp[3] & Stephen Brett[2,5]
[1]Royal Centre for Defence Medicine, Birmingham, UK; [2]Imperial College, London, UK; [3]Institute of Naval Medicine, Alverstoke, UK; [4]Leeds Beckett University, Leeds, UK; [5]Hammersmith Hospital, London, UK.

Background
Work in a hot environment can cause elevated core body temperature (Tc), circulatory insufficiency and death from Exertional Heat Illness (EHI). Failure to undergo successful heat acclimatisation (HA) is seen in ~5% of otherwise healthy volunteers and may lead to significant EHI, but pathways to severe illness remain poorly understood. Copeptin, a glycopeptide co-secreted with the pituitary hormone arginine vasopressin, reflects osmotic and cardiovascular stress and could inform assessment of EHI susceptibility.
Case report
Changes in body mass, Tc, heart rate and plasma copeptin were investigated in UK military volunteers performing structured exercise, both during and after heat acclimatisation (HA). Volunteer B had served in several hot countries, but reported difficulty acclimatising and poor performance in high humidity. In a field trial during early HA in Kenya ($n=15$), Volunteer B demonstrated marked loss of body mass from sweating vs the rest of the group, in association with elevated copeptin (35.1 vs 15.3 ± 8.4 pmol.l^{-1}) and failure to dissipate body heat.
In more controlled laboratory exposures during early HA in Cyprus ($n=25$), high loss of body mass in Volunteer B vs the group (4.3 ± 0.5 vs 2.0 ± 0.5%.h^{-1}) was accompanied by greater Tc (38.9 vs 38.2 ± 0.3 °C) and heart rate (176 vs 154 ± 19 b.min^{-1}) and exaggerated copeptin response (52.9 vs 15.6 ± 20.9 pmol.L^{-1}). With repeated exposures, heart rate and copeptin fell by 22 and 49%, respectively, though relative exuberance of sweating rate and Tc response persisted.
Discussion
Fluid depletion from maladaptive thermal sweating explained failure of initial HA in Volunteer B. This was reflected by plasma copeptin concentration, which did not fall until greater cardiovascular stability had been established with more advanced HA. Copeptin may have applicability in defining EHI mechanisms and could contribute to risk stratification during and after HA.

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P75

A case series of sodium glucose co-transporter-2 inhibitor (SGLT-2i) related diabetic ketoacidosis and literature review of the possible pathophysiology

Jawad Bashir[1,2], Steve Bain[2], Irfan Khan[3] & Tamar Saeed[4]
[1]Morriston Hospital, Swansea, UK; [2]Singleton Hospital, Swansea, UK; [3]Musgrove Park Hospital, Somerset, UK; [4]Royal Berkshire Hospital, Reading, UK.

As the SGLT-2i class gains popularity for management of type 2 diabetes (T2DM), the risk of diabetic ketoacidosis (DKA) has been recognised as a potential adverse event. However, all the reported cases of DKA associated with SGLT-2 inhibitors seem to have some additional predisposition to this condition and been exposed to alternative precipitants. We report a root-cause analysis of five locally presenting cases of DKA associated with dapagliflozin followed by a literature review of the pathophysiology.
Case 1
59-year-old T2DM for 17 years developed DKA after rapid reduction of insulin while being on SGLT-2i (pH = 7.16, HCO3 = 15 mmol/l, Glu = 41 mmol/l, ketones = 8 mmol/l).
Case 2
59-year-old T2DM for 14 years with multiple previous episodes of DKA was started on SGLT-2i and developed another DKA (pH = 7.21, HCO3 = 13.7 mmol/l, Glu = 27.8 mmol/l, ketones = 5.4 mmol/l).
Case 3
51-year-old lady diagnosed with T2DM 9 years ago and started on insulin in the same year was commenced on SGLT-2i. Within 2 months, she developed DKA (pH = 7.09, HCO3 = 8.3 mmol/l, Glu = 19.9 mmol/l, ketones = 6.6 mmol/l). Subsequently tested strongly positive for anti-GAD antibodies.
Case 4
52-year-old gentleman with T2DM for 15 years (diagnosed 2001) had recurrent episodes of idiopathic pancreatitis from 2005 onwards. He was commenced on dapagliflozin in 2013 and later on developed gastroparesis in 2014. He presented with mild DKA (pH = 7.32, HCO3 = 15.8 mmol/l, Glu = 32.3 mmol/l, ketones = 7.3 mmol/l) following flare up of his gastroparesis.
Case 5
37-year-old lady with T2DM was struggling to achieve improved glycaemic control or weight reduction while being on high dose of insulin. Her insulin was completely stopped and switched to dapagliflozin. She developed DKA (pH = 7.04, HCO3 = 5 mmol/l, Glu = 31.8 mmol/l, ketones = 3.9 mmol/l) after dental sepsis.
We did a literature search on all similar cases reported so far to determine the underlying pathophysiology and identify common precipitants. The aim of this review is to help physicians in proper patient selection for use of these novel agents (SGLT-2i) and early identification of potential precipitants.

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P76

Time taken for GH-treated adolescent patients, transitioning to adult services, to reach IGF1 levels within the upper normal range: Do we need to monitor more frequently?

Kerrie Grounds, Pauline Whittingham, Mo Didi & Aftab Ahmad
Royal Liverpool University Hospital, Liverpool, UK.

Introduction
According to NICE: adults receiving growth hormone (GH) treatment, IGF1 levels should reach therapeutic range by 9 months. Patients are reviewed at 1, 3, 6, 9, 12 months and 6 months thereafter in our clinics. GH dose is titrated by 0.1 mg each visit. This work aims to compare the time it takes to get the IGF1 in range, between adults and adolescent patients attending our specialist regional clinics.
Method
We performed a retrospective audit of 20 patients with GH deficiency. (ten attended Transitional clinic: men = 6, age 18–26 years, and ten attended the Adult GH clinic: men = 10, age 41–75 years. Data was gathered using patient case notes and hospital systems.
Results
Of the ten adolescent patients, 20% achieved the therapeutic IGF1 range within nine months (10% at 3 months and 10% at 9 months). 80% achieved IGF1 target outside the 9 month period (10% at 12 months, 10% at 15 months, 30% at 21 months, 30% are still yet to reach their therapeutic range).
Of the ten adult patients, 70% achieved therapeutic IGF1 target within 9 months (20% at 1 month, 10% at 3 months, 30% at 6 months and 10% at 9 months). 30% achieved therapeutic IGF1 levels outside the 9 month period (10% at 12 months and 20% at 18 months).
The mean maintenance dose of GH for the adolescent patients was 0.6 mg and for the adult patients 0.2 mg.
Conclusion
Our results suggest adolescents do not reach therapeutic IGF1 as quickly as adults using GH replacement, most likely due to the higher GH dose requirements, which takes longer to achieve at 0.1 mg increments at 3 month follow up intervals. We suggest either increasing the follow up frequency or GH dose increments of 0.2 mg at current follow up interval.

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P77

Nine year evaluation of a recall database of thyroid function tests in a combined antenatal-endocrine clinic

Naveed Khalily, Sheena Hodgett & David Barton
Princess Royal Hospital, Shrewsbury and Telford NHS Trust, Telford, UK.

Thyroid dysfunction is associated with well-recognised maternal and fetal complications. There is an increase in thyroxine requirement during pregnancy by 25–50% hence close monitoring of thyroid function and dose augmentation is vital in attaining euthyroid status. In our combined antenatal-endocrine clinic we aim to test thyroid function tests (TFTs) at booking, in the second and third trimesters. In order to reduce the need for patients to re-attend the clinic purely for TFTs we devised a Spread Sheet recording their follow-up results. In this study we evaluated the data using the Endocrine Society clinical practice guidelines (2012) as a standard. We examined data over a 9-year period with a total of 678 patients. Six hundred and five (605) were known hypothyroid, 13 hyperthyroid and 61 with varied diagnosis. A total of 1,114 TFTs were requested out of which 722 (64.8%) were performed and 392 (35.2%) were not done. Two hundred and forty three (243) patients required a dose adjustment of their thyroid replacement

with a further three patients initiated on treatment. Out of 243 patients, 109 had both second and third trimester TSH values available. Ninety six (96) showed improvement with 66 having TSH within the reference range for pregnancy (0.4–2.0 mU/l) and 13 showed no improvement or worsened.
In summary two-thirds of patients had been compliant with our novel system of outpatient TFTs monitoring and one third non-compliant. Around one-third had active intervention with nearly half showing improvement in their thyroid status of which two-thirds had results within the target TSH range for pregnancy.
In conclusion overall 552 clinic appointments were saved over a 9-year period, however there is still a need for further improvement in compliance with TFTs monitoring. This could be improved by use of mobile texting and close collaboration with maternity services to remind patients of when their investigations are due.

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P78

Management of multiple endocrine neoplasia type 1 (MEN1) and sporadic pancreatic neuroendocrine tumours (PNETS) in relation to the clinical guidelines: a single centre audit

Georgia Ntali[1], Paul J Newey[1,2], Victoria Stokes[1], Denis Talbot[3], Zahir Soonawalla[4], Greg Sadler[5], Niki Karavitaki[6,7], Ashley B Grossman[6] & Rajesh V Thakker[1]
[1]Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK; [2]Division of Cardiovascular and Diabetes Medicine, Level 5, Mailbox 12, Ninewells Hospital and Medical School, Dundee, UK; [3]Department of Oncology, University of Oxford, Cancer and Haematology Center, Churchill Hospital, Oxford, UK; [4]Department of Hepatobiliary and Pancreatic Surgery, Oxford University Hospitals NHS Trust, Oxford, UK; [5]Department of Endocrine Surgery, Oxford University Hospitals NHS Trust, University of Oxford, Oxford, UK; [6]Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK; [7]Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK.

Introduction and aim
Pancreatic neuroendocrine tumours (PNETs) may occur sporadically (sPNETs) or as part of the multiple endocrine neoplasia type 1(MEN1) syndrome, which is characterised by occurrence of PNETs, parathyroid and anterior pituitary tumours. Our aim was to review the management of these patients in relation to the clinical practice MEN1 guidelines, and the ENETS and UKINETS guidelines for PNETs.
Patients and methods
Patients attending with MEN1 or sporadic PNETs, during 2011–2013, were ascertained. All patients were reviewed at NET multidisciplinary team meetings. All PNETs were characterised using the WHO 2010 classification, TNM and ENETs staging system.
Results
Of 94 individuals (49 males and 45 females) with MEN1-associated tumours or a family history of MEN1, 67% had genetic testing to identify the MEN1 mutation, and a diagnosis of MEN1 was established in 81 (i.e. 86%) patients by genetic and clinical criteria; and the remaining 13 patients were unaffected relatives. Ninety-one percent of the MEN1 patients had primary hyperparathyroidism (PHPT); 67% had PNETs; and 36% had a pituitary tumour. Screening frequencies of 1, 2 and 3 times, during the 3 years were, respectively, as follows: for PHPT, using plasma calcium and parathyroid hormone (PTH) measurements, 20, 25 and 30%; for PNETs, using fasting gastro-intestinal hormones, 22.5, 30 and 27.5%, and using pancreatic-duodenal imaging, 15, 25 and 37.5%; and for pituitary tumours, using plasma prolactin and insulin-like growth factor 1 (IGF1), 15, 28 and 25%, and using MRI, 26, 6 and 2%. Of 59 patients (34 males and 25 females) with sPNETs, 39 had a non-functioning and 25 a functioning tumour (17 insulinomas, three glucagonomas, two gastrinomas, one hyperplasia of islet Langerhans, and two somatostatinomas).
Conclusions
Our audit shows compliance with guidelines, with MEN1 patients being regularly screened for the development of PHPT, PNETs and pituitary tumours.

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P79

Immunoassay cortisol day curve dangerously overestimates cortisol reserve in a metyrapone treated patient

Christine H M Leong[1], David R Taylor[2], Jackie Gilbert[1] & Benjamin C Whitelaw[1]
[1]Department of Endocrinology, King's College Hospital NHS Foundation Trust, London, UK; [2]Department of Clinical Biochemistry, Viapath Analytics, King's College Hospital NHS Foundation Trust, London, UK.

Background
Metyrapone is commonly used in medical management of Cushing's syndrome. It inhibits 11-β hydroxylase, which catalyses the conversion of 11-deoxycortisol to cortisol. The adequacy of metyrapone blockade can be assessed either clinically or biochemically using a target mean serum cortisol 150–300 nmol/l. Cortisol is normally measured by immunoassay.
Case report
A 21-year-old female presented with clinical and biochemical features of cortisol excess. 0900 h cortisol and basal ACTH were elevated at 1,168 nmol/l and 49 ng/l respectively. 24-h urinary free cortisol was markedly raised at 2,014 nmol/24 h (NR < 200 nmol/24 h). There was failure to suppress cortisol following 1 and 8 mg overnight dexamethasone suppression tests (cortisol 623 and 94 nmol/L). MRI revealed a 7 mm left-sided pituitary adenoma and baseline cortisol day curve demonstrated a mean cortisol of 751 nmol/l. Due to the severity of Cushing's preoperative medical blockade was initiated. Mean cortisol values on subsequent monthly Metyrapone Day curves were 565, 541 and 867 nmol/l. As cortisol values were markedly above target, metyrapone was increased from 500 mg TDS to 750 mg TDS.
She reported feeling increasingly tired and light-headed and repeat metyrapone day curve demonstrated an elevated mean cortisol of 678 nmol/l. Liquid chromatography-tandem mass spectrometry assay (LC-MS/MS) was then utilised to re-assess her cortisol samples and revealed mean LC-MS/MS cortisol of 87 nmol/l; overestimating cortisol by 591 nmol/l. LC-MS/MS analyses of the previous three samples revealed low mean cortisols of 132, 96 and 104 nmol/L respectively.
Conclusion
Metyrapone causes elevated circulating levels of 11-deoxycortisol which can cross-react in immunoassays. This can result in serum cortisol appearing normal or increased despite genuine hypocortisolaemia. The clinical consequences of this include potentially fatal hypocortisolaemic crisis. This case demonstrates that using LC-MS/MS is essential for accurate assessment of medical blockade with metyrapone. Centres that conduct metyrapone day curves using immunoassay may be exposed to dangerous cortisol overestimation.

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P80

Cortisol measurement using immunoassay versus liquid chromatography-tandem mass spectrometry: metyrapone dose-related discrepancies in cortisol values

Christine H M Leong[1], David R Taylor[2], Benjamin C Whitelaw[1] & Simon Aylwin[1]
[1]Department of Endocrinology, King's College Hospital NHS Foundation Trust, London, UK; [2]Department of Clinical Biochemistry, Viapath Analytics, King's College Hospital NHS Foundation Trust, London, UK.

Background
Metyrapone inhibits 11-β hydroxylase and causes a subsequent rise in the cortisol precursor, 11-deoxycortisol. Cortisol measurements by immunoassays are susceptible to interference and reagent antibody cross-reactivity with cortisol precursors when used in patients receiving metyrapone treatment. Clinicians rely on clinical and biochemical features of cortisol excess for dose titration of this medical blockade. The extent of this interference remains unclear. We compared serum cortisol measurement using immunoassay versus liquid chromatography-tandem mass spectrometry (LC-MS/MS) and assessed to see its correlation with metyrapone doses.
Method
We conducted a retrospective analysis of samples from 2015 that had paired measurements of cortisol using both immunoassay and LC-MS/MS. Only patients on metyrapone as a single medical blockade agent were included. Immunoassay of cortisol was performed using Centaur XP analyser.
Results
Nineteen patients were identified. 42% (8/19) had ACTH-dependent Pituitary Cushing's disease and the rest were ACTH-independent, of which 73% (8/11 patients) had ACTH-independent macronodular adrenal hyperplasia. 72 paired cortisol samples were analysed in total. With increasing daily metyrapone doses of 500, 750, 1,000, 1,500 and 2,250 mg, the mean delta cortisol (difference between immunoassay and LC-MS/MS cortisol levels) also increased by 15, 84, 68, 69 and 210 nmol/l respectively. Cortisol discordances were 7, 33, 33, 44 and 100% respectively. With most patients being on more than 1,500 mg of metyrapone daily,

there was significant overestimation of cortisol using immunoassays, which can lead to erroneous clinical decisions for metyrapone dose titrations. Moreover, with target range of mean cortisol of 150–300 nmol/l, this overestimation can mask genuine hypocortisolaemia and result in life-threatening consequences.
Conclusions
There is an exponential rise in cortisol discordance with increasing doses of metyrapone and clinicians need to be aware if using immunoassays for metyrapone day curves. Liquid chromatography-tandem mass spectrometry should be the gold standard platform used for cortisol measurement for patients on metyrapone treatment.

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P81

Male hypogonadism: an audit of initial investigation and management

Lyn Ferguson[1], Maurizio Panarelli[1] & Russell Drummond[2]
[1]Department of Clinical Biochemistry, Glasgow Royal Infirmary, Glasgow, UK; [2]Department of Diabetes and Endocrinology, Glasgow Royal Infirmary, Glasgow, UK.

Introduction
Male hypogonadism is a clinical syndrome comprising symptoms, signs and biochemical evidence of testosterone deficiency due to primary testicular failure or secondary pituitary/hypothalamic disease. Management may vary. This audit aimed to assess adherence to Endocrine Society Clinical Practice guidelines in investigation and management of male hypogonadism.
Methods
Electronic patient records for 25 men with hypogonadism attending endocrinology over 1 month were retrospectively reviewed. Baseline, repeat testosterone levels, gonadotrophins and DEXA scans where available were recorded, as well as serum prolactin, pituitary hormones, ferritin and pituitary MRI in secondary hypogonadism cases.
Results
25 out of 76 men (33%) attending endocrinology were referred with hypogonadism. Average age was 47 years. Average baseline total testosterone was 7.8 nmol/l. 12 (48%) were morning samples. 23 (92%) had repeat testosterone measured, however only 9 (36%) were morning samples. All had gonadotrophins measured. 11 (44%) underwent DEXA imaging. Out of 15 men with secondary hypogonadism, 14 (93%) had prolactin measured, 15 (100%) had TSH/free T_4 measured, 11 (73%) had IGF1 measured, 12 (80%) had serum cortisol/short synacthen test, 5 (33%) had ACTH, and 10 (67%) had ferritin measured. 12 (80%) had a MRI pituitary scan. 14 out of 19 men with confirmed hypogonadism (74%) commenced testosterone replacement. Average total testosterone level pre-treatment was 5.2 nmol/l, post-treatment 13.5 nmol/l. 13 (93%) on testosterone replacement had PSA and haematocrit measured. 11 (79%) reported symptom improvement, 2 (14%) had side effects, 2 (14%) stopped.
Conclusion
The majority of baseline testosterone levels merited endocrinology referral. Investigations and treatment were broadly in line with recommendations. Due to logistical reasons, the majority of repeat testosterone samples were afternoon samples. This may present diagnostic challenges due to the diurnal nature of serum testosterone. Due to increased osteoporosis risk, greater use of DEXA imaging may also be useful. These areas should be addressed in future practice.

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P82

The management of hypothyroidism in primary care without QOF – can we do better?

Anh Tran[1,2], Steve Hyer[2] & Andrew Rodin[2]
[1]Shadbolt Park House Surgery, Worcester Park, UK; [2]St Helier Hospital, Carshalton, UK.

Background
In 2014, Thy002 (the proportion of patients with hypothyroidism on the practice register with thyroid function tests recorded in the preceding 12 months) was removed as a Quality Outcome Framework (QOF) target.
Aim
To audit the current management of hypothyroidism in primary care two years following the QOF changes.
Method
Four local practices (total patient population: 37 200 (range 7300–1300 per Practice)) participated in the audit. An EMIS web population search was performed of all patients coded with 'hypothyroidism' or recorded as having been issued with Levothyroxine in the previous 6 months whether or not they had been coded. The proportion meeting the previous Thy002 target was calculated. The latest TSH value was also assessed according to the local reference range (0.35–5 mU/l) to determine the proportion of patients with results within range.
Results
1190 patients met the inclusion criteria; 1114 of these were coded with hypothyroidism (3% of total patient population). 80% of the coded group had had TSH checked within previous 12 months, compared with 100% prior to 2014. Levothyroxine was on repeat prescription in 97% of patients coded as having hypothyroidism and 92% of these had requested a prescription in the previous 6 months. The latest TSH was outside the local reference range in 33% of patients (32% $>$5 mU/l and 34% $<$0.1 mU/l). 7% of patients on Levothyroxine were not coded as having hypothyroidism, and 16% had not had thyroid function checked in the previous 12 months.
Conclusion
The removal of hypothyroidism from QOF targets has been associated with some deterioration in TSH monitoring in primary care. An EMIS web protocol with system alerts to remind about TSH check and also when TSH is outside local reference range has been developed to address areas needing improvement, and further studies will be carried out to assess its impact.

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P83

Audit on isolated pituitary stalk lesions/thickening in a tertiary hospital: Comprehensive guidelines needed

Karan Jolly[1], Hannah Cooke[2,3], William Smith[2,3], Metaxia Tampourlou[2,3], John Ayuk[2], Alessandro Paluzzi[4], Shahzada Ahmed[1] & Niki Karavitaki[2,3]
[1]Department of Otorhinolaryngology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [2]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK; [3]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK; [4]Department of Neurosurgery, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Background
Isolated pituitary stalk (PS) lesions/thickening detected on imaging pose challenging dilemmas.
Aim
Audit the diagnostic approach and management of patients with isolated PS lesions/thickening reported on MRI in a tertiary hospital.
Methods
Reports of pituitary/brain MRIs performed in our Radiology Department between 1/2013 and 12/2015 were searched for the terms 'stalk', 'infundibular', 'infundibulum'. Those with abnormality not limited to the stalk and cases with previous pituitary surgery were excluded.
Results
Fifteen cases were identified (nine females, median age 48 years; range 19–91) managed by various specialists. Reasons for MRI: possible diabetes insipidus ($n=3$), hyperprolactinaemia ($n=2$), history of hypopituitarism ($n=1$), neurosarcoidosis ($n=1$), anaplastic lymphoma ($n=1$), spinal ependymoma ($n=1$), investigation of other symptoms/signs ($n=6$;incidental finding).
Pituitary function
FSH/LH deficient 4/15, normal 5/15, not checked 6/15; hyperprolactinaemia 4/15 (resolved in 2), normal 5/15, not checked 6/15; ACTH normal 9/15, not checked 6/15 (one on steroids); TSH deficiency 4/15, normal 10/15, not checked 1/15;diabetes insipidus 2/15. No patient had stalk biopsy. Diagnoses were hypophysitis ($n=2$; based on imaging findings and later reduction of lesion), neurosarcoidosis ($n=2$; based on previous history and biopsy of other lesions), presumed Langerhans cell histiocytosis ($n=1$; diagnosed 8 years later from a skin lesion-remained stable during this interval), presumed Rathke's cleft cyst ($n=1$; no further follow-up deemed necessary), presumed metastasis from ependymona ($n=1$), progression of anaplastic lymphoma ($n=1$). Diagnosis was not clarified in 6 cases with stable imaging appearances (median follow-up 8 months (2–24)); their documented investigations included chest imaging $n=3/6$, vasculitis screen/aFP/hGC/inflammatory markers $n=2/6$, FDG-PET-CT $n=1/6$. In one case, further review was suggestive of 'normal variation' and had no further scans. Conclusions: Given that biopsy of isolated PS lesions/thickening is technically demanding, previous history, clinical/laboratory evaluation may narrow the diagnosis. However, in a number of cases, diagnosis is not established and investigations arranged seem to be non-comprehensive. As their natural history remains poorly understood, a robust diagnostic and management algorithm will guide all clinicians involved.

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P84

Cost-effective strategies to accelerate diagnosis and management of endocrine disorders in the outpatient setting

Rasheeta Sivapackianathan[1], Ahmed Siddiqi[1], C. Gouveia[1,2] & Karl Metcalfe[1]
[1]Newham University Hospital, London, UK; [2]Bartshealth NHS Trust, London, UK.

Introduction
The assessment of a new patient in the medical outpatients relies on thorough history taking as well as clinical examination. In particular, biochemical tests are pivotal in the diagnosis of endocrine conditions. Historically, our unit only mostly performed biochemical tests after new patients attended clinic. We proposed that diagnosis and management would be more efficient if this system was reverted, with the aim of minimising the number of clinic appointments. Additional strategies were considered including the use of a telephone clinic to manage patients with thyroid disease.
Methods
In 2016, clinicians and endocrine nurse specialists reviewed local protocols to determine the key tests required to confirm or refute most common endocrine disorders. Subsequently, a pilot system for processing new referrals was created. This system integrated a proforma for clinicians to request pre-clinic biochemical tests dependent on the referral category: examples include PCOS, hyperprolactinemia and hyperthyroidism. Tests were either carried out in the endocrine day unit or by the phlebotomy service. The secretarial team were then empowered to create standard letters for patients including diagnostic test request details. A model was designed to follow-up patients with thyroid disease via a telephone clinic. Long-term clinical outcomes were surveyed.
Results
The time from referral to confirming diagnosis and starting treatment was halved. Referred patients with unremarkable biochemical test results were also discharged earlier. All departmental staff involved in the project, felt the system improved patient care and should continue.
Discussion
The performance of pre-clinic investigations is a practical and cost-effective measure. It proves to be popular with both clinicians and nurse practitioners, and has dramatically improved our referral to treatment statistics by reducing the delays prior to diagnosis. From an economic perspective, the use of telephone clinics appears promising. This strategy could be utilised in the outpatient setting for all medical specialties.

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P85

Inpatient Endocrinology: a comprehensive specialty service audit and Quality Improvement Project in a large tertiary care centre

Joannis Vamvakopoulos[1,2], John Ayuk[2], Kristien Boelaert[1,2], Neil Gittoes[1,2], Niki Karavitaki[1,2], Brian Mtemererwa[2], Michael O'Reilly[1,2], Andrew Toogood[2] & Helena Gleeson[2]
[1]University of Birmingham, Birmingham, West Midlands, UK; [2]University Hospitals Birmingham NHSFT, Birmingham, West Midlands, UK.

Background
Endocrinology is well-established as an outpatient specialty. However, virtually no data exist on the volume, nature, management and disposal of inpatient referrals to inform the design and delivery of a quality-assured service.
Methods
We undertook an audit of all activity of the Inpatient Endocrine Service at University Hospitals Birmingham NHSFT (IES@UHB) between January 2010 and December 2015. Referrals received electronically via the Patient Information and Communication System (PICS) were collated and information was extracted pertaining to the timing, source, reason for and disposal of each referral; as well as to individual case outcomes (length of stay, readmission rate, mortality).
Results
A total of 2,817 actionable inpatient referrals were received over the audit period, 16% relating to readmissions. Referral volume grew at an average rate of 49.2% year-on-year, from 127 in 2010 to 885 in 2015. Multiple referrals for the same patient over the same episode of care made up 18.8% of the total workload. The majority of referrals originated from medical specialty teams (37.1%), followed by neurosurgery (20.8%); ENT (8.2%); trauma and orthopaedics (6.1%) and others ($<5\%$). Electrolyte derangement was by far the commonest referral reason, principally hyponatraemia (22.3%) and hypernatraemia (3.2%). Other common reasons included advice on hormone replacement therapy (14.6%); disorders of calcium metabolism (10%); and post-operative review of hypophysiectomised patients (6.4%). Median length of stay for referred cases was 15 days and the overall mortality rate over the audit period was 24.5%, with roughly one third of deaths occurring in hospital. Sixty-nine percent of cases with recurrent admissions were followed up in outpatients, compared to 36.5% with non-recurrent admissions.
Conclusions
The IES@UHB serves a high-risk patient population with a wide variety of acute and decompensated chronic endocrine problems. Audit findings are central in streamlining the service; as well as in developing appropriate educational resources for staff.

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P86

Improving the primary care management of erectile dysfunction and testosterone deficiency in men with or without Type 2 diabetes: findings from the REVITALISE audit

Janine David[1], David Edwards[2] & Patrick Wright[3]
[1]Porthcawl Group Practice, Porthcawl, UK; [2]Claridges Barn, Chipping Norton, UK; [3]The Belmont Surgery NHS Well Man Clinic, Durham, UK.

Introduction
Type 2 diabetes mellitus (T2DM) is associated with urological and endocrine complications, including erectile dysfunction (ED) and hypogonadism.
Aim
REVITALISE was conducted to assess men with/without T2DM at risk of ED and/or hypogonadism, and highlight gaps in current clinical management.
Methods
Data were collected from 13 UK primary care practices on incidence of ED, hypogonadism (defined as serum total testosterone <12 nmol/l), and use of phosphodiesterase type 5 inhibitors (PDE5i) and testosterone replacement therapy (TRT) in men with/without T2DM. Cardiovascular risk was assessed using the QRISK2 algorithm.
Results
Of 43 633 male patients analysed, 3185 had T2DM; prevalence 7.3%. 33.5% of men with T2DM were not asked about erection problems, which were more common in this group (19.7%) than in men without this condition (1.2%). 78.0% of men with T2DM and ED were not using PDE5i.
Data on testosterone levels during the 24 months preceding REVITALISE were available for 32.4%/39.8% of men with ED with/without T2DM, respectively. Among patients with T2DM and ED, 67.6% had not had a testosterone test (of whom 13.7% had QRISK2 score >10); 72.8% of those with testosterone levels <12 nmol/l did not receive TRT. Among patients with T2DM who had a testosterone test, 68.4% with testosterone levels ≤ 8 nmol/l (considered the cut-off value for low testosterone) were not receiving TRT, of whom 7.7% had QRISK2 score >20. Similarly, 76.7% of patients with testosterone levels >8 and ≤ 12 nmol/l did not receive TRT, of whom 9.1% had QRISK2 score >10. Among patients without T2DM, 23.1% had hypogonadism, of whom 42.6% were receiving TRT.
Conclusions
In REVITALISE, a substantial number of men with T2DM were not assessed for ED and/or hypogonadism, losing a valuable opportunity to improve their overall health and quality of life. Where diagnosed, management was suboptimal and often did not follow current UK guidelines.

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P87

Do guidelines improve practice? A re-audit of thyroid nodule ultrasound reporting at Northumbria Healthcare NHS foundation Trust post-BTA Thyroid Cancer Guidelines 2014

Ali Aldibbiat, Su Tee & Asgar Madathil
Northumbria Healthcare NHS Foundation Trust, North Shields, UK.

Introduction
BTA guidelines-2014 outlined the need for key features to be included in thyroid ultrasound scan (USS) reporting including risk stratification. The aim of this audit

was to evaluate the quality of thyroid-USS reporting at Northumbria Healthcare NHS Foundation Trust (NHCT); using BTA guidelines as the gold standard.
Methods
All thyroid/neck-USS between 1st November to 31st December 2015 were retrieved from radiology records at NHCT. Scans evaluating salivary glands, posterior neck, lipomas, and scans in patients <18 years old were excluded. Twelve domains were assessed and outcome compared to a pre-guidelines audit (2013). Fine needle aspiration cytology (FNAC) data was correlated to U-grading.
Results
134 of 256 scans identified were included. Nodules were identified in 104 scans (77%). Nodule size, lymph nodes and U-grading were reported in 89%, 72% and 67% of cases respectively. Scans were performed by 23 different sonographers and quality of reporting varied widely. Majority of nodules were graded U3 (50%) or U2 (43%). FNAC in those with U3 grading yielded 38% Thy1, 21% Thy2, 11% Thy3, 3% Thy4, and 3% Thy5; with 24% (n=9) having had no FNA done at the time of audit. Repeat USS and FNAC in those with Thy1 cytology resulted in 12% Thy1, 30% Thy2, 6% Thy3, while 35% were still awaiting repeat FNAC. In 18%, rescanning downgraded the nodules to U2. There was a significant improvement in overall reporting quality compared to the earlier audit, specifically with regards to risk stratification using U-grading (70% vs 37%) and lymph node evaluation (93% vs 27%).
Conclusions
Significant improvement in reporting quality has been achieved after introduction of BTA guidelines, however there remains room for improvement. Thy1 yield remains an issue. Majority of U3-graded nodules were benign on FNAC report. Further training for sonographers is needed in order to improve reporting outcomes.

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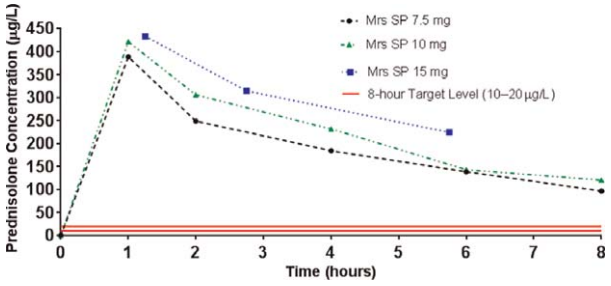
P88

Prednisolone and fludrocortisone as once daily treatment following adrenalectomy

Deborah Papadopoulou[1], Sirazum M Choudhury[1,2] & Karim Meeran[1,2]
[1]Imperial College London, London, UK; [2]Imperial College Healthcare NHS Trust, London, UK.

Mrs SP was a 50-year old patient who presented with typical features of Cushing's syndrome in 2003 and proceeded to pituitary surgery. Following this she was not cured, and elected to have a bilateral adrenalectomy. Following this, she was initially commenced on hydrocortisone 30 mg daily taken as 15 mg in the morning, 10 mg at noon and 5 mg at 1600 h, and fludrocortisone 100 µg daily. She continued on this for 10 years, but switched her glucocorticoid replacement to once daily prednisolone (7.5 mg). She developed diarrhoea and vomiting in 2015 due to an infection and the dose was increased to 15 mg for a day, and then reduced as she recovered. Prednisolone levels were measured as the dose was tapered (see figure) and an 8 h level on 10 mg was 120.2 µg/l and on 7.5 mg was 96.7 µg/l (target: 10 µg/l–20 µg/l). Given the high 8-hour serum concentrations, the dose was reduced to 5 mg daily, on which she feels well. Another prednisolone day profile is planned on 5 mg, with a view to reducing this further if appropriate. The conversion for hydrocortisone to prednisolone has traditionally been 4:1, but given that she feels better on 5mg prednisolone daily, would suggest a ratio of 6:1.
Once daily low dose prednisolone is a safe and effective replacement for patients who have had a bilateral adrenalectomy, and levels at 8h are a useful guide to dose adjustments.



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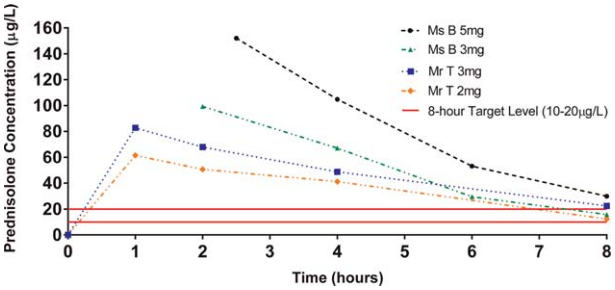
P89

The use of 8-h serum prednisolone concentrations to guide prednisolone dosing in replacement therapy

Deborah Papadopoulou[1], Sirazum M Choudhury[1,2], Karim Meeran[1,2] & Florian Wernig[1,2]
[1]Imperial College London, London, UK; [2]Imperial College Healthcare NHS Trust, London, UK.

We here report the cases of two patients receiving glucocorticoid replacement, whose treatment has been guided by serum prednisolone measurements and whose day curves are presented below. Ms B was a 33-year-old patient who presented 3 years ago with panhypopituitarism following transsphenoidal surgery in 2012, for a sellar mass in a foreign country. She had already commenced 5mg prednisolone daily in addition to DDAVP, levothyroxine and the COCP. Having noticed mild weight gain, a prednisolone profile was performed. Her 8-hour level was 29.9 µg/l (target: 10 µg/l-20 µg/l), suggesting over-replacement. A repeat day curve was performed on 3mg with an 8-hour level of 15.8 µg/l. She has continued on 3mg, remaining asymptomatic. We continue to monitor her weight. Mr T is a 57-year-old gentleman who presented 18 months ago with bitemporal hemianopia and headache secondary to pituitary macroadenoma. Following transsphenoidal resection 1 month later, he commenced prednisolone 5 mg, levothyroxine and testogel. He reported abdominal striae and adiposity, and was weaned down to 3 mg. A prednisolone profile showed an 8-h level of 22.4 µg/l. Given that he was over-replaced, another curve was done on 2 mg, showing this to be an appropriate dose (8-h level: 12.3 µg/l). Concurrent cortisol levels were noted to be 441 nmol/l at the time. Prednisolone was stopped and he is currently being monitored off replacement. Prednisolone 8-h serum levels have been successfully used to appropriately reduce replacement. Using prednisolone, we were able to identify recovery of the adrenal axis, which would have been more difficult using hydrocortisone therapy.



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Diabetes and Cardiovascular

P90

Effect of vitamin D supplementation on insulin resistance in type 2 DM subjects in Lagos, Nigeria

Anthony Anyanwu[1], Adetola Fasanmade[2,3], Herbert Coker[3] & Augustine Ohwovoriole[2,3]
[1]Federal Medical Centre, Owerri, Imo State, Nigeria; [2]Lagos University Teaching Hospital, Lagos, Nigeria; [3]University of Lagos, Idi-Araba, Lagos, Nigeria.

Background
Type 2 DM is a disease caused by both insulin resistance and an insulin secretory defect.
Reports suggest that vitamin D supplementation improves insulin resistance and pancreatic beta-cell function, however, there is paucity of data on vitamin D and glycaemia among type 2 diabetes mellitus in Nigeria.
Objective
To determine the effect of vitamin D supplementation on insulin resistance and pancreatic beta-cell function in type 2 DM subjects.
Methods
A single-blind prospective randomized placebo controlled trial, involving type 2 DM participants attending the Diabetes clinic of the Lagos University Teaching Hospital. The study participants consisted of 42 T2DM participants with poor glycaemic control and vitamin D deficiency selected following a prior cross sectional study on 114 type 2 DM participants for determination of vitamin D status and glycaemia. These participants were randomized into two equal groups of treatment and a placebo arms.

Levels of serum vitamin D, fasting glucose, HbA1c, calcium, albumin, phosphate, serum insulin, creatinine and alanine transaminase were determined. Vitamin D_3 supplements (3000 IU daily) were given to the participants in the treatment arm and placebo given to the placebo arm. Insulin resistance and pancreatic beta-cell function were determined at baseline and after 12 weeks of vitamin D_3 supplementation.
Results
There was a reduction from baseline in the mean insulin resistance level in both the treatment and placebo groups. However, this reduction was only statistically significant in the Treatment group ($P<0.01$). The proportion of subjects with improvement in insulin resistance status (HOMA-IR <2) was significantly higher in the treatment arm, $P<0.05$.
There was a reduction in the mean insulin secretory capacity in the treatment group ($Z=-0.402$; $P=0.29$) while it increased in the placebo group ($Z=-0.72$; $P=0.18$). This difference was however, not statistically significant.
Conclusion
Vitamin D_3 supplementation results in a reduction in insulin resistance but no effect on pancreatic beta-cell function in T2DM.

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P91

Oral glucose tolerance test or HbA1c assessment of subjects with coronary disease verified by angiography

Teodora Beljic Zivkovic[1,2], Biljana Jojic[2], Marina Andjelic Jelic[2], Goran Loncar[1,2], Aleksandar Davidovic[2] & Aleksandar Jankovic[2]
[1]Belgrade University School of Medicine, Belgrade, Serbia; [2]Zvezdara University Medical Center, Belgrade, Serbia.

Impaired glucoregulation is an important factor in the development of coronary heart disease. Numerous studies have reported a significant incidence of undiagnosed glucose intolerance in patients with coronary heart disease.
Aim
The aim of our study was to compare the utility of HbA1c versus oral glucose tolerance test (GTT) in detecting glucose tolerance abnormality in patients with coronary heart disease admitted for elective coronarography.
Participants and Methods
We have analyzed 100 subjects with no prior knowledge of glucose intolerance. Oral GTT with 75 g of glucose and HbA1c were performed prior to the coronarography. Based on the coronarography findings the subjects were divided in 4 groups: no significant stenosis (less than 50% stenosis), single vessel, two vessel or three vessel coronary artery disease (with stenosis $\geq 50\%$).
Results
Oral GTT showed that 23% subjects had normal glucose tolerance (NGT), 8% impaired fasting glucose, 39% glucose intolerance (IGT), while 30% were diagnosed with diabetes mellitus type 2 (DMT2). Based on HbA1c assessment, 24% subjects had NGT (HbA1c $<5.7\%$), 55% prediabetes (HbA1c 5.7–6.4%) and 21% DMT2 (HbAlc $\geq$ 6.5%). The incidence of patients with IGT and DMT2 correlated to the severity of coronary heart disease ($P<0.05$). No significant difference in HbA1c levels was observed between the groups with different degree of coronary heart disease. HbA1c had lower specificity and sensitivity compared to OGTT (Yuden index 0.06–0.49).
Conclusion
In conclusion, OGTT is superior to HbA1c in glucose tolerance assessment and should be applied as a routine screening procedure in patients with coronary heart disease.

Keywords: OGTT, HbA1c, coronarography
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P92

Temporal effect of bariatric surgery on predicted 10-year and lifetime cardiovascular risk at 1 and 6 months and 5 years

Thinzar Min[1,2], Scott Caplin[3], Jonathan Barry[3] & Jeffrey Stephens[1,2]
[1]Clinical Research Unit, Morriston Hospital, Swansea, UK; [2]Institute of Life Science, Diabetes Research Group, Swansea University, Swansea, UK; [3]Welsh Institute of Metabolic Surgery and Obesity, Morriston Hospital, Swansea, UK.

Background
Bariatric surgery aims to decrease cardiovascular risk factors. The Swedish Obese Subjects study reported that bariatric surgery was associated with reduction in long-term cardiovascular (CV) event. However, uncertainty remains regarding the effect of bariatric surgery on long-term CV risk. One way to predict long-term CV risk after bariatric surgery is to use cardiovascular risk assessment models.
Aim
The aim of this study is to investigate changes in the 10-year and lifetime predicted CV risk in subjects with impaired glucose regulation before, 1 month, 6 months and 5 years after bariatric surgery.
Method
A non-randomized prospective study of 45 participants (29 females) with impaired glucose regulation undergoing bariatric surgery. Body weight, BMI, blood pressure, lipid profile and HbA1c were recorded pre-operatively, 1 month, 6 months and 5 years post-operatively. Preoperative and postoperative predicted CV risk were calculated by using QRISK2, QRISK lifetime and JBS3 calculators.
Results
Follow-up rates were 93, 91 and 71% at 1 month, 6 months and 5 years, respectively. They had a mean age of 48.8 ± 7.0 years, a mean BMI 53.9 ± 11.1 kg/m^2, and a mean HbA1c $7.5\pm1.7\%$. The predicted 10-year QRISK2 score was reduced by 35, 54 and 24% at 1 month, 6 months and 5 years, respectively ($P<0.001$). The predicted lifetime risk was also reduced and maximum reduction (24.5% reduction in QRISK lifetime and 26.7% in JBS3 lifetime score) was observed at 5 years despite the patients being 5 years older.
Conclusion
Bariatric surgery in patients with impaired glucose regulation, was associated with a significant reduction in predicted 10-year and lifetime CV risk in a population that was on average 5 years older compared to baseline.

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P93

Type 2 DM risk evaluation in Nigerian undergraduates in Ile Ife: a comparison of the Finnish vs Indian risk scoring system

Olaoluwatomi Yusuff, Funmilayo Owolabi, Amina Lawal-Bello, Oluwadamilola Amjo, David Soyoye & Babatope Kolawole
Obafemi Awolowo Teaching Hospitals Complex, Ile Ife, Osun, Nigeria.

Background & objectives
Type 2 diabetes is on the increase especially among young people around the world due to increase in obesity and sedentary life style. Many risks scoring system has been developed and validated worldwide. Most are simple and inexpensive.
This research was to determine the applicability of these scoring systems in our environment and to compare the sensitivity of the Finnish versus the Indian scoring system in OAU undergraduates at Ile-Ife.
Methods
Hundred and eighty undergraduate students of OAU were recruited, the two questionnaires were administered which incorporated simple parameters such as age, abdominal obesity, BMI, physical activity, family history of DM, consumption of fruits and vegetable.
Results
73.3% had low risk while 26.7% had moderate risk, 0% had high risk using the IDRS. While FINDRISC had 87.2% with low risk, 12.2% slightly elevated risk and 0.6%with moderate risk. The IDRS was more sensitive in detecting those at risk compared to the FINDRISC.
Conclusions
Most of the respondents had low risk of developing type 2 DM, It is important to educate them on prevention of type 2 DM. A Nigerian DM risk score should be developed.

Keywords: T2DM, India Diabetes Risk Score (IDRS), Finnish Diabetes risk score (FINDRISC), Prevention.
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P94

Does precocious dexamethasone treatment advance fetal cardiac maturation?

Emma Batchen[1], Rachel Richardson[1,2], Adrian Thomson[1], Carmel Moran[1], Karen Sooy[1], Natalie Homer[1], Gillian Gray[1] & Karen Chapman[1]
[1]The University of Edinburgh, Edinburgh, UK; [2]Newcastle University, Newcastle, UK.

Synthetic glucocorticoids are administered to pregnant women at risk of pre-term delivery to mature organs and improve neonatal survival. We have shown that glucocorticoid action is essential to mature the fetal heart. Here, we tested the hypotheses that antenatal glucocorticoid exposure, prior to the normal increase in

glucocorticoid levels, will advance fetal heart maturation and this will depend on cardiovascular glucocorticoid receptor (GR).
Male SMGRKO mice, with *Sm22α-Cre* mediated deletion of GR in cardiomyocytes and vascular smooth muscle, were crossed with female control (*Cre-*) mice to generate SMGRKO and control fetuses within the same pregnancy. Dexamethasone (Dex, 100 μg/kg/d) or Vehicle (Veh) was administered in the drinking water of pregnant dams ($n=6$/group) from E12.5.
Liquid chromatography mass spectrometry showed that dexamethasone was measurable in livers of treated fetuses at E15.5, though levels were variable. Moreover, dexamethasone reduced fetal hepatic 11-dehydrocorticosterone levels ($P=0.0006$) with no corresponding increase in corticosterone, suggesting HPA axis suppression, though whether in fetus or dam is unclear.
In utero high frequency ultrasound performed at E15.5 showed that dexamethasone had no effect on most parameters related to cardiac function. However, 2-way ANOVA showed genotype and treatment differences in the mitral deceleration index (MDI), a marker of diastolic function. SMGRKO mice showed a lower MDI compared with control littermates ($P=0.027$). Dexamethasone also significantly lowered MDI ($P=0.029$), suggesting an improvement in fetal diastolic function in both control and SMGRKO mice.
Minimal differences in cardiac function were apparent at E15.5 in SMGRKO fetuses with cardiovascular GR deficiency. This differs from E17.5, when cardiac function is impaired in SMGRKO fetuses. Precocious glucocorticoid treatment modestly improved fetal diastolic cardiac function in E15.5 control and SMGRKO fetuses. The effects of precocious glucocorticoid administration upon cardiac function at a later time-point in development with the addition of a higher dosage will be examined in a future study.

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P95

Knowledge, attitude, and practice on prevention of type 2 diabetes mellitus among Nigerian undergraduates

John Ajiboye, Amina Lawal-Bello, Olaoluwatomi Yusuff, Funmilayo Owolabi, Okechukwu Ezekpo & Rosemary Ikem
Obafemi Awolowo Teaching Hospitals Complex, Ile Ife, Osun, Nigeria.

Background
Diabetes mellitus worldwide prevalence has risen significantly in the last two decades and type 2 diabetes mellitus makes up 90%. The control of this disease would largely be influenced by improved knowledge among the populace.
Objective
To assess the knowledge, attitude and practice on prevention of type 2 diabetes mellitus among undergraduate at Ile Ife.
Methods
A cross-sectional survey using simple random sampling technique was conducted on undergraduates at Obafemi Awolowo University Ile Ife. Questionnaires regarding attitude, knowledge and practice on prevention of T2DM were administered.
Results
A total of 180 undergraduates participated in the study; 95% of whom have heard of DM and 97.2% of them were able to define the condition correctly; 80% of them knew that DM can be prevented; 65.6% knows that DM can be prevented by exercise while 72.2% do daily physical activity of at least 30 min. Only 10% eat fruit and or vegetable daily; 90% falsely associated sugary food with development of DM; 88.3% of respondents were ready to screen for DM while 1.1% would prefer to seek spiritual help than orthodox treatment.
Conclusion
This study showed high awareness level of DM among participants and a positive attitude toward DM.
Keywords: Diabetic mellitus, knowledge, prevention, undergraduate.

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P96

Erectile dysfunction among male type 2 diabetics in a South Western Teaching Hospital, Nigeria

Christiana Omotola Ayandele[1,2], Chinedu Anizor[1,2], Funmilayo A. Owolabi[1], Olaoluwatomi T. Yusuff[1], John Kehinde Ajiboye[1], Okechukwu O. Ezekpo[1], Oluwadamilola O. Olusile[1], Adedeji O. Junaid[1], Amina Lawal- Bello[1], Olubukola Ala[1], Bukunmi Soyoye[1], Babatope A. Kolawole[1] & Rosemary T. Ikem[1]
[1]Obafemi Awolowo University Teaching Hospital, Ile-Ife, Osun State, Nigeria; [2]Delta State University Teaching Hospital, Oghara, Delta State, Nigeria.

Background
Diabetes is associated with multi-systemic complications. In male patients with diabetes, erectile dysfunction may be a worrisome condition and may result as an effect of diabetic complications, associated conditions such as hypertension and from the effects of drugs especially antihypertensives. Erectile dysfunction is increasingly being reported among diabetics with a resultant poor quality of life. This study seeks to determine the prevalence of erectile dysfunction and its associated sociodemographic and clinical correlates among patients with type 2 diabetes.
Method
This is a cross-sectional study involving 70 adult male participants with type 2 DM who were recruited from a diabetes clinic of a tertiary hospital in South-West Nigeria. Relevant history was obtained. Erectile dysfunction was assessed using the International Index of Erectile function-15 questionnaires. Statistical analysis was done using SPSS 22; P value of <0.05 was taken as significant.
Results
Mean age of the study subjects was 62.6 ± 9.9 years and mean duration of diabetes was 7.3 ± 6.4 years; 94.3% of the study subjects had erectile dysfunction of varying degrees. Moderate to severe ED was found in 47.9% of the study subjects; 66.7% of hypertensive diabetics had ED compared to 33.3% of non-hypertensives. All patients with poor glycaemic control had various degrees of erectile dysfunction with 33% of them having severe ED while 5.9% of subjects with good glycaemic control had no ED.
Conclusion
This study showed a high prevalence of erectile dysfunction among male patients with type 2 diabetes and is especially prevalent among patients also having hypertension.

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P97

SGLT2 inhibitors: results from clinical practice

Daniel K. Border[1,2] & Thomas M. Barber[1,2]
[1]University Hospitals Coventry and Warwickshire (UHCW), Coventry, UK; [2]Warwick Medical School, Coventry, UK.

Introduction
There is growing real-world experience of the SGLT2 inhibitor class for type 2 diabetes mellitus (T2D). We performed an audit of clinico-biochemical effects of SGLT2 inhibitor use for patients with diabesity in the context of a tier-3 obesity service within a UK-based teaching hospital.
Methods
We included patients with a confirmed diagnosis of T2D who had been treated with an SGLT2 inhibitor within licensed indications (monotherapy and addition to oral and insulin therapies) for at least 3 months. We ascertained changes in HbA1C and body weight on SGLT2 inhibitor (mean and standard deviation [S.D.]).
Results
Thirty-two patients were included (dapagliflozin [$n=13$], canagliflozin [$n=5$] and empagliflozin [$n=14$]). Mean baseline HbA1C and body weight were 79.3 mmol/mol and 110.1 kg respectively. At 3-months following SGLT2 inhibitor initiation, HbA1c reduced by 10.0 mmol/mol [S.D. = 11.2], and body weight by 3.3 kg [S.D. = 3.6]. At 6-months, HbA1c reduced by 16.5 mmol/mol [S.D. = 11.7] and body weight by 5.4 kg [S.D. = 7.2]. One patient had a 20% reduction of body weight at 6-months with an SGLT2-inhibitor agent and some patients ($n=9$) had HbA1c reduction of $>20\%$.
Conclusion
Our real-world evidence confirms that SGLT2 inhibitors in patients with T2D and obesity in the context of a tier-3 obesity service are efficacious, with reductions in both HbA1C and body weight being comparable to RCT data for these agents. Our data also suggest that some patients are 'super'-responders to SGLT2-inhibitors: future studies should identify further predictors of response.

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P98

Predictors and generation of risk equations for albuminuria progression in type 2 diabetes

Miriam Giordano Imbroll[1,2], Daniele Agius Lauretta[1], Trevor Tabone[1] & Stephen Fava[1,2]
[1]Diabetes and Endocrine Centre, Mater Dei Hospital, Malta, Malta; [2]University of Malta, Malta, Malta.

Background
Diabetes is the commonest cause of end-stage renal disease in the western world. However not all type 2 diabetic subjects develop renal disease, and of those who do, not all progress. At present it is not possible to identify patients who will progress.
Aim
The aim of the study was to identify baseline risk factors for the development and progression of renal disease in a cohort with type 2 diabetes and use this data to generate risk equations.
Patients and methods
Type 2 diabetic patients who had albumin:creatinine ratio (ACR) measurement in 2007–2008 were recruited, baseline characteristics were recorded and followed up for 8 years.
Results
Two hundred and sixty patients were included in the study. Of all the normo and microalbuminuric patients, 24.3% progressed and of all the micro and macroalbuminuric patients 22.1% regressed.
Baseline HbA1c, white cell count (WCC), smoking and duration of diabetes were associated with progression of renal disease in univariate analysis. Smoking ($P=0.064$) and duration of diabetes ($P=0.034$) were independently associated with progression in binary logistic regression.
Spearman correlation showed baseline HbA1c ($P=0.0016$), age ($P=0.0064$), serum creatinine ($P=0.0178$), serum potassium ($P=0.0414$), WCC ($P=0.0226$), serum triglycerides ($P=0.0156$), systolic blood pressure ($P=0.0164$) and duration of diabetes ($P=0.003$) to be positively correlated with % change in ACR, whilst baseline eGFR ($P=0.0278$), serum sodium ($P=0.039$), haemoglobin ($P=0.0006$) and haematocrit ($P=0.0002$) were negatively correlated. Duration of diabetes ($P=0.025$) and baseline HbA1c ($P=0.018$) was independently associated with % change in ACR in multivariate analysis.
Based on these results risk equations were generated.
Conclusions
We have identified baseline characteristics associated with progression of renal disease in type 2 diabetic subjects and generated equations to estimate risk of progression. If validated in other populations, these equations might be useful in predicting risk of progression in clinical practice.

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P99

Medical knowledge on DKA and management

Khaled Tofeec, Michelle Howarth, Moayed Alhelfi & Prasanna Rao-Balakrishna
Central Manchester Foundation Trust, Manchester, UK.

Introduction
We undertook a service development audit within our trust to review the Medical team's knowledge on DKA and the management involved in treating these patients. The aim was to identify where there was a lack of knowledge in this area so we could provide teaching sessions on DKA and aim at the specific areas highlighted from the audit. We went on to deliver education sessions on DKA management and pinpointed the areas lacking from the pre audit. The education sessions were delivered in August 2015 and the post audit took place in October 2015.
Method
The audit was completed with questionnaires which included a range of open and closed questions. The same questionnaire was used for the pre- and post-audits.
Results
The results from the pre teaching audit highlighted that there was a major need for education and development in relation to DKA management. The results showed that only 8% felt confident in managing DKA, 66% did not feel confident in prescribing insulin, only 28% said they would continue basal insulin whilst on fixed rate intravenous insulin infusion (FRIII) and no one identified the correct fluid regime to prescribe or when to obtain further bloods on DKA patients. Post teaching the results improved but still showed a need for education. The results showed that 55% said they felt confident in prescribing insulin, 70% said they would prescribe basal insulin whilst on FRIII, 30% identified the correct fluid regime in DKA and 27.5% recognised the correct time to obtain bloods.
Conclusion
From both the pre- and post-audit it is evident that there is a need for regular periodic education and training sessions if we want to ensure that DKA is diagnosed and managed effectively in all cases.

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P100

Captopril challenge test – is it useful for the diagnosis of primary aldosteronism?

Raluca Trifanescu[1,2], Alexandra Smarandoiu[2], Andra Caragheorgheopol[2], Sorina Schipor[2], Monica Gheorghiu[1,2] & Catalina Poiana[1,2]
[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [2]"C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania.

Background
Screening for primary aldosteronism (PA) needs aldosterone-to-renin ratio (ARR) measurement, followed by confirmative tests.
Aim
To assess the clinical value of captopril challenge test (CCT) in PA diagnosis.
Methods
Thirty patients were screened for secondary endocrine hypertension; study group consisted in 15 PA patients (7M/8F, aged 44.6 ± 13.3 years). Control group consisted in 15 patients (5M/10F) with negative screening for endocrine hypertension, matched for age (44.3 ± 13.2 years) and systolic blood pressure with PA group. Plasma aldosterone and direct renin were measured by chemiluminescence. In patients with increased ARR (3.8 ng/dl/ng/l), saline infusion test (SIT) and CCT were used as confirmative tests.
Results
Serum kalemia was significantly lower in PA patients (3.6 ± 0.7 mmol/l), than in controls (4 ± 0.6 mmol/l), $P=0.05$. In PA group, serum kalemia was significantly lower in patients who underwent CCT (3.2 ± 0.6 mmol/l) than in patients who underwent SIT (3.9 ± 0.5 mmol/l), $P=0.021$. AAR was greater in PA patients who underwent CCT (80.3 ± 53.6) than in patients who underwent SIT (8.2 ± 5.2), $P=0.007$. Median decrease in aldosterone levels during CCT tended to be lower (15.45%) in PA patients than in controls (41.9%), $P=0.2$. Median 4 h aldosterone levels after SIT were significantly higher (80.1 pg/ml, 25th percentile: 66.6 pg/ml, 75th percentile: 125 pg/ml) in PA patients than in controls (42.4 pg/ml, 25th percentile: 34.7 pg/ml, 75th percentile: 50.61 pg/ml), $P=0.02$.
Conclusion
In high-risk patients with severe hypertension and hypokalemia, CCT is a useful tool in the diagnosis of PA.

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P101

Effect of testosterone replacement in hypogonadal men with type 2 diabetes in routine clinical practice

Baljinder Kaur Sidhu[1], Eswari Chinnasamy[2] & Leighton Seal[1,2]
[1]St George's University of London, London, UK; [2]St George's University Hospitals NHS Foundation Trust, London, UK.

Approximately 25–40% of men with type 2 diabetes suffer from hypogonadism, mostly mixed type. Despite a clear association between diabetes and hypogonadism, the exact mechanism is not completely understood; insulin resistance, elevated oestradiol and inflammatory mediators may all have key roles. Studies so far, are conflicting on the benefits of testosterone on metabolic parameters in these men. Hughes et al and meta-analysis by Cai et al showed a significant improvement but others with conflicting results.
The aim of this audit was to examine the effects of testosterone treatment on metabolic and QOL parameters in routine clinical practice. We have retrospectively reviewed 23 diabetic patients on testosterone replacement with a minimum follow up of 6 months, for its impact on glycaemic control and lipid profile and quality of life.
Results are presented as mean $\pm$ S.D. Mean age 59 years ±10. With treatment total Testosterone rose from 7.87 ± 4.5 nmol/l to 17 ± 3 ($P=0.0002$). This was associated with fall in HbA1C in % (9.7 ± 2 to 7.9 ± 1.7, $P=0.01$), total cholesterol in mmol/l (4.1 ± 1 to 3.8 ± 0.98, $P=0.01$) and LDL in mmol/l (2.3 ± 0.9 to 2 ± 0.85, $P=0.02$) at 3–6 months. Except in 2 patients, the statin dose remained unchanged. Full details on changes to diabetes treatment were not available. Energy, drive and libido increased significantly from 5.1 ± 1.8 to 7.5 ± 1.3, 4.8 ± 2.4 to 7.7 ± 1.9, 5.3 ± 1.7 to 8 ± 1.3 respectively out of score of 10 ($P=0.001$).
This audit demonstrates that in routine clinical practice testosterone can be an effective adjunct in hypogonadal diabetic men and it also suggests that effect on HbA1c may be greater than previously reported. There are lots of limitations to this small retrospective audit but the findings are in line with reported literature.

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P102

Impact of diabetes mellitus on frequency and severity of hepatic encephalopathy in liver cirrhosis

Muhammad Fahad Arshad[1], Zeeshan Butt[2], Kamran Mushtaq[3] & Osman Salaria[2]
[1]Northern General Hospital, Sheffield, UK; [2]Mayo Hospital, Lahore, Pakistan; [3]Services Hospital, Lahore, Pakistan.

Objective
To analyze the effect of DM on frequency and severity of HE in patients with liver cirrhosis.
Methods
Three hundred and fifty-two patients with liver cirrhosis were prospectively assessed for severity of liver disease and presence of DM in a multicenter study. The presence and severity of HE was determined using West Haven criteria. Kolmogorov-Smirnov Goodness-of-Fit Test was used to check normality of continuous variables. Modified Child Pugh score and Model for End Stage Liver Disease scores (MELD) were calculated. Chi-square test for independence was used for categorical data while chi-squares test for trend was employed for ordered categorical variables. *T*-test and Mann–Whitney *U* test were used for continuous normal and continuous non-parametric data respectively.
Results
Hepatic encephalopathy (HE) was present in 50.3% of patients at time of admission and 33.5% of patients were diabetic. Chronic hepatitis C was the most common causes of cirrhosis (71.6%). Hepatic encephalopathy at admission was present in 58.5% of diabetics and 42.6% of non-diabetics (*P* value 0.03). Severity of hepatic encephalopathy was higher in patients with diabetes than those without diabetes (*P* value for trend 0.01). Chronic Hepatitis C, ascites, esophageal varices, modified Child-pugh class and MELD score were not different in diabetics as compared to non-diabetics. Trend for increasing serum creatinine was significant for diabetics while trend for increasing AST levels and serum bilirubin was significant for non-diabetics (*P* values 0.04, 0.03, 0.04 respectively). When stratified by age, more patients with diabetes presented with HE as compared to patients without diabetes (74.4 vs 53.2%, *P* value 0.02) albeit in the older age group only. Among gender subgroup analysis, only males with diabetes had increased HE prevalence (*P* value 0.03). In the multivariate model with age, gender, and diabetes as predictors and HE as dependent variable, both diabetes and older age were independently associated with HE (*P* values 0.03 and 0.006 respectively) while gender remained insignificant.
Conclusion
Cirrhotic patients with type 2 diabetes are more likely to present with hepatic encephalopathy than cirrhotic patients without type 2 diabetes. Moreover diabetes and age interact to cause increased prevalence of hepatic encephalopathy in decompensated cirrhosis.

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P103

Relationship of self-monitoring of blood glucose with glycemic control among patients attending a tertiary care hospital

Nauman Arif Jadoon[1,2], Muhammad Fahad Arshad[3], Mohammad Asif Shahzad[4] & Faheem Usman Sulehri[4]
[1]Hull Royal Infirmary, Hull, UK; [2]Ittefaq Hospital, Lahore, Pakistan; [3]Northern General Hospital, Sheffield, UK; [4]Diabetes Research Centre Medicine Unit 3, Nishtar Medical College Hospital, Multan, Pakistan.

Aim
The aim of this study was to estimate the frequency of SMBG among patients attending a tertiary care hospital and to evaluate the impact of SMBG on glycemic control in participants with diabetes mellitus.
Method
A random sample of 174 patients was selected for accrual in the study from the diabetic clinic of Nishtar Medical College Hospital Multan. Patients were interviewed using a structured questionnaire to elicit information about their self management practices and behaviors. Haemoglobin A1c (HbA1c) was measured from a capillary blood sample. Data was analyzed using SPSS 16 to determine the relationship between SMBG and glycemic control.
Results
Most of the patients (96.9%) of the patients recognized the importance of self management in the control of diabetes. Compliance with medication was reported by 95.5% of the patients, regular exercise was performed by 65.2% patients, dietary modification was practiced by 62.0% patients, while self monitoring of blood glucose was done by 64.2% of the individuals enrolled in the study. Younger participants with college education and those taking insulin were more likely to perform SMBG with no effect of gender. Multivariable linear regression analysis revealed that regular SMBG was associated with a lower HbA1c after adjusting for age, sex and insulin use, $P=0.005$. Performing SMBG was also associated with greater statistically significant odds of having good glycemic control (HbA1c $>7\%$), $P=0.04$. Self reported barriers to optimal self care included cost and access to healthcare, social factors, other health conditions and family problems.
Conclusion
The results of this study show that SMBG is associated with improvement in glycemic control.

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P104

Correlation between duration of diabetes mellitus and neuropathy in a Nigerian tertiary hospital

Olubiyi Adesina, F Adewusi, B Alalade, O Otukoya, G Olukunle & A Bello
Federal Medical Centre, Abeokuta, Ogun State, Nigeria.

Introduction
Diabetic neuropathy affects up to 50% of the patients with long standing diabetes mellitus. The duration of diabetes and glycaemic control are correlated with the development of neuropathy. Distal symmetrical neuropathy results in numbness which facilitates ulcer development. Biothesiometry provides a quantitative assessment of neuropathy. Patients with threshold >25 V (grade II) are at a high risk of developing ulcers later.
Aim
To detect peripheral diabetic neuropathy early and correlate it with the duration of diabetes at Federal Medical Centre, Abeokuta, Nigeria.
Methodology
A biothesiometer vibrometer machine was used. The amplitude of the stimulus (measured in volts) was gradually increased until the threshold of vibratory sensation was reached and the stimulus was appreciated by the patient. The results were recorded on a paper showing the neuropathy points on both right and left foot.
Results
Fifty diabetic patients were included in the study, out of which 28(56%) were females and 22(44%) were males. The duration of diabetes was 1month – 35years with a mean of 5.9 years. The mean value for the right and left foot was found to be 16.44 and 16.02 V respectively with the minimum values for both feet being 1 V and maximum for right and left foot 48 and 42 V respectively. Fifty per cent of patients with diabetes duration less than 5 years were considered to be normal (stimulus <15 V) while 50% had various degrees of neuropathy.
Discussion
Biothesiometer can detect sensory neuropathy even if the patient does not have any symptom of neuropathy. This study further shows the importance of early education on foot care in those with diabetes.
Conclusion
The biothesiometer detects peripheral neuropathy and grade its severity and thus predict future development of neuropathic foot ulcers. Steps needed to reduce the risk of ulcers and amputations can then be taken early.

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P105

Connexins and gap-junction mediated intercellular communication in the diabetic kidney

Claire E Hills, Gareth W Price & Paul E Squires
University of Lincoln, Lincoln, UK.

Background
Altered connexin expression and/or function is linked to the development and progression of secondary microvascular complications associated with diabetes. Despite this, we know little for the role of these small membrane proteins in the diabetic kidney. This study examines if glucose-evoked changes in TGF-β1 modulate connexin expression and gap junction-mediated intercellular communication in diabetic nephropathy.
Methods
Biopsy material was isolated from patients with diabetic nephropathy and stained for connexin-26 and connexin-43. Changes in expression, were corroborated by immunoblot analysis in model epithelial cells from human renal proximal tubules (HK2) cultured in either low glucose (5 mmol/l) +/− TGF-β1 (2–10 ng/ml) or high glucose (25 mmol/l) for 7 days. ELISA was used measured TGF-β1 secretion and paired-patch electrophysiology recorded junctional conductance in control versus TGF-β1 treated (10 ng/ml) HK2 cells.
Results
Connexin-26 expression was significantly up regulated in biopsy material from patients with diabetic nephropathy, compared to normal control (102 700 ± 6226 vs 21 030 ± 4727; $n=5$, $P<0.01$). Similarly, connexin-43 expression increased to 116 300 ± 5908 as compared to control 21 460 ± 10 920 ($n=5$, $P<0.01$). In response to high glucose (25 mmol/l) treatment for 7 days, HK2 cells increased TGFβ1 secretion to 994.4 ± 43.6 pg/ml compared to 5 mmol/l glucose (334 ± 14.9 pg/ml; $n=3$; $P<0.01$). Immunoblot analysis confirmed that TGFβ1 (10 ng/ml) up-regulates expression of connexin-26 and connexin-43 to 203.9 ± 7.5% and 151.1 ± 7.1% respectively compared to control ($n=4$; $P<0.001$). Whole cell paired-patch electrophysiology was used to determine the junctional conductance between coupled HK2 cells ± TGF-β1 (10 ng/ml). TGF-β1 produced decreased junctional conductance to 0.42 ± 0.2 nS compared to control 4.5 ± 1.3 nS ($n=5$; $P\leq0.05$).
Conclusion
Expression of connexin-26 and connexin-43 increased in biopsy material isolated form patients with diabetic nephropathy, changes corroborated in HK2 cells treated chronically with TGF-β1. Despite this gain in expression, gap junction mediated intercellular conductance was reduced, a feature linked to increased hemi-channel activity.

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P106

Connexins, hemi-channels and ATP release in the diabetic kidney

Paul E Squires, Gareth W Price & Claire E Hills
University of Lincoln, Lincoln, UK.

Background
Changes in the expression of connexins have been linked to renal damage in diabetes and both hemi-channels and gap junctions represent potential therapeutic targets for the treatment of diabetic nephropathy. In the current study, we utilize model epithelial cells from human renal proximal tubules (HK2), to demonstrate a role for glucose and its downstream beta1 isoform of the pro-fibrotic cytokine transforming growth factor (TGFβ1) on connexin expression and hemi-channel activity.
Methods
Connexin-26 and connexin-43 expression was assessed by immunoblot analysis in HK2 cells cultured in either low glucose (5 mmol/l) +/− TGFβ1 (10 ng/ml) or high glucose (25 mmol/l) for 7 days. ELISA was used to measure TGF-β1 secretion. Carboxyfluorescein uptake was used to measure hemi-channel activity in TGFβ1 treated HK2 cells at 7days, whilst ATP bio-sensing determined real time release of ATP.
Results
In response to high glucose (25 mmol/l) treatment for 7 days, HK2 cells increased TGFβ1 secretion to 994.4 ± 43.6 pg/ml compared to 5 mmol/l glucose (334 ± 14.9 pg/ml; $n=3$; $P<0.01$). Immunoblot analysis confirmed that TGFβ1 (10 ng/ml) up-regulates expression of both connexin-26 and connexin-43 to 203.9 ± 7.5% and 151.1 ± 7.1% respectively as compared to control ($n=4$; $P<0.001$). Dye uptake using carboxyfluorescein, demonstrated increased fluorescence in TGFβ1 treated (10 ng/ml) cells at 7 days compared to control (430 ± 18% increase), whilst pre-incubation with the hemi-channel blocker carbenoxolone (200 μM) significantly reduced uptake in both non-stimulated and TGFβ1 treated cells to 41 ± 2.7% and 64 ± 2.6% respectively ($n=3$ $P<0.001$). ATP bio-sensing confirmed that the TGFβ1 evoked increase in hemi-channel activity was paralleled by an increase in ATP release (1.99 ± 0.47 μM compared to control 0.29 ± 0.06 μM; $n=3$ $P<0.05$).
Conclusion
Recent studies link increased hemi-channel mediated ATP release to the progression and development of fibrosis in multiple tissue types. Understanding the contribution of connexin-mediated paracrine cell-to-cell communication in the pathogenesis of tubulointerstial fibrosis will help identify potential candidate proteins/pathways in the diabetic kidney ahead of future therapeutic intervention.

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P107

Elective hip arthroplasty rates and related complications in people with diabetes mellitus

Lindsey McVey[1], Nicholas Kane[2], Helen Murray[2], Brian Kennon[3], R M Dominic Meek[2] & Syed Faisal Ahmed[1]
[1]Developmental Endocrinology Research Group, Royal Hospital for Children, Glasgow, UK; [2]Department of Orthopaedics, Queen Elizabeth University Hospital, Glasgow, UK; [3]Department of Diabetes and Endocrinology, Queen Elizabeth University Hospital, Glasgow, UK.

Background
Diabetes mellitus (DM) affects nearly is reported to be present in approximately 8% of cases of elective hip arthroplasty and an HBA1c >53 mmol/mol may be associated with poorer outcomes in these cases.
Aims
To understand the demographics of DM patients in Glasgow undergoing elective hip arthroplasty over a 6 year period between Jan 2009 and Dec 2015 and the rate of post-operative complications.
Methods
Patients were identified through linking the hip arthroplasty patient list with the Scottish Care Information Diabetes dataset. Data were obtained through case note review and electronic patient records.
Results
Of the 2316 patients who had an elective hip arthroplasty at a single tertiary hospital, 102 (4.4%) patients had diabetes. Of these, 100 (98%) had Type 2 DM and 43 (42%) were diet controlled, 55 (54%) used oral antidiabetics and 4 (4%) required insulin. Median age was 71 years (range 39–88 years) and 60 (59%) were female. 16 (16%) were current smokers and 7 (0.1%) drank more than 10 units of alcohol per week. Median ASA (American Society of Anaesthesiologists) score was 2 (2.4) and median Scottish Index of Multiple Deprivation decile was 4 (1.10). Of the 70 cases where an HbA1c was available, HbA1c was >53 mmol/mol in 33 (47%) pre-operatively and >58 mmol/mol in 21 (30%). Five patients suffered early post-operative complications (1 with delirium, 2 with surgical site infections, 1 with acute renal failure and 1 with both a myocardial infarction and a lower respiratory tract infection). HbA1c was >53 mmol/mol in 4/5 of these cases (58, 55, 51, 59 and 54 respectively).
Discussion
The prevalence of DM is comparable to that of DM in the general population. Diabetic control in the current cohort was sub-optimal in half of the cases. The post-operative complication rate was low but was more common in those with sub-optimal control.

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P108

Exploring the mechanisms through which exercise influences beta cell health in Type 1 diabetes (T1D)

Michelle Curran
University of Birmingham, Birmingham, UK.

Aims
Exercise increases beta cell health in people at risk of, and with established type 2 diabetes (T2D). These benefits of exercise have not been characterised in T1D. Over 10% of beta cells are still present at the time of diagnosis with T1D, and exercise has the potential to preserve them. We aimed to explore the mechanisms through which exercise could improve beta cell health in T1D by investigating the effects of exercise serum on apoptosis and proliferation of the MIN6 mouse insulinoma cell line.
Methods
Fasted blood was taken from 10 healthy male subjects before and after 40 min of varied unsupervised moderate intensity exercise, and from 11 well-trained male

subjects before and after a 9 day intensive cycling exercise training study. Apoptosis was measured in MIN6 (24 h + 100 μM H_2O_2) by flow cytometry (AnnexinV-FITC, 7-AAD staining). Proliferation of MIN6 was measured using *PromegaCellTiter96aqueousOneCell* proliferation assay daily over four days. Experimental cultures were supplemented with 10% of either pre- or post-exercise serum.

Results

MIN6 incubated in post-exercise serum showed 6.2%(*s.d.* ± *pre:12.88, post:7.39*) reduced apoptosis ($P=0.03$) and 9% (*s.d.* ±*pre:0.339, post:0.237*) increased proliferation ($P=0.002$) compared to those incubated in pre-exercise serum, and further increased by 43% (*s.d.* ±*pre:0.256, post:0.367*) with serum following 9 days intensive training ($P \leq 0.001$).

Summary

Our results suggest exercise protects beta cells from apoptosis and increases their proliferation. Further benefits of exercise on beta cell health, and the mechanisms through which they manifest in T1D need characterisation. This provides a basis to explore exercise as a potential therapy for patients with T1D.

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P109

Does concomittant hypertension increase the risk of peripheral arterial disease in Nigerians with type 2 diabetes mellitus?

Olorunfemi J Adebayo[2], David O Soyoye[1], Christianah A Enikuomehin[1], Oluwagbemiga O Ayoola[1], Babatope A Kolawole[1] & Rosemary T Ikem[1]
[1]Obafemi Awolowo University Teaching Hospital, Ile-Ife, Osun, Nigeria; [2]Federal Medical Centre, Lokoja, Kogi, Nigeria.

Background

Peripheral arterial disease is a disorder due to obstruction of blood supply to extremities. Diabetes mellitus and hypertension are predisposing factors.

Objective

To determine if the presence of concurrent hypertension increases the risk of peripheral arterial disease (PAD) in Nigerians with type 2 diabetes.

Methods

This was a cross-sectional study that included 160 persons living with diabetes mellitus (60 subjects had type 2 diabetes (T2DM) while 100 subjects had concurrent diabetes and hypertension (DM-HTN)). The presence of PAD was determined by history of intermittent claudication, palpation of dorsalis pedis and posterior tibial arteries, ankle-brachial pressure indexes (ABPI), and measurement of intimal medial thickness [IMT] and spectral pattern on duplex ultrasound imaging of the femoropopliteal arteries. Fasting blood glucose (FBG), glycosylated haemoglobin (HbA_1C) and some other parameters were obtained from subjects in both groups. Comparisons were drawn between patients with diabetes alone and diabetic-hypertensives.

Results

Mean age of T2DM only was 56.4 ± 10.4 years and 59.4 ± 8.5 years in DM-HTN. FBG (mmol/l) in T2DM only was 7.9 ± 3.6 and 8.0 ± 3.4 in DM-HTN; HbA_1C (%) in T2DM group was 7.4 ± 2.2 and 7.3 ± 1.7 in DM-HTN. Prevalence of PAD was 74.9% in people with T2DM only and 70% among DM-HTN group using IMT as reference method. The prevalence of PAD in T2DM based on history of intermittent claudication, clinical palpation, ABPI and spectral pattern was 20.0, 26.7, 20.3, and 40.7% respectively while the prevalence of PAD in DM-HTN using history of intermittent claudication, clinical palpation, ABPI and spectral pattern was 26.0, 35.8, 22.0 and 50.0% respectively.

Conclusion

Prevalence of PAD is high among persons with diabetes mellitus. The presence of hypertension does not seem to confer any risk of PAD in people with T2DM only. In addition, traditional bedside methods of clinical pulse palpation and ankle-brachial pressure index of assessing PAD are still useful.

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P110

Volatile organic compounds: A potential biomarker for prediction of hypertension

Sahar Azharian[1], Matthew Neal[2], Iannos Kyrou[3], Milan Piya[1], Sudesh Kumar[1], James Covington[2], Philip McTernan[1], J Vrbikova[4], V Hainer[4], P Sramkova[5] & M Fried[5]
[1]Division of Biomedical Sciences, University of Warwick, Coventry, UK; [2]Warwick Systems Biology, University of Warwick, Coventry, UK; [3]Aston Medical School, Aston University, Birmingham, UK; [4]Institute of Endocrinology, Prague, Czech Republic; [5]OB Clinic, Prague, Czech Republic.

Background

Human obesity can significantly contribute to hypertension risk, often referred to as the 'silent killer', although targeting whom with weight gain becomes clinically hypertensive is unclear. Whilst therapeutic intervention such as bariatric surgery can mitigate both obesity and hypertension, it is not the most suitable solution for all patients. Therefore an early biomarker detection system to assess hypertension in subjects with weight gain could reduce mortality risk. Such a platform could be developed through a urine centred biomarker system identifying disease related signatures based upon volatile organic compounds (VOCs). The focus of this study was to determine whether urinary VOCs could be used as a potential monitoring tool for detection of blood pressure change in obese- hypertensive bariatric patients.

Methodology

Pre-surgery urine of 23 obese female patients undergoing bariatric surgery was analysed by Field-Asymmetric Ion Mobility Spectrometer (FAIMS). The data was processed by dividing the cohort into two classifications (high and low) based on individual median values: systolic and diastolic blood pressure, mean arterial pressure (MAP), C-reactive protein (CRP) and heart rate. Support Vector Machine (SVM) classifiers were trained with features selected using the Wilcoxon rank sum test. Performance was assessed using 10-fold cross-validation and the area under the ROC curve (AUC).

Results

FAIMS urinary VOC analysis highlighted a significant association with blood pressure markers as determined by systolic (ROC curve AUC: 0.918, $P<0.001$), MAP (AUC: 0.845 $P<0.001$), CRP (AUC: 0.932, $P<0.001$) and heart rate (AUC: 0.945, $P<0.001$); whilst diastolic did not attain significance (AUC: 0., P=N.S). Additionally the VOCs have predicted change in blood pressure factors 6 months post surgery.

Conclusion

This study suggests that urinary VOCs can be used for monitoring change in blood pressure in bariatric patients, additionally this technique could be utilised as a novel-screening tool for prediction of hypertension risk in subjects.

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P111

Diabetes admissions in a tertiary hospital: A one year review

Olubukola Ojo, Olalekan Ojo, Adebola Omosehin, Kayode Oluwatusa, Sulaeman Okoro & Ademola Bajowa
Federal Medical Centre, Owo, Ondo State, Nigeria.

Introduction

The prevalence of diabetes mellitus is increasing worldwide and people with diabetes have a 12–25% lifetime risk of developing a foot ulcer. This develops as a result of neuropathy, ischemia or both and is associated with significant morbidity and mortality. This study set out to determine the proportion and causes of diabetes related admissions and characterize the diabetic cases who presented with foot ulcer.

Methodology

This was a retrospective study involving 566 subjects. The case notes of patients admitted for medical conditions in 2015 were retrieved. The demographic and clinical data were extracted and analyzed using SPSS version 21.0.

Results

The mean age of subjects was 54.9 + 18.7 years, male to female ratio was approximately 1:1. Ninety-eight (98) of the subjects which constitutes 17.3% of the study population were admitted for diabetes related cases. Of this, 46 (46.94%) were admitted for poor glycemic control, 4 (4.08%) for hypoglycemia, 18 (18.37%) for hyperglycemic hyperosmolar state, 7 (7.14%) for Diabetes nephropathy and 20 (20.41%) for Diabetic foot and 2 (2.04%) for diabetic hand. Only 1 (1.02%) subject was admitted for Diabetic ketoacidosis. The mean age of subjects with DM foot was 57.4 + 16.9 years. There were more males than females, male to female ratio being 3:2. Their mean presenting RBS was 25.96 + 9.62 mmol/l. Out of the twelve cases of DM foot that were retrieved, 9 (75%) presented with gangrenous foot. Five (55.66%) subjects refused surgical intervention, 2 (22.2%) had below knee amputation, 1 (11.1%) had above knee amputation while 1 (11.1%) had Ray amputation.

Conclusions

The prevalence of diabetes foot ulcer is high mostly presenting with gangrenous foot leading to amputation. Diabetes foot education should be intensified at the community level and in the clinics.

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P112

Glycaemic load of commonly consumed beans among Nigerians with diabetes mellitus

Oluwarotimi Olopade[1], Ifedayo Odeniyi[1], Sandra Iwuala[1], Oluwatosin Kayode[1], Olufemi Fasanmade[1], Wale Ajala[2], Patience Chima[3] & Augustine Ohwovoriole[1]
[1]Endocrinology, Diabetes & Metabolism, Department of Medicine, Lagos University Teaching Hospital, Lagos, Nigeria; [2]Department of Chemical Pathology, General Hospital Lagos Island, Lagos, Nigeria; [3]Department of Dietetics, Lagos University Teaching Hospital, Lagos, Nigeria.

Introduction
Persons with Diabetes mellitus (DM) consume more of beans (Vigna unguiculata (Linn) Walp species) in Nigeria because of its low glycaemic index (GI). The quantity of beans consumed per meal has not been adequately considered.
Objective
To determine the glycaemic load (GL) of among persons with DM.
Methods
Twelve consenting T2DM persons and twelve healthy participants took part in this study. Anthropometric measurements were obtained. The reference food was glucose and the foods tested were three varieties of Vigna unguiculata (Linn) Walp species: 'oloyin', 'drum' and 'sokoto white'. Participants had a 50 g OGTT and 50 g of carbohydrate in the test bean meals after random stratification into four groups weekly. Serving sizes of test bean meals were served without restriction by participants. Venous blood was taken at 0, 30, 60, 90 and 120 min to estimate glucose. GI was determined using trapezoid rule. Comparison of medians of GI and GL by Friedman test was significant ($P<0.001$).
Results
Eleven persons with T2DM and 12 controls completed this study. Median ages of the DM and control groups being 53.0 years and 50.5 years ($Z=-0.617$, $P=0.537$). GI of the bean meal of 'oloyin', 'drum' and 'sokoto white' were 12.10, 17.64 and 12.04 (x2(2)=6.500, $P=0.039$). The GL of the DM group for 'oloyin', 'drum' and 'sokoto white' were 8.8, 12.9 and 10.3 (x2(2)=22.000, $P=0.0001$); that of the control were 14.3, 21.1 and 13.4 (x2(2)=22.167, $P=0.001$) respectively.
Discussion
GL is classified into low (0–10), moderate (11–19) and high (20+). Persons with DM consumed 'drum' and 'sokoto white' moderately, 'oloyin' in small quantity, the controls consumed 'oloyin', and 'sokoto white' moderately, 'drum' in high quantity. The GL differences are due to meal size, fibre and carbohydrate content of the test beans.
Conclusion
Diet of persons with DM should be low GL meals with high fibre content and reduced carbohydrate.

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P113

High risk populations: Attitudes to NAFLD among diabetologists

Thomas Marjot[1], Emilia Sbardella[1], Jonathan Hazlehurst[1], Ahmad Moolla[1], Jeremy Cobbold[2] & Jeremy Tomlinson[1]
[1]University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), Oxford, UK; [2]Department of Gastroenterology and Hepatology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

Introduction
Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) are common conditions that regularly coexist and can act synergistically to drive adverse outcomes. The prevalence of NAFLD in T2DM is 70%, with 16% having evidence of advanced hepatic fibrosis.
Aims
Our study therefore had two aims: Firstly, to define the attitudes and current clinical practice of diabetes specialists towards NAFLD across the UK and secondly, to implement an evidenced-based pathway for the assessment of NAFLD in patients attending diabetes outpatient clinics.
Materials and methods
An online survey was disseminated to diabetologists across the UK. Based on findings from this survey, all diabetic patients attending outpatient clinics at Oxford University Hospitals were screened for advanced fibrosis using a Fib-4 score. Those with elevated scores may then benefit from referral to the multidisciplinary metabolic hepatology clinic with combined hepatology and diabetes input.
Results
One hundred and sixteen diabetes specialists responded to the survey. Only 4.5% of responders correctly judged the prevalence of NAFLD in diabetic patients to be >50%. Even fewer (1.5%) correctly judged the prevalence of advanced fibrotic disease to be >15%. Whilst most diabetologists performed liver function tests, the majority (68%) had not used any non-invasive scoring system to assess risk of advanced disease. In light of these findings, a local 'think NAFLD' campaign was launched to educate diabetologists on the risk and assessment of NAFLD. In the subsequent 6 months 460 patients attending diabetic clinics were screened for advanced fibrosis using Fib-4. 16.5% of those screened had an elevated Fib-4.
Conclusions
Amongst diabetologists, there remains limited awareness of the prevalence and severity of NAFLD in the patients they treat. Fib-4 score can easily be used in clinical practice to identify patients at risk of advanced fibrosis who may then benefit from a dedicated multidisciplinary approach to their management.

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P114

The impact of thyroid autoimmunity on insulin secretion in pre-diabetic patients with normal thyroid function

Krystallenia Alexandraki[1], Stavros Liatis[2], Gregory Kaltsas[1] & Georgios Boutzios[1]
[1]Division of Endocrinology, Department of Pathophysiology, National and Kapodestrian University of Athens Medical School, Laiko General Hospital, Athens, Greece; [2]First Department of Propaedeutic Internal Medicine, Athens University Medical School, Laiko General Hospital, Athens, Greece.

Introduction
Autoimmune thyroid disease (AITD) and abnormal carbohydrate metabolism are the commonest endocrine disorders in the general population. However, the effect that AITD may exert in β-cell secretion and insulin action in patients pre-diabetes has not been investigated before.
Methods/design
One hundred and eighty-two patients (157 females) 46.5±14.2 years with pre-diabetes (impaired fasting glucose (IFG) or/and impaired glucose tolerance (IGT) or/and HbA1c≥5.7%) had oral glucose tolerance test (OGTT) with glucose (mg/dl) and insulin (μIU/ml) measurement at 0, 30′, 60′, 90′, 120′ min along with calculation of insulin resistance an secretion indices (IRI, ISI) analyzed according to the presence of AITD in an unselected sample. Age, gender, waist circumference (cm), and body mass index (BMI kg/m^2), TSH levels were recorded. HOMA, QUICKI as IRI and 1/fasting insulin, disposition index, AUCins/glu as ISI were assessed. Patients with abnormal TSH and/or DM2 were excluded from the study.
Results
Fifty-four (29.7%) had whereas 128 did not have AITD. 58.2% of patients had IFG (59.3% vs 57.8%, respectively) and 18.2% had IGT (11% vs 21.3%, respectively). IRI: Matsuda index was statistically significant higher in non-AITD patients ($P=0.009$). AUC ins/glu was higher with statistical significance in AITD group compared to non-AITD group ($P=0.045$). Univariate regression analysis showed that age, BMI, and AITD had significant impact on the index incAUCins/glu ($P=0.025$, $P=0.009$ and $P=0.031$, respectively) that remained significant in multivariate analysis.
Conclusion
Patients with AITD and pre-diabetes had higher AUCins/glu values and lower ISI(comp) compared to non-AITD. The presence of thyroid antibodies could be a possible factor modifying β-cell secretion in patients with established abnormality of carbohydrate metabolism.

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P115

Prevalence of dyslipidaemia in type 2 DM patients attending Obafemi Awolowo University Teaching Hospital Complex Ile Ife South West Nigeria

Adenike Enikuomehin[1,2], Fakhraddeen Mohammad[3], David Soyoye[2], Babatunde Kolawole[2], Rosemary Ikem[2] & Joseph Adebayo[2]
[1]State Specialist Hospital Akure, Ondo State, Akure, Ondo State, Nigeria; [2]Obafemi Awolowo University, Ile Ife, Osun State, Nigeria; [3]Kano University Teaching Hospital, Kano, Kano-State, Nigeria.

Many studies and treatment guidelines have emphasized that the treatment of DM extends beyond glycaemic control, but include lowering lipids, and blood pressure in people living with DM. According to The Task Force on Diabetes and Cardiovascular Disease of the European Society of Cardiology

(ESC) and of the European Association for the Study of Diabetes (EASD), dyslipidaemia is strongly related to increased CVD risk. This study determined the prevalence of dyslipidaemia in Type 2 DM patients attending the OAUTHC, Ile Ife South West Nigeria from January to November 2014.

Method

This cross-sectional descriptive study involved Three hundred (300) consecutive Type 2 diabetic presenting at OAUTHC, Ile-Ife. Relevant clinical information and physical examination was carried out. Venous blood was collected to determine total cholesterol, low density lipoprotein, high density lipoprotein and triglycerides. Lipid goals was based on total cholesterol <200 mg/dl, triglycerides <150 mg/dl, LDL <100 mg/dl and HDL <40 mg/dl in male and <50 mg/dl in female.

Results

A total of 300 type 2 Diabetes mellitus patients were recruited into the study. One hundred and three (35.3%) were males and 194 (64.7%) female. The mean age was $61.17+10.5$ years with a mean age of $62.0+10.9$ years for males and $60.7+10.3$ years females respectively. Of the 300 participants, One hundred and eleven (37.0%) subjects achieved optimal lipid control while 187 (63.0%) of the study subjects had dyslipidaemia. 85 (28.3%) study participants had total cholesterol of >200 mg/dl, 115 (38.3%) with LDL cholesterol above 100 mg/dl and 24.7% with triglycerides of >150 mg/dl and 28.3% for HDL of <40 mg/dl in men and 50 mg/dl in women.

Conclusions

The proportion of patient with poor lipid goal was high. Adequate management of dyslipidaemia should be paramount in the management of type 2 diabetes patients.

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P116

A case-control study of 24 hrs chronomics of BP/HR in terms of double amplitude, acrophase, hyperbaric index and its relation with circadian rhythm of Salivary cortisol in night shift nursing professionals

B Anjum[1,4], Narsingh Verma[1], Sandeep Tiwari[3], Ranjana Singh[2], Abbas Mahdi[2] & Madan Godbole[4]

[1]Department of Physiology, King George's Medical University, Lucknow, UP, India; [2]Department of Biochemistry, King George's Medical University, Lucknow, UP, India; [3]Department of Surgery(Gen), King George's Medical University, Lucknow, UP, India; [4]Department of Molecular Medicine & Biotechnology, King George's Medical University, Lucknow, UP, India.

Objective

The present study was aimed to investigate the 24 h chronomics of BP/HR in terms of Double amplitude, Acrophase and Hyperbaric index and its relation with circadian rhythm of salivary cortisol in night shift nurses and actual day workers.

Material and methods

Fifty-six night shift nurses, aged 20–40 years, performing day and night shift duties were recruited from the Trauma Center, KGMU, India, and 56 age sex matched actual day workers were also enrolled as controls. BP and HR were recorded by ABPM at every 30 min intervals in day time and each hour in night time synchronically with circadian rhythm of salivary cortisol during shift duties.

Results

Highly significant difference was found in double amplitude (2DA) of SBP between night (23.10 ± 14.68) and day shift (34.27 ± 16.44) ($P<0.0005$). In night shift, hyperbaric index (HBI) of mean SBP was found to be increased at 00–03 am (midnight) while during day shift, peak was found at 06–09 AM. HBI of mean HR was found to be increased at 18–21 PM during night shift while in controls, peak was found at 09–12 & again 15–18 PM of SBP, DBP & HR. Alterations in Acrophase of BP/HR were very common among night shift workers and Ecphasia was found in few night shift workers. Significant difference was found in night cortisol levels among night (4.08 ± 3.28) vs day shift (2.62 ± 2.37), ($P<0.005$) while in comparison to night shift or day shift with controls these difference was highly significant ($P<0.0005$).

Conclusion

Reverse pattern of acrophase and HBI of BP & HR along with increases salivary cortisol level at night during night shift represents desynchronization. It indicates that the circadian rhythm was disrupted during night shift and it may be a risk factor for cardiovascular and other metabolic diseases in future after longer duration of rotating night shift.

Keywords: Circadian rhythm, Night shift, Ecphasia, Salivary cortisol and Desynchronization

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P117

Insulin resistance, obesity indices and lipid profile in Nigerian patients with type 2 diabetes mellitus

Oyindamola Awofisoye, Racheal Okpiabhele, Arinola Esan & Jokotade Adeleye

University College Hospital, Ibadan, Oyo State, Nigeria.

Introduction

Insulin resistance (IR) is a fundamental defect in type 2 diabetes mellitus (T2DM) which is reported to be associated with other components of the metabolic syndrome including obesity and atherogenic dyslipidaemia. Routine measurement of insulin resistance in clinical practice is not practical, but other routinely measured clinical variables could predict the presence of IR. We aimed to determine the association of IR with obesity indices and lipid parameters in Nigerian patients with T2DM.

Patients and methods

One hundred and ten patients with T2DM who were not on insulin therapy were included in the study. Anthropometric indices including weight, height, waist and hip circumference were measured. We also measured fasting serum insulin (ELISA), fasting blood glucose and lipid profile. Insulin resistance was calculated using the Homeostasis Model Assessment for IR (HOMA-IR). Correlational analysis and linear regression was used to determine the association of IR with waist circumference and obesity indices.

Results

The mean age of the study subjects was 60.9 ± 9.7 years and 69.1% were females. The mean$\pm$S.D. of body mass index (BMI), waist circumference (WC) and waist-hip-ratio (WHR) were 27.1 ± 5.0 kg/m^2, 95.3 ± 10.3 cm and $0.97\pm.07$ respectively. The median (range) HOMA-IR was 1.65 (0.50–7.00). IR had a positive correlation with BMI ($r=0.26$, $P=0.007$), waist circumference ($r=0.28$, $P=0.003$), but not with WHR ($r=0.075$, $P=0.433$). IR was also positively correlated with serum triglycerides ($r=0.28$, $P=0.03$), but not with, total cholesterol, HDL, LDL cholesterol or estimated GFR. On linear regression analysis, serum triglycerides remained associated with IR ($\log_{10}$), independently of waist circumference or BMI.

Conclusion

Insulin resistance increased with WC, BMI and serum triglycerides. WC and BMI are better indices of IR compared to WHR.

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P118

Retrospective review of insulin degludec (Tresiba) started in patients at Royal Derby Hospital

Seifeldin Yahia, Abhiram Sahathevan & Roger Stanworth

Royal Derby Hospital, Derby, Derbyshire, UK.

Introduction

Patients with diabetes mellitus require insulin with disease progression to attain or maintain glycaemic targets. Patients and physicians work together to balance the advantages of improved glycaemic control with the risk of hypoglycaemia and increasing regimen complexity. Insulin Degludec (Tresiba) is an ultra-long-acting insulin analogue launched in the UK in March 2013 and is available in two strengths, 100 and 200 units/ml.

Method

Retrospective case note and hospital database review of patients initiated on degludec (Tresiba) at Royal Derby Hospital from December 2013 to January 2016.

Results

Six patients were identified (1 male, 5 females; 5 patients (83.3%)) with T1DM and one patient (16.7%) with T2DM). Mean age: 45.8 (range 19–56). Mean duration of diabetes prior to initiation of Degludec: 18.5 years (range 0.5–40). All patients were on preliminary insulin therapy prior to starting Degludec. Three (50%) patients were prescribed Degludec due to problems with hypoglycaemia (all T1DM). Poor compliance and requirement for basal OD insulin was the rationale for commencing Degludec in 66.6% of patients. In 3 (50%) patients, Insulin glargine was switched to Degludec. In the remaining patients, Biphasic Insulin regime was stopped and basal-bolus regime of Degludec + Novorapid commenced. HbA1c, where available, was reduced in 33.3% and increased in 33.3% of patients post-initiation of Degludec.

Conclusion

Overall, all of our patients were started on Degludec in compliance with NICE guidelines. The number of patients on Degludec is very limited as it is commonly reserved for last choice basal insulin therapy and requires specialist initiation in

view of its safety and cost concerns. Nonetheless, this audit is limited by the small cohort of patients and a multi-centre audit is recommended to provide further information regarding Degludec therapy within the population.

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P119

Freestyle Libre as a tool for management of hypoglycaemia in pregnancy complicated by type 1 diabetes mellitus

Valerie Gordon, Karen Towse, Priya Madhuvrata & Alia Munir
Sheffield Teaching Hospitals, Sheffield, UK.

Introduction
Pregnancy in women with pre-existing Type 1 diabetes (T1DM) is known to carry a 3–5 times increased frequency of severe hypoglycaemia (SH) in the first compared to the third trimester. The main predictors are: pre-gestational SH, HbA1C $<6.5\%$/48 mmol/mol, duration of diabetes and higher total daily insulin doses. Freestyle Libre or flash monitoring utilizes a 14 day tiny glucose sensor which is applied to the back of the arm and scanned with a reader, to obtain a glucose reading and excursion direction. Recent data where Freestyle Libre was used in Type 1 diabetics demonstrated a statistically significant reduction: in number of hours spent in hypoglycaemia (by 38%), nocturnal hypoglycaemia (40%), and SH (50%) without an increase in HbA1C at 6 months (IMPACT study). The Evaluation of Freestyle Libre (FL) – in Pregnancy Study (FLIPS) data is awaited.
Method
Three pregnant women with pre-existing T1DM from the high risk ANC were managed with FL. Two had undergone diagnostic trial and purchased their own systems. Impaired hypoglycaemia awareness being the primary indication. Standard capillary glucose monitoring was used alongside FL.
Results
Overall an improvement in: HbA1C, hypoglycaemia frequency, reported patient satisfaction, were noted. More extensive capillary glucose monitoring was prompted in all. Concerns over the low FL readings at 48 h lead to discontinuation in one patient.
Conclusion
The FL systems appear to be a useful tool in the management of complex T1DM pregnancies. Caveats: patient selection and ongoing capillary blood glucose monitoring. FL prompted pregnant patients to check capillary blood glucose more often thus avoiding hypoglycaemia.

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Neoplasia, Cancer and Late Effects

P120

Multiple endocrine neoplasia type 1: 'Are screening guidelines appropriate?' The importance of histology and correlation of clinical signs

Christopher Redford & Bijay Vaidya
Royal Devon and Exeter Foundation Trust, Exeter, Devon, UK.

We describe a 35 year old man who was referred back to the endocrinology service with a chronically raised amylase. He had previously been seen for early onset type 2 diabetes and for primary hyperparathyroidism. He had undergone a single gland parathyroidectomy, aged 32, for primary hyperparathyroidism in 2013 after which his calcium had remained normal. In clinic he was found to be overweight but otherwise well, with normal blood pressure and an HbA1c 49 mmol/mol. The most striking clinical finding was of numerous skin lipomas, mainly confined to his trunk. His history of primary hyperparathyroidism, although histology had reported adenoma/hyperplasia, and this finding raised the possibility of MEN 1. There was no relevant family history, suggesting a possible sporadic mutation. Initial investigations included a CT Abdomen/Pelvis and MEN 1 gene testing. CT showed a cystic islet cell tumour in the tail of the pancreas and MEN 1 testing confirmed a 1579C>T mutation. A subsequent Octreotide scan showed low grade avidity within the pancreatic lesion and fasting bloods revealed a raised Glucagon. The patient is now awaiting removal of his pancreatic lesion. Current guidelines suggest screening for MEN 1 should only be performed in patients developing primary hyperparathyroidism under 30 years of age. Clearly, cases such as this suggest that some will be missed using this cut off. The case also highlights the need for careful integration of clinical and histological findings. Current guidelines would recommend MEN 1 screening in individuals with primary hyperthyroidism and either skin lipomas or hyperplasia on histology.

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P121

Psychosocial impact of multiple endocrine neoplasia disorders

Joanna Grey & Kym Winter
Association for Multiple Endocrine Neoplasia Disorders (AMEND), Tunbridge Wells, Kent, UK.

Multiple endocrine neoplasia (MEN) disorders are autosomal dominantly inherited syndromes characterised by multi-glandular adenomas/carcinomas. AMEND is a charity providing support and information resources to MEN patients. A recent anonymous online patient survey was conducted by AMEND into the psycho-social impact of the conditions. 219 patients participated (n101 MEN1, n60 MEN2a, n26 MEN2b, n32 other) with a mean age of 47.5 years. 57% felt that their condition had a negative impact on their long-term mental/emotional well-being, 51% felt that their condition had a negative impact on their employment/career, and 54% felt that the condition had a negative impact on their family life. 83% of respondents felt confident discussing their condition with their specialist, but 55% felt that their GP did not understand the condition; results that correlate with an earlier study (1). Berglund *et al.* (2003) found that depression rates increased with disease burden in MEN1(2). In a 2013–2016 survey of AMEND's free counselling service, 84% of users rating the service as useful or very useful. It also showed common negative impact themes including dealing with diagnosis (73%), work-related issues (47%), relationship issues (50%), symptom/treatment management (83%) and fears for the future (80%). A notable 33% had suicidal thoughts.
Conclusion
Larger multi-centre studies are required to fully understand the needs of patients with chronic genetic conditions, and access to a range of psycho-social support services should be improved.
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P122

Investigation of the effects and interactions of a human neuroendocrine tumour (NET) cell binding peptide

Mark Stevenson[1], Kate Lines[1], Benjamin Thomas[2] & Rajesh Thakker[1]
[1]Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK; [2]Central Proteomics Facility, sir William Dunn School of Pathology, University of Oxford, Oxford, UK.

Pancreatic neuroendocrine tumours (PNETs) may occur as part of the multiple endocrine neoplasia type 1 (MEN1) syndrome or as non-familial (sporadic) tumours. PNETs, which include gastrinomas, insulinomas and non-functioning tumours occur in more than 80% of MEN1 patients and account for 50% of disease-specific deaths. This is because 25–40% of patients with PNETs will have metastasis at presentation, and current treatments, which include surgery, chemotherapy and radiotherapy for such advanced NETs rarely achieve a cure. Thus, additional therapies are required and we hypothesised that there maybe NET-specific receptors that could be targeted. We have therefore previously undertaken phage display screening using a human neuroendocrine cell line (BON-1) from a metastatic pancreatic carcinoid, to identify NET-binding peptides and reported a 12-mer peptide (P1). Confocal microscopy confirmed that P1 binds BON-1 cells, and trypan blue exclusion and Caspase-Glo 3/7 assays showed that P1 mediated a 70% decrease ($P<0.005$) in BON-1 cell proliferation and a 1.23-fold ($P<0.02$) increase in apoptosis respectively. To identify proteins that may interact with P1 on the surface of NET cells, BON-1 cell lysate was passed through streptavidin affinity chromatography columns loaded with biotinylated P1 or scrambled peptide control, fractions collected and digested with trypsin followed by mass spectrometry and protein identification software (MASCOT) analysis. A total of 247 proteins were identified that were unique to the P1 fractions. Using a MASCOT cut-off score of 50, these proteins included

isoform 2 of heterogeneous nuclear ribonucleoprotein M (HNRNPM), heat shock cognate 71kD protein (HSPA8), PRKAR2A protein (PRKAR2A), prohibitin (PHB), cell division control protein 42 (CDC42) and Ras-related protein Rab-3D (RAB3D), which are involved in regulating exocytosis, proliferation, migration and protein folding. Further characterisation of these proteins may help in elucidating the role of P1 and its possible receptors in NET biology and in developing novel therapies for targeting pancreatic NETs.

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P123

MicroRNA miR-3156-5p is down-regulated in serum of Multiple Endocrine neoplasia type 1 patients, and regulates expression of mortality factor 4-like protein 2 (MORF4L2)

Kate E Lines[1], Victoria Stokes[1], Simona Grozinsky-Glassberg[2], Christopher J Yates[1] & Rajesh V Thakker[1]
[1]Academic Endocrine Unit, OCDEM, University of Oxford, Oxford, UK; [2]Neuroendocrine Tumour Unit, Endocrinology and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Centre, Jerusalem, Israel.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterised by the combined occurrence of parathyroid tumours, and neuroendocrine tumours (NETs) of the pancreas and pituitary. Reliable biomarkers, ideally in plasma or serum, for the early detection and recurrence of MEN-1 associated tumours, and especially pancreatic NETs are required, and we explored the potential use of microRNAS (miRNAs), which are small non-coding RNAs that bind target mRNAs to negatively regulate gene translation, and are released from tumour cells into the circulation. We used Illumina miRNA sequencing to study miRNA expression in sera from four MEN1 patients (all with pancreatic NETs and parathyroid adenomas, and one also had a prolactinoma), and 4 control, gender-matched unaffected relatives. In total 45 miRNAs were up-regulated and 39 down-regulated (>1.5 fold-change) in all MEN1 patients when compared to controls. The most highly down-regulated (by 12-fold) miRNA, miR-3156-5p, was further investigated by treating human NET cells (BON-1 cells which are derived from a metastatic pancreatic carcinoid) with a specific miR-3156-5p inhibitor and mimic, and by studying the effects on expression of its predicted target gene, mortality factor 4-like protein 2 (*MORF4L2*, encoding MORF4L2), whose circulating transcripts have been reported to be correlated with NET disease progression. *MORF4L2* mRNA expression, assessed using quantitative real-time PCR, was similar in control untransfected cells and in cells transfected with inhibitor or mimic. However, MORF4L2 protein translation, assessed by Western blot analysis, was significantly higher (twofold, $P<0.05$) and lower (52% reduction, $P<0.05$) after miR3156-5p inhibitor and mimic transfection, respectively, when compared to control untransfected cells. Thus, our results demonstrate that miR-3156-5p regulates MORF2L2 protein expression, and that miR3156-5p is down-regulated in the serum of MEN1 patients, thereby indicating that miR-3156-5p, in combination with its target MORF4L2, may provide a novel biomarker for MEN1-associated tumours.

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P124

The prolactin receptor variant, Asn492Ile, results in activation of the Akt signalling pathway, and is found more frequently in patients with prolactinomas

Caroline Gorvin[1], Paul Newey[1,2], Victoria Stokes[1], Angela Rogers[1], Georgia Ntali[1], Peter Lees[3], Niki Karavitaki[4,5], Ashley Grossman[4] & Rajesh Thakker[1]
[1]University of Oxford, Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, Oxford, UK; [2]Division of Cardiovascular and Diabetes Medicine, Ninewells Hospital and Medical School, Dundee, UK; [3]Faculty of Medical Leadership and Management, London, UK; [4]Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK; [5]University of Birmingham, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, Birmingham, UK.

The prolactin receptor (PRLR) is a type-I cytokine receptor that plays critical roles in mammary gland development, lactation and glucose metabolism, and PRLR mutations have been associated with breast cancer and familial hyperprolactinaemia. The PRLR signals via Janus kinase-2-signal transducer and activator of transcription-5 (JAK2-STAT5) or phosphoinositide 3-kinase-Akt (PI3K-Akt) pathways to mediate changes in transcription, differentiation and proliferation, and we hypothesised that some PRLR variants may be associated with the occurrence of prolactinomas. We investigated leukocyte DNA from 46 patients (25 males and 21 females, mean age at diagnosis = 37.5 years) with prolactinomas, of which ~65% were macroadenomas. The PRLR Ile492 variant (wild-type Asn492) occurred more frequently in prolactinoma patients than normals in the exome variant server data from >6,500 individuals (19.57% versus 0.24%, $P<0.0001$). The effects of the PRLR WT Asn492 and variant Ile492 were assessed by transient transfection of WT and variant *PRLR* constructs in HEK293 cells that were treated with prolactin (0–1,000 ng/ml). Immediate signalling events were measured using phospho-STAT5 (pSTAT5) and phospho-Akt (pAkt) AlphaScreen assays, and later signalling events were assessed using a STAT5-dependent gene expression assay, utilising a cytokine inducible SH2-containing protein (*CISH*) luciferase reporter, and a CellTiter Blue proliferation assay. The prolactin-induced pSTAT5 and *CISH* luciferase reporter activity were similar in cells expressing PRLR Asn492 and Ile492, thereby demonstrating that Ile492 has no effect on JAK2-STAT5 signalling. However, pAkt signalling was significantly increased by >65% ($P<0.02$), and proliferation at 48, 72 and 96 h, by $123.96\pm60.06\%$, $194.75\pm83.18\%$ and $102.91\pm27.43\%$, $P<0.02$, respectively) in Ile492 expressing cells compared to wild-type (Asn492) expressing cells. Thus, the Ile492 PRLR variant, which increased Akt signalling and cell proliferation, occurs more frequently in patients with prolactinomas, thereby indicating that PRLR variants may contribute to pathogenicity by multiple signalling mechanisms.

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P125

Multiple endocrine neoplasia type 1 (MEN1) in identical twins, with different MEN1 tumours, is due to a deletion of the *MEN1* 5′ untranslated region (UTR)

Kreepa Kooblall[1], Treena Cranston[2], Kate Lines[1], Mark Stevenson[1], Angela Rogers[1], Simona Grozinsky-Glasberg[3], Daniel Flanagan[4] & Rajesh Thakker[1]
[1]Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford, UK; [2]Oxford Medical Genetics Laboratories, Oxford University Hospitals NHS Trust, Churchill Hospital, Oxford, UK; [3]Neuroendocrine Tumour Unit, Endocrine and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Centre, Jerusalem, Israel; [4]Department of Endocrinology, Derriford Hospital, Plymouth, UK.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterised by the occurrence of parathyroid, pancreatic and pituitary tumours, and is due to mutations of the MEN1 gene, which encodes menin. We have investigated identical twins with *MEN1*, one of whom developed primary hyperparathyroidism (PHPT) and a prolactinoma that caused pubertal arrest, and the other had PHPT only. DNA sequence analysis of the *MEN1* coding region had not identified any abnormalities and we hypothesised that deletions and mutations involving the untranslated regions may be involved, and we investigated these using patients' leukocyte DNA and combined Sanger DNA sequence and multiplex ligation-dependent probe amplification (MLPA) analysis. This revealed a heterozygous 596bp deletion between nucleotides −1,088 and −493 upstream of the translation start site, located within the *MEN1* 5′ untranslated region (UTR), and includes the core promoter and multiple cis-regulatory regions. To investigate the effects of this 5′UTR deletion on *MEN1* promoter activity, we generated luciferase reporter constructs, containing a wild-type 842bp or mutant 246bp *MEN1* promoter, and transfected them into human insulinoma BON-1 cells and human embryonic kidney HEK293 cells. This revealed the mutation to result in significant reductions by 17-fold ($P<0.0001$) and 30-fold ($P<0.0001$) in luciferase expression in BON-1 and HEK293 cells, respectively, when compared to the wild-type. The effects of this 5′UTR deletion on *MEN1* transcription and translation were assessed using qRT-PCR and Western blot analysis, respectively, of mRNA and protein lysates obtained from Epstein-Barr-virus transformed lymphoblastoid cells derived from the affected twins and unrelated controls ($N=4$). This demonstrated the 5′UTR deletion to result in significant reductions of 82% ($P<0.05$) and 88% ($P<0.05$) in *MEN1* mRNA and menin protein, respectively. Thus, our results report the first germline *MEN1* 5′UTR mutation and highlight the importance of investigating UTRs in MEN1 patients who do not have coding region mutations.

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P126

Radiological surveillance in multiple endocrine neoplasia type 1: A double edged sword?

Ruth Casey, Debbie Saunders, Ben Challis, Deborah Pitfield, Heok Cheow, Ashley Shaw & Helen Simpson
Cambridge University Hospital, NHS Foundation Trust, Cambridge, UK.

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary condition characterised by the predisposition to hyperplasia or the development of solitary adenomas of multiple endocrine gland. MEN1 related disease is responsible for death in two thirds of patients with this hereditary condition and the mean age at death is 55 years. This associated mortality necessitates a vigorous surveillance protocol, however all recommendations for radiological surveillance are based on non-prospective data and the clinical practice guideline recommendations were made despite a reported lack of consensus on the optimum radiological surveillance. This in mind, we sought to determine if cumulative radiation exposure as part of the recommended radiological surveillance programme posed a distinct and independent risk in this cohort of patients with hereditary endocrine neoplasia. A retrospective review of patients with MEN1 attending our institution was carried out and demographic and clinical information including clinical phenotype was obtained on all patients. A review of all radiological procedures performed as part of MEN1 surveillance between the time period; 2007–2015 was performed and an estimated radiation effective dose (ED) for each individual patient was calculated. A total of 43 patients were included in this study. The mean ED was 121 mSv and the estimated mean lifetime risk of cancer secondary to radiation exposure was calculated as 0.49%. Patients with malignant neuroendocrine tumours (NETS) had significantly higher ED levels compared to patients without metastatic disease (*P*-value <0.00002) and functional pancreatic neuroendocrine tumours (PNETS) were also associated with a higher ED (*P*-value 0.002). This study is a sharp reminder of the effects of long term radiological surveillance and the need for a multi-modality imaging approach to reduce exposure to ionising radiation in patients with hereditary cancer syndromes requiring life-long follow up.

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P127

A review of the diagnostic sensitivity of plasma metanephrine testing in patients with SDH gene mutations

Shalin Abraham, Ruth Casey, Deborah Pitfield, Ben Challis & Helen Simpson
Cambridge University Hospital, NHS Foundation Trust, Cambridge, UK.

Phaeochromocytomas (PC) are tumours of the adrenal medulla and paragangliomas (PGL) refer to their extra-adrenal counterpart arising from sympathetic or parasympathetic tissue. Mutations in the citric acid cycle enzyme succinate dehydrogenase (SDH) predispose to PC/PGL. Clinical practice guidelines suggest that plasma metanephrine and normetanephrine levels measured in the supine position should be used in the first instance for biochemical diagnosis, and those with positive results should have CT imaging for tumour localisation. The aim of this review was to determine if plasma metanephrine testing was a sensitive biochemical-screening test in patients with SDH mutations. A retrospective review of 32 patients (14 with SDH mutations) diagnosed with a PC/PGL in Cambridge University Hospital over a 10 year period was performed. A review of the plasma metanephrine levels at first diagnosis for each patient was carried out. In the SDH group mutations included: 66.6% in SDHB, 20% in SDHC, 6.7% in SDHD, and 6.7% in SDHA. The average age at diagnosis was 45.3 years, compared to 44.3 years in the no-mutation cohort. Phenotypes varied between groups; in the SDH cohort, 50% of tumours were head and neck paragangliomas and remaining 50% were abdominal paragangliomas. In the no-mutation cohort, 72% of tumours were adrenal phaeochromocytomas. In the SDH mutation cohort, the mean plasma metanephrine level was 199.5 pmol/l ($\pm$33.3 S.D.), compared to 1399.6 pmol/l ($\pm$2242.1 S.D.) in the no-mutation cohort (*P*-value 0.0364). The mean normetanephrine level was 1444.5 ($\pm$1964.4 S.D.), compared to 12 087.4 ($\pm$21 275 S.D.) in the no-mutation cohort (*P*-value 0.049). This study highlights that plasma metanephrine testing is a less sensitive biochemical-screening test in patients with SDH mutations due to the associated phenotype. Plasma methoxytyramine as an adjunct to plasma metanephrines may improve the sensitivity of biochemical screening in this cohort.

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P128

Timing and outcome of surgery for primary hyperparathyroidism in MEN1

Mamta Joshi, Barbara McGowan, Johnathan Hubbard, Jake Powrie, Louise Breen, Audrey Jacques, Louise Izatt & Paul Carroll
Guy's and St Thomas NHS Trust, London, UK.

Background
There is no consensus on the optimal timing of surgery for primary hyperparathyroidism (PHPT) in MEN1. Experienced centres recommend subtotal or total parathyroid surgery with three and a half gland surgery along with thymic removal as a favoured procedure; but long-term outcomes have rarely been reported.
Objective
To investigate the indications and outcomes for surgery in patients with PHPT in MEN1
Methods
Review of case notes, electronic records and clinical material from a cohort of MEN1 patients.
Results
Thirty-five patients with genetically confirmed MEN1 (21F(60%); age 42 years (range 11–83)) were included of whom 34 had PHPT. Twenty-eight of the 34 (82%) have had parathyroid surgery. Of these 28 patients 18 (64%) had significant symptoms of hypercalcemia or renal stones. Severe hypercalcemia with [Ca^{2+}] >3 mmol/l was present in only 1/28 patients. The pre-operative calcium was 2.78 ± 0.13 mmol/l (mean $\pm$ S.D.), the [PTH] was 115 ± 61 ng/l (10–65 ng/l). The favoured operation was 3.5 gland parathyroidectomy (18/28 (64%)), with total performed in 4/28 (14%). At 6 months post-surgery hypoparathyroidism was present in 9/28 (32%), persistent hypercalcemia in 8/28 (29%), and normocalcemia in 13/28 (46%). At longer term follow up 9/13 developed recurrent hypercalcemia. In our series, exon 3 mutation was associated with a higher chance of recurrence of PHPT on follow up.
Summary
Symptoms and renal calculi with elevated servum [Ca^{2+}] were the commonest reasons for surgical intervention. Post-operatively 1/3 patients have hypoparathyroidism and in the others recurrence/ persistence of hypercalcaemia occurs in the majority.
Conclusion
PHPT due to parathyroid hyperplasia is a different condition to parathyroid adenoma and applying the same criteria for first surgery in PHPT in MEN1 is inappropriate. In the absence of a standardised approach the decision to operate on parathyroid hyperplasia in MEN1 needs careful consideration, in the knowledge that long-term normalisation of [Ca^{2+}] is rarely achieved.

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P129

Low vitamin D is associated with increased bladder cancer risk; a systematic review and evidence of a potential mechanism

Rosemary Bland[1,2], Corina Chivu[1], Kieran Jefferson[2], Donald MacDonald[2], Gulnaz Iqbal[1] & Janet Dunn[1]
[1]The University of Warwick, Coventry, UK; [2]University Hospital Coventry and Warwickshire, Coventry, UK.

Vitamin D deficiency is associated with the development of some cancers and *in vitro* 1,25-dihydroxyvitamin D (1,25D) reduces cell proliferation. We suggest that modification of tissue specific immune responses, as a consequence of local synthesis of 1,25D, may be key. To assess the impact of serum 25D on the risk of bladder cancer we conducted a systematic review. To test our hypothesis, expression of vitamin D signalling components and the synthesis of 1,25D were examined in human bladder epithelial cell lines (T24/83 and RT4). A search of Embase, Web of Science, Medline and Cochrane library (April–May 2016) identified 287 citations. Following title and abstract review by two reviewers seven full papers were appraised. Studies varied in the number of participants (112–1125) and point of vitamin D measurement (pre-diagnosis, diagnosis, or follow-up). Low vitamin D levels were associated with bladder cancer risk in five of the seven studies. Higher vitamin D levels also correlated with better survival and outcomes. The vitamin D receptor and 25-hydroxyvitamin D 1α-hydroxylase (CYP27B1; 1α-OHase) mRNA and protein were expressed by both cell lines. 24-hydroxylase (24-OHase; metabolises 1,25D) mRNA was almost undetectable in unstimulated cells but was increased significantly by 1,25D (10 nM, 3–24 h; $P<0.05$). 24-OHase was also induced by 25D (100 nM, 6–24 h; $P<0.05$) indicating 1α-OHase activity. Synthesis of 1,25D was confirmed by EIA. Cathelicidin mRNA was induced by 1,25D and 25D in RT4 cells (10 nM/100 nM, 6 h; $P<0.05$). These data demonstrate that bladder cancer risk correlates with low

serum 25D levels. Transitional epithelial cells express functional vitamin D signalling and are able to synthesize sufficient 1,25D to stimulate a local immune response. We propose that in order to initiate a cell-mediated immune response to malignancy adequate levels of serum 25D are required for synthesis of 1,25D by bladder epithelial cells.

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P130

Diagnostic performance of adrenal imaging in a high risk population for adrenal malignancy

Danae Delivanis, Mark Nathan, Thomas Atwell, Patrick Eiken, Grant Schmit, Neena Natt, Dana Erickson, Spyridoula Maraka, William Young & Irina Bancos
Mayo Clinic, Rochester, Minnesota, USA.

Objective
There is limited evidence on the diagnostic accuracy of imaging tests in patients at high risk for adrenal malignancy. Our objective was to determine the performance of computed tomography (CT) and ^{18}FDG-PET/CT imaging in diagnosing a malignant adrenal mass in a high risk population of patients referred for CT-guided adrenal biopsy.
Methods
We retrospectively reviewed the medical records of 378 patients who had percutaneous adrenal core biopsies performed at Mayo Clinic Rochester between 1994 and 2014. Reference standard was based on histology in all patients. For FDG-PET, the standardized uptake value (SUV) was measured in the adrenal mass (SUV max) and liver (SUV liver). The SUV max to SUV liver ratios (ALR) were calculated.
Results
The median age of our cohort was 68 years (range 18–91) and 237/379 (62.5%) were men. Patients were referred for adrenal biopsy mainly due to suspected or confirmed extra-adrenal malignancy (303/378, 80%). Malignant adrenal lesions were found in 237 patients (62.5%). Benign adrenal cortical adenomas were diagnosed in 136 patients (36%). Unenhanced CT was performed in 352 patients (225 malignant, 127 benign lesions). All malignant adrenal lesions demonstrated a radiodensity of >10 Hounsfield units (HU) (sensitivity 100%, specificity 33%, positive predictive value (PPV) 73%, and negative predictive value (NPV) 100%). ^{18}FDG-PET/CT was performed in 91 patients. SUV max was higher in malignant lesions when compared to benign lesions (median 10.1 (range 1.9–29.4) vs 3.7 (range, 1.4–24.5), $P<.001$). Similarly, ALR in malignant lesions was higher than in benign lesions (median 3 (range, 0.5–13.4) vs 1.15 (range, 0.6–6.6), $P<0.001$). An ALR cutoff of 1.8 performed best in diagnosing adrenal malignancy (sensitivity 83%, specificity 84%, PPV 85%, and NPV 82%).
Conclusion
Noncontract CT HU of 10 or below is a good initial imaging approach as it excludes a malignant lesion. For lesions >10HU, ^{18}FDG PET/CT could be considered in a population at high risk for adrenal malignancy. However, both sensitivity and specificity of ^{18}FDG PET/CT are not perfect; therefore clinical judgment is warranted.

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P131

Metformin alters an anti-proliferative effect of Mitotane in a human adrenocortical cancer (H295R) cell line; preliminary results

Dorota Dworakowska[1,2], Paulina Szyszka[2], Gregory Weitsman[1], Salvador Diaz-Cano[1], Marta Korbonits[3], Ashley Grossman[4], Stefan Bornstein[1,5] & Tony Ng[1]
[1]Kings College London, London, UK; [2]Medical University of Gdansk, Gdansk, Poland; [3]Queen Mary University of London, London, UK; [4]OCDEM, Oxford, UK; [5]Medical University of Dresden, Dresden, Germany.

Introduction
Metformin is used as a first line treatment in type 2 diabetes. Several studies suggest that patients with type 2 diabetes treated with metformin may have reduced cancer risk. Recently it has been shown that Metformin acts directly on mitochondria to alter cellular bioenergetics and reduce tumorigenesis. We have shown that anti-proliferative effect of Mitotane is related with changes of expression of the genes involved in mitochondrial metabolism in human adrenocortical (H295R), breast, lung and colon cancer (ENDO 2015).
Aim
As both Metformin and Mitotane affect mitochondrial metabolism, the aim of the study was to assess the impact of combine treatment of Metformin and Mitotane on H295R cell line proliferation.
Material and methods
Human adrenocortical cancer cell lines (H295R) were cultured in 96 well plates and cell proliferation rate was assessed by resazurin assay.
Results
Optimum effect of Metformin was observed at 48-h of incubation, resulting in cytotoxicity of 6, 16, 28 and 55% at the concentration of 5, 10, 20 and 40 mM, respectively. Optimum effect of Mitotane (10 μM) was observed at 24-h of incubation, resulting in 30% of cytotoxicity and this concentration was used in combine treatments with Metformin. Even though both compounds inhibited proliferation separately, combine treatment resulted in either total loss of their anti-proliferative effect (Metformin at the concentration of 5 and 10 mM) or significant decrease in cytotoxicity to 9 ($P<0.001$) and 44% ($P<0.001$) for Metformin at the concentration of 20 and 40 mM, respectively.
Conclusions
Those preliminary results shows that even though Metformin alone can have an anti-proliferative effect on H295R cell line, it should be added to Mitotane with caution as their combine effect can negatively influence cytotoxic effect of Mitotane. The studies require further experiments.

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P132

Sparsely granulated somatotroph adenomas display aspects of epithelial-mesenchymal transition

Kathryn Dix, Ashley Grossman, Olaf Ansorge & Sarah Larkin
University of Oxford, Oxford, UK.

Somatotroph adenomas (SA) causing acromegaly exist as two major pathological variants: densely and sparsely granulated, according to the number and distribution of growth-hormone-containing secretory granules. These variants are increasingly recognised by neuropathologists and endocrinologists, but the consequences for tumour behaviour and patient outcome remain to be defined. Sparsely granulated SAs are associated with younger, female patients and are more invasive and proliferative than densely granulated SAs. In order to invade surrounding structures tumour cells must switch from a polarised, static, epithelial-like phenotype to a motile, proliferative mesenchymal-like phenotype. This process, termed epithelial-mesenchymal transition (EMT), is a feature of many invasive and metastatic neoplasms. Here we hypothesise that a change in phenotype from epithelial-like towards mesenchymal-like underlies the more invasive and proliferative behaviour of sparsely granulated SAs. We examined the expression of markers and mediators of EMT in a series of SAs ($n=21$) stratified by granulation pattern and compared the findings to clinical and biochemical characteristics. Sparsely granulated SAs were significantly ($P<0.05$) larger than densely granulated SAs. There was no significant difference in preoperative plasma IGF1 or growth hormone concentrations, sex or age in this series. However, quantification of a panel of EMT-related targets revealed that sparsely granulated SAs expressed significantly more mRNA encoding ZEB1 (Zinc Finger E-Box Binding Homeobox 1) and VIM (vimentin), consistent with EMT-like changes. In addition, protein components of the adherens junction (E-cadherin, α-catenin, β-catenin, JUP, p120) were expressed in densely granulated SAs, but were completely absent in sparsely granulated SAs. These findings suggest that lack of a functional adherens junction, along with a more mesenchymal-like pattern of mRNA expression, may contribute to the more invasive behaviour of sparsely granulated SAs, and that restoration of the adherens junction may offer the possibility to inhibit the more rapid growth of sparsely granulated SAs.

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P133

Adverse fibrin network profile in survivors of brain tumours with established hormonal deficiencies: A potential mechanism for increased vascular risk

Nikolaos Kyriakakis[1,2], Satish S Kumar[1], Natalie Oxley[2], Fladia Phoenix[2], Julie Lynch[1], Ramzi Ajjan[2] & Robert D Murray[1,2]
[1]Leeds Centre for Diabetes and Endocrinology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM), University of Leeds, Leeds, UK.

Introduction
Long-term survivors of childhood-onset brain tumours have increased risk of premature vascular disease by mechanisms that remain unclear. We hypothesised that a thrombotic fibrin network profile is one mechanism for the increased vascular risk in this population.
Methods
We undertook a cross-sectional study in 33 patients with previous history of brain tumours and 33 age and sex-matched healthy controls. We performed clot structure analysis using a validated turbidimetric assay and also assessed plasma levels of thrombotic and inflammatory vascular markers including fibrinogen, C-reactive protein (CRP) and complement C3.
Results
Thirty-three patients (19 males, mean age 31.5 ± 14.2 years), treated for primary brain tumours, were studied. All patients received cranial radiotherapy, while 75.8% and 39.4% had additional surgery and chemotherapy, respectively. 94% of patients had growth hormone deficiency, whereas gonadotrophin, ACTH and TSH deficiency was evident in 18%, 12% and 6%, respectively). The time from brain tumour diagnosis to the time of the study was 8.9 ± 6.2 years. Patients had raised clot maximum absorbance (a measure of clot density) compared with controls (0.412 ± 0.10 and 0.277 ± 0.09 arbitrary units (AU) respectively; $P<0.001$), increased clot lysis time (an indicator of fibrinolysis potential) (3695 ± 731 and 2720 ± 636 seconds, respectively; $P<0.001$) and larger lysis area (1949 ± 1390 and 906 ± 704 AU, respectively; $P<0.001$). Despite differences in fibrin network characteristics, fibrinogen levels were similar in patients and controls (3.38 ± 0.95 and 3.28 ± 1.15 mg/ml, respectively; $P=0.473$). In contrast, plasma CRP was higher in patients (3.08 ± 4.25 and 0.78 ± 1.08 mg/l, respectively; $P=0.006$) with similar findings for C3 (0.75 ± 0.13 and 0.67 ± 0.13 mg/ml; $P=0.027$).
Conclusions
We demonstrate, for the first time, that survivors of brain tumours with hypopituitarism display a thrombotic fibrin network profile, providing one mechanism for increased vascular risk in this population. Further longitudinal studies are required to clarify whether optimisation of the hormonal profile results in amelioration of the thrombotic environment in this population.

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P134

Somatastatin analogue tolerability testing in the management of neuro endocrine tumours (NETs), a single centre review of practice

Michael Tadman, Philip Charlton & Ashley Grossman
Oxford University Hospitals NHS Foundation Trust, Oxford, OXON, UK.

Background and aims
Immediate release somatostatin analogues (SAs) have routinely been administered to test tolerability prior to commencing long-acting SAs, though there is limited evidence to support this process. We aim to examine this practice at our centre.
Methods
Patients who received SA therapy for a neuro endocrine tumours (NET) between December 2012 and December 2014 were identified. Records were used to identify; start date, duration of test-dosing and side effects experienced during test dosing. Data was collected on the initial long-acting SA dose and subsequent side effects experienced during treatment.
Results
Sixty-nine patients, 40 male and 29 female, were identified during the defined period. 29 had functional tumours, 40 non-functional. 24 received in-patient test-doses with three immediate release octreotide doses over 24 hours; centre practice from 2012 to early 2013. 45 received test-dosing as a day-case, with a single immediate release dose of octreotide; centre practice from late 2013 onwards. Eight patients, 4 as inpatient and 4 as day-case, experienced side effects during test dosing, including nausea (3), steatorrhea (3) and possible bradycardia (1). No patients had symptoms severe enough to prevent starting a long acting SA. 42 (61%) patients experienced side effects from the long-acting SA. Only 4 (9.5%) of these experienced side effects during test dosing, 2 as in-patient and 2 as a day-case. There was a low correlation between test-dosing and overall side-effect profile.
Conclusions
There is lack of evidence to support ongoing test dosing for patients commencing long-acting SA. There is also a lack of correlation between side-effects from test dosing and overall side-effects on long-acting SA. We have now changed practice at our centre, commencing our patients on long-acting SA without a test-dose of immediate release octreotide. Further collaborative work is planned to review this approach in a cross-centre audit.

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P135

The effect of peptide receptor radionuclide therapy (PRRT) on symptoms and tumour burden in patients with metastatic neuroendocrine tumour (NET)

Stalin Abraham, Ruth Casey, Ben Challis, Deborah Pitfield, S Whitley, Ashley Shaw, Sarah Heard, Zia Saad, John Buscombe & Helen Simpson
Cambridge University Hospital NHS Foundation Trust, Cambridge, UK.

Peptide receptor radionuclide therapy (PRRT) is a targeted therapy using synthetic somatostatin analogues attached to a radionuclide, which binds to tumours expressing somatostatin receptors. The aim was to review the role of PRRT in a tertiary referral centre. We retrospectively reviewed a cohort of 25 patients (eight males, 17 females), with a median age of 65, who received Yttrium-90 DOTATATE or Lutetium-177 DOTATATE at Addenbrookes Hospital. The location of the primary tumour varied; small bowel (52%); pancreatic (16%), appendix (8%); paraganglioma (4%); other (12%). All patients had metastases, the liver (96%) and peritoneum (56%) were the most common sites of metastatic spread. 32% had other tumour manifestations pre-PRRT, including: pleural effusion (16%); SMV obstruction (12%); ascites (12%); hydronephrosis (4%) and varices (4%). Side effects from PRRT occurred in 76% and GI side effects were the most common occurring in 80%. Thromobocytopenia was the most common haematological side effect occurring in 32%. 36% of patients stopped PRRT before the four full cycles, 24% due to disease progression and 12% due to intolerance of treatment. Gut hormone hypersecretion was noted in 56% ($n=14$). Relief of symptoms caused by gut peptide hypersecretion was achieved in 79% ($n=11$) post PRRT. Disease stabilisation was analysed post PRRT initiation. 19 (76%) had tumour stabilisation and 6 (24%) had tumour progression. In conclusion, PRRT is an effective treatment option for clinical symptom relief, biochemical and tumour burden stabilisation. However, progression of other tumoral manifestations can occur, particularly ascites as seen in 8% of patients in this study, hence PRRT is not appropriate for patients with pre-existing ascites or signs of abdominal venous occlusion. Finally, PRRT is often a later treatment option for neuroendocrine tumour (NET), but our review highlights PRRT as an effective and well tolerated adjunctive treatment and patients may benefit from starting PRRT earlier in the treatment regime.

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P136

The role of primary cilia in the molecular pathogenesis of phaeochromocytoma

Sam O'Toole[1,2], Umasuthan Srirangalingam[1,2], William Drake[1,2] & Paul Chapple[2]
[1]Department of Endocrinology, St Bartholomew's Hospital, London, UK; [2]Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

Phaeochromocytomas are life-threatening catecholamine-producing tumours of the adrenal medulla. Our understanding of their pathogenesis is incomplete, with limited ability to predict malignant potential and disappointing treatment results in disseminated disease. Phaeochromocytomas occur in the inherited cancer syndrome von Hippel-Lindau (VHL). One function of VHL protein is in the formation and maintenance of primary cilia. These are microtubule-based organelles that protrude from cells, functioning in transduction of extracellular signals. This is dependent on localisation of signalling components to cilia, including pathways that are dysregulated in tumorigenesis. Moreover, cilia act as a checkpoint for cell division, because they assemble from the basal body, which is a modified centriole and thus required for spindle pole formation at the end of interphase. In this study we tested the hypothesis that primary cilia structure is disrupted in phaeochromocytomas and observed that primary cilia incidence and length is significantly reduced relative to normal adjacent tissue. This effect was greater in VHL patients compared to sporadic cases. Using the phaeochromocytoma-derived PC12 cell line we showed that abrogation of cilia, through knockdown of the ciliary protein IFT88, correlated with increased cell division, suggesting that cilia loss drives cellular proliferation. Next, we investigated whether hypoxia (a feature of the tumour microenvironment and specifically relevant to cluster 1 phaeochromocytomas) impacted on cilia function. Hypoxia resulted in the reduction of cilia incidence and length due to HIF-mediated increased activity of the HDAC6/AURKA cilia disassembly pathway. Pharmacological inhibition and siRNA-mediated knockdown of succinate dehydrogenase resulted in a ciliary phenotype that phenocopied the hypoxic response. Together,

our data demonstrate that primary cilia dysfunction is a feature of phaeochromocytomas and identify a mechanism by which it occurs in cluster one tumours. This identification of primary cilia as a novel contributor to phaeochromocytoma pathogenesis represents a potential target for future therapeutic intervention.

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P137

The effects of proton pump inhibitor therapy on neuroendocrine tumour biomarkers

Christoforos Constantinou, Neil Hill, Steve Bloom, Kevin Murphy & Paul Bech
Imperial College London, London, UK.

Introduction
Neuroendocrine tumours (NETs) comprise a heterogeneous group of tumours that constitute a diagnostic and therapeutic challenge. The most commonly used general NET circulating biomarker is Chromogranin A (CgA). CgA is elevated under other circumstances, notably by the use of Proton Pump Inhibitors (PPIs) and possibly via a gastrin-mediated mechanism. Chromogranin B (CgB) and Cocaine- and Amphetamine-Regulated transcript (CART) are two less commonly used NET biomarkers. Some studies have reported that CgB levels might remain unaffected by PPI use; the effects of PPI use on CART have not previously been described.
Methods
Blood samples from 45 patients on PPIs and 43 controls were collected and analysed at NHS Trust outpatient clinics. Patients with a history of NET disease or with evidence of impaired renal function were excluded from the analysis. Plasma gastrin, CgA, CgB and CART levels were quantified by RIA. CgA levels were also measured using a commercially available ELISA kit (DAKO).
Results
CgB and CART levels did not differ significantly between PPI users and controls ($P=0.576$ and $P=0.588$ respectively). The same was true for CgA levels determined using our in-house RIA ($P=0.207$). This is in contrast to gastrin and CgA (DAKO) levels, which were significantly elevated in PPI users (both $P<0.001$). Furthermore, gastrin levels positively correlated with CgA (DAKO) levels ($R=0.759$, $P<0.001$).
Conclusions
CgB and CART levels remain unaffected by PPI use. However, we demonstrate significant differences in the effect of PPI treatment on CgA measured by different assays. Further work is now required to determine the utility of these biomarkers in the diagnosis of NETs in PPI users.

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Neuroendocrinology and pituitary

P138

Copeptin as a marker of cardiovascular strain during occupational heat stress

Mike Stacey[1,2], David Woods[1,3], Lee Macconnachie[4], Sophie Britland[5], Simon Delves[5], Adrian Allsopp[5], Stephen Brett[2,6], Joanne Fallowfield[5] & Christopher Boos[3,4]
[1]Royal Centre for Defence Medicine, Birmingham, UK; [2]Imperial College, London, UK; [3]Leeds Beckett University, Leeds, UK; [4]Poole Hospital NHS Trust, Poole, UK; [5]Institute of Naval Medicine, Alverstoke, UK; [6]Hammersmith Hospital, London, UK.

Background
Regulation of core body temperature (Tc) can cause significant cardiovascular strain, leading to impaired performance, incapacitation and occupational hazard during work in the heat. Where continuous Tc and heart rate (HR) monitoring is not possible (e.g. during firefighting or on military operations), safer working could result from intermittent sampling of an integrated measure of physiological strain.
Aims
To assess the relationship between HR responses to occupational heat stress and copeptin, a 39-amino acid glycopeptide comprising the C-terminal part of the vasopressin precursor (CT-proAVP).
Methods
Peak HR during maximal exercise in the heat (HRpeak) was determined for 25 military volunteers. Following acclimatisation in Cyprus, volunteers participated in 5 h continuous field training (ambient temperature = 30 °C). HR was recorded every 10 min by ambulatory ECG. After training (POST), blood was sampled for plasma copeptin and osmolality.
Results
Heart rate during training was 102 [88, 123] b.min^{-1}, or 55 [47, 64] % HRpeak. Compared with baseline rest, training led to significant ($P<0.005$) increases in copeptin (8.3 ± 3.6 vs 21.0 ± 9.4 pmol/l) and osmolality (293 ± 4 vs 297 ± 4 mOsm/kg). While copeptin associated moderately with POST osmolality ($r=0.54$), it also correlated with POST HR ($r=0.64$) and % HRpeak ($r=0.73$), as well as with maximum % HRpeak achieved during training ($r=0.54$). Volunteers with copeptin ≥ 20 ($n=13$) vs <20 pmol/l ($n=12$) differed according to % HR peak (54 ± 6 vs 49 ± 4 pmol/l, $P<0.05$).
Discussion
Moderate-to-severe cardiovascular strain was achieved within ethical limits. Potential stimuli to copeptin/AVP secretion included osmolality, heart rate and other factors (e.g. baroreceptor activation). Copeptin could play a role in the investigation of exertional collapse, or identification of 'critical' cardiovascular strain before incapacitation. Its diagnostic/prognostic value should be established in more controlled settings, with higher exertional-heat stress, and in the post-collapse patient population.

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P139

LGR4 and *EAP1* mutations are implicated in the phenotype of self-limited delayed puberty

Alessandra Mancini[1], Sasha R Howard[1], Gerard Ruiz-Babot[1], Claudia P Cabrera[2,3], Michael R Barnes[2,3], Leonardo Guasti[1] & Leo Dunkel[1]
[1]Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [2]Centre for Translational Bioinformatics, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [3]NIHR Barts Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, UK.

Background
Aberrations in the timing of puberty may result in significant adverse health outcomes, including cancers, cardiovascular and neurological pathologies. Self-limited delayed puberty (DP) (i.e. constitutional delay of puberty) runs in families with either autosomal dominant or complex inheritance patterns in >70% of families, indicating a strong genetic basis of the trait. However, only a few genes have been identified underlying DP so far.
Objective and hypotheses
We hypothesise that genes causing DP are amenable to discovery through exome sequencing of our large cohort with familial DP.
Methods and results
Whole exome sequencing was performed on DNA from 111 individuals of 18 multi-generational families affected with DP. After filtering we identified 3 rare, potentially pathogenic missense variants in *LGR4* (16 individuals in four families) and one in-frame deletion and one rare missense variant in *EAP1* in two families (five affected individuals) that all segregated with the DP trait. *In vitro* analysis on *LGR4* and *EAP1* revealed specific expression in mice olfactory epithelium at different embryonic stages and in the peri-pubertal mice hypothalamus, respectively. The pathogenicity of each of variant is under investigation. *LGR4* variants have been produced by site directed mutagenesis and expressed in eukaryotic cell through transfection. Intracellular trafficking, ligand binding and signal transduction through Wnt-signalling are being investigated.
Conclusion
The preliminary results suggest a causal role for *LGR4* and *EAP1* in delayed puberty. Embryonic expression points to a role for *LGR4* in GnRH neuronal migration. *EAP1* may act upstream of GnRH to influence pubertal timing.

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P140

Complications of radiation therapy (RT) for acromegaly

Saodat Issaeva, Zamira Khalimova, Adliya Khalikova & Shokhsanam Safarova
Republican Specialized Scientific and Practical Medical Center of Endocrinology Uzbekistan, Tashkent, Uzbekistan.

The purpose of the study
To examine the incidence of neuroendocrine complications after RT of pituitary somatotropinomas.

Materials and methods
Thirty patients surveyed after receiving radiation therapy (RT) at a dose of 45 g in 25 fractions a day. Of these, 21 (70%) females, 9 (30%) men. The age of patients ranged from 36–71 years. 37% of them had pituitary macroadenoma with para-, supra-, infrasellar growth. Duration of illness was on average 15 years. Period of observation after RT averaged 10 years. The levels of GH, IGF1, PRL, TSH, LH, FSH, fr.T4, cortisol, estradiol, testosterone, CT/MRI of the brain covering pituitary, visual field and acuity tests, fundoscopy were assesed. All patients received RT in combination with drug therapy. Six of them (20%) received RT on the background of drug therapy, 11 (37%) after the TAG and 13 (43%) were primary. To assess the consequences of RT we checked all parameters before (I group) and a year or more after RT (II group).
Results of the study
The following impairments took place in I group: increased GH (M = 107), IGF1 (M = 1138) in 75%, and PRL in 33%; decreased gonadotropins in 80%, TSH and fr.T4 in 17%, cortisol in 10%, decreased visual acuity in 30%, menstrual disorder in 62%, impaired potency in 11% of patients. Group II showed the following results: GH (M = 33) and IGF1 (M = 434) in 38%, PRL in 9%; decreased gonadotrpins in 80%, TSH and fr.T4 in 30%, cortisol in 50%, menstrual disorder in 67%, impaired potency in 33%, decreased visual acuity in 57% of patients. Moreover, 20% developed ESS, 3% necrosis of brain tissue.
Conclusions
RT in pituitary somatotropinomas leads to the stabilization of the pathological process.

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P141

Hypobaric hypoxia-induced neurodegeneration and memory impairment is glucocorticoid receptor dependent

Iswar Baitharu[1,2], Satya Narayan Deep[1] & Govindasamy Ilavazhagan[1,3]
[1]Defense Institute of Physiology and Allied Sciences, New Delhi, Delhi, India; [2]Sambalpur University, Sambalpur, Odisha, India;
[3]Hindustan University, Chennai, Tamilnadu, India.

Chronic exposure to hypobaric hypoxia (HH) causes neurodegeneration and loss of memory. The underlying mechanisms of HH-induced memory impairment have been attributed to prolonged elevated corticosterone level in hippocampus leading to augmented glutamate excitotoxicity, oxidative stress, alteration of neurotransmitter level or their receptors and calcium mediated signaling. Whether this corticosterone mediated neurodegenerative effect occurs through over-stimulation of glucocorticoid receptors (GRs) or is independent of the GRs, is not known. Four groups of rats were taken and GR blocker mifepristone was administered intraperitoneally during exposure to HH from 3rd to 7th days. Our results showed duration dependent transcriptional upregulation of GRs and MRs following exposure to HH. Prolonged exposure to HH for 7 days augmented the translocation of GRs from cytosol to nucleus. Inhibition of GRs during hypoxic exposure improved the hippocampal ATP level and modulated the apoptotic markers like p53, Bcl2 and Bax. Decreased expression of L-type calcium channel and NR1 subunit of NMDA receptors were also observed following administration of mifepristone during hypoxic exposure. Morphological studies following mifepristone administration during hypoxic exposure showed decreased number of pyknotic cells in hippocampus and decrease in apoptotic and necrotic cells in the CA3 region of hippocampus. The study indicates that elevated corticosterone level during hypoxic exposure causes neurodegeneration and acts through its binding to GRs indicating that inhibition of GRs may provide therapeutic effect in ameliorating HH induced memory impairment.
Keywords: Corticosterone, memory impairment, hypobaric hypoxia, apoptosis, neurodegeneration

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P142

Hypopituitarism is associated with decreased oxytocin concentrations and reduced empathic ability

Katie Daughters[1], Antony Manstead[1] & Aled Rees[2]
[1]School of Psychology, Cardiff University, Cardiff, UK; [2]School of Medicine, Cardiff University, Cardiff, UK.

Background
Cranial diabetes insipidus (CDI) is characterised by arginine vasopressin (AVP) deficiency. Oxytocin (OT) is structurally related to AVP and is synthesised in the same hypothalamic nuclei, but a clinical syndrome of OT deficiency is not currently recognised. Psychological research has demonstrated that OT influences social and emotional behaviours, particularly empathic behaviour.
Aim
We hypothesised that patients with acquired CDI and anterior hypopituitarism would display OT deficiency, and consequently perform worse on empathy-related tasks, compared to age-matched clinical control (CC – isolated anterior hypopituitarism) and healthy control (HC) groups.
Method
Fifty-six participants (Age 46.54 ± 16.30 years; CDI: $n = 20$, 8 males; CC: $n = 15$, 6 males; HC: $n = 20$, 7 males) provided two saliva samples (pre- and post-empathy tasks) which were analysed for OT using an ELISA method, and undertook two empathy tasks: the Reading the Mind in the Eyes Task (RMET) and the Facial Expression Recognition (FER) task.
Results
CDI patients (mean OT = 86.1 pg/ml, S.E. = 15.9) and CC patients (mean OT = 86.6 pg/ml, S.E. = 18.4) had lower OT concentrations compared to HC participants (mean OT = 131.5 pg/ml, S.E. = 15.9), but this did not quite reach significance ($P = 0.084$). CDI and CC patients performed significantly worse on the RMET compared to HC participants ($P = 0.007$). Regression analyses revealed that patients' OT response during the study significantly predicted their RMET performance ($P = 0.025$). CDI and CC patients also performed significantly worse compared to HC participants at identifying high intensity facial expressions ($P = 0.004$).
Conclusions
Hypopituitarism may be associated with reduced OT concentrations and impaired empathic ability. Whilst further studies are needed to replicate these findings, our data suggest that OT replacement may offer a therapeutic approach to improve psychological well-being in patients with hypopituitarism.

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P143

Investigation of hyperprolactinaemia in patients with polycystic ovarian syndrome

Omar El Tokhy, Emma Hatfield & Tricia Tan
Imperial College London, London, UK.

Background
Hyperprolactinaemia is common in patients presenting with polycystic ovary syndrome (PCOS). Recent studies suggest that each condition has an independent aetiology, hence appropriate investigation of hyperprolactinaemia in the context of PCOS is required, for which separate treatment may then be provided. Appropriate investigation includes a serum macroprolactin screen, a specific drug history for drug-induced hyperprolactinaemia (DIH), blood tests to exclude secondary causes and, when indicated, a magnetic resonance imaging (MRI) examination of the pituitary gland. However, there is no current algorithm for appropriate investigation of hyperprolactinaemia in the setting of PCOS.
Objectives
To determine in patients with PCOS: (i) the prevalence of hyperprolactinaemia and its causes, (ii) the sequence of investigations for hyperprolactinaemia, and (iii) their subsequent management plan.
Methods
A retrospective audit of 493 PCOS patients who attended an Endocrinology Outpatient clinic between June 2012 and April 2016. Data was collected on demographics, presenting signs and symptoms, further imaging investigations, biochemical results as well as treatment plans.
Results
Only 334 (67.7%) patients with PCOS had serum prolactin levels measured at presentation. Fifty-eight (17.4%) female patients with PCOS presented with coexisting hyperprolactinaemia. Twenty-five (43.1%) patients presented with macroprolactinaemia, 18 (31.0%) with a pituitary adenoma and the remaining 15 (25.9%) with DIH. Excluding macroprolactinaemia, 33 (9.9%) patients from the total PCOS cohort demonstrated true hyperprolactinaemia. Twenty (52.7%) MRI pituitary scans performed were not necessary since diagnoses of macroprolactinaemia and DIH had already been made. Elimination of these scans could have resulted in financial savings.

Conclusion
All patients being evaluated for PCOS should have serum prolactin measured. We propose a diagnostic algorithm for appropriate investigation of hyperprolactinaemia in PCOS, which ensures accurate diagnosis and prevents superfluous investigation.
Keywords: PCOS, Hyperprolactinaemia, macroprolactin, pituitary adenoma, drug-induced, MRI.
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P144

Conservatively managed non-functioning pituitary adenoma – clinical and radiological course

Farooq Ahmed, Zafar Hashmi, Changez Jadun, Natarjan Saravanappa, Simon Shaw, John Ayuk & Biju Jose
Royal Stoke University Hospital, University Hospitals of North Midlands, Stoke-on-Trent, UK.

Introduction
Clinically non-functioning pituitary adenoma (NFPA) represents up to 30% of pituitary tumours. Management is dictated by their size or mass effect. The natural progression of NFPA attracts debate as the evidence-base is limited.
Methods
Conservatively managed NFPA patients were included. A single radiologist reviewed all images to avoid bias.
Results
Forty-six patients were identified, 21 female. Four presented acutely – two apoplexy, one headache and another visual disturbance; 26 were incidental diagnoses; 17 had hypogonadism, 14 requiring testosterone replacement. The mean tumour diameter was 19 mm (range 7-39 mm). 43 were macroadenoma. Majority were solid (38), the rest cystic or mixed. 28 had suprasellar extension. Of these, 13 were abutting, two were compressing and six were stretching the optic chiasm. 11 extended into the cavernous sinus. Three had haemorrhage in the lesion. The mean follow-up was 34 months. During this period, 13 shrank (-4.5 mm; range 1–24 mm). 17 remained unchanged. 16 showed enlargement ($+2.5$ mm; 1–11 mm). The longer the duration of follow-up, the larger was the increment. Eight had visual field defects, all had suprasellar tumour extension. Mean tumour size was 22 mm (7–39 mm). Among these, two increased in size by mean 7 mm over 52 months, but both had stable vision. The remaining had stable tumour. One had worsening vision, but tumour had shrunken by 5 mm. The decision to manage conservatively was either patient choice or the lack of progression of tumour/visual defect. One patient with worsening vision was unfit for surgery.
Conclusion
The natural progression of NFPA can be variable. In the absence of mass effect, these patients can be managed conservatively with radiological and orthoptic surveillance. Treatment decision should be made within a pituitary MDT setting involving the patient in decision-making. In those showing a tendency to grow, long term MRI surveillance is essential.
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P145

The epigenetic modifying compound, JQ1+, increases apoptosis in pituitary tumours

Kate E. Lines[1], Mark Stevenson[1], Panagis Filippakopoulos[2], Susanne Muller[2], Stefan Knapp[2], Chas Bountra[2] & Rajesh V Thakker[1]
[1]Academic Endocrine Unit, OCDEM, University of Oxford, Oxford, UK; [2]Structural Genomics Consortium, University of Oxford, Oxford, UK.

Epigenetic modifications and chromatin remodelling have been demonstrated to play a key role in the development, and progression of multiple cancers, and compounds regulating these mechanisms represent a novel class of anti-cancer drugs. Menin, which is encoded by the *MEN1* gene, whose mutations result in a syndrome characterised by pituitary, parathyroid and pancreatic islet tumours, binds histone modifying enzymes, including the histone methyltransferase MLL1. Furthermore, menin, together with the acetyl-lysine recognising bromo and extra terminal (BET) family protein, BRD4, has been shown to be an important mediator of transformation, e.g. in MLL-fusion leukemia, and blocking of binding of the BRD4 bromodomain to acetylated histones using the chemical inhibitor (+)-JQ1 (JQ1+) has been shown to have efficacy in several cancers, including *Men1*-associated pancreatic neuroendocrine tumours. We therefore hypothesised that JQ1+ may be effective in treating pituitary tumours, and we examined the efficacy of JQ1+ *in vitro* and *in vivo* using the mouse pituitary cell line, AtT20, and pituitary tumours developing in $Men1^{L/L}$/*RIP2-Cre* mice, respectively. JQ1+1 μM treatment at 96 h significantly reduced AtT20 cell proliferation (assessed by CellTitre Blue assay) by 95% ($P<0.0001$), and significantly increased apoptosis (assessed by CaspaseGlo assay) by 53-fold ($P<0.0001$), compared to cells treated with an inactive stereoisomer control, JQ1−. To examine the *in vivo* efficacy of JQ1+, female $Men1^{L/L}$/*RIP2-Cre* mice were injected twice weekly (i.p.) with either 50 mg/kg JQ1+ or JQ1−, or vehicle ($n=4$ mice per group), for one month and proliferation and apoptosis analysed in pituitary tumours using bromodeoxyuridine staining and TUNEL assay, respectively. JQ1+ significantly increased apoptosis when compared to JQ1− (3.4-fold increase, $P<0.005$) and vehicle (3.5-fold increase, $P<0.005$) treatments, but had no significant effects on pituitary tumour cell proliferation. Thus, BET protein inhibitors may represent novel compounds for the treatment of pituitary tumours.
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P146

Low risk of GH deficiency post subarachnoid haemorrhage

Sumithra Giritharan, Kanna Gnanalingham & Tara Kearney
Salford Royal NHS Foundation Trust, Salford, UK.

Introduction
Current literature suggests that the incidence of GH deficiency (GHD) post subarachnoid haemorrhage (SAH) ranges from 0 to 37%. We present the results from a large single centre study and discuss factors that should be considered when testing for GHD in this population.
Method
One hundred survivors of SAH were screened with a glucagon stimulation test (GST) for pituitary hormone deficiency. Participants with isolated GHD were required to undergo a confirmatory arginine stimulation test (AST).
Results
The incidence of hypopituitarism detected by GST was 37%. The most common hormone deficiency was Isolated GHD (27%). The confirmatory AST reduced the incidence of GHD to 14%. There was no association between GHD and gender, age, interval to pituitary hormone testing, site of aneurysm rupture, type of intervention or presenting GCS. Patients with GHD were significantly heavier than patients without (mean weight difference 16.0 kg, *P*-value <0.001). They also had a higher BMI and waist hip ratio (*P*-value <0.001). QoL-AGHDA scores of patients diagnosed with GHD were significantly worse than patients with normal GH status (<0.0001).
Conclusion
This is the largest series assessing pituitary function in SAH survivors. The incidence of GHD is lower than previously thought due to the use of confirmatory testing. However given that GH response has been shown to be weight and BMI dependent, it is unclear if these results are truly reflective of GH status in these patients. The QoL-AGHDA questionnaire may be useful preliminary screening tool for GHD in patients with SAH.
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P147

Incidental pituitary adenoma: clinical and radiological features

Zafar Hashmi, Gurmit Gill, Changez Jadun, Simon Shaw, Natarajan Saravanappa, John Ayuk & Biju Jose
Royal Stoke University Hospitals, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK.

Introduction
Incidental pituitary adenoma (IPA) is found in 10–20% autopsy and radiological series. These are being increasingly detected as access to sensitive imaging modalities improves.
Methods
Patients with incidental pituitary findings between 2012 and 2016 were identified from local database. Referral details, clinical features and radiological findings were analysed. A single radiologist reviewed all images to avoid bias.
Results
Sixty-five patients referred to MDT during the study period. Thirteen (20%) were excluded as there was no discernible lesion on review.
Fifty-two patients were selected for analysis, 25 female. Mean age was 57 (20–92). Bulk of referral came from neurology (19; 37%), followed by other local hospitals (7; 14%) and GP (6; 12%).
Forty-three were macroadenoma (83%), mean size 21 mm (10–45 mm range). Forty had suprasellar extension, of which 10 caused compression/stretching of the chiasm. Of these, four had abnormal field. Fifteen had cavernous sinus extension laterally, 6 of them encircling the carotids. Seven were seen extending inferiorly. Only one had evidence of blood product on MRI.
Majority are being followed up radiologically. Eleven (21%) were offered surgery, either due to functioning tumour or mass effect from large tumour. Nine proceeded. One delayed due to cancer diagnosis. One declined. Histology were prolactinoma, acromegaly, mixed GH and ACTH and cortiocotrophinoma, craniopharyngioma and four gonadotrophinoma.
Conclusion
IPA is an increasingly recognised clinical entity. Our series highlight several important aspects. Firstly, 20% did not have a tumour and therefore the role of a dedicated pituitary neuroradiologist in avoiding unnecessary anxiety for patients cannot be overstated. Secondly, the large majority (85%) were macroadenoma and have the potential to cause clinical concern during the course. A significant proportion (20%) required surgery. Moreover, these could be functioning tumours. All these make a formal assessment of all IPAs in a dedicated pituitary MDT setting vital.

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P148

Post-traumatic amnesia, but not acute CT brain findings, predicts pituitary dysfunction following traumatic brain injury

Triona O'Shea, Claire Feeney, Joanna Zaw-Linn, Carmen Tenorio Jimenez, Tim Han, David Baxter, David Sharp & Anthony Goldstone
Computational, Cognitive and Clinical Neuroimaging Laboratory, Division of Brain Sciences, Imperial College London, London, UK.

Pituitary dysfunction is a common, treatable consequence of traumatic brain injury (TBI), and is associated with poorer outcomes. Identifying prognostic factors that allow targeted endocrine testing will ensure that patients at higher risk of pituitary dysfunction are identified and screened.
Analysis of 176 adults at least 6 weeks after TBI attending the multidisciplinary Imperial TBI clinic found an overall prevalence of pituitary dysfunction of 13.7% (deficiency of growth hormone 7.4%, gonadotrophins 3.7%, ACTH 1.1%, hyperprolactinaemia 2.5%, SIADH 0.6%). Diagnosis of GH or ACTH deficiency required failure in 2 dynamic endocrine tests. Retrospective analysis was performed to find predictive factors related to TBI severity.
Using the Mayo classification for TBI severity (incorporating duration of post-traumatic amnesia (PTA) and loss of consciousness, lowest GCS and acute CT brain findings), the prevalence of pituitary dysfunction was 15.7% after moderate-severe TBI and 7.1% after possible-mild TBI.
Pituitary dysfunction was more prevalent in those with than without PTA >24 h ($n=160$, 19.7 vs 7.4%, OR 2.6, $P=0.02$) or >1week (25.0 vs 10.3%, OR 2.4, $P=0.04$). However findings on acute CT brain imaging ($n=132$) including presence of basal skull fracture, cerebral oedema, subdural haemorrhage, subarachnoid haemorrhage, intraventricular haemorrhage or cerebral contusions were not associated with greater prevalence of pituitary dysfunction ($P=0.4=0.9$). Neither were male sex, need for craniotomy, or post TBI epilepsy associated with post-TBI pituitary dysfunction.
Duration of PTA, an important marker of TBI severity, appears to be the best predictor of post-TBI pituitary dysfunction and could help target appropriate screening strategies.

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P149

Pituitary stalk thickening: use of an innovative MRI analysis to guide clinical management

Emilia Sbardella[1,2], Robin N Joseph[3], Bahram Jafar-Mohammadi[1], Andrea M Isidori[2], Simon Cudlip[4] & Ashley B Grossman[1]
[1]Department of Endocrinology, OCDEM, Churchill Hospital, Oxford, UK; [2]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy; [3]Department of Neuroradiology, John Radcliffe Hospital, Oxford, UK; [4]Department of Neurological Surgery, John Radcliffe Hospital, Oxford, UK.

Context
Disease processes that affect the pituitary stalk are broad, ranging from indolent lesions requiring simple observation to severe lesions with significant implications. Diagnosis and management of these lesions remains unclear.
Objective
The aim of this study was to assess the clinical presentation, biochemical and pathology characteristics of pituitary stalk thickening lesions and their association with specific MRI features in order to provide diagnostic and prognostic tools to guide the clinician in the management of these difficult patients.
Design and methods
We conducted a retrospective observational study of 36 patients (mean age 37 years, range 4–83) with pituitary stalk thickening evaluated at a university hospital in Oxford, UK, from 2007 to 2015. We reviewed morphology, signal intensity, enhancement and texture appearance at MRI (evaluated with *ImageJ* program), along with clinical, biochemical, pathology and long-term follow-up data.
Results
Histological diagnosis was available for 22 patients: 46% neoplastic, 32% inflammatory and 22% congenital lesions. In the remaining 14 patients, a diagnosis of a non-neoplastic disorder was assumed on the basis of long-term follow-up (mean 41.3 months, range: 12–84). Diabetes insipidus and headache were common features in 47 and 42% at presentation, with secondary hypogonadism the most frequent anterior pituitary defect. Neoplasia was suggested on size criteria or progression with 30% sensitivity. However, textural analysis of MRI scans revealed a significant correlation between the tumour pathology and pituitary stalk heterogeneity in sagittal pre- and post-gadolinium and in coronal pre- and post-gadolinium T1-weighted image (sensitivity: 89%, specificity: 92%).
Conclusions
New techniques of MRI imaging analysis may identify clinically significant neoplastic lesions, helping to direct future therapy. We propose possible textural heterogeneity criteria of the pituitary stalk on sagittal and coronal pre- and post-gadolinium T1 images with the aim of differentiating between neoplastic and non-neoplastic lesions with high accuracy.

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P150

Morvan's syndrome: could insulin like growth factor-1 be a marker?

Simon Edeghere, Duncan Browne & Brendan McLean
Royal Cornwall Hospital, Truro, UK.

Morvan's syndrome is a rare autoimmune disease characterised by peripheral nerve hyper excitability, CNS symptoms and autonomic dysfunction which can mimic other endocrine presentations with symptoms including hyperhidrosis, weight loss, neuromyotonia and insomnia. Morvan's is associated with malignancy, in particular thymomas, suggesting paraneoplastic aetiology. This case is the first to associate Morvan's with renal carcinoma and proposes insulin like growth factor 1 (IgF1) as a marker of disease activity.
A 52 year old man presented with non-specific symptoms including weight loss, hyperhidrosis and paraesthesia. He was extensively investigated and a CT scan revealed an incidental 5.4×5.1 cm left renal mass which was confirmed to be renal cell carcinoma following a curative nephrectomy. His symptoms persisted three months following surgery and a phaeochromocytoma, carcinoid tumour, thyrotoxicosis and Cushing's syndrome were excluded. Furthermore, he had a normal positron emission tomographic scan that ruled out metastatic spread or a secondary malignancy. Interestingly, his IgF1 was found to be elevated at 103 nmol/l (normal range 8–39 nmol/l) which was confirmed on subsequent testing (although he had a normal oral glucose tolerance test excluding acromegaly). Voltage gated potassium antibodies (diagnostic of Morvan's) were positive at 843 pM (normal <100 pM) confirming Morvan's syndrome. He received an immunoglobulin infusion and high dose prednisolone and his symptoms improved significantly with a stepwise improvement in his IgF1 to 91 nmol/l then presently 42 nmol/l.

This case report is significant because it is the first case of Morvan's syndrome with renal cell carcinoma and not a thymoma and proposes IgF1 as a marker of disease as the patient's levels progressively improved with treatment and resolution of symptoms. Furthermore, voltage gated potassium channel antibodies should be considered in unexplained autonomic symptoms associated with malignancy and further research into the association of raised IgF1 with Morvan's disease activity is indicated.

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P151

MicroTSHoma: an emerging clinical entity with 'atypical' biochemical features and often 'normal' imaging characteristics on MRI

Olympia Koulouri[1,2], Carla Moran[1,2], Sarah Heard[2], Greta Lyons[1,2], Rob Smith[1], Franklin Aigbirhio[1], Nagui Antoun[2], Heok Cheow[2], David Halsall[2], Krish Chatterjee[1,2] & Mark Gurnell[1,2]
[1]University of Cambridge, Cambridge, UK; [2]Addenbrooke's Hospital, Cambridge, UK.

Background
Heightened awareness, as well as frequent thyroid function testing, have contributed to a recent rise in the incidence of thyrotropinomas. Microadenomas are now increasingly being recognized. The classical textbook description of thyrotropinomas is based on historically reported features in patients who typically had large/invasive lesions. The phenotype of microTSHomas could therefore differ.
Methods
We reviewed the records of all TSHomas referred to our centre in the last 5 years. Investigations in all patients included TFTs, alpha-subunit (ASU) and ASU:TSH molar ratio, SHBG, TRH stimulation testing and pituitary MRI. A subgroup of these patients additionally underwent detailed metabolic/physiological studies including measurement of resting energy expenditure (REE), sleeping heart rate (SHR), DXA and pituitary imaging with SPGR MRI and ^{11}C-Methionine PET/CT.
Results
Forty-three prospective cases were identified, 22 of which were microTSHomas (51%). ASU was normal in 70% of microTSHomas and was significantly lower than in the macro cases (1.9 IU/l vs 4.8 IU/l, $P=0.04$). SHBG was not elevated in one third of cases. Response to TRH stimulation was more pronounced in micro- compared to macroTSHomas (1.97- vs 1.17-fold rise, $P=0.0075$), but remained 'flat' in both groups. Pituitary MRI was reported as normal or inconclusive in 51% of cases. Detailed imaging with SPGR MRI and ^{11}C-Methionine PET/CT identified the culprit lesion in 9/13 (69%) cases with 'negative' MRI. Although many patients were relatively asymptomatic, they had raised REE and SHR and low BMD.
Conclusion
Despite, in many cases, very few overt symptoms, patients with microTSHoma demonstrate sequelae of thyrotoxicosis. Traditional tests employed in the diagnosis of TSHoma can yield normal results and conventional imaging will potentially miss half of the micro-lesions. Modern algorithms should focus on the combination of TRH testing and trial of depot somatostatin analogue, in order not to miss the diagnosis. SPGR MRI and functional pituitary imaging with ^{11}C-Methionine can be used to detect microlesions that are not visible on conventional pituitary MRI sequences, thus facilitating targeted treatment.

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P152

Development of an interactive patient database for the University Teaching Hospital Trust's neuroendocrine tumour service; and auditing early baseline biochemical investigations for gastroenteropancreatic neuroendocrine tumours

Joseph Boylan, Sally-Ann Botchey, Aftab Ahmad & Mahmud Ahmad
Royal Liverpool and Broadgreen University Hospital Trust, Liverpool, Merseyside, UK.

Background
The University Teaching Hospital Trust has a regional neuroendocrine tumour (NET) service that requires a database exclusively for NET patient information. UK and Ireland NET Society (UKINETS) guidelines for gastroenteropancreatic (GEP) NETs recommend plasma Chromogranin-A (Cg-A) and 24 h urinary 5-hydroxyindoacetic acid (24 h Ur 5-HIAA) as baseline investigations. This audit investigated both guideline adherence and the value of these tests in making the diagnosis of GEP NETs.
Method
A retrospective dataset analysis was performed using clinical records (i.e. NET clinic letters and Multidisciplinary Team (MDT) forms) and the hospital's software systems (online since 2004). NET patients' details, including Cg-A and 24 h Ur 5-HIAA levels, were recorded onto the database.
Results
56/101 (55.45%) patients under the NET service were diagnosed with GEP NETs by investigations including biopsy and imaging. 47/56 (83.93%) GEP NET patients had Cg-A levels and 15/47 (31.91%) had a significantly raised level (>150 pmol/l). 35/56 (62.50%) GEP NET patients had 24 h Ur 5-HIAA levels, 10/35 had significantly raised levels (>50 pmol/l) and 5/10 had symptoms of carcinoid syndrome. 3/35 (8.57%) confirmed GEP NET patients had symptoms of carcinoid syndrome and 24 h 5-HIAA levels below 50 pmol/l.
Discussion
83.93% and 62.50% of GEP NET patients had documented Cg-A and 24 h Ur-5HIAA levels respectively. Therefore, UKINETS guideline adherence could be improved. The results show a false negative rate of 68.09 and 8.57% in Cg-A and 24 h Ur-5HIAA tests respectively suggesting these baseline tests are of limited use in diagnosing GEP NETs. However, confounding factors (e.g. sample size) might have influenced these findings. It was unclear whether patients with raised 24 h Ur 5-HIAA levels without symptoms of carcinoid syndrome was due to incomplete records or because they were asymptomatic. Clinic and MDT letter templates were recommended to rectify this and a future re-audit is required to confirm quality improvement.

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P153

Clinical and radiological presentation of craniopharyngioma in a mixed cohort of children and adult patients

Cristina Capatina[1,2], Mihaela Bodnarescu[2], Anda Dumitrascu[2], Andra Caragheorgheopol[2] & Catalina Poiana[1,2]
[1]Carol Davila UMPh, Bucharest, Romania; [2]CI Parhon National Institue of Endocrinology, Bucharest, Romania.

Background
Craniopharyngioma is a rare epithelial tumor of the central nervous system, affecting both children and adults and associated with significant morbidity.
Objective
To study the potential differences in the clinical and radiological presentation of craniopharyngioma in children versus adults in a large mixed cohort.
Material and methods
We performed a retrospective review of craniopharyngioma patients evaluated in the National Institute of Endocrinology in Bucharest between 1990 and 2016.
Results
A total of 82 patients (59 adults, 39.27 ± 15.5 years-old; 23 children, 12.96 ± 4.2 years-old) with a mean follow-up of 6.85 years were included. The presenting symptoms were mostly headache (83% adults, 91.3% children), visual impairment, symptoms of hypopituitarism, diabetes insipidus. Some symptoms or hormonal abnormalities were significantly more prevalent in the children group: nausea, vomiting (47.82% children, 16.94% adults; $P=0.006$), photophobia (5% adults, 21.73% children; $P=0.036$), diabetes insipidus (8.4% adults, 30.43% children; $P=0.018$), GH deficiency (69.56% children; 13.5% adults; $P=0.000$). Headache, convulsions, cranial nerves paresis, hydrocephalus and ventriculoperitoneal shunt insertion were all more frequent in children, but no statistical significance was reached. Impaired visual acuity (43.13% adults, 13.63% children, $P=0.017$) or visual fields (69.23% adults, 36.36% children, $P=0.006$), optic atrophy (47.82% children, 60% adults; $P=0.001$) were more frequent in adults. The tumor dimensions was similar in both groups. Intratumoral calcifications and cystic components were significantly more prevalent in children (73.91 and 86.95%) than in adults (48.25% and 65.51%); $P=0.031$ and 0.045, respectively. Massive suprasellar extension reaching the third ventricle was frequently present (27.3% children, 19.23% adults).
Conclusions
Despite similar tumor dimensions and extension compared to adults, craniopharyngioma in children is more frequently associated with signs of intracranial pressure or meningeal irritation. Visual impairment appears to be comparatively less frequent in children with craniopharyngioma.

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P154

Non-functioning pituitary adenomas: characteristics and outcomes after trans-sphenoidal surgery

Rebecca Symes & Fraser Gibb
University of Edinburgh, Edinburgh, UK.

Introduction
Non-functioning pituitary adenomas (NFPAs) constitute a large proportion of pituitary adenomas and can lead to hypopituitarism and visual field defects. Trans-sphenoidal surgery is the treatment of choice but as a consequence patients may suffer from long-term hormone deficiencies and diabetes insipidus. We sought to examine clinical, pathological, and imaging characteristics of those presenting with NFPAs and subsequent post-surgical outcomes.
Methods
Clinical data was collected from NHS Lothian care records for patients who underwent primary trans-sphenoidal surgery for NFPAs between 2005 and 2014 ($n=81$). This retrospective analysis looked at patient characteristics, tumour pathology, tumour imaging and biochemical profiles. Mean follow-up was 5.52 ± 2.41 years.
Results
Visual disturbance and headache were the commonest presenting symptoms at 67 and 30% respectively. Pathological analysis identified most tumours to be either gonadotroph cell (38.8%) or null cell (37.5%) adenomas. Repeat surgery was required in 6.2% of patients. The percentage of patients with hormone deficiencies decreased from 64.2 to 56.8% after surgery. An inadequate day 3 morning cortisol of <460 nmol/l had a low positive predictive value of 28.1% for 6 week postoperative adrenocorticotrophic hormone deficiency. Those patients who developed hypopituitarism at follow up were more likely to be male than female (76.2 vs 35.9%, $P\leq0.001$) due to the large amount of males with hypogonadism. Patients with hormone deficiencies at follow up had larger preoperative tumours (30.4 ± 8.3 mm vs 24.7 ± 8.9 mm, $P=0.016$). Diabetes insipidus postoperatively was associated with higher preoperative sodium levels (141.0 ± 4 vs 139.0 ± 5, $P=0.042$).
Conclusions
These results show encouraging postoperative outcomes and can help clinicians identify those at risk of complications. Active follow-up should be targeted at those who are male, have large preoperative tumours and higher preoperative sodium levels.

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P155

Biliary ultrasound and liver function testing in acromegaly before and after 6 months of somatostatin analogue therapy

Rosanne M A Cope[1], Andrew S Powlson[2], Sarah J Case[1], Olympia Koulouri[2] & Mark Gurnell[1,2]
[1]School of Clinical Medicine, University of Cambridge, Cambridge, UK; [2]Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge & NIHR Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge, UK.

Background and aims
We have previously reported an increased prevalence of gallbladder polyps in treatment-naive acromegaly when compared with the general population (29 vs 4.6%), with potential implications for future malignant transformation and screening. However, little is known about biochemical markers of liver function in active acromegaly, or in response to treatment. Furthermore, somatostatin analogue (SSA) therapy is associated with the development of gallstones. Here, we examine biliary ultrasound findings and biochemical liver function before and after SSA treatment in newly-diagnosed acromegaly.
Method
Biliary ultrasound findings and biochemical liver status was assessed in 39 newly diagnosed, treatment naïve patients with acromegaly, at baseline and after six months of SSA therapy.
Results
Somatostatin analogue treatment was effective in reducing GH and IGF-1 levels (mean changes: GH, – 13.92 μg/l, $P<0.03$; IGF-1, – 1.83× upper limit of normal, $P<0.00001$). Biochemical markers of liver function (ALT, ALP, bilirubin, albumin) were within reference ranges at baseline, with no significant effect after 6 months of SSA therapy. Thirteen of thirty-nine (33%) patients had gallbladder polyps at baseline. Interestingly, only 7 of the 39 (18%) still had visible polyps after SSA. Gallstones (3/39 pre- and 8/39 post-SSA) and gallbladder sludge/debris (0/39 pre-and 6/39 post-SSA) both increased after 6 months of medical treatment.
Conclusions
Within the limitations of sample size and follow-up duration, our results confirm a high prevalence of gallbladder polyps in de novo acromegaly, and an increased risk of gallstones and gallbladder sludge/debris following SSA treatment. We saw no significant effect of acromegaly or SSA treatment on biochemical liver function. The finding that SSA therapy was associated with an apparent reduction in the prevalence of gallbladder polyps is interesting, and provides further suggestion that this should be considered a potential consequence of uncontrolled acromegaly, to be taken into consideration in screening for comorbidities.

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P156

The role of the microenvironment in the invasive phenotype of familial pituitary tumours

Sayka Barry[1], Eivind Carlsen[3], Emanuela Gadaleta[2], Dan Berney[2], Claude Chelala[2], Tatjana Crnogorac-Jurcevic[2] & Márta Korbonits[1]
[1]WHRI/QMUL, London, UK; [2]BCI/QMUL, London, UK; [3]Department of Pathology, Skien, Norway.

Background
Patients with heterozygote germline mutations in the aryl-hydrocarbon receptor interacting protein (AIP) gene (AIPpos) develop often aggressively growing tumours in early teenage years. The mechanism of this behaviour is not clear.
Aim
The role of the microenvironment in the invasive phenotype of AIPpos pituitary tumours.
Methods and results
We established that AIPpos GH-secreting tumours are infiltrated by a large number of macrophages and our microarray data on human AIP-mutant tissue samples compared to sporadic somatotrophinomas identified the 'epithelial-to-mesenchymal transition' (EMT)-pathway as one of the most significantly altered pathways in AIPpos tumours. Down-regulation of E-cadherin, beta-catenin, PERP, ESRP1 and up-regulation of ZEB1 ($P<0.05-<0.0001$). There is a functional relationship between tumour associated macrophages and EMT. Following validation of selected genes (RT-qPCR and immunohistochemistry), EMT was induced on stable AIP-knockdown GH3 cells using rat bone marrow macrophage-derived conditioned media (MCM) and assessed by Western blotting and immunofluorescence. MCM induced EMT-like phenotype, increased migratory and invasive properties, as assessed by transwell and matrigel invasion chambers, of AIP-KD cells. On the other hand, AIP-KD cell-derived media significantly increased macrophage migration. As chemoattractant CCL5 was highly up-regulated in AIPpos tumours, addition of CCL5 also increased macrophage migration and was blocked by CCL5-receptor inhibitor maraviroc by 50%.
Conclusions
This study showed the potential crosstalk between the pituitary adenomas with its microenvironment. Macrophages increased invasion of AIP-KD cells while tumour cell supernatant increased macrophage migration at least partly via CCL5. Data from this study will help us to understand the role of microenvironment in invasive pituitary tumour development which might lead to novel treatment targets.

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P157

Use of biguanides in the treatment of pituitary adenomas, an *in vitro* approach

Alejandro Ibáñez-Costa[1,2], Ma Carmen Vázquez-Borrego[2], Antonio C. Fuentes-Fayos[2], Eva Venegas-Moreno[3], Ma Ángeles Gálvez[4], Alfonso Soto-Moreno[3], Rhonda D. Kineman[5], Justo P. Castaño[2] & Raúl M. Luque[2]
[1]Centre for Endocrinology, William Harvey Research Institute, Queen Mary University of London, London, UK; [2]Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC); Department of Cell Biology, Physiology and Immunology, University of Córdoba; Hospital Universitario Reina Sofía (HURS); Campus de, Córdoba, Spain; [3]Metabolism and Nutrition Unit, Hospital Virgen del Rocío; Instituto de Biomedicina de Sevilla Sevilla (IBIS), Sevilla, Spain; [4]Service of Endocrinology and Nutrition, HURS/IMIBIC, Córdoba, Spain; [5]Research and Development Division, Jesse Brown Veterans Affairs Medical Center and Department of Medicine, Section of Endocrinology, Diabetes and Metabolism, University of Illinois at Chicago, Chicago, Illinois, USA.

Pituitary adenomas (PA) comprise a commonly underestimated pathology in terms of incidence and associated morbi-mortality. Although somatostatin analogs and dopamine antagonists constitute the main medical treatments for PAs, an appreciable subset of patients are resistant or poorly responsive to these drugs and hence is crucial the search for new therapies. Biguanides such as metformin (MF; commonly used to treat type-2 diabetes), phenformin (PF) and buformin (BF) have been shown to exert antitumour actions in in different tumour types (brain, prostate, breast and lung cancers) but their actions in PA cells have not been reported. The aim of this study was to determine the *in vitro* effect of these biguanides on key functional parameters (hormone expression/secretion, signaling pathways and cell viability) in: normal pituitaries of two primate models (*Papio anubis* and *Macaca fascicularis*) and a series of 15 functioning (GH- and ACTH-secreting) and non-functioning PAs (NFPAs). The treatment with biguanides in normal primate pituitary cultures decreased GH, ACTH and FSH secretion and GH and ACTH mRNA expression. MF and PF treatment did not alter cell viability in both species, while reduced the cell viability, in a dose-dependent manner, in GH- and ACTH-secreting PAs and NFPAs. In primates, the use of inhibitors of different signalling pathways revealed that the inhibitory effect of MF on pituitary hormone release involved the activation of mTOR, PI3K intracellular calcium signaling and/or MAPK pathways. In line with this, in PA primary cultures the effect of biguanides might involve a calcium-dependent mechanism, since treatment with these biguanides clearly altered the kinetics of cytosolic free calcium. Taken together, our results reveal a clear inhibitory effect of biguanides on pituitary adenoma cell viability *in vitro*, and given their demonstrated clinical safety suggest a potential therapeutic role of these compounds for the treatment of PA patients.

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P158

Follow up of patients with SDHB mutations attending a tertiary endocrine service in Greater Glasgow and Clyde

Stefanie Lip, Claire Middleton, Guftar Shaikh, Nicola Bradshaw, Marie Freel, Robert Lindsay & Colin Perry
Endocrine Service, Queen Elizabeth University Hospital, Glasgow, UK.

Introduction
Patients with mutations in the Succinate Dehydrogenase Complex Subunit B (SDHB) gene are predisposed to neuroendocrine tumours such as paranganglio-mas, phaeochromocytomas and gastrointestinal stromal tumours. Individuals who are carriers but have no manifestation of disease require regular surveillance. Our tertiary endocrine service provides follow up/surveillance for these patients and we cover a wide geographical area throughout the West of Scotland.
Aims
Our aim was to report follow up rates for individuals carrying a mutation in the SDHB gene (with and without disease) who were attending a tertiary endocrine service. We hypothesised that patients with a mutation but with no clinical manifestations would be less likely to attend clinic than those with clinical evidence of disease.
Methods
A list of patients with a mutation in the SDHB gene and who were known to the endocrine genetics service was obtained from outpatient clinic work lists from 2013 to 2015. Demographic data, follow up, genetic status, biochemical and imaging results were obtained. Patients were defined as having disease if they had characteristic imaging or pathology and carried an SDHB mutation. Data were collected in a secure excel spreadsheet.
Results
From year 2013 to 2015, there were 113 patients with SDHB mutations who were known to the service. Fifty-four (48%) were male and 59 (52%) were female. Average age of patients was 44.6 years (range 10–93 years). Eighty-three (74%) patients attended the clinic in that time period. Of the 83 patients who attended, 31 (37%) had disease and 52 (62%) did not have disease. Of the 30 not attending the clinic in 2013–2015, those who had died or were followed up elsewhere were excluded (10/113), leaving 20 (19%) who were lost to follow up, which consisted of 9/40 (23%) patients who had disease and 11/63 (17%) without disease.
Conclusion
We conclude that a majority of patients with SDHB attended the service. In terms of follow up, patients without disease manifestations may be less likely to attend but numbers are small. Further work needs to be undertaken in improving follow up especially in patients who are mutation positive without disease.

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P159

Dynamic hormonal diagnostics of acromegaly and Cushing's disease

Katerina Simunkova[1], Georgina Russel[1], Thomas Upton[1], Eystein Husebye[2], Paal Methlie[2], Kristian Lovas[2] & Stafford Lightman[1]
[1]University of Bristol, Bristol, UK; [2]University of Bergen, Bergen, Norway.

Pituitary and adrenal gland assessment, is one of the most important aspects of the management of a pituitary and adrenal adenoma.
Clinical practice varies widely with regard to assessment of pituitary and adrenal status pre- and post-operative. Pre-operative testing includes dynamic testing to assess function which is not practical in the immediate post-operative period. Instead a single morning serum total hormones are measured while a more definitive assessment is usually determined from a repeat dynamic testing 4–12 weeks after the surgery. What is evident from current literature is that not only is there a lack of consensus on the best test but also that the details of the most appropriate time of measurement and the correct cut-off values. Almost all hormones oscillate either under circadian or ultradian fashion and it contributes to render the interpretation of diagnostic test results more difficult since current diagnostic procedures are static and does not take into account this rhythmicity. Frequent automated blood sampling is available but it is laborious. To overcome this we (Prof Lightman research group) have developed a novel collection device linked to a microdialysis technique that automatically collects timed dialysate samples from subcutaneous tissue for 24 h or longer. The entire system has been already validated. It's safe, easy to use and needs little time commitment from the patient or from the surgical or nursing staff. By utilizing this system we obtain a full 24 h profile of hormones without disturbing the individual.
We will be able to recognize these patients earlier and with higher sensitivity compared to current diagnostic procedures and will be in a position to decide when replacement therapy is indicated. On the basis of some pilot studies we would be able to create a national collaboration network to introduce new guidelines for management of acromegaly and Cushing's disease.

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P160

Measurement of urinary 5-hydroxyindole acetic acid: correlation between spot vs 24-h urine collection

Matilde Calanchini, Michael Tadman, Jesper Krogh, Andrea Fabbri, Ashely Grossman & Brian Shine
Oxford Centre for Diabetes, Endocrinology and Metabolism – Churchill Hospital, University of Oxford, Oxford, UK.

Introduction
In patients with neuroendocrine tumours (NETs), the urinary concentration of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) is used to monitor disease progression or response to treatment. The sensitivity and specificity in the presence of the carcinoid syndrome are approximately 70 and 90%, respectively. However, there are problems with the accurate meaurement of a 24-h collection, and this is often inconvenient for patients. In addition, serotonin-containing foods may increase urinary 5-HIAA levels and require food avoidance. The aim of this study was to assess the correlation between 5-HIAA concentration in a spot-urine sample with the 24h-urine collection.
Methods
Consecutive patients with NETs or symptoms suggestive of NETs seen in our Endocrine-Oncology Clinic provided a 24h-urine collection and a spot-urine for 5-HIAA assessment. Written advice to avoid serotonin-rich food for three days prior to collection was given. Urine 5-HIAA was analysed by high-performance liquid chromatography (HPLC). As previously suggested by the group at King's Hospital London, a cut-off value of 5 mol/mmol for spot urinary 5-HIAA was used as the upper reference limit.
Results
We included 102 paired samples from 85 patients: 49/85 (58%) were male, the mean age was 64.7 (s.d. 14.1) years, and 76/85 (89%) had a previous NET diagnosis. Based on the 24h-urine collection, 58 measurements were above the reference value (5-HIAA >40 μmol/24 h) and 52 from spot specimens were above the upper limit of 5 mol/mmol. A spot-urine was concordant with 24h-urine results in 88.2%. The Spearman correlation between 5-HIAA measured in the 24h-urine and the spot-urine was $+0.88$. Using the 24h-urine collection as a gold standard, the spot-urine had a sensitivity of 84.5% and a specificity of 93.1%.
Conclusions
These results suggest that spot-urine is a simple and promising sample type for 5-HIAA analysis, in particular for follow-up in patients with known elevated 5-HIAA levels.

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P161

Bone turnover is significantly increased in patients with active acromegaly while bone mineral density remains normal

Marko Stojanovic[1,2], Dragana Miljic[1,2], Sandra Pekic[1,2], Mirjana Doknic[1,2], Milan Petakov[1,2] & Vera Popovic[1,2]
[1]Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia; [2]University of Belgrade, School of Medicine, Belgrade, Serbia.

Introduction
Skeletal complications are among most persistent and invalidating systemic impacts of acromegaly. Assessment of bone health in acromegaly by dual-X-ray absorptiometry (DXA) alone might be insufficient or even misleading.
Patients and methods
Patients with acromegaly ($n=170$) were classified as active ($n=104$), operatively cured ($n=34$) or medically controlled ($n=32$). We excluded patients with metabolic bone diseases, thyreotoxicosis, primary hyperparathyroidism, anti-resorptive therapy, renal failure and postoperative GH deficiency. A total of 57 males and 113 females were included, 52.8 (22.0–78.5) years old. Serum osteocalcin (OC) and beta-cross-laps (CTx) were analyzed in all patients by Roche ECLIA immunoassay on Cobas Analyzer. Gender, age and menopausal status speciffic reference values for OC and CTx were used. Results were expressed as % of upper limit of normal (ULN). Bone mineral density (BMD) was assessed at L1-L4 and Femoral neck using DXA Hologic Discovery-W-QDR (Apex 2.3.2 software). BMD results were expressed as Z score, accounting for age and gender.
Results
Lumbar spine BMD was normal in all patients and not significantly different in active (Zsc: 0.61 ± 0.13) cured (Zsc: 0.32 ± 0.25) or controlled acromegaly (Zsc: 0.17 ± 0.32). Femoral neck BMD was normal in all patients and not significantly different in active (Zsc: 0.61 ± 0.11) cured (Zsc: 0.59 ± 0.19) or controlled acromegaly (Zsc: 0.49 ± 0.22). OC was significantly elevated ($P<0.01$) in active acromegaly (1.01 ± 0.06%ULN) compared to cured (0.49 ± 0.05%ULN) or controlled (0.55 ± 0.06%ULN). CTx was significantly elevated ($P<0.01$) in active acromegaly (1.25 ± 0.09%ULN) compared to cured (0.59 ± 0.08%ULN) or controlled (0.70 ± 0.15%ULN).
Conclusion
Serum markers of bone formation (OC) and resorption (CTx) were significantly elevated in active acromegaly compared to cured or controlled, in a large cohort of patients. Bone mineral density was normal and not different in regard to disease activity. Increased bone turnover may be the cause of structural and biomechanical deterioration leading to vertebral fractures despite preserved BMD.

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P162

The clinical, pathological and molecular differences between sparsely and densely granulated somatotroph adenomas

Mario Shaid, Sayka Barry, Emanuela Gadaleta, Claude Chelala & Márta Korbonits
Queen Mary University of London (QMUL), London, UK.

Introduction
Somatotroph adenomas are GH producing pituitary adenomas. There are two main types based on granulation pattern: sparsely and densely granulated. Each type also has their own fibrous body pattern. Sparsely granulated (SG) have a 'dot-like' fibrous body pattern and the densely granulated (DG) have a 'perinuclear' fibrous body pattern. The fibrous bodies are mainly composed of keratin 8. Previous microarray analysis revealed six differentially expressed cytoskeleton specific genes (ANLN, DSP, SDC4, DSG2, IQGAP2 and TAGLN) that may be responsible for the different fibrous body patterns.
Aims/objectives
To validate the genes of interest using RT-qPCR in human samples and to induce fibrous bodies in the GH3 rat somatomammotroph cell line using drugs.
Methods
RT-qPCR was performed for the validation of the six genes using human sparsely, densely and normal pituitaries. GH3 cells were treated with the drugs Nocodazole or Griseofulvin for 72 h and immunocytochemistry (ICC) was subsequently performed for cytokeratin 8, actin or tubulin.
Results
RT-qPCR revealed a significant decrease in expression for DSP, SDC4, DSG2 and IQGAP2 when comparing both SG and DG to normal pituitaries. When comparing SG to DG, IQGAP2 was significantly decreased. From the immunocytochemistry, Nocodazole-treated cytokeratin-8 stained cells showed a 'dot-like' pattern similar to that observed in human SG tumours. All other treated cells produced multiple 'dot-like' structures.
Conclusion
We have demonstrated a differential expression of several cytoskeleton specific genes between tumour and normal pituitaries and identified differential expression of one of the genes when comparing sparsely and densely granulated adenomas. The cytoskeleton may play a role in the development of fibrous bodies. Fibrous body-like structures can be induced by the drugs we applied. The role of fibrous bodies in the clinical behaviour of somatotroph adenoma requires further studies.

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P163

Stereotactic radiosurgery as salvage therapy in refractory Cushings's disease: long term outcome from a single institution

Kirun Gunganah[1], Mohammed Abdalla[1], S A Akker[1], S J B Aylwin[2], P N Plowman[1], J P Monson[1], Ian Sabin[1] & W M Drake[1]
[1]Department of Endocrinology, St Bartholomew's Hospital, London, UK; [2]Department of Endocrinology, Kings College Hospital NHS Trust, London, UK.

Background
Untreated Cushing's disease has a high mortality rate. Transsphenoidal surgery is usually first line treatment and in the hands of a skilled experienced surgeon can achieve a cure rate of up to 80%. For those with recurrent or un-resectable disease, a combination of external beam radiotherapy, stereotactic radiotherapy, repeat transsphenoidal surgery, bilateral adrenalectomy and chemotherapy may be used. We investigated the safety and efficacy of stereotactic radiosurgery as salvage therapy in patients with recurrent Cushings's disease refractory to a combination of conventional treatments.
Method
This was a single-centre retrospective study of patients with recurrent Cushing's disease following a combination of surgery, external beam radiotherapy and/or chemotherapy, treated with stereotactic radiosurgery. We investigated achievement of biochemical and radiological control as well as clinical outcomes and adverse effects of stereotactic radiosurgery.
Result
From 2000 to 2016, 14 patients met our criteria. They were followed up for a median of 5 years (12–96 months). Following stereotactic radiosurgery, cortisol control was achieved in 86% of patients (12 out of 14) and reduction in tumour volume was seen in 79% of patients (11 out of 14). Three patients died due a combination of tumour progression and complications of cortisol excess (36, 60 and 72 months after stereotactic radiosurgery). One patient had recurrence of disease 5 years following initial biochemical and radiological control after stereotactic radiosurgery. Main adverse events included hypopituitarism (9 out of 14), neuromytonia (2 out of 14) and stroke (1 out of 14).
Conclusion
Stereotactic radiosurgery is an effective and safe treatment option for patients with Cushing's disease refractory to conventional therapies. Hypopituitarism was the main adverse event. Longer term follow-up is required to determine the recurrence rate of Cushing's disease post stereotactic surgery in this group of patient.

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P164

Investigation of the appearance of adenohypophyseal folliculostellate cells during embryonic chick development

Iona Talintyre, Jo Begbie & Helen Christian
University of Oxford, Oxford, UK.

Folliculostellate (FS) cells constitute around 10% of the adenohypophyseal cell population. Various functions of these non-endocrine cells have been elucidated, including the paracrine control of the function of local endocrine cells. FS cell development is currently very poorly understood. In this study FS cell appearance during embryonic chick development between pre-natal stages (st)17-37 was examined. Gene and protein expression of the FS marker proteins annexin A1 (AnxA1) and S100β were detected by *in situ* hybridisation and immunohisto-chemistry/immunogold staining respectively. In addition, the emergence of cells with FS-like morphology was investigated by electron microscopy (EM). EM analysis of st30-35 pituitary glands revealed the pre-natal appearance of FS-like cells. Expression of Islet1 in st30-37, known to be expressed in the embryonic

chick pituitary gland, was verified. However, *in situ* hybridisation and immunohistochemistry/immunogold staining for AnxA1 and S100β at the same stages demonstrated a lack of expression. AnxA1 expression was observed elsewhere in choroid plexus, mesonephros and pro-epicardium. These findings support the idea that a subset of FS cells, act as progenitors in the pituitary before differentiated marker expression is evident.

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P165

Olfactory neuroblastoma: a multi centre clinical and pathological review

Karen Young[1,4], Nara Orban[2], Peter Clarke[2], Ann Sandison[2], Catherine Gilkes[3], Ghassan Alusi[4] & Marta Korbonits[1]
[1]William Harvey Research Institution, London, UK; [2]Charing Cross Hospital, London, UK; [3]The Walton Centre, Liverpool, UK; [4]Barts and the Royal London Hospital, London, UK.

Olfactory neuroblastoma (ONB) is a rare neuroendocrine tumour arising within the sino-nasal cavity. It occurs world wide, affecting both sexes, all ages and all races with no underlying predilection having yet been identified. ONB exhibits a range of phenotypes from indolent to very aggressive, and up to 5% cases are associated with ectopic hormone secretion. Despite current gold-standard treatment of surgical resection (either endoscopic or craniofacial resection) followed by post op radiotherapy ± chemotherapy patients remain at lifelong risk of recurrence. Early stage disease has recurrence rates of up to 60%, and patients presenting with advanced (stage 4) or metastatic disease have a poor prognosis. At present very little is known about the molecular mechanisms underlying tumourigenesis in ONB. New disease biomarkers and treatments are therefore urgently needed.

Our multi-centre patient cohort ($n=48$) shows a wide age range at diagnosis and no clear difference between sex and race. The average age at presentation is 56 years, however stratification of our data reveals that patients presenting with intracranial disease are typically younger (48 years) as are patients who go on to develop metastatic disease (47 years). In our cohort all patients under 40 years presented with advanced disease (stage 3 or 4) and stage 4 disease was the most commonly diagnosed stage at presentation in all patients under 50 years. Stage 2 disease was most common in the 50–70 age group. Overall there was a 41% recurrence rate in our cohort, with multiple recurrences affecting 11%.

We summarise our patterns of recurrence, metastatic disease and outcomes related to patient age, stage and grade at presentation and treatment modalities used. We also highlight atypical features seen in some groups, and demonstrate altered immuno-histochemical profiles in some patient subgroups which may represent de-differentiation of the tumour to a more aggressive phenotype.

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P166

Corticosteroid-driven response of synaptic plasticity-associated targets are differentially regulated in the rodent brain: transcriptional actions of receptor modulators

Chinedu Udeh-Momoh[1,2], Francesca Spiga[2], Eleanor Waite[3], Fiona Thomson[4] & Stafford Lightman[2]
[1]Imperial College London, London, UK; [2]University of Bristol, Bristol, UK; [3]Oxford University, Oxford, UK; [4]Glasgow University, Glasgow, UK.

Actions of the stress hormone, glucocorticoid (GC), are essential for the modulation of implicated biological processes such as synaptic transmission. In disease paradigms that feature a hormone hyper-secretion phenotype (e.g. neurocognitive disorders), the normalcy of receptor signaling is compromised.

The pro-cognate role of Glucocorticoid receptor (GR) inhibition via hormone analogues bearing anti-glucocorticoid properties is well described. A key example is RU-486 (Mifepristone), an effective GR blocker. Though widely used experimentally, this compound exhibits partial agonist activity creating a need for potent antagonists that exhibit greater receptor-selectivity. Org A; a novel non-steroidal anti-glucocorticoid is one such candidate. Highly selective for GR, it reverses the deleterious effects of abnormal GC exposure.

Although data exists for the actions of these GR antagonists on signaling parameters like receptor translocation and activation; little is known about their effect on target gene modulation, more-so markers related to synaptic plasticity. Such information is critical since gene regulation is a key mechanism by which GCs modulate such neuronal processes.

In this study, we show that exposure to high GC levels (3 mg/kg i.p.) elicits an increase in plasma corticosterone levels sufficient to induce GR nuclear translocation, and subsequent hormone-mediated receptor activation. These effects remained unaltered by investigated compounds, **RU-486** (20 mg/kg s.c.) and **Org A** (20 mg/kg s.c.).

Differential regulation of synaptic plasticity transcripts (adcy8, sgk-1, pkaca and gria-1 mRNA) were observed in the rodent hippocampus and amygdala**.** These modulatory effects occurred in a **gene and tissue specific manner,** with both antagonists eliciting differing transcriptional responses to the GC signal.

Our results provide novel information on the differential effects of select GR antagonists on GC-mediated transcriptional responses. Given the potential use of this class of compounds for targeted- treatment of associated diseases, further research into the reported distinct transcriptional regulation during a hyper-corticosterone state is needed.

Reference

Spiga F, Lightman SL, Differential effect of glucocorticoid receptor antagonists on glucocorticoid receptor nuclear translocation and DNA binding. *Journal of Psychopharmacology* 2011 **25**, 211–221.

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P167

Polymorphism or mutation? – The role of the R304Q missense *AIP* mutation in the predisposition to pituitary adenoma

Nadira B Mothojakan[1], Francesco Ferraù[2], Mary N Dang[3], Anne Barlier[4], Philippe Chanson[5], Gianluca Occhi[6], Adrian F Daly[7], Christof Schöfl[8], Jakob Dal[9], Mônica R Gadelha[10], Mark Ludman[11], Sonal Kapur[3], Donato Iacovazzo[3] & Márta Korbonits[3]
[1]Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [2]Department of Clinical and Experimental Medicine – Endocrinology Unit, University of Messina, Messina, Italy; [3]Centre for Endocrinology, Barts and the London School of Medicine, Queen Mary University of London, London, UK; [4]Aix Marseille University CNRS, Marseille, France; [5]Endocrinology and Reproductive Diseases, Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud (site Bicêtre), Le Kremlin- Bicêtre, France; [6]Department of Biology, University of Padua, Padua, Italy; [7]Department of Endocrinology, University of Liège, Liège, Belgium; [8]Division of Endocrinology and Diabetes, Department of Medicine I, University Hospital Erlangen, Friedrich-Alexander-University, Erlangen-Nuremberg, Germany; [9]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; [10]Endocrinology Unit, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; [11]Institute of Genetics, Meir Medical Center, Kfar Saba, Israel.

Introduction

Heterozygous mutations in the *AIP* gene are associated with young-onset pituitary adenomas while homozygous loss of *AIP* in animal models is lethal. As early diagnosis could lead to better outcomes, family members of *AIP* mutation-positive patients need follow up. The R304Q variant is commonly described as pathogenic based on clinical assessment. However, it is also present in the general population (minor-allele-frequency (MAF) 0.0007–EVS, 0.0015–ExAc) and the European population included homozygote subjects. Functional studies are unable to unequivocally identify abnormal function.

Method

Clinical, histological and family history data were collected on 30 R304Q cases (including four families and 13 known sporadic cases) from the literature, other centres and our own centre. Loss-of-heterozygosity (LOH) analysis was performed on tumour tissue. *In silico* and experimental data on protein function was reviewed and screening of our large patient cohort (FIPA consortium) was compared to general population databases.

Results

With nine affected patients, the MAF in our pituitary adenoma patient cohort (1149 probands) was not significantly different from that of the ExAc database ($P=0.15$). No LOH was detected in five tumour samples. *In silico* predictions using 11 different programs suggest that this is a benign variant, as do functional studies which found that R304Q was similar to the wild-type in 6/7 assays (PDE4A5-assay, AIP-RET interaction, two half-life studies and two fruit fly models), while an *in vitro* study assessing aryl hydrocarbon receptor-target Cyp1a1 expression showed intermediate results.

Conclusion

Several familial and young-onset sporadic pituitary adenoma cases carry the R304Q *AIP* variant. *In vitro* studies, *in silico* predictions and MAF data suggests that R304Q is a benign polymorphism. This discrepancy between clinical data and experimental results provides a controversial situation sometimes seen in clinical genetics which has potential implications for clinical practice, especially the screening of family members and follow up of carriers.

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P168

Combining conventional treatment and complementary therapies benefits pituitary patients

Zosanglura Bawlchhim[1], Isuri Kurera[1], Val Corser[1], Roselle Herring[1,2], Anne Pike[1], David Russell-jones[1], Victoria Hordern[1] & Sue Davidson[1]
[1]Royal Surrey County Hospital, Guildford, Surrey, UK; [2]University of Surrey, Guildford, Surrey, UK.

Complementary therapies are becoming a recognised adjunctin cancer care as they address the psychological burden of coping with cancer. When provided in addition to standard treatments they can help provide patient centred holistic care. Patients with pituitary conditions may develop debilitating symptoms that are not easily addressed despite appropriate medical treatment.
Aim
To determine whether Complementary therapies lead to improvements in Quality of life in a group of Pituitary patients.
Method
A randomised control study involving 42 patients with a pituitary disease for at least 6 months. Of the 42 patients, 24 were offered therapy at start with a further 18 patients in the control group. The patients in the control group were offered access to therapies after a 4 months delay. The Nottingham Health Profile questionnaire was used to compare the quality of life in the two groups at 4 months intervals throughout the study. The therapies offered included Massage, Reflexology, Reiki and Cranio-sacral therapy.
Results
Total quality of life score showed a significant improvement at 12 months with complementary therapy (P value $= 0.01$). Though the sample size was small, sub-analysis of the individual quality of life parameters, showed a significant improvement at 12 months in physical mobility ($P=0.04$) and a positive trend in pain reduction scores ($P=0.05$) in the complementary therapy group.
All participants who had therapy gave positive feedback with all patients feeling that they had benefited from the therapy and would consider continuing on long-term basis.
Conclusion
This is one of the first studies to show a link between complementary therapy and symptom reduction in pituitary patients. This opens up opportunities for further research in combined therapies, compared to conventional treatments.

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P169

Significance of cumulative GH exposure in patients with acromegaly: comparison between patients in whom control was achieved and patients with active disease

Lakshminarayanan Varadhan & Richard Clayton
University Hospitals of North Midlands NHS Trust, Stoke on Trent, UK.

Aim
The aim of the study was to assess the differences between patients in remission in acromegaly and those with active ongoing disease, using cumulative GH measurement as risk factor for various complications.
Methods
A retrospective observational analysis of all patients with acromegaly treated at a tertiary referral centre since the initiation of service ($\sim$50 years) was conducted. Cumulative GH exposure was calculated as a sum of averages of GH levels measured in each calendar year, added up to the entire duration of follow up of the patient at our centre. Basic biochemical and metabolic details were collected by review of case notes. All GH values were converted to μg/l. Control was achieved if latest GH was consistently <1.5 μg/l. Development of diabetes, hypertension or new cardiovascular events and mortality were assessed.
Results
Results of 141 patients were analysed. Mean age was 48.2 years and mean duration of follow up was 146 months (4–467). Control of acromegaly had been achieved in 107 patients and mean duration to achieve control was 60 months (1–273). Comparing the 'control-achieved' vs the 'active disease' groups: mortality 29.9% vs 55.9% ($P<0.01$); Radiotherapy used 54.2% vs 61.8% ($P=$NS); Surgery attempted 62.6% vs 70.6% ($P=$NS); new incident hypertension 20.6% vs 17.6% ($P=$NS); incident diabetes 8.4% vs 8.8% ($P=$NS); new incident cardiovascular events 16.8% vs 23.5% ($P=$NS). The cumulative GH measurement was 42.7 μg/l in patients who achieved control, compared to 81.8 μg/l during the follow up period ($P=0.01$). The last measured GH was 0.7 μg/l vs 6.2 μg/l ($P<0.0001$).
Conclusion
The study shows that despite control being achieved in a significant proportion of patients with acromegaly, the risk of morbidity from acromegaly remains higher. Mortality was higher in 'active disease' group. The 'latest' GH may not be a good predictor of this risk. Cumulative GH exposure, which measures magnitude and duration of GH exposure, could be an important predictor of morbidity and mortality in acromegaly.

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P170

Audit of adult GH replacement therapy in Derby

Seifeldin Yahia, Edmond Quah, Rebecca Kinton, Hisham Ali & Roger Stanworth
Royal Derby Hospital, Derby, Derbyshire, UK.

Introduction
In 2003, the UK National Institute for Clinical Excellence (NICE) established guidelines on the use of GH in adults. These guidelines state that recombinant GH should be used only for adults with a severe GH deficiency that severely affects their quality of life. To assess current practice in relation to these guidelines, a review of patients receiving GH treatment was performed. The aims were to assess if adults with GH deficiency met NICE criteria for GH therapy and to identify reasons for initiating or continuing GH treatment if NICE criteria were not met.
Methods
Retrospective case note review of adults and young adults in transition receiving growth hormone therapy at the Royal Derby Hospital up to May 2016.
Results
Thirteen patients (ten males and three females) included in this study, two were excluded (one male and one female). Two patients had previous pituitary surgery. Six patients had Multiple Pituitary Hormones Deficiency (MPHD). All thirteen patients were assessed as adults requiring GH replacement. All patients fulfilled all criteria for commencing GH therapy. the diagnosis was secured with Insulin Stimulation test (ITT) in 8 patients (61.5%) and with Glucagon Stimulation test (GST) in the rest. 6 (46.15%) patients were treated with Surepal, 5 (38.46%) with Saizen, 1 (7.28%) with Genotropin and 1 (7.28%) with Humatrop respectively. 13 (100%) of patients were assessed with QOL-AGHDA questionnaire at baseline and all were reassessed within 12 months and met criteria to continue. There were no records of any initiation of treatment for childhood GH deficiency in this study.
Conclusion
All patients meet the NICE criteria for GH replacement therapy. The QOL-AGHDA questionnaire may have limitations given the subjective nature of questionnaires and comorbidities influencing quality of life. Additionally, consideration of both clinical evidence and patients' wishes may prove to be beneficial when commencing and reassessing patients on GH treatment.

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P171

The role of kisspeptin in the medial amygdala on male sexual behaviour in rats

Rebecca Gresham, Shengyun Li Li, Daniel Adekunbi, Minghan Hu, Xiao Feng Li Li & Kevin O'Byrne
King's College London, London, UK.

The medial amygdala (MeA) is crucial for sexual behavior; kisspeptin (Kiss1) also plays a role in sexual function. Kisspeptin receptor (Kiss1r) knockout mice display no sexual behavior. Recently Kiss1 and Kiss1r have been discovered in the posterodorsal subnucleus of the medial amygdala (MePD). We hypothesized that Kiss1 in the MePD may have an influence on male sexual behavior. To test this we bilaterally cannulated the MePD and infused kisspeptin-10 in male rats. This caused the rats to have multiple erections, an effect specific to Kiss1 receptor activation, because Kiss1r antagonism blocked the erectile response. When Kiss1 was infused into the lateral cerebroventricle, there were no observed erections. We also measured the plasma levels of LH when Kiss1 is infused into the MePD or lateral cerebroventricle; Kiss1 increased plasma LH to comparable levels when infused into both sites. We conclude that Kiss1 has a role in male sexual behavior, which is specific to the MePD.

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Nursing Practice

P172

Steroid replacement education: are we getting it right?

Veronica Kieffer, Emma Bremner, Carole Robinson, Ragini Bhake, Narendra Reddy & Miles Levy
Leicester Royal Infirmary, Leicester, Leicestershire, UK.

Patients with Adrenal Insufficiency are potentially at risk of life threatening events if during intercurrent illness they do not take adequate glucocorticoid replacement. The National Institute for Health and Care Excellence Clinical Knowledge Summaries for this patient group recommend that they should: know how to self inject intramuscular hydrocortisone in an emergency; how to adjust their steroid replacement in response to illness; understand the importance of medical identification.
Current education in our department is given during clinic visits, supported by written information. Patients identified by clinicians are seen by the endocrine specialist nurse for education and supply of an emergency kit. There is little evidence of subsequent reinforcement of this knowledge.
Method
Four hundred and fifty-nine questionnaires were sent to those currently on steroid replacement questioning: possession of in date injection kits and knowledge of use; knowledge of dose adjustment; possession of steroid dependence identification and recent hospital admissions. Two hundred and fifty-eight valid replies were received.
Results
Seventy-two per cent had emergency kits; 57% were in date. 50% knew how to give the injection. Seventy-five per cent carried identification of steroid dependence. Seventy-one per cent felt they knew enough to alter the doses but $<45\%$ gave correct answers to action required for severe illness. Ten per cent had hospital admissions possibly related to hypoadrenalism in the last year.
Conclusion
Possession of in date emergency kits is inadequate; Knowledge of how to self-inject is inadequate; there is insufficient knowledge of dose adjustment in severe illness.
Actions planned
Bigger and brighter posters on 'sick day' rules and emergency kits to be produced; design a new concise information sheet and send to all on steroid replacement; Produce a prompt list to remind clinicians to question knowledge of 'sick day' rules and possession of in date emergency kits at each clinic visit. Repeat audit in 1 year.

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Acromegaly tea party: a way of providing education in a relaxed environment

Amanda Morcombe, Clare Whicher & Jean Munday
Queen Alexandra Hospital, Portsmouth, UK.

Background
Portsmouth endocrine department does not have a dedicated acromegaly clinic. This group of patient are seen in general consultant endocrine clinic and those who need treatment with Somatostatin analogues have their initial injections with our endocrine specialist nurses (ENS). Once on a stable injection dose they are handed over to their practice nurse (PN) for on-going administration. Patients often comment that they like the initial monthly ENS contact at the centre and miss this when it ceases.
Innovation
The endocrine team therefore invited twenty of our acromegaly patient to an informal afternoon meeting in April 2016. All patients arrived together and the event was held in an allocated room with refreshments. A specialist registrar (SpR) and ENS ran the event. We also used this as an opportunity to also update the participants on new innovations. This included the opportunity to download an APP which looked at ways by which patients could personally track their care. Attendees were also invited to write anonymous questions that they wished to ask either to the group or to the event organisers. Attendees filled in written anonymous feedback forms at the end.
Results
Sixty per cent of patients invited attended.
Ninety per cent felt the group was of great benefit. Hundred per cent of those who attended said that they would like a similar event to be organised.
Future plans
It was striking that the majority of our acromegalic patients had never met someone else with the same condition and how beneficial they found the experience. We therefore have plans to run this group again with the aim to make it an annual event and extend invitation to all acromegalic patients on our database. We are also considering other endocrine conditions which may benefit from patients meeting each other and having education delivered in this way.

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Obesity and Metabolism

P174

Expression of insulin receptor and glucose transporter-4 in the skeletal muscle of chronically stressed rats

Ayodele Morakinyo, Bolanle Iranloye, Titilola Samuel, Adekunle Mofolorunso & Adefunke Adegoke
University of Lagos, Lagos, Nigeria.

Stress defined as a disruption in the normal homeostatic functions of an organism caused by a stressor (a physiological or psychological challenge) is an unavoidable experience of life. Previous studies suggest that stress hormones have acute adverse effects on glycaemic control. The aim of this study was to assess the effect of chronic psychological and physical stress on the expression of insulin receptor (INSR) and glucose transporter-4 (GLUT4) in male Sprague–Dawley rats.
Male rats (12 weeks old) were randomly distributed into 3 groups: control, water avoidance stress (WAS), forced swimming stress (FSS). The stress procedures were performed between 0900 and 1100 to minimize the effect of circadian rhythm and lasted for 28 consecutive days. Levels of insulin and corticosterone in the blood were determined using enzyme-linked immunosorbent assay. Glucose metabolism was assessed by glucose tolerance test (GTT) and insulin tolerance test (ITT), and expression of INSR and GLUT4 in skeletal muscle. Food intake and final body weight were also measured.
The FSS rats had decreased food intake as well as final body weight; and without adverse changes in GTT, stress worsened insulin sensitivity in FSS rats and increased serum insulin level. Stress also increased corticosterone, decreased INSR and GLUT4 in the skeletal muscle of both groups. In conclusion, chronic stress impairs insulin sensitivity and alters glucose metabolism through the down-regulation of INSR and GLUT4 in skeletal muscles.

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P175

Impaired glucose tolerance due to altered expression of INSR and GLUT4 receptors in restraint stress rat

Ayodele Morakinyo[1], Kolawole Ajiboye[2] & Olufeyi Adegoke[1]
[1]University of Lagos, Lagos, Nigeria; [2]Babcock University, Ilishan Remo, Ogun, Nigeria.

The study investigated the potential alteration in the level of insulin and adiponectin, as well as the expression of INSR and GLUT-4 in chronic restraint stress rats. Sprague–Dawley rats were randomly divided into two groups: the control group and stress group in which the rats were exposed to one of the four different restraint stressors; 1 h, twice daily for a period of 7 days (S7D), 14 days (S14D) and 28 days (S28D). To minimize habituation, the sequence of the stressors was randomized for both the morning and afternoon sessions of the first week of exposure, and was repeated during the second week with the morning and afternoon sequences exchanged. Glucose tolerance and insulin sensitivity were evaluated following the final stress exposure. ELISA were performed to assess the level of insulin and adiponectin as well as expression of INSR and GLUT4 protein in skeletal muscle. Plasma corticosterone level was also determined a marker of stress exposure.
Restraint stress for 7 days caused transient glucose intolerance, while S14D rats demonstrated increased glucose intolerance and mild insulin insensitivity. However, restraint stress for 28 days had no effect on glucose tolerance, but did cause an increase in glucose response to insulin challenge. The serum level of adiponectin was significantly ($P<0.05$) lower compared with the control value while insulin remained unchanged except at in S28D rats that had a significant ($P<0.05$) increase. The expression of INSR and GLUT4 receptors were significantly ($P<0.05$) decreased in the skeletal muscle of restraint stress exposed rats. There was a significant ($P<0.05$) increase in the plasma corticosterone level of the stress rats compared with their control counterparts.
Restraint stress caused glucose intolerance in male Sprague–Dawley rats but becomes abated with prolonged exposure arguably due to the blunted insulin signalling in skeletal muscle.

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P176

Five years on: A qualitative exploration of beliefs prior to and following gastric banding using a Theory of Planned Behaviour framework

Jude Hancock[2], Sue Jackson[1] & Andrew Johnson[2]
[1]University of the West of England, Bristol, UK; [2]Southmead Hospital, Bristol, UK.

Introduction
Despite the usefulness of using theory to underpin analysis, there is a paucity of literature applying this to experiences of gastric banding (GB) surgery. The Theory of Planned Behaviour (TPB) is useful for exploring beliefs underlying behaviour. The present study uses a TPB framework to explore individuals' beliefs towards GB both prior to and five years post-surgery.
Methods
A prospective longitudinal qualitative study. Semi-structured interviews were conducted with 20 individuals (aged 31 to 58 years, 16 female, 19 White, 16 with diabetes) twice: prior to, and five years post-GB. Content analysis was carried out using the TPB constructs as an explicit coding framework to determine salient beliefs pre- and post-GB surgery; while *t*-tests were used to explore weight loss.
Results
Participants lost a significant amount of weight following GB ($P<.001$). Prior to GB, salient beliefs included feeling unhappy with current self, experiencing social stigma as a result of being overweight, a good understanding of what GB would do, and both approval and disapproval of GB from family. Five years post-surgery salient beliefs included feeling happy, life improvements, experiencing problems with the band, approval and disapproval of GB from family, and social stigma due to having had GB.
Conclusion
Weight loss does happen following GB, but not all experiences of living with a band are positive. Many individuals experienced problems with their band, which they felt hindered their weight loss. Beliefs identified in this study may need to be considered during clinical consultations and planning future interventions to support individuals with their weight loss following surgery.

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P177

Glucocorticoid treatment rapidly increases AgRP and food intake with delayed effects on other metabolic systems

Erika Harno[1], Alison Davies[1], Tiffany-Jayne Allen[1], Charlotte Sefton[1], Jonathan R Wray[1], Thanuja Gali Ramamoorthy[1], Anthony P Coll[2] & Anne White[1]
[1]University of Manchester, Manchester, UK; [2]University of Cambridge, Cambridge, UK.

Glucocorticoids are widely prescribed therapeutic agents, however long term treatment can cause increased morbidity from adverse metabolic events, including weight gain and hyperglycaemia. The mechanisms and site of action which underpin these side-effects are not fully understood. The aim of this study was to characterise phenotypic, biochemical and neurohormonal responses in mice administered corticosterone, with a particular focus on changes seen in the early stages of chronic treatment.
In 12 week old male mice given corticosterone (CORT, 75 μg/ml)-supplemented drinking water, food intake was increased after 24 h and remained elevated over 3 weeks. This was accompanied by immediate and persistent increases in the orexigenic neuropeptide *Agrp*, without any consistent changes in other hypothalamic factors associated with energy balance. This model caused an increase in body weight after 14 days and increased white adipose tissue (WAT) after 3 weeks. In brown adipose tissue, expression levels of genes involved in thermogenesis (*Ucp-1*, *Ppargc1a*, *Cidea* and *Prdm16*) were unchanged at day 2. However, after chronic CORT treatment, expression of all four genes was decreased, indicative of reduced energy expenditure. CORT treatment also increased circulating insulin 5-fold at 24 h but levels increased 35-fold compared to vehicle treated mice at 3 weeks. *Irs-1* expression decreased after 2 days, only in skeletal muscle, but was also decreased in liver and WAT at 3 weeks, suggestive of widespread insulin resistance. Chronic CORT also caused hyperglycaemia accompanied by increased hepatic gluconeogenic genes, which was not present at 2 days.
In summary, CORT induces a sustained increase in food intake, with persistent increases in *Agrp*. However with chronic glucocorticoid treatment, a more widespread pattern of adverse metabolic sequelae emerge. Understanding these mechanisms may help in the design of therapeutic strategies to counteract the side-effects.

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P178

Dramatic weight loss induced by dapagliflozin and tier 3 obesity service support

Daniel K Border[1,2] & Thomas M Barber[1,2]
[1]University Hospitals Coventry and Warwickshire (UHCW), Coventry, UK; [2]Warwick Medical School, Coventry, UK.

The importance of weight reduction in the management of diabesity is well-established. However, significant weight loss can be difficult to achieve without bariatric surgery, even within specialist tier 3 obesity services. Here we describe the case of a 52 year old man who presented to weight management clinic. He had made multiple weight loss attempts, but with little success. On presentation, his weight was 140.8 kg with a BMI of 40.3 kg/m2, and he had now been static at this weight for approximately 10 years, despite best efforts.
He began management under the weight management team (dietetics, psychology, medical team), and was considering weight loss surgery. He qualified for this with his BMI and weight, but also had a diagnosis of type 2 diabetes mellitus (T2D) diagnosed 6 years previously. He was taking metformin 500 mg TDS and sitagliptin 100 mg OD, with a poorly-controlled HbA1c of 84. The SGLT-2 inhibitor dapagliflozin was initiated, and he was for medical review in 6 months with dietetics input in the interim. He lost weight consistently, and motivation/lifestyle change increased as a result. At 6 month review he weighed 107.8 kg (a **33kg loss**), and BMI was 33.5 kg/m2 (down from 43.3 kg/m2). His HbA1c had halved, at 43 mmol/mol.
He now had excellent glycaemic control, and a reduced weight such that he no longer required weight loss surgery.
This case highlights some important learning points:
1. SGLT-2 inhibitors in the context of diabesity can effect significant weight loss and improved glycaemic control.
2. It highlights the importance of pharmaceutical and lifestyle management of diabesity in the first instance as some patients do extremely well, no longer requiring surgery.
3. In this case, the pharmaceutical agent and weight management team support acted synergistically to effect weight loss where motivation alone had failed for some years.

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P179

Metabolic endotoxaemia impairs mitochondrial respiration and insulin sensitivity in human adipocytes

Lucia Martinez de la Escalera, Laura Jackisch, Alice Murphy, Milan Piya, Sudhesh Kumar, Gyanendra Tripathi & Philip G McTernan
University of Warwick, Coventry, UK.

Background
Metabolic endotoxaemia (raised bacterial endotoxin in serum after high-fat feeding) has been shown to reduce insulin sensitivity in humans through systemic inflammation and oxidative stress. Mitochondria represent the main source of cellular reactive oxygen species and mutations in mitochondrial DNA often result in a diabetic phenotype. However, the direct cellular impact of endotoxin on mitochondrial respiration and DNA integrity, particularly within the context of type-2 diabetes (T2DM), is not known.
Methods
Morbidly obese women with T2DM ($n=44$) undergoing bariatric surgery consented to participate in this ethics-approved prospective study. Serum and abdominal subcutaneous adipose tissue biopsies collected before and six months after surgery were used to determine circulating endotoxin and mitochondrial gene expression, respectively. Human obese subcutaneous adipocytes ChubS7 were treated for 24 hours with (10 ng/ml; 100 ng/ml) or without endotoxin.
Results
A strong negative correlation was observed between serum LPS and mitochondrial number in adipose biopsies across all surgical cohorts ($r^2=-0.485$, $P=0.005$**, $n=32$). Patients with lower serum endotoxin levels also exhibited greater weight, HbA1c and lipidaemia reduction in tandem with improvements in mitochondrial gene regulation. The *in vitro* endotoxin exposure up-regulated TNFα mRNA ($P=0.004$) and oxidative stress ($P=0.009$) whilst down-regulating activity of endogenous antioxidants superoxide dismutase ($P=0.016$) and catalase ($P=0.008$), and impairing glucose uptake ($P<0.001$) via inhibition of Insulin Receptor Substrate 1 protein ($P<0.05$). Furthermore, endotoxin resulted in 8 to 15% mitochondrial DNA deletion ($P=0.008$), mitochondrial protein depletion ($P=0.007$) and mitochondrial number reduction ($P=0.034$) compared with controls. This mitochondrial damage functionally manifested in a shift from aerobic to anaerobic respiration ($P=0.03$) and an impaired ability to cope with a seahorse stress test ($P<0.01$).

Conclusion
Taken together, our findings indicate that metabolic endotoxaemia drives insulin resistance in human adipose tissue, at least in part, via up-regulation of mitochondrial dysfunction, oxidative stress and inflammation.

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P180

Metabolic surgery with Roux-en-y Gastric bypass is an effective treatment in patients with Familial Partial Lipodystrophy and Body Mass Index Less than 35 kg/m^2

Claire Adams[1], David Savage[2], Lisa Gaff[1], Catherine Flanagan[1], Charlotte Jenkins-Liu[1], Robert Semple[2], Elaine Withers[2], Stephen O'Rahilly[2] & Anna Stears[1]
[1]Wolfsen Diabetes & Endocrine Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [2]Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK.

Introduction
Familial Partial Lipodystrophy Type 1 (FPLD1) is characterised by loss of gluteal and limb subcutaneous fat and increased abdominal fat. The genetic basis is currently unknown. FPLD1 is frequently associated with metabolic problems including diabetes, insulin resistance, dyslipidaemia and non-alcoholic fatty liver disease. Despite central adiposity and severe metabolic abnormalities, this group of patients often do not qualify for NHS funding for bariatric surgery as they often have a Body Mass Index (BMI) below 30 kg/m^2.
Patients 1 & 2
Two female patients with an FPLD1 phenotype and poor glycaemic control were referred to the National Severe Insulin Resistance Service. Despite trying metformin, intensification of insulin therapy and specialist dietary input (one patient undertook a liquid diet), HbA1c in both women remained >100 mmol/mol. Exceptional funding requests were made for Roux-en-Y gastric bypass (RYGB) surgery.
Results
Post RYBG, BMI fell from 33.2 to 27.8 kg/m^2 in Patient 1 and from 29.7 kg to 22.9 kg/m^2 in Patient 2. HbA1c returned to the normal range in both women (114 to 55 mmol/mol and 113 to 47 mmol/mol respectively) and diabetes medication was stopped other than metformin in Patient 1. MRI-based measures of liver fat normalised in both women, with a dramatic reduction from 20% to 4.5% in patient 2. Fasting triglycerides, LDL-cholesterol and liver function tests also reduced. Patient 1 is now 3 years post RYGB and her weight and metabolic control remain stable.
Conclusion
These case studies suggest that RYGB is safe and can be highly effective in improving insulin sensitivity and diabetes control in patients with FPLD1. Access to RYGB is currently limited in accordance with NICE guidance. However RYGB should also be considered for selected patients with FPLD and severe metabolic disease despite a relatively normal BMI. This could be viewed as a key 'metabolic' – rather than an 'obesity' intervention in this setting.

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P181

The impact of a tier three weight loss service on Quality of Life (QoL): A retrospective, service evaluation project

Esme Ingram[1,2], Anjali Zalin[1,2], Charlotte Quarrie[1], Kevin Shotliff[1,2], Daniel Morganstein[1], Veronica Greener[1,2] & Lucy Turnbull[1]
[1]Nutrition and Dietetics Department, Central London Community Healthcare, London, UK; [2]Beta Cell Department, Chelsea and Westminster Hospital, NHS Foundation Trust, London, UK.

Introduction
The NHS Commissioning Board recommends the introduction of multi-disciplinary Tier 3 Specialist Weight Management Services (SWMS) for adults with obesity. Unfortunately, these services are yet to be commissioned in many areas and this largely reflects financial barriers to their development. We have noted, through observation and feedback, that our Tier 3 service is highly valued by patients. Supportive evidence in the literature - although encouraging - is limited. In the current financial climate, it is important that long-term data are collected in order to evaluate the wider effects of implementing such services.
Methods
Retrospective service evaluation of all patients ($n=179$) engaging with the Central London Community Healthcare SWMS for at least 6-months from 2011 onwards. Outcome measures, including weight, Body Mass Index (BMI), blood pressure, HbA1C, Epworth Sleepiness Scale (ESS) and measures of QoL (EQ-5D-3L) and anxiety and depression (GAD7, PHQ9) were collected at baseline and then at 6-monthly intervals during the patient's period of engagement with the service. Data collection is ongoing and provisional analyses of the first 46 patients are detailed.
Results
The mean time from baseline assessment to first follow-up was 187.9 days. There was a significant reduction in weight (mean 1.8 kg, $P=0.002$) between baseline and first follow-up, with an associated reduction in BMI (mean reduction BMI 0.9, $P=0.001$). Reductions between baseline and follow-up ESS and PHQ9 scores were also noted although these findings did not reach statistical significance.
Conclusions
Provisional results confirm that a Tier 3 SWMS can achieve weight loss through lifestyle changes. The noted trends in reduction of ESS and PHQ9 scores, the latter of which was also noted in previous local work (PHQ9 scores improved in up to 74% of patients) suggest that these services may also provide a positive effect on an individuals' overall wellbeing. This warrants further study.

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P182

Concentrations of endocrine disrupting chemicals in liver and adipose tissue in United Kingdom

Thozhukat Sathyapalan[1], Lesa Aylward[2], Martin Rose[3], Steve Petch[3], Natalie Thatcher[4] & Stephen Atkin[5]
[1]Hull York Medical School, University of Hull, Hull, UK; [2]Summit Toxicology, LLP, Falls Church, VA, USA; [3]Fera, Sand Hutton, York, UK; [4]European Food Safety Authority, Parma, Italy; [5]Weill Cornell Medical College in Qatar, Ar-Rayyan, Qatar.

The prevalence of obesity is increasing in most populations. The aim of this study was to provide baseline data on the concentrations of chlorinated and brominated dioxins and related compounds as well as polybrominated diphenyl ethers to assess whether concentrations of these compounds are higher in obese than control subjects.
Materials and Methods
Patients undergoing Roux-en-y gastric bypass surgery for weight loss and control patients who were undergoing abdominal surgery for non-bariatric reasons were recruited with informed consent for the study. Anthropometric parameters were measured at the day of surgery. During surgery, visceral and subcutaneous adipose tissue biopsies, liver biopsy and blood samples were taken.
Results
Patients undergoing bariatric surgery were younger on average than control patients (47.9 (12.7) vs 68.5 (14.2) years) and on average had higher BMI. Tissue concentrations were measured in samples of visceral and subcutaneous fat and in liver biopsies. Brominated TEQ concentrations were relatively low compared to chlorinated TEQ, constituting less than 5% of adipose tissue TEQ and less than 10% of liver TEQ. The most frequently detected PBDD/F compounds were 2,3,7,8-tetrabromodibenzodioxin, 2,3,7,8-tetrabromodibenzofuran, and 2,3,4,7,8-pentabromodibenzofuran. The PBDE compounds presented here are those that were consistently detected in the samples. Of these, BDE 153 was present at the highest concentrations, followed by BDE 47.
Multivariate linear regressions showed chlorinated TEQ in visceral fat was significantly positively associated with both age and BMI. In contrast, brominated TEQ compounds showed no significant association with any of the factors considered. BDE 47 was borderline significantly negatively associated with age, while BDE 153 showed a borderline significant negative relationship to BMI. Gender was not a significant factor for any analyte.
Conclusion
Subcutaneous fat concentrations were highly correlated with visceral fat concentrations for all analytes. This confirms that concentrations of these compounds in fat depots in the body appear to be generally in equilibrium, an observation previously made for chlorinated TEQ compounds but not previously demonstrated in humans for PBDD/Fs and PBDEs.

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P183

Impact of paternal cholestasis on the metabolic phenotype of female offspring

Vanessa Pataia, Georgia Papacleovoulou, Lucilla Poston & Catherine Williamson
King's College London, London, UK.

Introduction
Accumulating evidence has shown that not only maternal health during pregnancy, but also the paternal metabolic status at the time of conception may have an impact on the subsequent health of the offspring. Cholestatic liver diseases are metabolic conditions characterised by increased circulating serum bile acid and lipid levels. In this study we hypothesised that paternal cholestasis alters disease susceptibility in the offspring.
Methods
7–9 week-old male mice were fed a Normal-Chow (NC) diet or 0.5% cholic acid supplemented diet (CA diet) for 10 weeks. At completion of feeding, males were mated to NC-fed females. Offspring were weaned onto NC diet and at 12 weeks old offspring were either kept on a NC diet or challenged with an obesogenic Western Diet (WD) for 8 weeks. Offspring groups were defined according to the paternal and offspring diet: NC NC, CA NC, NC WD and CA WD. Glucose and lipid homeostasis parameters were assessed in the offspring.
Results
Female offspring of cholestatic fathers showed a significant decrease in Respiratory Exchange Rate (RER) both in NC NC vs CA NC and NC WD vs CA WD comparisons ($n=4$–6, P-value ≤ 0.05). Moreover, hepatic free fatty acid (FFA) content was significantly increased in CA WD female offspring as compared to NC WD females ($n=4$–6, P-value ≤ 0.05). However, following a glucose tolerance test (GTT) challenge, female CA WD offspring showed a significant improvement in glucose levels at 30 min as compared to NC WD females.
Conclusions
Despite the increased levels of hepatic FFA and decreased RER in females from CA fathers, both features of metabolic syndrome, these mice had improved glucose tolerance. This may suggest a compromise of the lipid homeostatic set-points as a consequence of paternal cholestasis. In parallel, a homeostatic feedback response appears to be in place to counteract the metabolic imbalance.

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Prevalence and factors associated with Dyslipidaemia among Hiv patients in Kano, Northwestern Nigeria

Fakhraddeen Muhammad[1], Andrew Uloko[2], Ibrahim Gezawa[2], Adenike Enikuomehin[3], Aliyu Mukhtar[4] & Fauziyya Muhammad[5]
[1]Muhammad Abdullahi Wase Specialist Hospital, Kano, Nigeria; [2]Aminu Kano Teaching Hospital, Kano, Nigeria; [3]Obafemi Awolowo University Teaching Hospital, Ile Ife, Nigeria; [4]Health Management Board, Kano, Nigeria; [5]GSS Shadawanka, Bauchi, Nigeria.

Introduction
Lipid abnormalities are very common among HIV patients particularly those on Highly Active Antiretroviral Therapy (HAART). Infection with HIV causes decline in HDL cholesterol and a raise in triglyceride. Treatment with HAART causes Dyslipidaemia in a variety of ways.
Aims
To determine the prevalence and factors associated with Dyslipidaemia among HAART naïve and HAART exposed HIV patients.
Methodology
Three hundred consented HIV infected patients were recruited for the study. Half were HAART naïve and the other half were on HAART. Anthropometric indices were done. Total serum cholesterol and triglyceride were estimated using enzymatic reactions. The estimation of HDL was by precipitation method while LDL was calculated using Friedewald formula. Dyslipidaemia was assessed using ATP III guideline.
Results
The mean age for the HAART exposed group was 35.7 ± 10.0 years while that for the HAART naive was 34.0 ± 9.7 years. The prevalence of Dyslipidaemia among HAART exposed was 70 and 58% among HAART naïve $P=0.03$. Total prevalence among all was 64%. Elevated total cholesterol was found among 44 and 7.3% respectively ($P<0.000$), low HDL was found among 40 and 50.7% respectively ($P=0.064$), raised triglyceride occurred in 26.7 and 10.7% respectively ($P<0.000$), elevated LDL occurred in 6 and 1.3% respectively ($P=0.032$). Low HDL was the most predominant dyslipidaemia, 70.3 and 50.7% among all participants and among HAART naïve respectively. Among HAART exposed, it was elevated total cholesterol 44%. Exposure to HAART, Male gender, Age, hypertension, elevated FPG were found to be significantly associated with the development of Dyslipidaemia ($P<0.05$). Only hypertension was found to be an independent predictor for the development of Dyslipidaemia $P=0.019$ (OR 2.74, 95% CI 1.179–6.354).
Conclusion
Infection with HIV and exposure to HAART cause dyslipidaemia, which is a major cardiovascular risk factor among these patients. Lifestyle and statin therapy should be part of management.
Key words: HIV, Dyslipidaemia, Kano

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P185

A retrospective study assessing the effects of OSA in women with PCOS attending the weight management clinic

Hassan Kahal[1,2], George K. Dimitriadis[1,2], Ioannis Kyrou[1,3], Asad Ali[4], Abd A Tahrani[5] & Harpal Randeva[1,2]
[1]Division of Translational and Experimental Medicine, Warwick Medical School, University of Warwick, Coventry, UK; [2]Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism, University Hospitals of Coventry and Warwickshire NHS Trust, Coventry, UK; [3]Aston Medical Research Institute, Aston Medical School, Aston University, Birmingham, UK; [4]Department of Respiratory Medicine, University Hospital Coventry, University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK; [5]Institute of Metabolism and Systems Research, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK.

Introduction
Obstructive Sleep Apnoea (OSA) is more common in women with Polycystic Ovary Syndrome (PCOS). There is paucity of data regarding the impact of OSA in women with PCOS.
Methods
We conducted a retrospective study using electronic patients' records of premenopausal women with PCOS who were first seen in the weight management clinic (WMC) between March/2008 and November/2014. PCOS diagnosis was documented either by referring clinician or established at the WMC using the Rotterdam Criteria. OSA risk was assessed clinically based on history of snoring and daytime sleepiness. Those with high risk of OSA were referred for sleep studies. Based on the results of the clinical assessment and sleep studies, patients were classified into three groups: (1) PCOS and low risk of OSA (not requiring sleep studies); (2) PCOS without OSA (negative sleep studies); and (3) PCOS with OSA (diagnosed as apnoea/hypopnoea index ≥ 5 events/hour).
Results
Seventy-five women were identified, 31 women were excluded (25 had no documented assessment of OSA risk, whilst 6 failed to complete sleep studies). Out of the remaining 44 women: 16 (36.3%) had PCOS and low risk of OSA; 15 (34.1%) had PCOS without OSA; and 13 had (29.6%) PCOS with OSA. There were no between groups differences in age (31.6 (± 6.3) vs 30.1 (± 8.0) vs 28.9 (± 4.3) years, $P=0.49$, respectively). The body mass index (44.9 (± 7.3) vs 47.2 (± 4.9) vs 50.6 (± 3.6) kg/m^2, $P=0.03$); and the prevalence of depression (4 (25%) vs 6 (40%) vs 10 (76.9%), $P=0.02$) were greater in the OSA group. Following adjustment for BMI, OSA remained associated with depression (odds ratio: 6.5, 95% confidence interval = 1.1 – 39.3, $P=0.042$). There were no between groups differences in testosterone, SHBG, FSH, LH, ALT, HbA1C, and lipids.
Conclusions
OSA is associated with depression in morbidly obese women with PCOS. The impact of OSA treatment on depression need to be examined.

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Suppression of isoproterenol-induced lipolysis by insulin in rat visceral adipose tissue explants is increased with aging: Consequences on adiposity

Alejandro Fernandez, Cristina Pintado, Sergio Gomez, Carmen Arribas, Nilda Gallardo & Antonio Andres
University of Castilla La Mancha, Ciudad Real/Toledo, Spain.

Although the effect of aging on adipose tissue metabolism have been thoroughly studied for years, changes in the antilipolytic action of insulin in visceral white adipose tissue from aged rats are still not completely understood. By fact, some

contradictory data on the inhibition of isoproterenol-induced lipolysis by insulin with aging have been reported. As aging is a significant risk factor for increasing adiposity and the development of obesity, we hypothesized that the inhibition of isoproterenol-induced lipolysis by insulin in rat visceral adipose tissue explants (vWAT) may be increased in aged rats.
Experiments were performed in ad libitum (AL) or caloric restricted for 3-months (CR) male Wistar rats of 3, 8 and 24 months. All rats were fasted for 36 h before euthanized under CO_2 and sacrificed by decapitation. Adiposity index, adipose cell size, FA composition by GC from vWAT TAG and serum concentrations of glycerol, TAG, NEFA, lactate and KB were measured. Glycerol and NEFA release were measured in the medium of vWAT explants (100 mg) incubated for 3 h in the absence or presence of 1 μM isoproterenol without or with 1 μM insulin. The mRNA and total protein levels of ATGL, AQ7, HSL, as well as the phospohrylation of HSL, were studied by real-time PCR and immunoblotting.
Results
As expected, basal and isoproterenol-induced lipolysis were markedly decreased in the older and fatter rats. Surprisingly, the inhibition of isoproterenol-induced lipolysis by insulin in vWAT explants was higher in 24-month AL or CR compared to younger rats. Although vWAT TAG 18:1/18:0 ratio, which correlated negatively with insulin sensitivity, was significantly increased in old rats, our results were associated to lower ATGL, HSL protein and activation levels.
Conclusion
Higher antilipolytic action of insulin in rat vWAT with aging is associated to increased adiposity in older rats.

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NAD+ supplementation normalises central carbon metabolism in skeletal muscle: a mechanistic insight into the energetic consequences of age-related NAD+ decline

Lucy Oldacre-Bartley, Rachel Fletcher, Kate Hollinshead, Yasir Elhassan, Craig Doig, Daniel Tennant, Christian Ludwig & Gareth Lavery
University of Birmingham, Birmingham, UK.

A decline in skeletal muscle nicotinamide adenine dinucleotide (NAD+) can decrease mitochondrial function and energy metabolism in age-related metabolic disease. Restoration of NAD+ using the precursor nicotinamide riboside (NR) may serve to support age and disease driven impairment of mitochondrial energy metabolism. Manipulating NAD+, and consequently cellular pyridine nucleotide NAD(P)(H) pools, may impact the flux of glucose through intermediary energy metabolism pathways. To examine this we have used NMR spectroscopy and metabolic tracer analysis in NAD+ depleted (10 μM FK866 (inhibitor of the NAD^+ salvage enzyme nicotinamide phosphoribosyltransferase NAMPT) for 48 h), and NAD+ replete (0.5 mM NR) C2C12 myotubes grown in 10 mM $^{13}C_2$-[1,2]-D-Glucose. FK866 treatment impaired cellular energetic status, reducing NAD+ (>90%), NADP+ (>50%), ATP (>30%), and basal mitochondrial respiration (50% using seahorse technology), but without inducing apoptosis or affecting cell viability. Compensatory adaptations in redox-sensitive metabolic pathways were observed, including a reduction in use of the pentose phosphate pathway (PPP) and a block in glycolysis at the NAD+ dependant glyceraldehyde-3-phosphate dehydrogenase step. Supplementing NR to FK866 treated cells for only 4 h rescued NAD^+ levels and normalised these metabolic pathways. NAD^+ repletion in 'healthy' cells supplemented with NR for 4h in the absence of FK866 resulted in a 53% increase in NAD^+ and 20% increase in NADP+ without affecting ATP or basal mitochondrial respiration. The excess NAD^+ reduced PPP flux while increasing contributions to glycolytic flux and TCA cycle activity from non-glucose carbon sources. Our results show NAMPT as a critical enzyme for NAD^+ homeostasis, with low NAD^+ impairing glucose flux and TCA cycle activity, providing mechanistic information as to why age-related decline in NAD+ affects overall health. While NR supplementation may be effective to 'normalise' glucose flux in the low NAD+ state, excess NAD+ may have unintended consequences for glucose turnover and intermediary energy metabolism in muscle requiring further evaluation.

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P188

Low maternal B12 associates with higher leptin in maternal adipose tissue, placental tissue and cord blood

Antonysunil Adaikalakoteswari[1], Manu Vatish[2], Ilona Goljan[3] & Ponnusamy Saravanan[1,3]
[1]University of Warwick, Warwick, UK; [2]University of Oxford, Oxford, UK; [3]George Eliot Hospital, Nuneaton, UK.

Background
Evidences show that maternal vitaminB12 deficiency at periods of development influence metabolic status and degree of metabolic syndrome of the offspring into adulthood. VitaminB12 is required for the synthesis of methionine, which is the precursor of S-adenosyl-methionine, a key methyl donor for DNA methylation. So vitaminB12 deficiency might cause methylation changes, which are thought to alter gene expression of regulatory factors and could result in adverse metabolic phenotypes. Our recent study showed that low maternal vitaminB12 was associated with adverse cord blood lipid profile and higher BMI which provided the clue to explore the link between the adiposity marker, leptin, and vitaminB12. We hypothesize that maternal B12 might program leptin levels *in-utero*. Therefore we investigated whether maternal B12 levels associate with leptin in maternal adipose tissue, placental tissue and cord blood.
Methods
Paired maternal venous and cord blood samples ($n=91$), adipose tissue ($n=42$) and placental tissue ($n=83$) were collected at delivery. Serum vitaminB12 was determined by electro-chemiluminescent immunoassay. Leptin levels were measured by ELISA. To assess the underlying mechanism, human pre-adipocyte cell line (Chub-S7) was differentiated in various B12 concentrations (1) Control: (B12-500 nM); (2) LowB12 (0.15 nM) (3) Control + methylation inhibitor (AZ): (B12-500 nM +5-Aza-dC-200 nM).
Results
B12 deficiency (<150 pmol/l) was common (mothers-40%; neonates-29%). In regression analysis, adjusted for likely confounders, maternal B12 independently associated with neonatal leptin ($\beta=-0.662$; $P=0.002$; $R^2=12.7\%$). Leptin gene expression was higher in adipose tissue and placental tissue from mothers with low B12. Leptin gene was higher in adipocytes (Chubs-S7) cultured with low B12 (0.15 nM) and treated with normal B12 (500 nM) in the presence of methylation inhibitor (5-Aza-dC).
Conclusion
Our study highlights that low maternal B12 associates with higher leptin in cord blood, maternal adipose tissue and placental tissue, suggesting leptin gene could represent a mechanism of adverse programming either in the placental tissue or maternal adipose tissue.

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P189

Mechanisms of ageing metabolic decline revealed by targeted metabolomics and energy metabolism in NAD+ depleted skeletal muscle

Rachel Fletcher[1,2], Lucy Oldacre-Bartley[1,2], Craig Doig[1,2], Charles Brenner[3] & Gareth Lavery[1,2]
[1]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT, UK; [2]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, B15 2TT, UK; [3]University of Iowa, Iowa City, Iowa, USA.

Nicotinamide adenine dinucleotide (NAD^+) levels increase during metabolic stress, which acts as a consumed substrate by, amongst other proteins, the sirtuins, which adapt transcriptional programmes to increase energy availability and regulate insulin sensitivity. Thus, maintaining appropriate skeletal muscle NAD^+ availability is critical for regulating systemic energy homeostasis. In order to gain better insight into ageing muscle NAD+ dynamics we used targeted LC/MS-based metabolomics and assessed NAD^+ associated metabolome in young (3-months) and aged (30-months) mouse quadriceps ($n=8$). In aged muscle we identified significantly reduced NAD+ (~20%). ADPribose was also significantly reduced (~30%). ADPribose is a product of NAD+ consumption and signalling molecule, implying reduced sirtuin mediated NAD+ turnover and impaired energy harvesting. Thus, low NAD+ and ADPribose levels corroborate the significantly reduced ATP levels (~40%). Following NAD+ consumption, nicotinamide is also released. Nicotinamide is recycled by the enzyme nicotinamide phosphoribosyltransferase (NAMPT) and critical to maintaining intracellular NAD+ levels. To model aged-related NAD^+ decline, we exposed primary muscle myotubes (C57BL/6J quadriceps) to the NAMPT inhibitor FK866 (100 nM, 48–72 h) to deplete NAD^+. After 48–72 h basal oxygen consumption was significantly reduced by 50% implying severely impaired

mitochondrial function. Furthermore we also observed increased caspase 3 activity after 72 h indicative of cellular apoptosis initiation. 72 h FK866 treated myotubes were supplemented with the NAD^+ precursor nicotinamide riboside (NR) for the final 24 h, which fully restored NAD^+ levels, mitochondrial function and cell viability. Nicotinamide was unable to rescue these effects and supports the notion that muscle has a limited NAD+ salvage system which comprises NAMPT, and NR kinases (NMRK) 1/2 to maintain NAD^+ availability from extracellular sources. Overall these data identify perturbed NAD^+ dynamics in aged muscle and its potential impact on energy homeostasis that may underpin age-related metabolic decline. Enhancing NAD^+ by NR supplementation may prove a useful nutraceutical approach to combat age-related muscle decline.

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P190

Maternal high fat diet exposure and offspring metabolism: a meta-regression analysis of animal models

George Ribaroff[4], Elizabeth Wastnedge[3], Amanda Drake[2], Richard Sharpe[1] & Thomas Chambers[1,3]
[1]MRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, 47 Little France Crescent, Edinburgh, UK; [2]British Heart foundation Centre for Cardiovascular Sciences, Queen's Medical Research Institute, University of Edinburgh, 47 Little France Crescent, Edinburgh, UK; [3]NHS Lothian, University Hospitals Division, Edinburgh, UK; [4]University of Edinburgh Medical School, The Chancellor's Building, 49 Little France Crescent, Edinburgh, UK.

Background
Maternal high fat diet (HFD) exposure is thought to perturb offspring metabolism, however the literature on experimental animal studies is inconsistent.
Objectives
(i) In experimental studies, appraise data regarding metabolic parameters in offspring of mothers who consumed a HFD, (ii) assess possible predictors for these, and (iii) explore the quality of the evidence base.
Methods
Searches were performed in four electronic databases (MEDLINE, CAB, SCOPUS and Web of Science) in July 2015. Eligible papers investigated offspring outcomes following maternal HFD exposure in animals. After removal of duplicates, 1848 abstracts were screened. 171 papers met the inclusion criteria and were included for meta-analysis, providing a total of 6047 offspring. Meta-regression was based on predefined factors: macronutrient content of diet, species, strain, whether lactational exposure, and gestational weight gain. Egger's regression test was used to identify publication bias. Results. Maternal exposure to HFD resulted in increased wean weight, final body weight, adiposity, hypertriglyceridaemia, hypercholesterolaemia and hyperinsulinaemia in both female and male offspring. Hyperglycaemia was found in female offspring only. No effect was found on birth weight. Meta-regression analysis identified exposure during lactation as a key moderator. Carbohydrate content of the diet was predictive of male wean weight. Use of randomisation and taking account of litters in experimental design reduced the effect sizes found. There was significant evidence for publication bias.
Conclusions
A comprehensive analysis of models of maternal HFD exposure demonstrates perturbed metabolism in offspring. This is influenced by lactational exposure, sex of offspring and dietary macronutrients. This analysis goes some way towards explaining some of the inconsistencies in the literature and identifies several factors that should be taken into account in future study design. It also adds to the growing body of experimental and epidemiological evidence that the early life environment programs future health.

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P191

Freeze dried broccoli extract relieves ER stress and mitochondrial inefficiency in differentiated human pre-adipocyte cells

Alice Murphy, Lucia Martinez de la Escalera Clapp, Laura Jackisch, Sahar Azharian, Alanoud Aladel, Guy Barker, Gyanendra Tripathi, Michael Chappell & Philip McTernan
University of Warwick, Coventry, UK.

Background
In obesity, excess nutrients can disrupt protein folding in the endoplasmic reticulum (ER) which activates the unfolded protein response (UPR) and alters mitochondrial function. These changes can induce inflammation, oxidative stress and insulin resistance. The aim of the study was to investigate whether broccoli extract can protect against cellular damage in human adipocytes, which with mathematical modelling may help predict pathway response.
Methods
Differentiated Chub-S7 cells were treated over a 72 hr time course with 10 ng/ml freeze-dried broccoli extract (hybrid Brassica oleracea var. italic) alone or combined with ER stress inducer, tunicamycin (750 ng/ml). UPR markers (ATF6, ATF4, CHOP, ERO1α, P-PERK, PERK, P-eIF2α, eIF2α, P-IRE1α and IRE1α) were measured by qRT-PCR and Western blot. Mitochondrial genes (MFN2, OPA1, UCP2, SOD2, POLG) were also measured. Mathematical modelling was undertaken.
Results
Tunicamycin led to a significant increase in UPR gene expression ($P<0.05$), whilst broccoli extract combined with tunicamycin significantly reduced the expression of UPR markers compared with those treated only with tunicamycin, in a time dependent manner. Tunicamycin had a detrimental effect on mitochondrial genes ($P<0.05$); the presence of broccoli appeared to protect against these effects. This *in-vitro* time-series data are being used to realistically parameterise an existing mathematical model.
Conclusion
Broccoli extract appears to positively influence protein folding in ER stressed adipocytes, reducing UPR gene expression and causing influential changes in mitochondria. As such broccoli supplementation in the daily diet may reduce the inflammatory response posed by adipose tissue during weight gain. The mathematical model of the UPR offers the possibility of *in silico* optimisation for the supplementation.

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P192

RNA-seq of mouse arcuate nuclei reveals pathways perturbed by glucocorticoid treatment

Jonathan Wray[1], Erika Harno[1], Alison Davies[1], Charlotte Sefton[1], Tiffany-Jayne Allen[1], Brian Y.H. Lam[2], Giles S.H. Yeo[2] & Anne White[1]
[1]Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; [2]University of Cambridge Metabolic Research Labs, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK.

Glucocorticoids (GCs) are widely prescribed to treat a number of inflammatory and autoimmune conditions. However, patients receiving GCs often develop adverse metabolic effects such as hyperphagia leading to weight gain and hyperglycaemia. Little is known about the central effects of GCs; however they can act in the hypothalamic arcuate nucleus (ARC), a region involved in the integration of other energy regulatory hormones such as leptin, insulin and ghrelin. Therefore, the aim of this study was to identify genes and pathways differentially expressed in the ARC following GC treatment. Male C57BL/6J mice were given ad libitum access to corticosterone (CORT; 75 μg/ml) in their drinking water for 2 days, producing a robust increase in circulating corticosterone. Food intake was increased ($\sim$30%) in CORT treated mice from day 1 onwards, but no change in body weight was observed. Following treatment, arcuate nuclei were isolated using laser capture microdissection before RNA was extracted and amplified for RNA-seq. RNA-seq results indicate that of the 15,277 genes identified in the ARC, 224 were differentially expressed ($>$1.5-fold; $P<0.01$) with CORT treatment (90 downregulated; 124 upregulated). This subset contained genes already known to be regulated by GCs, including *Mt1*, *Mt2*, *Cdkn1a*, as well as some involved in the control of food intake and energy balance, e.g. Agrp, Ghsr, Lepr. This change in *Agrp* expression (1.8-fold increase) provides a likely explanation for the observed hyperphagia, as AgRP has potent orexigenic effects. Using Ingenuity Pathway Analysis we revealed effects of GC treatment on genes involved in glucose metabolism, such as *Spp1*, *Bmp2* and *Atgr1*. These genes are predicted to be regulated by the histone deacetylases (HDACs), with *Hdac5* being altered in our dataset (60% decrease). Therefore this study has identified strong candidate genes in the hypothalamus that may be mediating GC induced metabolic dysfunction.

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P193

Tunicamycin-induced ER stress mediates mitochondrial dysfunction in human adipocytes

Laura Jackisch[1], Lucia Martinez de la Escalera[1], Alice Murphy[1], Nasser Al-Daghri[1,2], Philip McTernan[1], Harpal Randeva[1] & Gyanendra Tripathi[1,2]
[1]Warwick Medical School, University of Warwick, Coventry, UK; [2]Biomarkers Research Program and Prince Mutaib Chair for Biomarkers of Osteoporosis, Biochemistry Department, College of Science, King Saud University, Riyadh, Saudi Arabia.

Background
The pathogenesis of obesity and T2DM mediates mitochondrial dysfunction which, in part, may arise as a consequence of endoplasmic reticulum (ER) stress. However, the potential impact of ER stress on mitochondria dysfunction is unclear. Therefore, we investigated whether induction of ER stress contributes to mitochondrial dysfunction in human adipocytes using 1) human differentiated adipocyte cell line (Chub-S7, $n=12$); and 2) primary differentiated lean and obese abdominal subcutaneous adipocytes (AbdSc Ad; $n=3$ respectively).
Methods
ER stress was induced in post-differentiated Chub-S7 (AbdSc Ad) using tunicamycin (Tn) (0.25 μg/ml, 0.75 μg/ml) for 24 hrs, 48 hrs and 72 hrs. Assessment of mitochondrial function post Tn treatment was undertaken using the Extracellular Flux Analyser – evaluating oxygen consumption rate (OCR) and proton excretion (glycolysis; extracellular acidification rates (ECAR)). Flux stressors (oligomycin, FCCP, rotenone/antimycin A) were given to Chub-S7 adipocytes treated with Tn to measure mitochondrial response. Mitochondrial dynamics were also evaluated using RT-PCR and confocal microscopy.
Results
The Seahorse stress test identified that Tn (0.25 μg/ml, 0.75 μg/ml) induced mitochondrial stress with a 14% rise in OCR (Basal: 472 pMoles/min vs Tn: 537 pMoles/min; $P=0.002$) and a maximum 78% increase in ECAR (Basal: 124 mpH/minute vs Tn: 228 mpH/minute; $P=0.006$). This Tn induced mitochondrial stress was maintained over 72 hrs. Coupled with the observed functional data, mRNA expression analysis highlighted that fission (Drp1, Fis 1; $P<0.01$) and fusion (Mfn2, Opa1; $P<0.01$) were both increased by Tn (0.25 μg/ml, 0.75 μg/ml). Confocal microscopy was used to further verify this result.
Conclusions
These studies highlight unfavourable changes in mitochondrial function and gene expression arise in adipocytes, in response to an inducer of ER stress; this may mimick an obese phenotype. Taken together, these results indicate that therapeutics to reduce ER stress could have a beneficial influence on alleviating mitochondrial dysfunction and its pathogenic consequences.

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P194

Impact of weight gain on long term outcomes in women with turner syndrome: The turner syndrome life course project

Antoinette Pimblett, Thomas J King, Vikram Talaulikar, Melanie Davies & Gerard Conway
University College London Hospitals, London, UK.

Turner syndrome (TS) affects over 15,000 females in the UK and is defined by the loss of X chromosome material. In the setting of an adult clinic we can observe adverse outcomes and determine their risk factors. For instance women with TS have an excess risk of hypertension, diabetes, fatty liver and osteoporosis. The Turner Syndrome Life Course Project at UCLH has collected data from over 750 women with TS over 20 years. Here we report the influence of weight on these outcomes.
Full data sets were available for 659 women with TS who were subdivided by BMI quintiles of 132 women in each group. Comparisons were made using ANOVA (***$=P<0.001$; **$=P<0.01$; *$=P<0.05$. Data in the table are presented for mean (SEM) Diastolic blood pressure (BP), glycated haemoglobin (HbA1c), gamma glutamyl transferase (GGT) and t-score at the lumbar spine measured by DEXA.

Quintile	1	2	3	4	5
BMI (kg/m^2)	<20.6	20.6–23.2	23.2–26.3	26.3–31.0	>31
Diastolic BP	71.4 (1.1)	71.4 (0.9)	74.2 (1.0)	76.7 (1.1)	78.1 (1.1)***
HbA1c %	5.3 (0.09)	5.4 (0.10)	5.4 (0.08)	5.6 (0.012)	5.7 (0.09)*
GGT mu/L	60.1 (7.6)	51.4 (5.7)	56.2 (7.3)	97.1 (13.5)	102 (12.0)***
Spine t-score	−1.10 (0.12)	−1.35 (0.11)	−1.04 (0.11)	−0.83 (0.12)	−0.67 (0.13)**

The results show that weight has a major influence on health risk factors in women with TS. This information emphasises the need to incorporate weight loss programs as part of routine care in adult clinics.

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P195

Adrenal insufficiency post gastric bypass surgery

Vinod Joseph, Manish Kushe, Suresha Muniyappa & Chinnadorai Rajeswaran
Dewsbury District Hospital, Dewsbury, Wakefield, West Yorkshire, UK.

Introduction
Bariatric surgery is now a common surgical procedure for weight management recommended by NICE. Complications such as dumping syndrome, micro-nutrient deficiencies are well documented in the literature. Here we discuss a lesser reported complication of adrenal insufficiency and its management in five patients following gastric bypass surgery.
Case reports
All patients presented with one or more of the following symptoms: sweating, anxiety, weight regain, hypoglycaemia, collapse with transient loss of consciousness and profound weight loss.
Baseline cortisol and cortisol response following a challenge with synacthen were all suboptimal. All patients had normal pituitary function and imaging, adrenal antibody was negative. Patients were commenced on oral hydrocortisone with resulting improvement in only three of them.
Discussion
The cause of adrenal insufficiency in the above cases remains unexplained. Possible mechanisms are malabsorption of bile affecting cholesterol leading to reduced precursor for steroid synthesis, malabsorption of trace elements and vitamins (especially selenium and vitamin B5) that are steroid biosynthesis cofactors, re-setting of hypothalamo-pituitary–adrenal axis due to weight loss as in anorexia nervosa and perioperative complications such as blood loss causing pituitary/adrenal infarct or apoplexy or reduction in steroid metabolites produced by adipose tissue. Rapid weight loss, which is expected with bariatric surgery, may mask symptoms of adrenal insufficiency.
Patients who did not have an improvement in symptoms had abnormal cortisol day curve, which was due to malabsorption of oral hydrocortisone. Parental hydrocortisone resulted in improvement of symptoms but resulted in significant weight gain. One of these patients had been commenced on a subcutaneous hydrocortisone pump with significantly reduced dose of hydrocortisone and improvement in symptoms.
Conclusion
These cases highlight the importance of long-term follow-up of patient's post-bariatric surgery and bariatric team needs to consider the possibility of adrenal insufficiency, when patient's presents with unexplained symptoms.

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P196

L-Phenylalanine modulates gut hormone release, and suppresses food intake in rodents via the Calcium Sensing Receptor

Mariana Norton, Amin Alamshah, Eleanor Spreckley, James S. Kinsey-Jones, Anjali Amin, Fanyi Li, Ishani Canisius, Rebecca Johnson, Elina Akalestou, Zainab Malik, Stephen R. Bloom & Kevin G. Murphy
Imperial College London, London, UK.

High protein diets suppress appetite, but are difficult to adhere to. Understanding how the gut senses protein may identify mechanisms to drive satiety. Amino acid products of protein digestion are thought to be sensed by G protein coupled receptors in the gut, including the calcium sensing receptor (CaSR). Calcium ions are the major ligand of the CaSR, but aromatic amino acids, particularly L-phenylalanine (L-Phe), allosterically modulate CaSR activity.
Our pilot studies suggested oral administration of L-Phe could reduce food intake in rodents. We therefore aimed to investigate the mechanisms that may underlie these anorectic effect of L-Phe.

We examined the effect of L-Phe on food intake, energy expenditure, behaviour, gut hormone secretion and neuronal activation, in rodents. Additionally, we explored the role of the CaSR in mediating gut hormone secretion in vitro and food intake *in vivo*.

In vitro, L-Phe stimulated secretion of the anorectic gut hormone glucagon-like peptide-1 (GLP-1) from STC-1 cells, an effect attenuated by CaSR antagonist. *In vivo*, orally administered L-Phe reduced food intake, increased circulating levels of GLP-1, supressed circulating levels of the orexigenic gastric hormone ghrelin, increased locomotor behaviour, and modulated neuronal activity in appetite regulating centres of the brain. Intra-ileal administration of L-Phe in rats supressed food intake, and this effect was attenuated by CaSR antagonist. Chronically, L-Phe decreased food intake and body weight in diet induced obese mice.

Further work is required to confirm whether the effects of L-Phe on gut hormone release mediate its effects on food intake and neuronal activation. L-Phe and the CaSR may represent new therapeutic targets for functional foods or drugs designed to regulate appetite and body weight.

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Administration of FGF21 analogue ameliorates hyperglycemia in streptozotocin-induced diabetic mice

In-Kyu Lee
Kyungpook National University School of Medicine, Daegu, Republic of Korea.

This study was performed to investigate the effects of LY2405319, an analogue of fibroblast growth factor 21 (FGF21), on glucose homeostasis in streptozotocin (STZ)-induced insulin-deficient mice. Nine-week-old male C57BL/6J mice were administered a single intraperitoneal injection of STZ (150 mg/kg). One week later, after confirmation of hyperglycaemia, saline or LY2405319 (5 mg/kg) was injected subcutaneously daily for 4 weeks. The STZ-induced diabetic mice had elevated blood glucose and reduced plasma FGF21 levels, impaired glucose uptake in the BAT, and BAT mitochondria with absent or swollen cristae and fewer lipid vacuoles. FGF21 analogue LY2405319 significantly reduced blood glucose levels and this was associated with increased BAT glucose uptake and changes in gene expression and morphology, indicating improved mitochondrial lipid metabolism in the BAT. Importantly, the ability of LY2405319 to lower blood glucose in STZ-induced diabetic mice was compromised after removing interscapular BAT. Taken together, our results show that LY2405319 reduces blood glucose levels in insulin-deficient diabetes by improving BAT function. Additional studies investigating the therapeutic potential of FGF21 for the treatment of type 1 diabetes are warranted.

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Progesterone and estrogen regulation of gene expression related to acylation stimulating protein production and function in *ex vivo* adipose tissue explant culture

Bashair Al Riyami[1], Simon Langley-Evans[1], Andrew Salter[1] & Jumana Saleh[2]
[1]The University of Nottingham, Nottingham, UK; [2]Sultan Qaboos University, Muscat, Oman.

Acylation stimulating protein (ASP) synthesis occurs through the interaction between complement C3, factor B and adipsin in adipose tissue. ASP demonstrates potent lipogenic effects that are modulated by sex hormones *in vivo* and *in vitro*. In this study, an *ex vivo* investigation was carried out to analyse expression of genes related to ASP production and function. Adipose tissue was harvested from ovariectomized rats ($n=6$), and treated with sex steroids at physiological concentrations (progesterone, estrogen, P&E and testosterone) and chylomicrons. The addition of chylomicrons to the media of cultured adipocytes has been shown to stimulate ASP production. Tissue explants were cultured for 24 hours at 37 °C and 5% CO2. The results showed that ASP production was only influenced by co-treatment with P&E in both visceral and subcutaneous tissue ($P=0.011$ and $P=0.007$, respectively) compared to the control group. Interestingly, in P&E treated subcutaneous tissue along with a reduction in ASP concentration, factor B gene expression decreased significantly ($P=0.032$) and C5L2 receptor expression increased significantly ($P=0.05$) compared to the control. DGAT1 expression increased significantly ($P=0.032$) and correlated positively with C5L2 receptor ($P=0.045$, $r=0.51$). In addition, factor B and factor D were positively correlated with ASP concentration ($P=0.012$, $r=0.61$ and $P=0.013$, $r=0.61$ respectively).

In summary, the findings showed that ASP concentration and expression of precursors and related lipogenic factors may regulated only under the combined (P&E) treatment compared to individual hormone effects. The unexpected decrease in ASP production in subcutaneous tissue may be explained by the increased expression of C5L2 receptor and this suggest increased uptake of ASP by adipocytes. The positive correlation between C5L2 and DGAT suggests a regulatory effect of P&E hormones on the ASP-C5L2 signaling pathway and triglyceride uptake. Further analysis of the mechanism involved may clarify the influence of female hormones on fat storage and distribution.

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P199

Endocannabinoid receptor blockade increases vascular endothelial growth factor and inflammatory markers in obese women with PCOS

Thozhukat Sathyapalan[1], Zeeshan Javed[1], Eric S Kilpatrick[3], Anne-Marie Coady[4] & Stephen L Atkin[2]
[1]Department of Academic Endocrinology, Diabetes and Metabolism, University of Hull, Hull, UK; [2]Weill Cornell Medicine Qatar, Doha, Qatar; [3]Sidra Research Centre, Doha, Qatar; [4]Department of Obstetric Ultrasound, Hull & East Yorkshire Women's & Children's Hospital, Hull, UK.

Context

There is growing evidence that cannabinoid receptor-1 (CB-1) blockade reduces inflammation and neovascularization by decreasing vascular endothelial growth factor (VEGF) levels associated with a reduction in inflammatory markers, thereby potentially reducing cardiovascular risk.

Objective

To determine the impact of CB1 antagonism by rimonabant on VEGF and inflammatory markers in obese PCOS women.

Design

Randomised, open-labelled parallel study.

Setting

Endocrinology outpatient clinic in a referral centre.

Subjects

Twenty patients with PCOS and biochemical hyperandrogenaemia with a body mass index of $\geq$ 30 kg/m^2 were recruited. Patients were randomised to 1.5 g daily of metformin or 20 mg daily of rimonabant.

Main Outcome Measures

Post hoc review to detect VEGF and pro-inflammatory cytokines TNF-α, IL-1β, IL-1ra, IL-2, IL6, IL-8, IL-10, MCP-1 and Eotaxin before and after 12 weeks treatment.

Results

After 12 weeks of rimonabant there was a significant increase in VEGF (99.2$\pm$17.6 vs 116.2$\pm$15.8 pg/ml, $P<0.01$) but not after metformin (110.3$\pm$25.2 vs 111.5$\pm$24.8, $P=0.7$). There was no significant difference in the pro-inflammatory cytokines following either treatment except IL-8 (7.4$\pm$11.0 vs 18.1$\pm$13.2 pg/ml, $P<0.05$) and Eotaxin (52.7$\pm$9.2 vs 64.9$\pm$14.6 pg/ml, $P<0.05$), which were raised significantly after rimonabant and metformin treatment, respectively.

Conclusion

This study suggests that rimonabant CB-I blockade paradoxically raises VEGF and some pro-inflammatory markers in obese women with PCOS, which may offset the potential benefits associated with weight loss.

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P200

Defining uterine insulin resistance

Ruijin Shao[1], Yuehui Zhang[1,2], Min Hu[1] & Håkan Billig[1]
[1]Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden; [2]Key Laboratory and Unit of Infertility in Chinese Medicine, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin, China.

Peripheral insulin resistance and hyperandrogenism are the primary features of polycystic ovary syndrome (PCOS). However, how insulin resistance and hyperandrogenism affect uterine function and contribute to the pathogenesis of PCOS are open questions. Rodent models of insulin and human chorionic gonadotropin (hCG) treatment have provided systems in which to study ovarian insulin resistance, ovarian stromal hyperplasia, follicular cyst formation, and impaired mitochondrial function in oocytes as well as to identify the underlying molecular mechanisms behind hyperinsulinemia and hyperandrogenism. Using these rodent models, this study was designed to answer whether the uterus develops insulin resistance *in vivo*. We showed that peripheral insulin resistance and hyperandrogenism alter uterine morphology, cell phenotype, and cell function, especially in glandular epithelial cells. These defects are associated with an aberration in the PI3K/Akt signaling pathway that is used as an indicator for the onset of insulin resistance in classical metabolic tissues. Next, we determined the expression pattern of glycolytic enzymes and intermediates during insulin resistance and hyperandrogenism in the uterus. The results of this study highlight for the first time the in vivo effects of chronic insulin and hCG exposure on the development of uterine insulin resistance. In addition, our results demonstrate that dysregulation of the IR-mediated PI3K/Akt signaling pathway and glycolytic metabolism in the uterus is strongly associated with insulin resistance and hyperandrogenism.

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P201

Alterations of specific caveolin isoforms in the rat uterus under insulin resistance and hyperandrogenism conditions: does metformin contributes to their regulation?

Min Hu[1], Yuehui Zhang[2], Xue Sun[2], Xiaoyan Sun[2], Fanci Meng[2], Ruijin Shao[1] & Håkan Billig[1]
[1]University of Gothenburg, Gothenburg, Sweden; [2]Heilongjiang University of Chinese Medicine, Harbin, China.

The caveolin (CAV) consists of three isoforms (CAV1, CAV2, and CAV3) and contributes to insulin-regulated glucose metabolism. It has been reported that decreased caveolin-1 phosphorylation in the endometrium is linked with insulin resistant state in women with polycystic ovary syndrome (PCOS). Because PCOS patients often display hyperandrogenism, whether hyperandrogenism in addition to insulin resistant is involved in the regulation of caveolin expression and activation in the uterus remain unknown. In this study, we treated female rats with insulin alone or in combination with human chorionic gonadotropin (hCG), and showed that insulin resistance and hyperandrogenism change the different caveolin isoform expression in the uterus, especially in smooth muscle cells. While no significant difference in CAV1 expression was detected in all groups, we found that CAV1 (Tyr14) phosphorylation was increased in hCG-treated uterus. Further, we showed that CAV2 expression was lower in insulin-, hCG- and insulin + hCG-treated uterus than control uterus, and CAV3 expression was decreased in insulin- and hCG-treated uterus. Treatment with metformin, an insulin-sensitizer, is reported to decrease circulating insulin and androgen levels, and reduce insulin resistance in most women with PCOS. In parallel to the improvement of insulin resistance and reduction of androgen synthesis, we observed that treatment with metformin reduced CAV2 expression but not CAV1/3 expression and CAV1 (Tyr14) phosphorylation in insulin + hCG-treated uterus. Our results suggest that specific caveolin isoforms and their regulation may be influenced by the environment of insulin resistance and hyperandrogenism in the rat uterus.

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P202

Understanding and supporting women with polycystic ovary syndrome: a qualitative study in an ethnically diverse UK sample

Michelle Hadjiconstantinou[1], Hamidreza Mani[1,2], Naina Patel[1], Miles Levy[2], Melanie Davies[1,2], Kamlesh Khunti[1] & Margaret Stone[1]
[1]University of Leicester, Leicester, UK; [2]University Hospitals of Leicester NHS TRust, Leicester, UK.

Background and aims
Polycystic Ovary syndrome (PCOS) is a common, lifelong condition. Its associated symptoms have been linked with psychological consequences, but less attention has been given to the daily implications of living with the condition. We aimed to explore women's experiences of living with PCOS, including a specific focus on practical implications and methods of providing support such as structured group-based patient education.
Methods
Women with PCOS were recruited from an ethnically diverse UK community. Twelve semi-structured interviews were conducted. Analysis was underpinned by the constant comparative approach and involved identification and exploration of key themes.
Results
Participants reported a range of symptoms linked with PCOS, including problems relating to menstruation and difficulties with weight. Hirsutism was reported as the most distressing symptom. Emergent themes included perceptions about symptoms and delays in receiving a diagnosis; psychological distress; practical implications of living with the condition; coping with PCOS and perceived support needs. Some findings were suggested to be specific to women from different cultural backgrounds, for example, failure to recognise symptoms that were seen as normal within their ethnic group. Participants were generally supportive of the idea of group education for women with PCOS and suggested a need to provide education within the wider community and for health care providers.
Conclusion
Women with PCOS experience high psychological distress and difficulties with coping with their condition. Suggested strategies for support include increased provision of education at various levels that could help reduce the negative psychological and practical impact of symptoms.

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P203

Elicitation of estrogenic and antiandrogenic mechanisms by oleic acid in pubertal male rats

Oluwakemi Oyelowo[1] & Adeyombo Bolarinwa[2]
[1]University of Lagos, Lagos, Nigeria; [2]University of Ibadan, Ibadan, Nigeria.

This study was designed to determine if prenatal exposure to oleic acid would alter testicular endocrine functions in either an estrogenic or antiandrogenic manner at puberty. Gravid dams were distributed into four groups of five rats each as follows: Control group (1 ml/kg olive oil throughout pregnancy), pre-treatment group (1000 mg/kg of oleic acid for 7 days before mating), preimplantation group (1000 mg/kg of oleic acid for the period of preimplantation), Organogenesis group (1000 mg/kg of oleic acid for the period of organogenesis). Dams delivered naturally and male offspring were studied into puberty. Morphological landmarks, hormone levels and sex accessory gland development were assessed. Estrogenic properties included shortened AGI, decrease in serum LH and T ($P < 0.001$), increase in prolactin level in the organogenesis group. Antiandrogenic properties included delayed pubertal maturation, altered serum LH and T levels ($P < 0.001$), epididymal sperm numbers in all treated groups. The results provide *in vivo* example of a pronounced degree of target tissue selectivity to an environmental endocrine-disruptor.

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P204

Gonadotropin Induction of Spermatogenesis in Men with Hypogonadotrophic Hypogonadism: an audit

Pushpa Jinadev[1], Tomas Ahern[1,2], Lakshmi Pichaipillai[1], Khaled Tofeec[1], Christine Gibson[1], Nicci Komlosy[1] & Frederick Wu[1]
[1]Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK; [2]Christie Hospital, Manchester, UK.

Introduction
Infertility affects 15% of couples worldwide. Male factors account for half of cases seeking medical care.
Objectives and methods
To ascertain whether the American Association of Clinical Endocrinologists (AACE) guidelines regarding gonadotrophin induction of spermatogenesis in men with hypogonadism are being followed in our unit. Data were collected retrospectively from clinical records.
Results
26 couples were identified. The presence of hypogonadotropic hypogonadism was confirmed by an endocrinologist in all cases. Assessment of the female partner's fertility was recorded in 17 couples (65%).
Hypogonadotropic hypogonadism was due to a congenital cause in 54% of cases. βHCG was the initial therapy in all cases. In men with persistent azoospermia, recombinant follicular stimulating hormone (rFSH) therapy was added in 17 couples (65%) 9 months (median, range 6 to 16 months) after commencement of βHCG therapy.
Serum testosterone levels were measured and semen samples were analysed every 3.6 ± 1.1 (mean $\pm$ S.D.) months.
Pregnancy was achieved in 4 couples (15%) treated with βHCG monotherapy and in 7 couples (27%) in receipt of combination βHCG and rFSH therapy.
βHCG was continued until 2nd trimester in at least 8 couples (31%). Testosterone replacement therapy was restarted in 12 patients (46%).
Conclusion
Gonadotrophin induction of spermatogenesis in our unit is in line with AACE recommendations. This study shows that infertility due to secondary hypogonadism is treatable with exogenous Gonadotrophins. We also suggest that a dedicated unified proforma will enable us to follow the protocol for management of infertility and assist us for data collection for future studies.

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P205

An audit of success rates of the induction of spermatogenesis clinic at University College London Hospitals

Anastasia Dimakopoulou[1], Taofeek Ojewuyi[2], Sofia Llahana[1], Stephanie Baldeweg[1] & Gerard Conway[1]
[1]UCLH, London, UK; [2]Whittington Hospital, London, UK.

Introduction and aim
In the UK, 15% of couples are affected by infertility which is due to primary or secondary male factors in 30%. Induction of spermatogenesis with gonadotrophins is a long established endocrine treatment for gonadotrophin deficiency. However, there are concerns that some patient groups have very low success rates. The aim of our audit was to define success of spermatogenesis and fertility rates amongst these men.
Methods
We retrospectively reviewed records from the male reproductive clinic at UCLH. All men presented with azoospermia or oligospermia (<15 millions/ml) and received human chorionic gonadotropin therapy or combination with recombinant follicle-stimulating hormone.
Results
Fifty five men were included in this audit of whom 58% had hypogonadotrophic hypogonadism, 36% hypopituitarism and 6% partial testicular failure. Eight (15%) achieved sperm cryopreservation, 11 men (20%) stopped attending our clinic for personal reasons and 36 (65%) wanted immediate fertility. Pregnancy was achieved for 26 out of 36 men (72%) who attempted fertility. Spontaneous conception was achieved for 16/36 men (44%), with 15/16 live births (94%) and 1/16 miscarriage (6%). Median conception time was 16 (range 5–36) months. Ten out of 36 (28%) men proceeded to *in vitro* fertilization (IVF) which resulted in 5/10 live births (50%), 3/10 miscarriages (30%) and 2/10 failed conception (20%). Median conception time for this group was 19.5 (range 6–44) months. Testicular sperm extraction (TESE) with was performed for 10/36 men (28%) resulting in 2/10 live births (20%) whilst 8/10 failed conception (80%). Median time to TESE was 19 (range 5–62) months.
Conclusion
This study reports real life fertility rates in men with secondary subfertility of different aetiologies. Closer assessment of factors predicting successful outcome will allow us to identify good and poor responders in order make the program more effective.

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P206

The effects of Vitamin D on the outcomes of controlled ovarian stimulation in women with and without Polycystic Ovary Syndrome undergoing *in vitro* fertilisation

Thomas Cunningham[1,2], Victoria Allgar[3], Stephen Atkin[4], Eric Kilpatrick[5], Stephen Maguiness[1] & Thozahukat Sathyapalan[2]
[1]The Hull IVF Unit, Hull, UK; [2]Centre for Cardiovascular and Metabolic Research, Hull York Medical School, University of Hull, Hull, UK; [3]Statistics Department, Hull York Medical School, University of Hull, Hull, UK; [4]Weill Cornell Medicine Qatar, Doha, Qatar; [5]Sidra Medical and Research Centre, Doha, Qatar.

Background
Vitamin D deficiency has become the most common nutritional deficiency throughout the world. 67–85% of Polycystic Ovary Syndrome (PCOS) patients have low serum levels of Vitamin D. Studies have reported conflicting data as to whether or not Vitamin D may play a role in human reproduction. The objective of this prospective cohort study was to investigate what effect vitamin D had on parameters within an *in vitro* fertilisation (IVF) cycle in a population of infertile women with and without Polycystic Ovary Syndrome (PCOS).
Method
PCOS was diagnosed using the Rotterdam ESHRE/ASRM consensus criteria. Serum levels of Vitamin D [25(OH)D] were measured using liquid chromatography mass spectrometry during the menstrual cycle prior to commencing a short antagonist cycle of IVF. 25(OH)D levels were compared against patient demographics and IVF cycle parameters between PCOS and non-PCOS groups.
Results
59 women participated, 29 PCOS and 30 non-PCOS. 83% of the women had vitamin D insufficiency (25(OH)D $<$ 50 nmol/l); there was no statistical significance in vitamin D levels between the groups ($P=0.12$). There was no significant difference in clinical pregnancy rates per IVF cycle in the non-PCOS group compared to the PCOS group (33% vs 24%; $P=0.57$). There was a significant positive correlation ($P=0.03$) between vitamin D levels and fertilisation rates in women with PCOS.
Conclusion
The Vitamin D status in our patients appears to reflect that of the general population. There was a significant correlation between Vitamin D levels and fertilisation rates in the PCOS group indicating a possible relationship between Vitamin D and oocyte maturation in this distinct population of women. This is an important finding as replenishing Vitamin D in PCOS patients may in fact increase their chances of achieving a pregnancy. How this process is achieved is unclear and would require further work and larger studies.

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P207

Bacterial isolates associated with semen and mouth of infertile men

Titilola Samuel[1], Omobonike Olagunju[1] & Segun Nwhator[2]
[1]University of Lagos, Lagos, Nigeria; [2]Obafemi Awolowo University, Ile Ife, Nigeria.

Background
This study was aimed at examining the association between the fertility parameters and periodontal status of men, with reference to the bacterial culture analysis of the semen and mouth swab, seminal fluid parameters and blood serum parameters.
Method
43 men consisting 30 infertile men as test subject, and 13 fertile men as control aged 30–50 years were selected for this research. Semen samples were analysed to determine microbial presence, as well as the qualitative and quantitative features using standard methods. Blood serum samples were analyzed to determine Biochemical parameters using standard kit assays, as well as Hormonal parameters were determined by enzyme immunoassay kits.

Results
Staphylococcus aureus accounted for the highest frequency (36.7%) of bacterial isolate from both semen culture and mouth swab. There was a significant decrease ($P<0.05$) in the semen volume, concentration and motility of the test group compared to the control group, with a corresponding significant increase ($P<0.05$) in the abnormal semen morphology of the test group compared to the control.
Conclusions
The results suggest a relationship between infections in the semen and mouth, and increase in seminal fluid infections, elicits a decrease in sperm concentration, volume, motility and morphology.
Keywords: Male infertility, periodontal infection, *Staphylococcus aureus*
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P208

Anti-Müllerian Hormone (AMH) and Antral Follicle Count (AFC) are predictive markers in the assessment of patients with menstrual disturbance

Ali Abbara[1], Sophie Clarke[1], Rachel Roberts[1], Sunitha Vimalesvaran[1], Alexander Comninos[1], Georgios Christopoulos[2], Rumana Islam[2], Steven Franks[1], Geoffrey Trew[2] & Waljit Dhillo[1]
[1]Imperial College London, London, UK; [2]Imperial College Healthcare NHS Trust, London, UK.

Background
Anti-Müllerian Hormone (AMH) and Antral Follicle Count (AFC) are both principally used as markers of ovarian reserve and available in all UK hospitals. The utility of these markers in the binary diagnosis of Polycystic Ovarian Syndrome (PCOS) by published criteria, such as Rotterdam, has been previously reported. We evaluated their utility in the evaluation of oligo/amenorrhoea in healthy young non-obese women.
Methods
Women with both ovaries in situ, under the age of 35 years, with BMI <30 kg/m^2, seeking fertility treatment at Imperial College Healthcare NHS Trust were included in the study. 186 women were screened with menstrual cycle history, follicular-phase AFC on ultrasound, ovarian morphology (normal, multicystic ovaries MCO, or polycystic ovaries PCO), serum AMH level (pmol/l; Beckman-Coulter 3rd generation assay), and other reproductive hormones. Oligo/amenorrhoea was defined as average menstrual cycle length (ACL) greater than 35 days.
Results
There was a linear correlation between serum AMH and AFC on ultrasound, with the following equation describing the relationship (AFC = AMH X0.5 + 12). Rather than AMH and AFC being elevated only in women with oligo/amenorrhoea, there was a gradual increase in these markers with increasing ACL even in eumenorrhoeic women (median AMH 20 pmol/l in ACL <27 days, 28 pmol/l in ACL 28–29 days, 47 pmol/l in ACL 30–34 days, 66 pmol/l in ACL >35 days). There was an increased prevalence of oligo/amenorrhoea with increasing AMH, or AFC, (5% oligo/amenorrhoea in AMH <15 pmol/l, 24% oligo/amenorrhoea in AMH 30–45 pmol/l, 61% oligo/amenorrhoea in AMH >60 pmol/l). Oligo/amenorrhoea was less prevalent in those with at least one normal ovary (0–7%) when compared with those with those with 2 MCO (11%), or 2 PCO (47%) ovaries.
Conclusion
AMH and AFC are reliable predictive markers of menstrual cyclicity, even in women currently regarded as being eumenorrhoeic. Thus, AMH and AFC are useful adjuncts in the clinical assessment of patients with menstrual disturbance.
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P209

Profiling the decidualisation response of women with endometriosis reveals diverse patterns of steroid responsiveness

Ioannis Simitsidellis[1], Douglas A. Gibson[1], Olympia Kelepouri[1], Andrew W Horne[2] & Philippa T K Saunders[1]
[1]The University of Edinburgh, MRC Centre for Inflammation Research, Edinburgh, UK; [2]The University of Edinburgh, MRC Centre for Reproductive Health, Edinburgh, UK.

Endometriosis is a chronic hormone-dependent disorder, characterised by growth of 'ectopic' endometrial tissue outside the uterus. It has been reported that 30–40% of women who are sub/infertile have endometriosis. Infertility in women with severe endometriosis may be the result of either scarring or pelvic distortion, but in women with mild/moderate disease it is believed subfertility may result from disturbances in endometrial tissue function. Transformation of human endometrial stromal fibroblasts (hESC) into specialised secretory cells (decidualisation) is fundamental to the establishment of a receptive endometrial microenvironment which can support and maintain pregnancy. Evidence suggests that women with endometriosis have an impaired decidualisation response. In the current study, we have compared the decidualisation response of women with and without endometriosis, examined the temporal expression of decidualisation factors and steroidogenic enzymes and explored the impact of steroid receptor ligands.
Primary hESCs from women with and without endometriosis were recovered during the proliferative phase of the menstrual cycle and incubated with progesterone and cAMP to model decidualisation *in vitro*. Co-treatment with androgen receptor ligands (DHT, flutamide) was performed. Culture media, RNA and protein samples were recovered on days 1, 2, 4 and 8 of treatment. Expression of decidualisation markers (IGFBP1, PRL, HOXA10, FOXO1) and steroidogenic enzymes (AKRIC3, SRD5A1) was determined and concentrations of secreted IGFBP1, PRL and DHT measured by ELISA.
Results revealed striking and consistent time-dependent changes in gene and protein expression, with evidence that local (intracrine) biosynthesis of androgens plays a role in regulation of decidualisation. In contrast to those of control cells, responses of hESCs from women with endometriosis were not uniform, with several exhibiting rapid/transient responses consistent with blunted decidualisation. In conclusion, hESC from women with endometriosis appear to retain a 'memory' of altered *in vivo* responsiveness providing a platform for development of novel therapies.
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P210

Safety and tolerability of inducing completion of puberty with IM testosterone over 1 year in older men with congenital hypogonadism and absent puberty

Agniezska Pazderska[2,3], Satish Artham[1], Margaret Miller[1], Margaret Morris[1], Steve Ball[4] & Richard Quinton[1,2]
[1]Endocrine Unit, Newcastle-upon-Tyne Hospitals Foundation NHS Trust, Newcastle, UK; [2]Institute of Genetic Medicine, University of Newcastle-upon-Tyne, Newcastle, UK; [3]Directorate of Diabetes & Endocrinology, Norfolk & Norwich University Hospitals NHS Trust, Norwich, UK; [4]Department of Endocrinology, Manchester Royal Infirmary, Manchester, UK.

Background
Guidance on pubertal-induction in hypogonadal adult men is sparse. For adolescent boys, in whom delay is usually constitutional, treatment is typically initiated with pulsed low-dose IM testosterone (T); the dose being progressively increased if/when it becomes clear that endogenous gonadotrophin secretion is not being initiated. In teenagers with organic hypogonadism, the aims are to recapitulate the normal tempo of puberty over 2–3 years and optimise linear growth. However, such regimes may be inappropriate for older apubertal men, who have already attained near-final height, exhibit segmental disproportion and, having experienced years-decades of treatment-delay, typically wish to complete the process as rapidly as possible.
Aim
To review the effectiveness and tolerability of a 1-year pubertal-induction regime with IM T in adult men with congenital hypogonadism presenting with absent puberty.
Methods
Records of 9 older men with congenital hypogonadotrophic hypogonadism (CHH) who underwent pubertal-induction (2000–16) were reviewed, comprising Kallmann's ($n=4$), normosmic CHH ($n=4$) and CHARGE syndrome ($n=1$). One man had major physical and learning impairments and another presented following major self-harm episode. Median age at commencement of pubertal induction was 53.4 years (range 22.9 − 70). Treatment over the 1st year was with T undecanoate 1g injections (TU) spaced around 4-monthly ($n=8$), or Sustanon® 250 mg/monthly ($n=1$).
Results
All patients had completed pubertal development within a year of treatment-initiation and there were no recorded adverse physical or psychological events (apart from male-pattern baldness, $n=1$), nor any excursions of trough serum T or haematocrit. Extended follow-up revealed major improvement in bone density in all but the oldest.
Conclusions
Patients' experiences were overwhelmingly positive and similar to published data on older Trans-Men (F2M) receiving virilising cross-hormone treatment, reflecting the paucity of evidence behind traditional concerns about relatively

rapid elevation of serum T into the adult male range causing behaviour-disturbance in T-naïve adults. To this end, 4-monthly TU injections are safe, convenient and effective, and can minimise clinic visits.

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P211

Insight into the molecular mechanisms underlying alterations in gonadotropin receptor activity in polycystic ovarian syndrome

Lisa Owens, Avi Lerner, Silvia Sposini, George Christopoulos, Shiran Khanjani, Razia Islam, Stuart Lavery, Vicky Tsui, Kate Hardy, Stephen Franks & Aylin Hanyaloglu
Imperial College London, London, UK.

Introduction
Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 5–10% of women of reproductive age, and is the major cause of anovulatory infertility. Aberrant secretion and/or action of gonadotropins are implicated but, to date, we have only limited knowledge about the precise mechanisms involved. Recent genome wide association studies have discovered signals at loci close to the genes coding for gonadotropin receptors. The functional significance of these polymorphisms is, as yet, unclear and represents a key area for research.
Methods
In this study granulosa-lutein (GL) cells were obtained from women with and without PCOS undergoing IVF. HEK293 cells were also used as an ovarian PCOS model by stable transfection with FLAG-LHR, transient transfection with HA-FSHR and 24-hour treatment with DHT. RNA was extracted and qPCR performed to analyse differential gene expression. Cyclic AMP production was measured after administration of luteinising hormone (LH) and follicle stimulating hormone (FSH) to cultured cells using a second messenger accumulation assay. Intracellular calcium signalling was measured after administering LH using calcium fluorescent indicators.
Results
Increased expression of full-length FSH ($P=0.02$) and LH ($P=0.05$) receptor RNA was seen in PCOS GL cells, along with increased expression of signaling/trafficking molecules β arrestin-2 ($P=0.03$), PDZ-protein GIPC ($P=0.07$) and APPL1 ($P=0.005$). No significant differences were seen in expression of LH receptor splice variants. CyclicAMP level measured after administration of LH for 5 minutes was higher in GL cells from PCOS than from controls (x4 fold). Similarly cAMP produced after administration of LH to HEK cells was higher in cells pre-treated with DHT (x3.5fold). cAMP measured after administration of FSH was however negligible in all groups, suggesting involvement of an alternative to the traditional Gs pathway. Administration of LH activated a calcium signaling response.
Conclusion
These results reveal multiple molecular alterations of LH receptor action and downstream signaling in GL cells from women with PCOS.

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P212

Gonadotrophin secretion is a useful adjunct in the diagnosis of patients with hyperprolactinaemia

S Clarke, A Abbara, A Nesbitt, S Ali, AN Comninos, E Hatfield, NM Martin, A Sam, K Meeran & W Dhillo
Imperial College Healthcare NHS Trust, London, UK.

Background
Hyperprolactinaemia accounts for 1 in 7 patients presenting with amenorrhoea. Recent data suggests that prolactin acts at the hypothalamus to reduce GnRH-pulsatility. Conditions in which GnRH-pulsatility is reduced, such as hypothalamic amenorrhoea, favour FSH over LH secretion from the pituitary gland. We examined gonadotrophin secretion in hyperprolactinaemic patients as a surrogate marker of GnRH-pulsatility.
Methods
A retrospective analysis of gonadotrophin secretion in patients with hyperprolactinaemia over the gender-specific reference range during 2012–2015 was performed at Imperial College Healthcare NHS Trust.
Results
Of 470 patient-records reviewed, 275 (Female 210, Male 65) had raised serum monomeric prolactin levels concomitant with serum gonadotrophin (FSH/LH) levels. Frequent diagnoses included microprolactinoma ($n=80$), macroprolactinoma ($n=46$), non-functioning macroadenoma (NFA; $n=72$), drug-induced hyperprolactinaemia (DIH; $n=22$) and polycystic ovarian syndrome (PCOS; $n=15$).
In PCOS, LH-predominant secretion was observed consistent with increased GnRH-pulsatility (FSH 4.0iU/L, LH 7.2iU/L, FSH-LH -3.2iU/L). Conversely in DIH, FSH-predominant secretion was observed, consistent with reduced GnRH-pulsatility (FSH 5.5iU/L, LH 3.4iU/L, FSH-LH +2.1iU/L; FSH-LH $P=0.0006$ vs PCOS).
In patients with prolactinoma, there was a progressive increase in 'FSH-LH' differential with increasing serum prolactin level, consistent with a progressive fall in GnRH-pulsatility. However, both FSH and LH secretion were reduced in patients with prolactin levels >4000 mU/l, consistent with intrinsic pituitary gonadotroph hypofunction in larger prolactinomas.
In patients with macroadenomas, extremes of gonadotrophin secretion were more frequently observed in NFAs when compared with macroprolactinomas. This observation was not accounted for by the effect of prolactin on GnRH-pulsatility and was more consistent with autonomous intrinsic pituitary gonadotrophin secretion in NFA (100% of FSH+LH>15iU/L had NFA vs 47% with FSH+LH <5iU/L).
Conclusion
Raised prolactin acts at the hypothalamus to reduce GnRH pulsatility, resulting in FSH-predominant secretion. In larger prolactinomas, gonadotrophin secretion is reduced due to pituitary gonadotroph hypofunction. Thus, gonadotrophin levels are a useful adjunct in the diagnosis of patients with hyperprolactinaemia.

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P213

The relation of liver enzymes and insulin resistance in women with polycystic ovary syndrome (PCOS)

Djuro Macut[1], Ivana Bozic-Antic[1], Konstantinos Tziomalos[2], Jelica Bjekic-Macut[3], Dusan Ilic[1], Danijela Vojnovic-Milutinovic[4], Olivera Stanojlovic[5] & Dimitrios Panidis[2]
[1]Clinic of Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia; [2]Department of Medicine, University of Thessaloniki, Thessaloniki, Greece; [3]CHC Bezanijska Kosa, Belgrade, Serbia; [4]IBISS, University of Belgrade, Belgrade, Serbia; [5]Institute of Physiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Introduction
There is a link between polycystic ovary syndrome (PCOS) and nonalcoholic fatty liver disease (NAFLD). Here, we analyzed transaminazes and their relation to insulin resistance (IR) in PCOS women.
Methods
We analyzed 600 women with PCOS diagnosed using ESHRE/ASRM criteria (age:25.6±5.9 years, BMI: 30.6±6.9 kg/m^2), and 125 BMI-matched healthy controls (age: 31.4±5.3 years, BMI: 29.6±6.8 kg/m^2). IR was evaluated using HOMA-IR cut-off 2.5. Subjects were divided into: PCOS-IR ($N=384$), PCOS-nonIR ($N=216$), Controls-IR ($N=53$) and Controls-nonIR ($N=72$). Analyses were age and BMI adjusted.
Results
The highest AST was found in PCOS-IR and significantly differed in comparison to PCOS-nonIR (20.75±8.31 vs 17.99±5.04 U/l, respectively, $P<0.05$). There was no difference in AST between Controls-IR and Controls-nonIR (18.96±6.66 vs 18.38±5.63 U/l, respectively, $P>0.05$). ALT was highest in PCOS-IR and significantly differed from PCOS-nonIR (25.36±16.21 vs 18.59±10.08 U/l, respectively, $P<0.05$), while ALT levels were the same in Controls-IR compared to Controls-nonIR (24.60±12.97 vs 19.97±10.94 U/l, respectively, $P>0.05$). In PCOS HOMA-IR correlated with both AST ($\rho=0.202$, $P<0.001$) and ALT ($\rho=0.315$, $P<0.001$) while in Controls only with ALT ($\rho=0.254$, $P=0.004$).
Conclusions
Although our PCOS women had normal values of liver enzymes, they were higher in comparison to controls. It seems that IR could additionally contribute to the disturbance of liver enzymes in PCOS.

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P214

Correlation of maternal serum Insulin growth factor 1 and 2 to predict foetal outcome

Amrit Gupta, Swasti Tiwari & Nisha Singh
SGPGIMS, Lucknow, Uttar Pradesh, India.

The intrauterine foetal environment is crucial for foetal survival and long term health. The insulin-like growth factors (IGF)-I and -II have a predominant role in fetal growth and development. Insulin-like growth factor 1 (IGF-1) is an anabolic hormone with several biological activities, such as proliferation, mitochondrial protection, cell survival, tissue growth and development.

Aims & Objectives

To find the association of Maternal insulin Growth Factors 1 & 2, in normal and pregnancy with Intrauterine Growth Restriction of foetus.

Methodology

This was a prospective case control study conducted in collaboration with Post graduate institute, (SGPGIMS, Lucknow, India) over a period of two years.

Inclusion criteria for control group included normal pregnant women with singleton pregnancy and growth parameters appropriate for gestational age. In the study group all cases diagnosed to have intrauterine growth restriction by under stated criteria:

- Gestational age confirmed by USG in first trimester
- IUGR suspected by a lag of >3 weeks in fetal biometry on serial USG after 20w
- Birth weight below 10th centile for the gestational age
- IUGR was confirmed after birth by weight in accordance with gestational age

A total of 120 mothers were recruited, 100 maternal serum samples were collected between gestational age of 32–38 weeks. 68 maternal samples were analysed for IGF-I, by chemi-lumnescent immunometric assay. 60 maternal serum samples were analysed for IGF 2 by Radio-immno assay.

Results

In maternal serum, the mean serum IGF-I levels were 251 ng/ml in control group vs 214.48 ng/ml (F-test$=0.005$) in study group, and were positively correlated with the birth weight. On other hand, IGF2 was negatively correlated 521.163 ng/ml in control group vs 618.473 ng/ml in study group (F-test$=0.029$).

Conclusion

Maternal blood IGF-I, plays an important role in the regulation of fetal and neonatal growth. It is likely that IGF2 in maternal blood may influence the growth potential of foetus.

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P215

Fertility effects of Curcumin-a kitchen Spice on Male Wistar Rat

Bolanle Iranloye & Oghochukwu Uweru
Reproductive and Endocrine Unit, Department of Physiology, College of Medicine of the University of Lagos, Lagos, Nigeria.

Surprisingly, up to 50% of cases of infertility among couples worldwide are male-related. But despite this alarming prevalence of male infertility, most studies continue to focus on analysis of infertility from female perspective. Curcumin (CUM), a food additive with international numbering code E100 has been shown to exhibit therapeutic potential against some illnesses (cancer, diabetes, testicular damage) in which free radicals plays a crucial role (Aggarwal and Harikumar 2009). Thus, this study examines the effect of curcumin on sperm profile and serum testosterone level.

The extraction of curcumin from turmeric rhizome was carried out according to the method described by Liu et al. (2008). Twenty adult male rats were randomly divided into four equal groups: group A (control) received distilled water, groups B, C and D received 50 mg/kg, 100 mg/kg and 150 mg/kg of CUM respectively. The CUM-treated animals received this compound intra-peritoneally once daily for fourteen days after which they were sacrificed by cervical dislocation. Epididymal sperm profile (motility, morphology and concentration), serum testosterone level and the micro-architecture of the seminiferous tubule were examined.

The different concentrations of CUM significantly ($P<0.05$) increased the percentage value of spermatozoa with normal morphology (77.75 ± 3.83, 74.50 ± 2.10, 85.25 ± 2.06 respectively) as compared to the control group (62.50 ± 1.44). Sperm motility and concentration were significantly increased ($P<0.05$) with a concomitant apparent increase in spermatogenic activity in the seminiferous tubule of the CUM-treated groups. CUM significantly increase ($P<0.05$) serum testosterone level particularly in the 150 mg/kg CUM group (14.45 ± 0.14 nmol/l) as compared to the control group (9.51 ± 0.98 nmol/l). This study suggests that curcumin enhances fertility in male wistar rats as evidenced by increased sperm profile and serum testosterone level.

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P216

Androsterone Glucuronide to dehydroepiandrosterone sulphate ratio is higher in obese Caucasian women with Polycystic Ovary Syndrome

Thozhukat Sathyapalan[1], Lina Ahmed[4], Brian Keevil[2], Adrian Miller[2], Eric Kilpatrick[3] & Stephen Atkin[4]
[1]Hull York Medical School, Hull, UK; [2]Wythenshaw Hospital, Manchester, UK; [3]Sidra Medical Research Centre, Doha, Qatar; [4]Weill Cornell Medicine, Doha, Qatar.

Objective

Androsterone glucuronide (ADTG) concentrations have been suggested as a more reliable marker of the effects of androgens at the target tissue level and they are significantly elevated in hirsute compared to non-hirsute women with PCOS. This study compared the different precursors of testosterone, including dehydroepiandrosterone sulphate (DHEAS), ADTG and androstenedione in non-obese compared to obese women with PCOS, and in normal subjects and their implications on cardiovascular risk.

Design and Method

Eleven non-obese and 14 obese women with PCOS were recruited and compared to 11 control women without PCOS. DHEAS, ADTG, androstenedione and total testosterone were analysed using tandem mass spectrometry and comparison made between the three groups.

Results

ADTG and androstendione levels did not differ between non-obese and obese PCOS but were significantly higher than for controls ($P<0.01$). However, the ADTG to DHEAS ratio was significantly elevated 39 ± 6 ($P<0.01$) in obese PCOS in comparison to non obese PCOS and controls (28 ± 5 and 29 ± 4, respectively). Both non-obese and obese PCOS were equally hyperandrogenic as measured by total testosterone ($P=0.74$), but the FAI and insulin resistance (HOMA-IR) was significantly higher in obese PCOS (both $P<0.01$). DHEAS was significantly higher in the non-obese versus obese PCOS ($P<0.02$). All androgen parameters were significantly lower and SHBG significantly higher in normal subjects compared to those with obese and non-obese PCOS.

Conclusion

ADTG:DHEAS ratio was significantly elevated in obese PCOS compared to non-obese PCOS and controls suggesting that this may be a novel biomarker. It is likely that this raised ratio may be due to higher hepatic 5α reductase activity increasing the conversion of its precursors to ADTG likely driven by increased insulin resistance seen in obese women with PCOS.

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P217

A prospective cohort study investigating Endocrine Disrupting Agents and Polycystic Ovary Syndrome within an IVF setting

Thomas Cunningham[1,2], Victoria Allgar[3], Stephen Atkin[4], Eric Kilpatrick[5], Stephen Maguiness[1] & Thozahukat Sathyapalan[2]
[1]The Hull IVF Unit, Hull, UK; [2]Centre for Cardiovascular and Metabolic Research, Hull York Medical School, University of Hull, Hull, UK; [3]Statistics Department, Hull York Medical School, University of Hull, Hull, UK; [4]Weill Cornell Medicine, Doha, Qatar; [5]Sidra Medical and Research Centre, Doha, Qatar.

Background

Endocrine Disrupting Agents (EDAs) are external substances that have the potential to interfere with the natural endocrine pathways such as the reproductive axis. Polycystic ovary syndrome (PCOS) is a common endocrine condition resulting in, hyperinsulinaemia, hyperandrogenaemia and subfertility. This study was conducted to see whether there was any association between EDAs and PCOS.

Methods

Blood samples were collected from 59 women (29 PCOS and 30 controls) undergoing IVF/ICSI. Serum samples were analysed using gas chromatography combined with mass spectrometry to identify the presence of common EDAs including, 14 polyfluoroalkyl congeners (PFAAs), 7 Polychlorinated Biphenyl (PCB) congeners, 7 Polybrominated diphenyl ether (BDE) congeners, hexabromocyclododexanes (α-HBCDD, β-HBCDD, γ-HBCDD), and the pesticides perclorobenene (PeCB), hexachlorobenzene (HCB), hexachlorocyclohexanes

(γ, α, and β-HCH), chlordanes (trans (γ) chlordane, Cis (α) Chlordane), dichlorodiphenyltrichloroethane (p,p-DDT) and its metabolites (op-DDE, pp-DDE, op-DDD), and Mirex. Statistical analysis was undertaken for potential associations with the EDAs, pregnancy rates and various characteristics of an IVF cycle between the PCOS and control groups.
Results
The levels of EDAs in the serum were comparable in each group with only the PFAA congener PFOS having a significantly higher concentration in the PCOS group, (4.11 ± 1.62 ng/ml vs 3.11 ± 1.05 ng/ml, $P=0.03$). The PFAAs had significant positive correlations with testosterone in both the control ($P=0.02$) and PCOS ($P=0.03$) groups. The PFAAs, PCBs and p,p-DDE demonstrated significant positive correlations with cleavage rates ($P=0.04$, 0.01, and 0.04 respectively). There was no correlation between the levels of EDAs and pregnancy in either group.
Conclusion
EDAs are detectable within subfertile women and that PFOS is significantly higher in PCOS women. There is evidence that these chemicals may disrupt not only endocrine pathways but also affect the cleavage stage in early embryo development. This study demonstrates EDA concentrations continue to decline and the UK has much lower levels than other western industrialized nations.

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P218

Validation and implementation of a diagnostic NGS panel in Scotland for disorders of sex development

LA Diver[1], V Cerqueira[1], A Purvis[1], R Nixon[2], ES Tobias[1,2], R McGowan[1], SF Ahmed[1,2] & N Williams[1]
[1]NHS Greater Glasgow & Clyde, Glasgow, UK; [2]University of Glasgow, Glasgow, UK

Disorders of sex development (DSD) are a collection of rare congenital conditions with diverse features and pathophysiology. Patients usually present at birth with atypical genitalia or with delayed puberty in adolescence. Biochemical and cytogenetic investigations may provide guidance on the underlying cause, however molecular genetic analysis is usually required to provide a definitive diagnosis and allows for personalised management of the patient. The current diagnostic service for the Scottish population in the West of Scotland Genetics Service detects pathogenic variants in ~10% of cases of XY DSD. Patient samples may also be sent to laboratories in England for further investigations which not only results in additional cost to the National Health Service in Scotland, but also delays treatment and increases anxiety and waiting times for patients and their families. The development of next generation sequencing (NGS) allows multiple genes to be investigated simultaneously at reduced cost and time compared with current methods. A targeted custom SureSelect hybridisation comprehensive gene panel has been designed and validated on the Illumina MiSeq NGS platform. Data analysis was performed using the commercially available software CLC Genomics Workbench and VarSeq. Variant interpretation was conducted using a combination of in silico tools and a specialist multidisciplinary Diagnostic Board with input from endocrinology, clinical and molecular genetics and steroid biochemistry. The validity and clinical utility of this extended gene panel in the diagnostic laboratory has been assessed and will be presented alongside initial results from patients with no previous molecular diagnosis.

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P219

Regulation of the renin-angiotensin system by salt in BeWo and JEG-3 cells

Raheel Klossner[1], Paula Williams[2], Nicole Eisele[1], Lesia Kurlak[2], Markus Mohaupt[1] & Hiten Mistry[2]
[1]University of Bern, Bern, Switzerland; [2]University of Nottingham, Nottingham, UK

Introduction
The renin-angiotensin system (RAS) become upregulated very early on in pregnancy and is crucial in maintaining blood pressure. In addition to the peripheral RAS there is a uteroplacental RAS, which is also important in regulating placental function and development. Recent work has shown extra-renal sodium storage in the skin; it is suggested that the placenta may also function as a salt sensing organ and is important in regulating maternal blood pressure.
Objectives
To test the hypothesis that increased sodium leads to a decrease in expression of RAS components involved in vasoconstriction and increased expression of those components involved in vasodilation.
Methods
The human choriocarcinoma cell lines BeWo and JEG3 were incubated in medium containing 110 mM (control), 140 mM or 170 mM Na^+ (in the form of NaCl). Cells were harvested after 6 hour incubation and RNA was extracted. TaqMan PCR was performed to determine mRNA expression of renin, (pro)renin receptor (PRR), angiotensinogen (AGT), angiotensin-converting enzyme (ACE), angiotensin-II receptor type 1 or 2 (AGTR1, AGTR2), and mineralocorticoid receptor (MR). Relative quantification was performed and results normalised to the housekeeping gene cyclophilin A.
Results
Following NaCl incubation decreased mRNA expression was found for MR (0.4 fold, $P<0.001$ in BeWo; 0.5 fold, $P<0.001$ in JEG3 at 170 mM) and AGT (0.5 fold, $P<0.001$ in BeWo; 0.7 fold, $P<0.05$ in JEG3 at 170 mM). ACE mRNA expression was low in both BeWo and JEG3 but increased following NaCl treatment (1.5 fold, $P<0.05$ in BeWo; 150-fold, $P<0.05$ in JEG3 at 170 mM). mRNA expression of PRR was not found to differ in either BeWo or JEG3 cells following NaCl treatment. Renin, AGTR1 and AGTR2 mRNA expression was not detected in either cell line.
Conclusion
This study is the first to show that Na^+ effects placental mRNA expression of MR, AGT and ACE. Therefore the placenta could be acting as a salt sensitive site and may be involved in the regulation of maternal blood pressure regulation. Further work is needed to confirm if these mRNA changes are translated to functional changes and also if they can be replicated in isolated human primary trophoblast cells.

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P220

Management of Turner's syndrome women with liver involvement: FIB-4 score is a promising marker of fibrosis

Matilde Calanchini[1], Ahmad Moolla[1], Jeremy W Tomlinson[1], Jeremy Cobbold[2], Andrea Fabbri[1], Ashley Grossman[1] & Helen Turner[1]
[1]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, University of Oxford, Oxford, UK; [2]Translational Gastroenterology Unit, Department of Gastroenterology and Hepatology, John Radcliffe Hospital, University of Oxford, Oxford, UK.

Introduction
Liver involvement is frequent in Turner's syndrome (TS). We have shown that 35% TS women have elevated liver function tests (↑LFTs). Most common hepatic changes include steatosis and steatohepatitis; however, progression to advanced fibrosis and cirrhosis is reported. This study assessed a simple noninvasive test for liver fibrosis, FIB-4, which combines standard biochemical values (platelets, ALT, AST) and age in order to evaluate its diagnostic performance in TS.
Methods
From a total of 104 patients attending our dedicated adult TS-clinic, we selected cases corresponding to the following criteria: 1) laboratory assessments allowing FIB-4 calculation; 2) absence of heavy alcohol consumption; 3) absence of other liver comorbidities. Karyotype, clinical and metabolic data were collected. A FIB-4 >1.3 was used, as a validated cut-off of increased risk of advanced fibrosis. Comparisons between FIB-4, liver biopsy and noninvasive (serologic and morphologic) markers of fibrosis were performed.
Results
Fifty-nine women, including 26 with ↑LFTs had a FIB-4 evaluation. FIB-4 scores ranged between 0.24 and 3.03, median 0.68. In the ↑LFTs-group median was 0.84 (range 0.4–3.03). Strong correlations were found between FIB-4 and GGT ($P=0.009$), ALP ($P=0.005$), duration of ↑LFTs ($P=0.002$) and AST-Platelet-Ratio-Index ($P=0.001$). FIB-4 was >1.3 in 9 women, 7 with ↑LFTs. Of these, one (FIB-4 1.3), Fibroscan 8.9 kPa (>7 kPa suggestive of fibrosis, >11 kPa of cirrhosis) and MRCP showing poor intrahepatic filling. One (FIB-4 1.48) had a biopsy finding of periductal fibrosis and one (FIB-4 3.03) Fibroscan 30.1 kPa and biopsy showing cirrhosis. The other patients were referred for Fibroscan. Biopsy was performed in 3 women with normal FIB-4, but ↑LFTs: none of which demostrated fibrosis.
Conclusions
Comparison between FIB-4 and liver biopsy showed a high concordance, suggesting that FIB-4 may be a useful noninvasive tool to screen for significant fibrotic liver disease in TS women and exclude those who do not require biopsy.

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P221

Turner's syndrome and liver involvement: prevalence and characterisation of a large population with Turner's syndrome

Matilde Calanchini[1,2]
[1]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford, UK; [2]Translational Gastroenterology Unit, Department of Gastroenterology and Hepatology, John Radcliffe Hospital, Oxford, UK.

Aims
Elevated liver function tests (↑LFTs) are frequent in Turner's Syndrome (TS). The cause and clinical significance are unclear. The aim of this study was to analyse the association between ↑LFTs and a comprehensive panel of TS-related conditions, focusing on metabolic and cardiovascular diseases in order to further elucidate the pathophysiological mechanisms underlying this condition.
Methods
We reviewed our adult TS cohort. LFTs were collected, along with karyoptype, anthropometric, metabolic and TS-related diseases and treatments. Ascending aorta diameters, measured with echocardiography and cardiac MR, were analyzed.
Results
We analysed data from 104 women with TS (45X0 44/104), mean age 36y (±46SD), height 149.5 (±7.8SD) cm, weight 62.1 (±14.6) Kg and BMI 28.3 (±7SD) kg/m^2. Liver enzymes were elevated in 35 (34%) patients, with a duration of 7y (±6.2SD) and age at the first finding of ↑LFTs 34y (±12.9SD). The most frequently abnormality was a raised GGT in 91% of cases; ↑ALT and ALP were found in 40%. Significant differences between the ↑LFTs-group and the normal-LFTs-group were found for age ($P=0.01$), HRT duration ($P=0.004$), Tot-Chol ($P=0.009$) and LDL-Chol ($P=0.011$). Adjusting for age, HRT-duration was not significantly different between the two groups. No differences were noted analysing karyotype, anthropometric values, HbA1c, and history of diabetes, hypertension, congenital heart abnormalities or autoimmunity. Ascending aorta diameter was significantly greater in the ↑LFTs-group ($P=0.002$). Liver biopsy was performed in six women with ↑LFTs: one normal, two nonalcoholic fatty-liver, one non-specific hepatitis, one mild fibrosis and one cirrhosis.
Conclusions
This study shows – first, ↑LFTs in TS are common and important to detect given the high prevalence at a young age and possible progression towards advanced fibrosis; secondly, a relationship between ↑LFTs and aortic dilatation was found, suggesting that liver involvement may be associated with a primary vascular process; thirdly, we suggest that HRT can be safely continued in TS women with ↑LFTs.

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P222

The Role of the Epidermal Growth Factor (EGF) Receptors (ErbBs) in Mouse Preantral Follicle Development

Kacie Thomson[1], Victoria Atess[1], Mhairi Laird[2], Stephen Franks[1] & Kate Hardy[1]
[1]Imperial College London, London, UK; [2]University of Reading, Reading, UK.

The factors responsible for regulating primordial follicle activation and early preantral follicle growth remain poorly understood, despite their importance in determining a female's reproductive lifespan. The essential role of the epidermal growth factor (EGF) family of receptors (ErbBs) during ovulation is well established; however there is emerging evidence that ErbBs may also be important regulators of early follicle development. This study aimed to investigate the role of EGF and ErbBs during preantral follicle development in the mouse. Previous work has shown high mRNA levels of ErbB subtypes, ErbB1 (EGFR) and ErbB2, in PND16 mouse ovaries and preantral follicles, ErbB3 is present but at low levels (Atess, unpublished). EGFR and ERBB2 protein can be detected in preantral follicles by western blotting, with ERBB2 immunolocalised at the cell surface of granulosa cells (GCs) from the transitional stage onward. Preantral follicles isolated from PND16 mouse ovaries (C57BL/6) were cultured for 72 hours with EGF (10 ng/ml). EGF significantly increased follicle growth by inducing GC proliferation ($P<0.01$), as demonstrated by increased Ki67 immunostaining ($P<0.001$). The addition of AG1478 (10 μM), an EGFR inhibitor, reversed the stimulatory effect of EGF on follicle growth ($P<0.01$), and showed no inhibitory effects when added to culture alone. Inhibition of ErbB2 had no effect on baseline or EGF stimulated follicle growth. The addition of the MEK inhibitor U0126 (10 μM) also reduced EGF stimulated growth ($P<0.05$). EGF treatment altered mRNA levels of key genes involved in follicle growth. At 24 hours EGF significantly increased *Bcl2* and *Egr1* mRNA levels and decreased *Fshr, Esr1, Esr2, Bmp15, Gdf9, Amh, Amhr2, Egfr*, *Erbb2* mRNA levels in cultured follicles. In conclusion, preantral follicles express EGFR and ErbB2 and are responsive to EGF, signalling primarily through the EGFR and MAPK pathway. This suggests a role for ErbBs in regulating early follicle development in the mouse.

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P223

Outcome of ovarian stimulation for oocyte cryopreservation in women with Turner Syndrome

Vikram Talaulikar, Antoinette Pimblett, Melanie Davies & Gerard Conway
University College London Hospitals, London, UK.

Approximately 20% of women with Turner syndrome (TS) proceed normally through puberty with spontaneous menstruation. An increasing number of women with TS are taking advantage of oocyte cryopreservation which is becoming widely available. It may be expected however, that controlled ovarian stimulation would result in fewer than expected number of oocytes compared to women without TS. We report our initial results from women with TS undergoing this procedure.
Five women with TS requested oocyte cryopreservation. Clinical details and outcome of ovarian stimulation are shown in the table.

Age	Karyotype	Age at diagnosis	Baseline FSH	AMH (pmol/L)	Antral follicles	Oocytes retrieved
22	45,X	15	6.9	3.5	3+4	9
18	45,X/46,XX	14	3.2	3.0	4+5	13
18	45,X/46,XX	15	7.4	7.0	5+6	9
25	45,X/46,XX/47,XXX	0.1	2.9	9.5	5+7	10
21	45,iX/46,XX	2.5	6.2	3.5	3+2	4

Results
The majority (4/5) all women had a mosaic form of TS. Despite relatively low serum AMH concentrations, oocyte retrieval was successful in all attempts with an average of 9 oocytes.
Conclusion
Oocyte cryopreservation is an option for women with Turner syndrome who have preserved ovarian function with oocyte retrieval very similar to published data from women without TS. The outcome in terms of live birth rate is yet to be determined and will be adversely affected by additional procedures such as preimplantation genetic diagnosis in order to minimise the chance of chromosomal anomalies in offspring.

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P224

Case series of 10 46,XX DSD males

Artemis Vogazianou[1,2], Mahesh Deore[1] & Gerard Conway[1]
[1]University College London Hospital, London, UK; [2]North Middlesex University Hospital, London, UK.

Introduction
46,XX disorder of sexual development (DSD) is a rare cause of sex reversal. Only a few hundred cases have been described. The clinical spectrum can be divided into 3 groups of males according to genital appearance: normal male, atypical variants such as hypospadias or cryptorchidism, and those with both male and female genitalia.
Subcategories of 46,XX DSD include ovotesticular DSD, which is characterised by the presence of both testicular and ovarian tissue in the gonads of the same individual and testicular DSD characterised by a full development of both gonads as testes without any evidence of ovarian tissue. Most cases (~80%) have normal external genitalia at birth and are usually diagnosed after puberty when they present with hypogonadism, gynaecomastia and/or infertility. They usually have normal pubic hair, normal penile size but small testes and sterility due to azoospermia. Approximately 10% of affected individuals have mild or severe genital ambiguity.

Case Series
We present our series of 10 men, 1 with CAH, 1 with SRY translocation, 3 confirmed SRY negative and 5 with as yet unknown SRY status. Two of the individuals are brothers. Gonadal status included 3 men with gonadal dysgenesis and 4 ovotestes. Genitalia appearance comprised 1 hypospadia, 1 normal genitalia with infertility and 1 virilisation requiring a penile implant.
Discussion
Because central London has such a genetically diverse population and as our centre has a longstanding interest in DSD we have found a spectrum of conditions under the heading of 46,XX DSD. As genetic diagnosis improves so the precision of our knowledge of each condition will develop. Management requires a multidisciplinary approach with specialist urology, endocrinology and psychology input.

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P225

Spontaneous pregnancy in Turner's Syndrome: An optimistic analysis

Matilde Calanchini
Oxford Centre Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK.

Aims
Spontaneous pregnancy (SP) in Turner's syndrome (TS) has been reported, with a prevalence of 2 to 7%. The aim of this study was to evaluate the prevalence and the outcome from spontaneous pregnancies (SPs) in a cohort of women with TS from a single centre, in order to give realistic counselling regarding options for fertility.
Methods
We considered the following data: karyotype, age at diagnosis of TS, age at the time of the study, cardiac, and metabolic comorbidities. Reproductive history was collected.
Results
We analysed 104 adult women with TS, median age 33y (range 18–73). Diagnosis of TS was at a median age of 13y (range 0–58) and 44/104 had a 45X0 karyotype. There were 26 successfull (live offspring at term) pregnancies: 22 were SPs and 4 assisted-pregnancies. 13 women (12.5%) had successfull SPs: the numbers of SPs per patient was one (8pts), two (4pts), three (6pts) and four (1pt). Complications were: one stillbirth, one termination and five women had miscarriages. No aortic dissection or cardiac complications were observed. Three patients with karyotype 45X0 had successful SPs. Of them one woman had 4 successfull SPs and 17 miscarriages. No fetal complications were reported. One daughter was diagnosed with TS. The only predictive factor for SP comparing the 13 women with SPs with the non-pregnant TS patients was 45X, 46XX and/or 47XXX mosaicism (46% versus 9.8%).
Conclusions
This study shows a higher rate of SP in women with TS than previously reported; that karyotypes with mosaicism 45X0, 46XX and/or 47XXX are predictive for SP, but importantly that a non mosaic karyotype (45X0) does not absolutely preclude SP. This emphasises the importance of counselling for young TS women regarding fertility including potential for SP, contraception, and education regarding complications in pregnancy.

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P226

A multidisciplinary specialist team for pregnancy in Turner's syndrome improves survival and maternal and fetal outcomes

Gayathri Kumarasinghe[1], Matilde Calanchini[2], Lucy Mackillop[3], Emma Weingart[1], Elizabeth Orchard[1] & Helen Turner[2]
[1]Department of Cardiology, John Radcliffe Hospital, Oxford University Hospitals, NHS, Oxford, UK; [2]Department of Endocrinology, Churchill Hospital, Oxford University Hospitals NHS, Oxford, UK; [3]Department of Obstetrics, John Radcliffe Hospital, Oxford University Hospitals, NSW, Oxford, UK.

Aims
Turner's syndrome (TS) is associated with bicuspid aortic valve (BAV), ascending aortic dilatation (AD), aortic coarctation, and hypertension. Pregnancy in TS is associated with increased risk of aortic dissection (2%), gestational hypertension, pre-eclampsia and a 2% risk of maternal mortality.
This retrospective study aimed to assess the effectiveness of a multidisciplinary team (MDT) comprising endocrinologist, cardiologist and maternal medicine obstetrician providing risk-assessment, pre-conception counselling and close follow-up, on safety and improving pregnancy outcomes in TS.
Methods
From a total of 104 women attending our dedicated TS clinic, we identified 23 spontaneous pregnancies (SP, 3/23 45XO) and six pregnancies with oocyte donation (OD). Clinical data, blood pressure measurements and aortic dimensions (indexed for body surface area) were analysed. Echocardiography, cardiac magnetic resonance (CMR), pre-conception counselling and risk-assessment were performed. Surveillance echocardiography and cardiologist review were performed each trimester and monthly if AD was detected. Echocardiography and CMR were repeated six months post-delivery.
Results
Total 26 successful pregnancies (3 following OD), maternal age 28 ± 7 years. Pre-conception cardiovascular risk-assessment identified hypertension in 6 women, BAV in 7 (1 with moderate aortic stenosis), AD (>2.0 cm/m^2) in 4, coarctation repair and correction of congenital heart disease in 1 and thoracic aortic graft in 1. Seven women developed mild aortic dilatation (1 ± 2 mm). Aortic dimensions increased slightly after pregnancy: aortic root 1.79 ± 0.32 cm/m^2 (1.84 ± 0.37 cm/m^2; $P=0.07$) and ascending aorta 1.69 ± 0.40 cm/m^2 (1.71 ± 0.41 cm/m^2; $P=0.83$).
Complications were low: gestational hypertension ($n=1$), diabetes ($n=1$), aortic dissection ($n=0$), pre-eclampsia ($n=0$), and no mortalities. Delivery was at 39 ± 1 weeks, birth weight 3.1 ± 0.6 kg, with 81% caesarian deliveries, $n=1$ child with TS and $n=1$ stillbirth.
Conclusions
Pre-conception counselling including risk-assessment by a dedicated MDT, along with close surveillance by a cardiologist with serial echocardiography, ensures low complications and excellent maternal and fetal outcomes, suggesting a more optimistic approach to pregnancy is appropriate in TS women.

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P227

Re-evaluation of safety in pregnancy following oocyte donation in Turner's Syndrome; is it time to modify the guidelines?

Gayathri Kumarasinghe[1], Matilde Calanchini[2], Lucy Mackillop[3], Emma Weingart[1], Elizabeth Orchard[1] & Helen Turner[2]
[1]Department of Cardiology, John Radcliffe Hospital, Oxford University Hospitals NHS, Oxford, UK; [2]Department of Endocrinology, Churchill Hospital, Oxford University Hospitals NSW, Oxford, UK; [3]Department of Obstetrics, John Radcliffe Hospital, Oxford University Hospitals NHS, Oxford, UK.

Aims
Oocyte donation (OD) is increasingly utilised in women with Turner's syndrome (TS). However, guidelines state TS a 'relative contraindication' for pregnancy, due to increased risk of aortic dissection (AD 2%) and maternal mortality (2%). Recent data on OD-related morbidity and mortality in TS has raised further concern. We aimed to analyse cardiovascular risk profiles of TS women undergoing OD and those with spontaneous pregnancy (SP), and determine outcomes in a setting of rigorous peri-pregnancy monitoring by a multidisciplinary team.
Methods
Of 104 women seen at a dedicated multidisciplinary TS clinic, 14 had SP (3/14 45XO) and 6 OD (3/6 45XO). Cardiovascular risk factors, aortic sinuses (AS) and ascending aorta (AA) measurements, maternal and fetal morbidity and mortality were analysed.
Results
There were 26 successful pregnancies (3 from OD). Baseline features in SP vs OD were: age at pregnancy 24 ± 6 years vs 35 ± 4 years ($P<0.001$); hypertension 15% vs 66% ($P<0.05$); bicuspid aortic valve 23% vs 50% ($P<0.05$); AS 1.69 ± 0.17 cm/m^2 vs 2.02 ± 0.41 cm/m^2 ($P<0.05$); AA 1.50 ± 0.22 vs 2.04 ± 0.44 cm/m^2 ($P<0.01$). There were no differences in BMI 27.6 ± 3.1 vs 29.0 ± 6.4, comorbidities 21% vs 66%, or previous aortic surgery 8% vs 17%. Post-pregnancy aortic dimensions were: AS 1.70 ± 0.23 (SP) vs 2.16 ± 0.48 (OD, $P<0.05$) and AA 1.58 ± 0.22 vs 2.10 ± 0.61 ($P<0.05$), but Δ increase was not significant (AS: Δ 0.07 ± 0.14 vs 0.10 ± 0.16; AA: Δ 0.03 ± 0.11 vs -0.02 ± 0.27, $P=$ns). There were no cases of AD, pre-eclampsia or maternal mortalities. Delivery was at 39 ± 1 week vs 38 ± 0 weeks ($P=$ns), with caesarean deliveries in 77% vs 100% ($P=$ns) and one still-birth (SP).
Conclusions
Women with TS undergoing OD were older and had more cardiovascular risk factors. However, pregnancy outcomes were comparable to the SP group with minimal maternal complications and excellent survival. Rigorous risk-assessment, peri-pregnancy monitoring and follow-up by a specialist multidisciplinary team can result in safe and successful outcomes in these women.

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P228

Causes of primary amenorrhea in women evaluated in an academic center of adult endocrinology

Monica Livia Gheorghiu[1,2], Constantin Cucu[1,2], Raluca Alexandra Trifanescu[1,2] & Corin Badiu[1,2]
[1]C Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]CI Parhon National Institute of Endocrinology, Bucharest, Romania.

Introduction
Primary amenorrhea is defined as the absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics, or at 13 years, if there is no breast development. We retrospectively assessed the causes of primary amenorrhea in a series from an academic center of adult endocrinology.
Patients and methods
We retrieved data from the files of 111 consecutive patients with primary amenorrhea evaluated in our center between 2000 and 2016 – mean age at admission 23.8 years (14–58 years), mean age at diagnosis 19.5 years (7–38years).
Results
Gonadal dysgenesis (Turner syndrome included) was present in 26 patients (23.4%); idiopatic isolated hypogonadotropic hypogonadism in 22 patients (19.8%); hypopituitarism in 12 patients, usually pluritropic (10.8%); prolactinoma in 11 patients (9.9%); Müllerian agenesis or abnormalities in 7 patients (6.3%); other sellar or suprasellar tumors in 7 patients (6.3%), constitutional delay of puberty in 5 patients (4.5%); polycystic ovarian syndrome in 5 patients (4.5%); congenital adrenal hyperplasia in 5 patients (4.5%); central nervous system or cranial defects in 4 patients (3.6%), complete androgen insensitivity in 3 patients (2.7%), other causes in 4 patients. A few cases (3) with initially elevated serum FSH levels had either normal response to dipherelin test or subsequently normal gonadotropin levels, menses and even pregnancy in 1 case. Abnormalities of gonadotropin receptors have been suspected in these cases.
Compared to other reported large series, in our settings (mainly adult endocrinology care) we observe an increased prevalence of isolated hypogonadotropic hypogonadism and hypopituitarism, and fewer cases of constitutional delay of puberty. The large majority of the women with primary amenorrhea in our series did not recover the normal reproductive potential.
Conclusion
The most frequent causes of primary amenorrhea in patients evaluated in an academic center for adult endocrinology are gonadal dysgenesis, idiopatic isolated hypogonadotropic hypogonadism and hypopituitarism.

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P229

Effect of predator-induced psychosocial stress on implantation and pregnancy outcome in rats

Bolanle Iranloye, Oluwatoyin Medubi & Olufeyisipe Adegoke
Reproductive and Endocrine Unit, Department of Physiology, College of Medicine of the University of Lagos, Lagos, Nigeria.

Maternal stress is commonly cited as a potential cause for idiopathic pregnancy loss (Knackstedt et al., 2005). However, the mechanisms through which stress affects implantation and pregnancy are yet to be totally deciphered. This study was designed to determine the effect of predator-induced psychosocial stress on implantation and pregnancy in rat. Cycling rats ($n=48$) at proestrus phase were paired overnight with sexually experienced male in ratio 2:1. Following confirmation of mating in the morning, rats were registered to be on day one of pregnancy and randomly assigned to either control ($n=24$) or stress ($n=24$) group. Stress was induced by the method of Figueiredo et al., 2003; exposing rats to cat for 60 minutes/day for 14 consecutive days. Subsequently, six animals from each group were sacrificed by cervical dislocation on days 6, 8, and 19 and blood was collected through cardiac puncture for hormonal analysis. Remaining six animals in each group were allowed to deliver at term. Number, weight of implantation sites (IS) and litter size were determined as described by Iranloye et al., 2010. Results reveal significant ($P<0.05$) reduction in number and weight of IS on day 8 (6.40 ± 0.72, 0.035 ± 0.002 g) compared with control (10.83 ± 0.48, 0.064 ± 0.010 g). There is a significant ($P<0.05$) reduction in the number of fetuses and litters on day 19 (6.00 ± 0.37) at term (6.17 ± 1.01) compared with their corresponding days in control (9.00 ± 0.37 and 9.83 ± 0.54). Hormonal analysis reveal significant ($P<0.05$) elevation of corticosterone in the stress group (320.80 ± 22.45; 423.30 ± 35.28; 285.50 ± 25.70) ng/ml compared with control (152.80 ± 32.68; 170.20 ± 38.63; 178.20 ± 38.07) ng/ml, on days 6, 8, and 19. Prolactin concentration was significantly ($P<0.05$) reduced in stress group with control on days 6, 8 and 19. Gestation was also significantly ($P<0.05$) extended in the stress group. This study suggests that predator-induced psychosocial stress reduce implantation and pregnancy outcome as a result of stress-induced hormonal perturbation.

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P230

Serum total cholesterol, thyroid hormone concentrations and haematological variables in cyclic and acyclic Nili-Ravi buffaloes

Muhammad Usman Ghani, Ijaz Ahmad, Nazir Ahmad, Ashar Mehfooz & Nabeel Ijaz
University of Agriculture, Faisalabad, Pakistan.

Buffalo is a major dairy animal in many countries of the world, including Pakistan. However, the productive and reproductive performance of this species is affected by many physiological problems such as anestrous. Therefore, this study was conducted to compare serum total cholesterol, thyroid hormone concentrations and haematological variables in cyclic and acyclic Nili-Ravi buffaloes. For this purpose, 60 adult Nili-Ravi buffaloes were divided into two equal groups i.e. cyclic and acyclic, depending upon the presence or absence of active corpus luteum on the ovaries. Blood samples with and without anticoagulant were collected from each animal. The blood samples without anticoagulant were used for separation of serum, which was utilized for estimation of serum total cholesterol, T_3 and T_4, using appropriate kit method. The samples containing anticoagulant were used for determination of haematological variables viz. RBC count, Hb, PCV, ESR, MCV, MCH, MCHC, TLC, DLC and platelets count. Results showed that serum total cholesterol (142.85 ± 7.43 V 88.84 ± 5.53 mg/dl) was higher in cyclic than acyclic buffaloes ($P\leq0.05$), while levels of T_3 and T_4 did not differ between the two groups. Among haematological variables, RBC count (6.29 ± 0.97 V $4.87\pm1.62\times10^6$/µl), Hb concentration (11.54 ± 1.61 V 9.89 ± 1.14 g/dl), PCV (40.28 ± 6.06 V $36.80\pm3.0\%$), MCV (62.1 ± 3.55 V 56.81 ± 5.35 fl), MCH (21.58 ± 5.47 V 15.99 ± 1.84 pg) and MCHC (29.32 ± 2.52 V 26.95 ± 2.03 g/dl) were higher in cyclic than acyclic buffaloes ($P\leq0.05$), while reverse was true for TLC and platelet counts. However, ESR, lymphocytes, monocytes, eosinophils and neutrophil percentages did not differ between two groups. In conclusion, low level of serum cholesterol might have been among causes of anestrous in these buffaloes, as cholesterol is the precursor of sex hormones like progesterone and estradiol, and its level was lower in acyclic than cyclic buffaloes. However, thyroid hormones do not seem to play any significant role in the occurrence of this problem.

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P231

Hormonal profiling to detect male mini-puberty: a rapid and accurate diagnostic approach in suspected cases of congenital hypogonadotrophic hypogonadism

Yaasir Mamoojee[1], Tim Cheetham[2,3], Alison Murdoch[4] & Richard Quinton[1,3]
[1]Department of Endocrinology, Newcastle-upon-Tyne Hospitals, Newcastle upon tyne, UK; [2]Department of Paediatric Endocrinology, Newcastle-upon-Tyne Hospitals, Newcastle upon tyne, UK; [3]Institute of Genetic Medicine, Newcastle upon tyne, UK; [4]Newcastle Fertility Centre at Life, Newcastle-upon-Tyne Hospitals, Newcastle upon tyne, UK.

Activation of the hypothalamo-pituitary-gonadal axis, from the third trimester of pregnancy to the first post-natal months in males, results in serum concentrations of gonadotrophins and testosterone approaching adult levels. This phase, known as male mini-puberty, represents a key window of opportunity to identify congenital GnRH deficiency in early childhood.
We present a case to illustrate the diagnostic efficiency of screening for mini-puberty in a male neonate born to a mother with congenital hypogonadotrophic hypogonadism (CHH). She conceived with her second cycle of IVF, having failed to fall pregnant with natural-cycle ovulation induction and on her 1st IVF cycle. She had an unremarkable pregnancy and delivered at term via an elective caesarean section. Prior to conception research-based genotyping failed to identify any known CHH-associated mutation. She did not exhibit any non-reproductive phenotypes, such as anosmia, clefting, or hearing impairment. She was concerned about the risk of her son having inherited CHH. At birth there was no strong indication for absent male mini-puberty; namely he had normal genitalia and bilateral descended testes, but we nevertheless proceeded to serum assay of gonadotrophins and testosterone at 2 months. These were unequivocally normal: testosterone 8.9 nmol/l, LH 3.0 IU/l and FSH 2.3 IU/l.

In male neonates with suspected CHH a single serum sample (between 4 and 8 weeks of life) can detect early GnRH deficiency far more rapidly and with much greater accuracy than any number of dynamic tests performed in adolescence. Hormonal profiling during mini-puberty has been demonstrated to offer better diagnostic specificity than genetic studies in predicting the adult phenotype, with the exception of ANOS1 mutation. Early diagnosis of CHH through hormonal profiling to detect absent mini-puberty in high-risk cases would allow for a more coordinated monitoring and therapeutic intervention schedule for timely pubertal progression, thus maximising later fertility potential, physical and psychosexual well-being.

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P232

Levels of reactive oxygen species (ROS) in the seminal plasma predicts the effectiveness of L-carnitine to improve sperm function in men with infertility

Wayne Vessey[1], Cassandra McDonald[1], Ashraf Virmani[3], P. Almeida[2], Channa Jayasena[1] & Jonathan Ramsay[1]
[1]Imperial College London, London, UK; [2]Chelsea & Westminster Hospital, London, UK; [3]Sigma-Tau, Utrecht, The Netherlands.

Background
Oxidative stress is implicated in the pathogenesis of primary male infertility. Some studies suggest that administration of the amino acid derivative anti-oxidant, L-carnitine, may improve sperm quality. No previous study has investigated whether the anti-oxidant effects of L-carnitine relate to changes in sperm quality in men with infertility.
Aim
Investigate whether L-carnetine significantly improves sperm function, and whether baseline levels of seminal plasma reactive oxygen species (ROS) predicts its effectiveness.
Methods
Men with oligoaesthenospermia were administered L-carnitine (Proxeed Plus) for 90 days ($n=29$). Semen analysis and ROS levels were measured immediately before and following L-carnitine. ROS was measured in relative light units/s (RLU/s) using an established chemiluminescence assay.
Results
L-carnetine reduced ROS markedly in subjects (ROS in RLU/s: 105 ± 83, pre-treatment; 6.6 ± 1.8, post-treatment, $P<0.05$ vs pre-treatment) but did not change sperm total motile count (TMC) significantly ($n=29$). In subjects with a pre-treatment ROS >10RLU/s ($n=12$), L-carnitine increased sperm TMC more than 2-fold (sperm TMC in millions: 18.6 ± 8.8, pre-treatment; 51.2 ± 27.0, post-treatment, $P<0.01$ vs pre-treatment).
Discussion
There is currently no approved therapy to improve sperm quality in men with primary infertility. Our data suggest that increased levels of oxidative stress may underlie a subgroup oligoaesthenospermia which is potentially amenable to L-carnetine therapy. This study has important potential implications for the treatment of men with primary infertility.

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Thyroid

P233

The use of the radiologically determined U grading for Thyroid Nodules prior to Fine Needle Aspiration is a reliable and highly Predictive way to determine Abnormal Cytology

Ehtasham Ahmad, Aleksandra Plictha & Stonny Joseph
East Kent Hospitals University NHS Foundation Trust, Margate, Kent, UK.

Controversy exists as to the best way to determine which thyroid nodules we should have fine needle aspiration (FNA). The lack of consensus in the British and American Thyroid Association guidelines has not helped to clarify this. The use of ultrasound scan (USS) determined U grading versus a composite of nodule size and pre-determined number of suspicious features continues to be debated. We therefore set out to compare the accuracy of U grading with other identified USS features in predicting an abnormal cytology.
A retrospective analysis Thyroid USS and FNA in 2015 was performed. Reports were analysed for calcification, echogenicity, vascularity, USS grading (U), cytology (Thy) and histology. The number of abnormal cytology in the U group was compared with that seen in other features. Data are expressed as n(%) of findings.
We identified 40USS performed (37 female, mean age range 45–60 years) for thyroid nodules (10 solitary). Scans according to U grading: 8U2, 27U3, 3U4, 2U5. There were 14 abnormal cytology ($>$Thy3) and these yielded 6 follicular adenoma and 4 papillary carcinoma histologically. 8(30%)U3 grading had abnormal cytology with 2 each from (90%)U4 and (100%)U5; a total of 12(92%) abnormal cytology were correctly predicted by U3 grading and above. Abnormal cytology was found if nodules had central vascularity 6(46%), calcification 5(38%) and mixed echogenicity nodules 5(38%). Abnormal cytology also reliably predicted abnormal histology in 80% of biopsies.
Our data show that the U grading of thyroid nodules is a highly predictive way of determining abnormal cytology on FNA. This predictability is better than in any single USS feature. We conclude that nodules with U3 grading and above should proceed to FNA without the need for further USS assessment. The small numbers in our study would however suggest that larger studies will need to be done to support our findings.

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P234

Serum thyroid function, mortality and disability in a cohort of 85 year olds

Salman Razvi[1], Mohammad Yadegarfar[1], Carmen Martin-Ruiz[1], Andrew Kingston[1], Joanna Collerton[1], Theo Visser[2], Tom Kirkwood[1], Carol Jagger[1] & Simon Pearce[1]
[1]Newcastle University, Newcastle upon Tyne, UK; [2]Erasmus Medical Center, Rotterdam, The Netherlands.

Perturbations in thyroid function are common in older individuals but their significance in the very old is not fully understood. We examined thyroid hormone status (serum TSH, FT_4, FT_3, rT_3) at baseline in a cohort of 643 85-year-olds and followed their mortality and disability outcomes for 9 years. All cause mortality, cardiovascular mortality and disability according to categorical thyroid disease status and baseline thyroid hormone parameters were examined. Models were adjusted for age, sex, education, body mass index, smoking and disease count.
Patients with either subclinical hypothyroidism ($n=79$) or subclinical hyperthyroidism ($n=19$) did not have adverse outcomes. All cause mortality was associated with baseline serum rT_3, and FT_3, but after adjustments for age, sex and potential confounders only rT_3 remained significantly associated ($P=0.001$). Baseline serum TSH ($P=0.038$) and rT_3 ($P=0.04$) predicted future disability trajectories in men and women, respectively.
Our study is reassuring that individuals aged 85 yrs with either subclinical hyper- or hypo-thyroidism did not have a significantly worse survival over 9 years than their euthyroid peers. However thyroid function tests did predict disability, with higher serum TSH levels predicting better outcomes. These data strengthen the argument for routine use of age-specific thyroid function reference ranges.

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P235

Hypothyroidism induces hyperplasia of unilocular adipocytes in perirenal adipose tissue of the ovine fetus

Shelley E Harris[1], Miles J De Blasio[2], FB Peter Wooding[2], Dominique Blache[3], David Meredith[1], Abigail L Fowden[2] & Alison J Forhead[1,2]
[1]Oxford Brookes University, Oxford, UK; [2]University of Cambridge, Cambridge, UK; [3]University of Western Australia, Crawley, Australia.

Thyroid hormones are important regulators of fetal growth, although their mechanism of action remains unclear. In the sheep fetus, thyroid hormone deficiency increases plasma insulin and leptin concentrations. This study investigated the effects of hypothyroidism on perirenal adipose tissue (PAT) development and adipose insulin signalling pathways in fetal sheep.
All procedures were performed under the UK Animals (Scientific Procedures) Act 1986. In 10 twin-bearing pregnant ewes at 105–110 days of gestation (d; term$\sim$145d) and under general anaesthesia, one fetus was thyroidectomised (TX), while the other was sham-operated. After maternal and fetal euthanasia, PAT was collected from the fetuses at 143d, weighed, and frozen or processed for histology and stereological assessment. Protein and mRNA content was determined by Western blotting and qRT-PCR. Data (mean$\pm$SEM) were assessed by Student's *t*-test.

Relative PAT mass was increased in TX fetuses compared to sham fetuses (sham 3.1 ± 0.3 g/kg, TX 4.8 ± 0.4 g/kg $P < 0.05$). This was due to a 2-fold increase in relative mass of unilocular (white) adipocytes (sham 1.1 ± 0.2 g/kg, TX 2.3 ± 0.3 g/kg, $P < 0.05$), with no change in the mass of multilocular (brown) adipocytes. Relative unilocular adipocyte mass correlated positively with plasma insulin ($r = 0.76$, $P < 0.001$) and leptin ($r = 0.64$, $P < 0.002$). Unilocular adipocyte perimeter was unaffected by TX which indicated that thyroid hormone deficiency *in utero* induced hyperplasia rather than hypertrophy of unilocular adipocytes. In PAT from TX fetuses, increases were observed in protein levels of proliferating cell nuclear antigen, the insulin-sensitive glucose transporter-4 and phosphorylated S6-kinase, and in mRNA and protein levels of the differentiation marker, peroxisome proliferator-activated receptor-γ ($P < 0.05$). In the ovine fetus, development of unilocular adipocyte mass in PAT is sensitive to changes in thyroid hormones, which may be related, in part, to altered insulin concentrations *in utero*. These findings have implications for the control of adipose function and leptin secretion before and after birth.

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P236

Increasing awareness of Graves' orbitopathy with "Early Warning" cards – a TEAMeD multicentre quality improvement project

Anna L Mitchell[1,5], Nicola Zammitt[3], Ramzi Ajjan[4], Bijay Vaidya[6], Janis Hickey[7], Petros Perros[5] & Colin Dayan[2]
[1]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; [2]Institute of Molecular and Experimental Medicine, Cardiff University, Cardiff, UK; [3]Department of Endocrinology, Royal Infirmary of Edinburgh, Edinburgh, UK; [4]Department of Endocrinology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [5]Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, UK; [6]Department of Endocrinology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK; [7]British Thyroid Foundation, Harrogate, UK.

Background
Clinically significant Graves' orbitopathy (GO) develops in 20% of those with Graves' Disease (GD). Up to 90% of cases present at the same time as, or after, hyperthyroidism develops. Most cases of GD in the UK are managed in endocrinology clinics. Despite this, patients report significant delays before a correct diagnosis of GO is made. We argued that measures to increase awareness of the early signs of GO in those with GD and establishing a fast-track referral pathway to specialist care should overcome these delays and improve outcomes.
Aims
(1) To determine whether issuing a "GO early warning card" to all patients with an established diagnosis of GD raises awareness of GO and facilitates early diagnosis.
(2) To determine what percentage of cards result in a telephone contact.
(3) To determine the number of "false reports" from card carriers.
Methods
We designed early warning cards, detailing common symptoms of GO and a telephone contact number for patients who develop eye symptoms. Cards were distributed to 171 patients with a diagnosis of GD, but without known GO, attending endocrine clinics in Newcastle, Exeter, Cardiff, Edinburgh and Leeds. We recorded telephone contacts over 3 months and feedback from patients regarding their experience of this initiative.
Results
Over 3 months, 10 telephone contacts were received (6% of cards issued). One patient called twice. 1/10 (10%) calls were managed with telephone advice alone, while the other 9 resulted in an additional clinic review. Overall, 4 diagnoses of GO were made. Feedback received to date suggests that most patients felt that having a card was useful and increased their awareness of GO.
Conclusions
In this pilot study, we found that it is feasible to distribute GO early warning cards to patients in busy endocrine clinics and that this does not result in an excessive burden of telephone enquiries. Patients generally appreciated the additional information offered and viewed the project positively.

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P237

Management and investigations of woman with hypothyroidism before and during pregnancy in a joint Medical/Obstetric clinic a DGH

Tala Balafshan, Paula Chattington & Oliver Llewellyn
Warrington Hospital, Warrington, UK.

Maternal thyroid hormones play a critical role in foetal brain development in the first 12 weeks of gestation. Children born to hypothyroid mothers, especially those undertreated, are more likely to suffer lower IQ. Based on BES guidance 2007 and NICE 2011 at confirmation of pregnancy a woman with hypothyroidism should immediately increase the dose of levothyroxine by 25–50 mcg with aim TSH of less than 2.5 mu/l as soon as possible with monitoring of TFT every 4 weeks.
We carried out a retrospective cohort study of 41 pregnant women with hypothyroidism in Warrington hospital medical/Obs clinic between 2009 and 2016. Data was collected using patient's case notes and SUNQUEST ICE, the hospital pathology system. ICE was interrogated for TSH results from up to 6 months pre-conception, and in each trimester of pregnancy.
53% of patients received TFT checks in the 6 months pre- conception. Of these, 59% had TSH levels outside recommended levels. 22% received correct treatment before pregnancy. 62% of patients received their 1st TFT of pregnancy in the 1st trimester, 17% in the 2nd trimester, and 2% in the 3rd trimester. 6% were first checked post-delivery, and 13% were never checked. In patients found to be hypothyroid, 96% received appropriate levothyroxine dose adjustment at review in Medical/Obs clinic.
Unfortunately many patients were not referred by their GP or midwives in a timely manner. Just 62% were referred to our clinic in the first trimester, 15% in second trimester and 3% in third. More work is needed to ensure patients receive their first TFT pre-conception and early in their pregnancy and then follow BES and NICE guidance. We need to increase GP and patients awareness of potential problems as many patients with hypothyroidism are not under hospital care. Referral to joint medical/Obs clinic is associated with much tighter control.

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P238

Five year follow-up of patients who received radio-iodine therapy at district general hospital

Hussam Abusahmin
Wrexham Maelor Hospital, Wrexham, UK.

Background
Radioiodine is used as a method of treating hyperthyroidism secondary to Grave's disease and toxic goitres. Radioiodine therapy most often results in patients becoming hypothyroid, however a small percentage of patients (around 10–20%) require repeated doses to treat persistent hyperthyroidism.
Aim
The aim of this audit was to determine the outcome of patients who received radioiodine for hyperthyroidism over 5 years period.
Method
This was a retrospective audit looking at patients who received radioiodine for hyperthyroidism at Wrexham Maelor hospital, from January 2007 to December 2011. The total number of patients was 118. Information collected included: age, gender, diagnosis, dose of radioiodine, length of time to becoming hypothyroid, and rates of relapse following treatment.
Results
The majority of patients (68%) became hypothyroid with the average length of time taking 6 months (48%). This is in fitting with the general expected outcome of radioiodine therapy. The dose of radioiodine fell on average between 540 and 590 which is also in fitting with what is expected by the Royal College of Physicians. Unfortunately, our data collection determined 9% of the total number patients who received the treatment were lost to follow up for reasons including moving to a different area and having their follow up conducted in a different trust. In addition, 13% of patients had no documented diagnosis prior to treatment.
Conclusion
We conclude that the service offered in our hospital falls well within the remit specified by the Royal College of Physicians. Guidelines recommend regular review of thyroid function tests in patients who have undergone radioiodine treatment and therefore we recommend the need to ensure adequate follow is conducted, particularly in view of patients being lost to follow up. In addition, improved record keeping is needed with regards to documentation of diagnosis and a designated follow up clinician.

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P239

Optimising the medical treatment of Graves' Disease through developing a novel carbimazole dosing-algorithm

Rosalind Brewster, Ali Abbara, Sophie Clarke, Alexander Comninos, Deborah Peters, Amir Sam, Karim Meeran & Waljit Dhillo
Imperial College Healthcare NHS Trust, London, UK.

Introduction
Graves' disease is the commonest cause of hyperthyroidism accounting for 80% of all cases. The first line treatment for Graves' disease in the UK is medical therapy, most frequently using a 'dose-titration' regimen. Currently, there is a lack of guidance to aid clinicians in carrying out optimal dose-titration of carbimazole, resulting in a risk of under- or over-treatment. Thus, we aimed to develop a carbimazole dosing-algorithm for the medical management of Graves' disease.
Methods
A retrospective analysis of 415 patients treated with medical therapy for Graves' disease at Imperial College Healthcare NHS Trust during 2009–2016 identified 324 patients for inclusion to the study. Dose of antithyroid drug prescribed, thyroid hormones levels, antibody status and relevant clinical data were collated.
Results
During medical therapy, 30% of patients were over-treated and rendered hypothyroid, occurring at a median of 101 days post-initiation. Patients with highest titres of Thyroid Peroxidase Antibody had greatest risk of over-treatment following carbimazole (70% of patients with TPOAb titre >1000 u/ml were over-treated vs 24% in those with undetectable TPOAb).
There was a significant association between the median percentage fall in thyroid hormones over a 4 week period and carbimazole dose ($P=0.0003$; r^2 0.97), identifying a dose-response relationship for carbimazole. Neither weight-based, nor split-dosing, were of significant benefit in the dosing of carbimazole ($P=0.48$ and $P=0.67$, respectively).
The risk of relapse following withdrawal of medical therapy was highest in men, current smokers, British-Caucasian patients, in those with high initial freeT_4 levels, or high TSH receptor antibody titres.
Discussion
We have developed a dosing-algorithm for carbimazole prescription based on the dose-response relationship elicited. A scoring system (Relapse Rate Score; RRS) based on risk factors identified to confer an increased risk for persistent disease was derived. The RRS can be used to identify patients more appropriately triaged towards definitive management than medical therapy.

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P240

Epidemiology, management and outcomes of Graves' disease in a U.K. Population – a Retrospective Cohort Study

Yusuf Hussain[1], Jessica Hookham[1], Amit Allahabadia[1,2] & Sapabathy Balasubramanian[1,2]
[1]University of Sheffield, Sheffield, UK; [2]Royal Hallamshire Hospital, Sheffield, UK.

Background
Graves' disease is the commonest cause of hyperthyroidism. Although first line and definitive treatment options are clearly defined, management practices and the natural history in terms of outcomes of treatment in a large consecutive cohort of Graves' disease has not been well characterised.
Aims
To describe incidence, presentation, diagnosis, management strategies and medium term outcomes following anti-thyroid drug treatment, radio-iodine ablation and surgery in a consecutive cohort of patients presenting with Graves' disease.
Methods
Retrospective cohort study of all patients ($n=659$) who received treatment for a new diagnosis of Graves' disease in secondary care over a five year period. Median (IQR) follow up was 42.9 (29.0–57.5) months.
Results
Incidence of adult onset Graves' disease was 24.8 per 100,000 per year (11.0 and 37.9 for males and females respectively). TRAb was positive in 91.7% ($n=341$) and TPO in 73.1% ($n=236$). 93.1% ($n=581$) achieved initial control with thionamide medication and 73.1% ($n=428$) achieved remission. At last follow up, 36.7% ($n=157$) relapsed. The risk of relapse was higher in patients who received block and replace therapy ($P=0.013$) versus titration, TRAb positive patients ($P=0.035$) and those with higher pre-treatment FT_3 ($P<0.001$) and FT_4 ($P<0.001$) levels.
Of 144 patients who had RIA treatment, 5.6% ($n=8$) relapsed. Of 119 patients having surgery, 5.2% ($n=6$) had long term hypoparathyroidism and no one had documented long term RLN palsy. Surgery was performed more often in younger, female patients with more severe disease.
Conclusions
This is the first study to report incidence of Graves' disease in a UK population. In the short to medium term, 39.9% ($n=263$) of patients required surgery or RIA; both of which have little morbidity. Up to two-thirds of patients who achieved remission did not relapse. This information on effectiveness of various treatments for Graves' disease will help clinicians and patients in decision making.

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P241

Contrasting phenotypes in Resistance to Thyroid Hormone α correlate with divergent properties of thyroid hormone receptor α1 mutant proteins

Carla Moran[1], Maura Agostini[1], Anne McGowan[1], Erik Schoenmakers[1], Louise Fairall[3], Greta Lyons[1], Odelia Rajanayagam[1], Laura Watson[2], Amaka Offish[4], John Barton[5], Susan Price[6], John Schwabe[3] & Krishna Chatterjee[1]
[1]Wellcome-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK; [2]NIHR/Wellcome Trust Clinical Research Facility, University of Cambridge, Cambridge, UK; [3]Department of Molecular & Cell Biology, University of Leicester, Leicester, UK; [4]Academic Unit of Child Health, University of Sheffield, Sheffield, UK; [5]Department of Paediatric Endocrinology & Diabetes, Bristol Royal Hospital for Children, Bristol, UK; [6]Department of Clinical Genetics, Northampton General Hospital, Northampton, UK.

Resistance to Thyroid Hormone alpha (RTHα) is characterised by tissue-selective hypothyroidism with near-normal thyroid function tests, and is due to thyroid receptor α gene mutations. We sought to correlate the clinical characteristics and response to thyroxine treatment of two RTHα patients with the properties of their defective TRα proteins.
Clinical, biochemical and physiological parameters were assessed in each patient at baseline and after thyroxine therapy.
Heterozygous *THRA* mutations were identified in a 17y.o male with mild pubertal and growth retardation (P1; A263V mutation), and a 15y.o male (P2; L274P mutation) with short stature (0.4^{th} centile), skeletal dysplasia, dysmorphic facies and global developmental delay. Both exhibited typical features of RTHα; macrocephaly, delayed dentition, constipation, low T_4/T_3 ratio, low reverse T_3 levels and mild anaemia.
In vitro, A263V mutant TRα1 was transcriptionally impaired and inhibited the function of its wild type counterpart at low (0.01–10 nM) T_3 levels, with higher T_3 concentrations (100nM–1nM) reversing dysfunction and dominant negative inhibition. In contrast, L274P mutant TRα1 was transcriptionally inert, exerting significant dominant negative activity, only overcome with 10nM T_3. Normal expression of KLF9, a TH-responsive target gene, was achieved in A263V mutation-containing peripheral blood mononuclear cells (PBMCs) following 1nM T_3 exposure, but reduced expression levels were seen in L274P mutation-containing PBMCs even with 10 nM T_3. Following thyroxine therapy growth, BMI, dyspraxia and constipation improved in P1, whereas growth retardation and constipation in P2 were unchanged.
A milder clinical phenotype with favourable response to thyroxine therapy was evident in our patient (P1) with mutant TRα1 which exhibited partial, T_3-reversible, loss-of-function *in vitro*. In contrast, a more severe clinical phenotype, refractory to hormone treatment, was evident in our patient (P2) with severe, virtually irreversible, dysfunction of mutant TRα1 *in vitro*. These differing clinical phenotypes and responses to treatment suggest a genotype-phenotype correlation exists amongst individuals with RTHα.

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P242

Occupational disability and access to psychological tools in thyroid eye disease

Jennifer Kim[1], Anne Cook[1] & Claire Higham[2]
[1]Manchester Royal Eye Hospital, Manchester, UK; [2]Christie NHS Foundation Trust, Manchester, UK.

Purpose
To evaluate the impact of thyroid eye disease (TED) on occupational disability and access to psychological input. Previous European studies have demonstrated a negative effect of TED on occupation but there are no similar UK studies.
Methods
102 outpatients under the age of 75 were identified for participation from a joint thyroid eye clinic at a tertiary centre. 42 completed a standardised fixed-choice questionnaire about occupational disability and access to psychological therapies.
Results
15% reported losing their job as a direct result of TED and 12% changed their jobs as they were deemed unfit for work. 44% had difficulty managing their job with 63% recording problems at work secondary to the physical impact of TED. 44% took time off work and this was due to double vision (39%), depression (34%), visual disturbances (39%), pain (24%), unsteadiness (22%) and appearance (14%). 44% of respondents accomplished less than they would have liked to at work and 44% were unable to focus due to low mood. 3% were currently undergoing or previously received psychological input, 8% reported that they would like to pursue psychological therapy. 15% reported being on anti-depressants prior to diagnosis of TED, and further 20% were started on antidepressants following diagnosis.
Conclusion
TED has a direct impact on patients' vision resulting in stress and occupational impairment, including a significant number of patients suffering unnecessary job loss. This study confirms reports from other European countries (with higher rates of job loss in our study) and highlights the need for larger UK confirmatory studies, with a particular focus on occupational education and increasing understanding of the condition by employers and employees. Limited access to psychological therapies despite high levels of antidepressant use was also found, highlighting the importance of improving access to these services and increasing support for patients.

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P243

Evaluation of clinical diagnosis of Graves' or Non-Graves' Hyperthyroidism Compared to Gold-Standard TRAb Test

Lauren Bell[1,2] & Akheel Syed[1,2]
[1]Department of Endocrinology, Salford Royal NHS Foundation Trust, Salford, UK; [2]Manchester Medical School, The University of Manchester, Manchester, UK.

Background
TSH receptor antibody (TRAb) measurement, with a sensitivity of $>97\%$ and specificity of 100%, is considered the gold standard investigation for diagnosing Graves' disease (GD).
Aim
To evaluate clinical diagnosis of GD or non- GD hyperthyroidism at a University Teaching Hospital compared to TRAb result.
Methods
Electronic records of patients who had a TRAb measurement between December 2009 and October 2015 were studied retrospectively for a pre-TRAb clinical diagnosis of GD or non-GD. We examined descriptive statistics and binary classification tests; Fisher exact test was used to analyse contingency tables.
Results
We identified 316 patients seen in the Endocrinology service aged 18–89 years with a mean $\pm$ standard error of 45.2 ± 2.5 years; 247 (78%) were women. A clear pre-test clinical diagnosis was identified in 160 patients; the remaining 156 patients had differential diagnoses and were excluded for this analysis. Of the 166 patients, a clinical diagnosis of GD was identified in 93 patients, of which 67 were TRAb-positive, 19 were TRAb-negative and 7 were TRAb-borderline; 67 patients had a pre-test clinical diagnosis of non-GD, of which 47 were TRAb-negative, 15 TRAb-positive and 5 TRAb-borderline. After excluding TRAb-borderline patients, clinical diagnosis had a sensitivity of 82%, specificity 71%, positive predictive value 78%, negative predictive value 76%, false negative rate 18%, and false positive rate 29% ($P < 0.0001$). Incorrect initial clinical diagnoses were corrected at subsequent appointments based on the TRAb result.
Conclusion(s)
Clinicians were liable to incorrectly make an initial clinical diagnosis of non-GD in 1 in 5 patients with TRAb-positive GD, whilst 3 in 10 patients with TRAb-negative non-GD were incorrectly mislabelled as GD clinically. The TRAb test can help reduce the number of incorrect or unknown diagnoses in the initial clinical assessment of patients presenting with hyperthyroidism.

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P244

TIGIT gene variants and thyroid disease susceptibility in dogs and humans

Ishita Bhatnagar[1], Jonathan Massey[2], Lorna Kennedy[2], William Ollier[2], Heather Cordell[1], Simon Pearce[1] & Anna Mitchell[1]
[1]Newcastle University, Institute of Genetic Medicine, Newcastle upon Tyne, UK; [2]University of Manchester, Centre of Integrated Genmoic Medical Research, Manchester, UK.

Background
The autoimmune thyroid diseases, primary autoimmune hypothyroidism (AH) and Graves' hyperthyroidism (GD), represent the most prevalent endocrine disorders. Although clinically distinct, they share several genetic susceptibility loci, many of which remain unidentified.
TIGIT (T cell immunoreceptor with immunoglobulin and ITIM domains), expressed on the surface of T-cells, interacts with CD-155 on dendritic cells to form an alternative costimulatory pathway. It therefore drives a more tolerogenic phenotype making it a plausible candidate gene for autoimmune diseases. A TIGIT variant in the canine genome has been associated with lymphocytic thyroiditis in a genome-wide meta-analysis in the Rhodesian Ridgeback and Dobermann pedigree dogs (unpublished data), however no links to human thyroid diseases have been established.
Hypothesis
We hypothesise that variants in TIGIT may be associated with susceptibility to GD in humans.
Subjects and Methods
We performed a case-control association study of two TIGIT single nucleotide polymorphisms (SNPs; rs10934259 and rs2693052). These were genotyped using Taqman chemistry (Life Technologies) in 426 GD patients. Results were compared to data from 5097 healthy individuals available from the Wellcome Trust (WTCCC2) using PLINK.
Results
For rs10934259, the AA genotype was present in 48 cases (12%) compared to 567 controls (11%). 186 cases (46%) and 2353 controls (46%) were heterozygous. The frequency of the minor A allele was 0.35 and 0.34 in cases and controls respectively ($P > 0.05$). For rs2693052, the TT genotype was present in 75 cases (18%) compared to 833 controls (16%). 178 cases (42%) were heterozygous compared to 2409 controls (47%). The frequency of the minor T allele was 0.39 and 0.40 in cases and controls respectively ($P > 0.05$).
Conclusions
This study suggests that TIGIT is not playing a significant role in susceptibility to GD in humans. Further studies are now needed to determine whether TIGIT variants contribute to susceptibility to AH.

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P245

Thyroid autoimmunity as a biomarker of breast cancer outcome: large-scale study using data from the Taxotere as Adjuvant Chemotherapy Trial (TACT: CRUK01/001)

Ilaria Muller[1], Lucy Kilburn[2], Peter Taylor[1], Peter Barrett-Lee[3], Judith Bliss[2], Ellis Paul[4], Ludgate Marian[1] & Colin Dayan[1]
[1]Thyroid Research Group, Division of Infection & Immunity, School of Medicine, Cardiff University, Cardiff, UK; [2]The Institute of Cancer Research – Clinical Trials & Statistics Unit (ICR-CTSU), London, UK; [3]Breast Cancer Centre, Velindre NHS Trust, Cardiff, UK; [4]Guy's Hospital & King's College, London, UK.

Background
An association between breast cancer (BC) and thyroid autoimmunity has been frequently observed, and several small-scale studies correlated the presence of autoantibodies to thyroid peroxidase (TPOAb) with an improved BC outcome. We aimed to clarify in a large cohort of patients whether circulating TPOAb are prognostic for BC recurrence.

Materials and methods
Available plasma samples for patients with node-positive or high-risk node-negative early BC previously enrolled in TACT trial (Ellis et al. Lancet 2009, Bliss et al. Cancer Res Suppl. 2012) were measured (standard assays) for TPOAb (positive $\geq$6kU/L), free-thyroxine and thyroid stimulating hormone (combined as euthyroid, hypothyroid, hyperthyroid status). Prognostic significance of these markers was assessed for disease free survival (DFS), overall survival (OS) and time to recurrence (TTR) using Cox regression models stratified by chemotherapy regimen and ER status. Univariate and multivariable analyses were performed, considering other known prognostic factors for BC (nodal status, HER2 status, age, tumour grade, tumour size) and type of surgery.
Results
1974 (47.4%) patients had plasma available, taken 15.5 months (median) after BC surgery, with majority taken during/after adjuvant treatment for BC. 406 (20.6%) patients were TPOAb positive. The median follow-up was 96.7 months. There was no evidence of difference in DFS by TPOAb status (unadjusted hazard ratio [HR] = 0.97, 95%CI: 0.78–1.19; $P = 0.75$) and/or thyroid function (unadjusted HR (hypothyroid versus normal) = 1.15 95%CI: 0.79–1.68; $P = 0.46$, HR (hyperthyroid versus normal) = 1.14, 95%CI: 0.82–1.61; $P = 0.44$). Similar results were obtained for OS and TTR. Sensitivity analyses in a 123 patients subgroup with plasma collected before BC adjuvant therapy also showed no evidence of TPOAb prognostic ability.
Conclusions
No evidence for a prognostic role of TPOAb and/or thyroid function in moderate-high risk early BC was found in the largest and longest observational study to date. Confounding due to BC adjuvant treatments is unlikely.

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P246

High tumoral expression of PBF and PTTG modulates the DNA damage response and is associated with poor survival in thyroid cancer

Martin Read[1], Jim Fong[1], Waraporn Imruetaicharoenchoke[1], Hannah Nieto[1], Bhavika Modasia[1], Alice Fletcher[1], Rebecca Thompson[1], Neil Sharma[1,2], Andrea Bacon[3], John Watkinson[1,4], Kristien Boelaert[1], Andrew Turnell[2], Vicki Smith[1] & Christopher McCabe[1]
[1]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK; [2]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK; [3]School of Immunity and Infection, University of Birmingham, Birmingham, UK; [4]University Hospitals Birmingham National Health Service Foundation Trust, Birmingham, UK.

Despite extensive genomic profiling a better understanding of the contributory factors that promote aggressive thyroid cancer is urgently needed. The proto-oncogenes PBF and PTTG have been implicated in thyroid cancer but there is a lack of information regarding their co-expression and specific roles in tumour progression. Separate studies have previously indicated that PBF and PTTG may disrupt pathways associated with the tumour suppressor p53 that are central to DNA-damage repair (DDR), cell growth and apoptosis. To further investigate this, we examined the association of PBF and PTTG with p53-related genes in the human thyroid TCGA cancer dataset, as well as in a bi-transgenic murine model (Bi-Tg) overexpressing PBF and PTTG specifically in the thyroid gland.
Characterisation of primary murine Bi-Tg thyrocytes revealed that co-expression of PBF and PTTG caused extensive repression of DDR genes (31/82 genes; $>$1.5-fold; $P < 0.05$), including genes with key roles in maintaining genomic integrity such as *Brca1*. Irradiation exposure to cause DNA damage gave further evidence of significant repression of DDR genes ($n = 82$) between irradiated Bi-Tg and wild-type thyrocytes ($P = 2.4 \times 10^{-4}$) that was greater than either PBF-Tg ($P = 1.5 \times 10^{-3}$) or PTTG-Tg thyrocytes (P = NS). By comparison in the TCGA dataset, there were striking correlations with PBF and PTTG in well-characterised p53-related gene panels ($P < 0.05$; 82–96 genes per panel; $n = 322$ TCGA tumour samples). Importantly, nearly half of the DDR gene alterations in Bi-Tg thyrocytes were also present in TCGA comparing tumours with either low or high PBF/PTTG expression. Furthermore, the overall survival ($P = 1.91 \times 10^{-5}$) and disease-free survival ($P = 4.9 \times 10^{-5}$) was poorer for TCGA individuals with high tumoral PBF/PTTG expression and mutationally activated BRAF than for all other patients.
Together our study provides important insights into the role of PBF and PTTG in modulating p53-related genes to promote tumorigenesis. We also identify using PBF and PTTG together as a new clinical indicator for aggressive thyroid cancer.

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P247

Aiming for a serum TSH in the higher reference range in older levothyroxine treated hypothyroid individuals – a randomized controlled proof of concept trial (SORTED 1)

Salman Razvi[1,2,3]
[1]Newcastle University, Newcastle upon Tyne, UK; [2]Gateshead Health NHS Foundation Trust, Gateshead, UK; [3]Sunderland University, Sunderland, UK.

Context
Serum TSH reference range increases with age but target TSH is similar in younger and older hypothyroid patients on treatment. It is unknown if quality of life (QoL), hypothyroid symptoms and cardiovascular (CV) risk factors change in older patients in whom a higher serum TSH is aimed for.
Objective
To assess if a higher target serum TSH of 4.01–8.0 mU/l is feasible in and acceptable to older treated hypothyroid patients.
Design
Single-blind randomised controlled trial.
Participants
Forty eight hypothyroid patients aged $\geq$80 years on established and stable levothyroxine therapy with serum TSH levels within the reference range (0.4–4.0 mU/l).
Intervention
Usual dose (standard TSH group or ST group) or lower dose (higher TSH group or HT group) levothyroxine for 24 weeks.
Outcome measures
Hypothyroid-specific QoL, symptoms and general health. CV risk factors such as total cholesterol and blood pressure and serum marker of bone resorption were also assessed.
Results
Mean ($\pm$ S.D.) serum TSH was 1.39 (0.98) and 6.43 (3.15) mU/l at the end of the trial in the ST and HT groups, respectively. Corresponding mean ($\pm$ S.D.) daily levothyroxine doses were 82.1 (26.4) and 59.2 (23.8) micrograms. There were no significant differences between the two groups with regards to QoL, symptoms or general health status. Furthermore, there were no significant changes in cardiovascular risk factors or marker of bone resorption between the two groups.
Conclusions
A higher target serum TSH in hypothyroid patients on levothyroxine therapy aged $\geq$80 years is not associated with an adverse impact on patient reported outcomes, CV risk factors or bone resorption marker over 24 weeks. A larger trial assessing hard outcomes in this age group is now required.

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P248

One third of thyroid radionuclide uptake scans is deferentially interpreted leading to potentially differential treatment for patients with thyrotoxicosis

Aftab Aziz, Tamar Avades, Richard Poyner, Bijay Vaidya & Kashyap Patel
Royal Devon and Exeter NHS Foundation Trust, Exeter, UK.

Background
Accurate diagnosis of an underlying cause of thyrotoxicosis is critical for targeted therapy. Thyroid radionuclide uptake scan is a useful second line investigation in patients who lack TSH receptor antibody. The uptake scan patterns identify patients who can be preferentially treated with anti-thyroid drugs (diffuse pattern - Graves' disease) or radio-iodine treatment (patchy uptake - multinodular or localised uptake – toxic adenoma) or simple monitoring (no update – thyroiditis). Therefore, accurate interpretation of the uptake scan is critical for the correct treatment and differential interpretation will lead to different treatment. We aim to identify inter-individual agreement for interpretation of the thyroid radionuclide uptake scan.
Method
Three assessors (two senior registrars and one consultant endocrinologist) independently reviewed thyroid uptake scans ($n = 173$) carried out in a single university hospital from Sep 2006 to Aug 2014 for patients with thyrotoxicosis who were negative for TSH receptor antibody. All three assessors graded each scan for three patterns – diffuse update, no uptake and patchy/localised uptake according to published criteria. Inter-assessor agreement was analysed using kappa statistics.
Results
All three assessors were in agreement for 71% ($n = 123$) of the scans. The overall kappa was 0.67 (95% CI 0.62–0.71). The highest agreement was with 'no uptake'

outcome (kappa 0.86), least with 'patchy/localised uptake' outcome (0.62) and with 'diffuse uptake' outcome (0.65). In scans that lacked agreement ($n=50$), assessor one would have offered radioiodine as a first line treatment to 66% ($n=33$) of patients (pathy/localised uptake), assessor two to 46% and assessor three to 20% of patients.
Conclusion
There is a high overall agreement for the interpretation of thyroid uptake scan but inter-individual variation in one third of uptake scans lead to potentially different treatment for patients with thyrotoxicosis.

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P249

ESR2 mutations in *RET* mutation-negative familial medullary thyroid carcinoma

Wazir K. Afghan[1], Donato Iacovazzo[1], Maria Alevizaki[2], William Foulkes[3], Francesca Lugli[4], Maralyn Druce[1], Pinaki Dutta[5], Mary N. Dang[1], Plamena Gabrovska[1], Patrick J. Morrison[6], Martina Owens[7], Sian Ellard[7], Julian Sampson[8], Laura De Marinis[4] & Márta Korbonits[1]
[1]Centre for Endocrinology, Barts and The London School of Medicine, London, UK; [2]Endocrine Unit, Athens University Medical School, Athens, Greece; [3]Departments of Medicine, Oncology and Human Genetics, McGill University, Montreal, Canada; [4]Endocrinology, Università Cattolica Del Sacro Cuore, Rome, Italy; [5]Endocrinology, PGIMER, Chandigarh, India; [6]Centre for Cancer Research and Cell Biology, Queens University, Belfast, UK; [7]Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK; [8]Institute of Medical Genetics, Cardiff University, Cardiff, UK.

Introduction
Approximately 25% of medullary thyroid cancer (MTC) cases arise in a familial setting, either as MEN2 or fMTC. While most of these are caused by mutations in the *RET* gene, a few families have unidentified mutations. Recently, a frameshift mutation in the *ESR2* gene (coding oestrogen receptor beta) was found in a family with *RET*-negative fMTC associated with C-cell hyperplasia. *In vitro*, transfection of mutant *ESR2* led to unopposed oestrogen receptor alpha-mediated RET expression. Tissue samples showed RET overexpression. The aim of this study was to investigate the prevalence of *ESR2* mutations in *RET*-negative fMTC/CCH kindreds and patients diagnosed with *RET*-negative sporadic MTC.
Methods
DNA samples from six *RET*-negative fMTC/CCH families and 12 *RET*-negative sporadic MTC patients were collected. The eight *ESR2* coding exons and exon-intron boundaries were amplified by PCR and sequenced through Sanger sequencing. *In silico* prediction tools were used to assess the functional impact of identified variants. Immunohistochemistry for RET was performed in samples of *RET*-negative fMTC and in a series of sporadic MTC controls.
Results
No *ESR2* variants were identified in five *RET*-negative fMTC/CCH families, while two common single nucleotide polymorphisms were found in the proband from one other family. Two rare missense variants (c.748G>A p.G250S, minor allele frequency (MAF) 0.08% and c.1508G>A p.C503Y, MAF 0.01%) were found in two patients with sporadic MTC. *In silico* predictions did not support a pathogenic role for these variants. Immunohistochemistry in *RET*-negative fMTC samples showed either absent or weak RET expression, significantly lower compared with sporadic controls.
Conclusion
No pathogenic *ESR2* mutations were identified in our *RET* negative fMTC/CCH families, suggesting that *ESR2* is not commonly involved in *RET*-negative fMTC. Lack of RET overexpression suggests that RET-independent mechanisms underlie the pathogenesis of MTC in these families. Further studies are needed to identify alternative causative mutations in *RET*-negative fMTC.

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P250

Auditing outcomes post radioiodine therapy in patients with hyperthyroidism

Venugopal Vimal, Vito Carone, Thrasos Macriyiannis & Miles Levy
University Hospitals Leicester, Leicester, UK.

Objectives
To evaluate outcomes post radioiodine (I-131) therapy for hyperthyroidism at a tertiary hospital in a two-year period.
Method
The local database (Leicester Clinical Workstation) was used to identify patients with hyperthyroidism who had received radioiodine therapy (RAI) between January 1st 2010 and December 31st 2011 and their records were retrospectively analysed.
Results
84 patients were identified, 65 (77%) were female and 19 (23%) were male. Graves' disease comprised 48 patients (57%), multinodular goitre 22 patients (26%), solitary toxic nodule 6 patients (7%), autonomous thyroid function of unspecified aetiology 8 patients (10%). The mean duration between first diagnosis of thyrotoxicosis and time of first radioiodine was 1507 days (range=62–6532). 14 patients (16%) had ophthalmopathy – of whom 4 were given steroids. 1 patient had worsening of existing ophthalmopathy, and 1 patient only developed clinically apparent ophthalmopathy post RAI. In both these patients the eye disease remained mild in severity. At 2 years post RAI, 59 patients (70%) were hypothyroid, 18 patients (21%) were euthyroid and 7 patients (8%) remained hyperthyroid. 5 patients went on to have a second dose of RAI and 2 patients underwent thyroidectomy. Of the 5 patients who received RAI for the second time, 3 (60%) became hypothyroid and 2 (40%) became euthyroid.
Conclusion
Overall rates of hypothyroidism (70%), euthyroidism (21%) and hyperthyroidism (8%) at 2 years were similar to previous data published by our group in 2008 (67, 27 and 6% respectively). Although only 2 patients developed worsening eye disease, this remains an important potential complication in patients with Graves' receiving RAI. Although there were similar single centre data published previously there were no nationwide data to compare with, thus we recommend a nationwide audit into outcomes and complications post RAI for hyperthyroidism.

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P251

Distribution of free T_4 levels in patients with low-risk thyroid cancer on thyroid hormone replacement and pituitary diseases: comparison with the normal population

Khyatisha Seejore[1], Nikolaos Kyriakakis[1], Georgina Gerrard[2], Vanessa Gill[2] & Robert D Murray[1]
[1]Department of Endocrinology, Leeds Centre for Diabetes and Endocrinology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]Department of Clinical Oncology, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK.

Background
Diagnosing secondary hypothyroidism can be challenging, particularly for patients with low-normal free T_4 (fT_4). Thyroid hormone replacement (THR) in these cases is guided by the normal population fT_4 range. The aim of this study was to compare thyroid function tests in thyroid cancer patients on THR and patients with pituitary diseases with or without central hypothyroidism.
Methods
We retrospectively collected data from low-risk thyroid cancer patients, post-total thyroidectomy with TSH 0.2–2.0 miu/l and patients with hypopituitarism, with or without TSH deficiency, who were reviewed in Outpatient Clinics during March 2015-February 2016. Patients with primary hypothyroidism/hyperthyroidism and TSHomas were excluded. The fT4 reference range for our laboratory is 10.0–20.0 pmol/l.
Results
119 patients with low risk thyroid cancer (Group 1, age 55.5 ± 16.1 years), 144 hypopituitary patients with TSH deficiency on THR (Group 2, age 60.9 ± 15.1 years) and 79 hypopituitary patients not on THR (Group 3, age 56.1 ± 13.7 years) were studied. Mean fT_4 was higher in Group 1 compared with Group 2 (19.1 ± 3.1 vs 15.9 ± 2.9 pmol/l, $P<0.001$) and Group 3 (19.1 ± 3.1 vs 13.4 ± 2.0 pmol/l, $P<0.001$). Additionally, patients in Group 2 had significantly higher mean fT_4 compared with Group 3 (15.9 ± 2.9 vs 13.4 ± 2.0 pmol/l, $P<0.001$). The distribution of fT_4 values in Group 2 was similar to the normal population fT_4 range. In contrast, a right-sided shift of fT_4 distribution was observed in Group 1 and a left-sided shift was noted in Group 3. Only 1.6% of patients in Group 1 had fT_4 values of <13 pmol/l, compared with 19.4% in Group 2 and 43% in Group 3.
Conclusion
Low risk thyroid cancer patients on THR demonstrate a different fT_4 distribution range compared with patients with pituitary diseases and normal population, while maintaining normal TSH levels. The higher fT_4 range in this thyroid cancer group may guide THR in pituitary patients to avoid under-diagnosis and under-treatment of central hypothyroidism.

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P252

Weight-related concerns in endocrine outpatients and its relationship to thyroid function

Angelos Kyriacou[1,2], Alexis Kyriacou[1,3] & Nicholas Economides[1]
[1]Centre of Endocrinology Diabetes & Metabolism (CEDM), Limassol, Cyprus; [2]Salford Royal NHS Foundation Trust, Salford, Greater Manchester, UK; [3]University of Stirling, Stirling, UK.

Introduction
Weight concerns are common in endocrine outpatients. Weight indices seem to have a complex interaction with thyroid function. The two have not been studied in eastern Mediterranean populations.
Methods
Prospective collection of baseline data on weight, BMI and thyroid function on consecutive patients presenting to an endocrinology outpatients. The setting included a medical centre in Limassol, Cyprus. Exclusion criteria were as follows: age less than 16 years, pregnant status and lack of data of any of fT_4, TSH, weight or height or a failure to obtain consent. The frequency of weight-related complaints was assessed as well as the relationship between weight and BMI versus fT4 and TSH.
Results
Fifty patients were included. Mean age was 47.8 years (S.D. = 15.8) and 72% were female. Mean fT_4 was 15.1 pmol/l (S.D. 6.3) and mean TSH was 2.36mIU/L (S.D. 2.8). Mean weight was 77.5 kg (S.D. 21.8) and mean BMI was 27.9 kg/m^2 (S.D. 6.36); 60% of the patients were either overweight or obese. Weight problems were the presenting complaint of 56, 50 and 60% among the overall, normal BMI and euthyroid cohort, respectively. Thyroid function did not relate to weight indices apart from fT_4 being negatively and weakly associated with BMI (rho = -0.2984, $P = 0.0353$); this relationship was no longer significant on multivariate linear regression analysis ($P = 0.185$; adjusted for age, gender, smoking and thyroid medication status).
Discussion
Thyroid function does not appear to be related to weight and BMI. However, this may be due to the small number of subjects participating in this study. Interestingly, the majority of patients presenting to the endocrinology clinic perceive to have weight problems as their major concern and this is true for euthyroid and normoweight patients. Hence, the endocrinologist needs to be better trained in tackling weight-related concerns and better infrastructure is required from supporting specialties, such as dietetics and psychology.

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P253

Prognostic factors of unsuccessful medical treatment of hyperthyroidism; longitudinal analysis of outcomes in the cohort of 538 patients

Barbara Torlinska[1], Oliver Johnson[2] & Kristien Boelaert[1]
[1]University of Birmigham, Birmingham, UK; [2]UHB NHS Foundation Trust, Birmingham, UK.

A prolonged course of antithyroid drugs (ATD) is commonly used as first line treatment in patients with hyperthyroidism, although long term cure rates are poor – 40–50%. We performed a longitudinal analysis of outcomes in patients treated with a complete course of ATD and identified factors predicting remission.
583 consecutive patients with newly diagnosed hyperthyroidism presenting between 2005 and 2014 and treated with ATD for a minimum of 6 months were retrospectively analysed. Remission, defined as biochemical euthyroidism for a minimum of 6 months following ATD discontinuation, was achieved in 322 (55%). Among the remaining, 170 (29%) were given definite treatment with radioiodine or surgery, 76 (13%) stayed on a long-term ATD and 15 were lost for follow-up or died.
Binary logistic regression indicated that younger patients (AOR = 1.03/per year; $P < 0.001$) were more likely to achieve remission whereas ATD had lower likelihood of success in smokers (AOR = 3.6; $P < 0.001$), those with medium/large goitres (AOR = 5.9; $P < 0.001$) and subjects with thyroid eye disease (AOR = 1.7, $P = 0.04$). Gender, biochemical severity of hyperthyroidism at presentation, presence of TPO antibodies or family history of thyroid disease did not significantly influence the likelihood of remission.
Subsequently we determined remission-free survival during 36 months following treatment completion in those achieving remission ($n = 322$). 75 (23%) subjects relapsed, most frequently during the first year following treatment ($n = 41$). In univariate Cox regression models, the severity of hyperthyroidism at presentation (HR = 1.01 per pmol/l; $P = 0.02$) and presence of medium/large goitre (HR = 2.1; $P = 0.03$) significantly predicted risk of relapse at any point of follow-up period.
Conclusion
Medical therapy of hyperthyroidism with thionamides is associated with poor remission rates and high risk of relapse during follow-up. Patients with larger goitres, those with thyroid eye disease, subjects with more severe hyperthyroidism and smokers are less likely to be cured and early consideration of definitive treatment is needed in these subgroups.

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P254

An Audit on Fixed dose (555 MBq) Radioactive-iodine for Hyperthyroidism at a University Hospital

Arun Muthukaruppan Alagar Vijay, Julie Cooper, Lakshminarayanan Varadhan & Ananth U Nayak
University Hospitals of North Midlands, Stoke-on-Trent, UK.

Background/Aim
Radioactive-iodine (RAI) therapy aims to cure hyperthyroidism, with some International authorities recommending a sufficient RAI dose to render patients hypothyroid. An audit on low dose RAI (< 400 MBq) at our University Hospital in 2014 suggested above national average rates of Thyrotoxicosis relapse (24%) and lower rates of hypothyroidism (41%) 6-months post RAI. From 2015, a fixed dose (555 MBq) RAI was utilised and we present the audit outcomes using this 555MBq dose.
Methods
Demographics, clinical and biochemical data on all patients at our Hospital who received 1st dose of RAI for hyperthyroidism in the year 2015 was obtained ($n = 69$). Thyroid status at 6 weeks, 3–6 months and 12 months was determined to analyse the rates of relapse and Hypothyroidism post RAI.
Results
Demographics of cohort: Age 54.5 ± 13.8 (mean ± S.D.) years; Caucasians 90%; Females 78%; Graves' disease 70%; Pre-existing TED 10%. RAI was used as primary treatment in 5.8% and others post ATD treatment with mean duration 13.6 months. Mean duration of thyrotoxicosis 45.2 ± 41.1 months. The proportion with relapse of Thyrotoxicosis and those who developed hypothyroidism at 6 months were 15.5 and 55.2% respectively. On retrospective analysis, among patients who were thyrotoxic at 6 months (15.5% of $n = 58$ with 6 months data), their status at 6 weeks post RAI review were: Euthyroid 22.2%, Hypothyroid 0%, Subclinical Hypothyroid 0%, Subclinical Thyrotoxic 11.1% and Thyrotoxic 66.7%. Of patients who were thyrotoxic at 12 months (8.3% of $n = 36$ with 12 months data), 100% were Thyrotoxic at 6 months post RAI. On logistic regression neither demographics nor biochemical parameters predicted Thyrotoxicosis relapse at 6 or 12 months post RAI.
Conclusion
Standardisation of RAI dose to 555 MBq for treatment of hyperthyroidism improved cure rates of hyperthyroidism, reducing the risk of relapse of thyrotoxicosis and with higher hypothyroidism rates. The incidence of transient Eu/Hypothyroid state post RAI progressing to overt Thyrotoxicosis was low with 555 MBq.

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P255

Comparison of post-operative histology versus pre-operative cytology in thyroidectomy patients who had two pre-operative fine needle aspirates (FNA)

Gurmit Gill, Sushuma Kalidindi, Paul Wilson, Karthik Kalyansundaram, George Varughese & Lakshminarayanan Varadhan
University Hospital North Midlands, Stoke On Trent, UK.

Aim
Patients with thyroid nodules, usually undergo FNA, prior to considering surgery however the results may not be conclusive. Our aim is to compare the cytology results in patients who have had two FNA's with post-operative histology.
Methods
All patients who have had thyroidectomy and two pre-operative FNA's over 7 years were identified. Post-operative histology and FNA cytology was collected from pathology records. Standard 'Thy' classification was used for FNA cytology.
Results
Fifty nine patients were analysed of whom 14 patients had malignant nodules on histology. Forty two patients (71%) had Thy1 on first FNA and 21 (36%) had Thy 1 on second FNA. The proportions of malignancy to abnormal FNA were:

- Thy 1+ Thy 1: n=19, malignant 4
- Thy 1+ Thy 2: n=4, malignant 0
- Thy 1+ Thy 3: n=17, malignant 6
- Thy 1+ Thy 4: n=1, malignant 1
- Thy 1+ Thy 5: n=1, malignant 0
- Thy 2+ Thy 2: n=4, malignant 0
- Thy 2+ Thy 3: n=2, malignant 0
- Thy 3+ Thy 1: n=1, malignant 1
- Thy 3+ Thy 3: n=4, malignant 1
- Thy 5+ Thy 5: n=1, malignant 1

Conclusion
There is a 21% chance of having a malignant lesion if patient has two Thy1 samples. Patients with two Thy2 samples did not have malignancy. Seven out of twenty patients with at least one Thy3 were malignant. Multiple clinical factors and MDT decision making is vital in approaching patients with thyroid nodules.

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P256

How effective are thyroid ultrasound and cytology compared to histology in identifying thyroid malignancy in thyroidectomy patients?

Sushuma Kalidindi, Gurmit Gill, George Varughese & Lakshminarayanan Varadan
University Hospital North Midlands, Stoke on Trent, UK.

Aim
Investigation of thyroid nodules usually involves an ultrasound and fine needle aspiration (FNA); however it could still be challenging to devise a management plan based on these. The aim of our study was to compare the reliability of two thyroid FNA's and ultrasound in comparison to post-operative histology in managing thyroid nodules.
Methods
The data on patients who had underwent thyroidectomy and had at least two FNAs and Ultrasound pre-operatively were analysed. Patients who had ultrasound done prior to the introduction of 'U' staging were excluded. Patients with a history of hyperthyroidism were excluded. Post-operative histology was used as gold-standard, FNA and ultrasound results were compared. Results of sixteen patients were analysed.
Results

- *Malignant on histology* (n=5): Ultrasound was reported as U2 (benign) in two of these patients and correctly identified malignancy in 60% of patients. FNA during the first attempt identified just one patient as Thy 3f, all others were reported as Thy 1. Repeat FNA confirmed cytology of Thy 3 or higher. Cytology correctly identified malignancy in 25% of cases on first attempt and 100% on second attempt.
- *Benign on histology*: (n=11): Ultrasound confirmed nine of the eleven nodules as U2. A patient with follicular adenoma was reported as U3 (suspicious) on ultrasound and was noted to have THY1 on two separate cytology samples. Another patient with U4 findings on ultrasound was found to have THY3A/THY2 on cytology. Histology subsequently revealed a hyperplastic nodule in multi nodular goitre with no malignancy.

Conclusions
Isolated ultrasound imaging is insufficient to exclude thyroid malignancy. In our small sample, cytology on second attempt was superior to ultrasound on detecting malignancy. Combination of both ultrasound and FNA is needed along with a MDT approach for management of thyroid nodules.

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P257

Vitamin D supplementation in Graves' disease and risk of relapse

Suhel Ashraff, Caroline Addison, Vasilieos Tsatlidis & Salman Razvi
Queen Elizabeth Hospital, Gateshead, UK.

Background
Graves' disease (GD) is an auto-immune condition where the thyroid gland produces excess hormones due to stimulation of the TSH receptor. Treatments for GD have largely remained unchanged for over 60 years. The commonest treatment strategy is to use anti-thyroid drugs (ATD) which has limited efficacy and may have serious side-effects. Newer therapies are required that will supplement existing therapies and impact on the underlying immune mechanisms of GD. Vitamin D (D) is a potent immune modulator and its deficiency/insufficiency has been linked with several other auto-immune conditions such as type 1 diabetes and multiple sclerosis. We therefore assessed if supplementation with D in patients with GD and D insufficiency/deficiency impacts on risk of relapse at 12 months.
Methods
All consecutive patients with GD and D insufficiency/deficiency (25-OH-D <50 nmol/l) were treated with D3 20,000 IU weekly for the duration of ATD therapy. After ATD cessation regular thyroid function monitoring was performed up to 12 months to assess relapse. Patients with sufficient D levels ($\geq$ 50 nmol/l) were used as controls.
Results
Amongst patients with GD treated with ATD for 12–18 months, those who were also treated with D for co-existing D insufficiency/deficiency ($n=71$) had lower relapse rate at 12 months post ATD cessation, compared to those that did not have D therapy ($n=71$); 19.7 vs 32.4%, $P=0.02$. In addition, TSH receptor antibody (TRAb) levels were lower in the D treated group at ATD cessation than in those with no D treatment (1.7 vs 3.1 U/l, $P=0.04$). No patient with D treatment had hypercalcemia at the time of ATD cessation. ΔTRab was significantly correlated with ΔD (Pearson's correlation $=-0.22$, $P=0.04$). In further linear modelling after accounting for baseline D levels, ΔTRab continued to be significantly associated with ΔD levels (standardised beta co-efficient -0.36, $P=0.02$). Moreover, this relationship continued to show a significant negative association when other clinical variables that are recognised to have an impact on TBII levels such as age, gender and smoking status were included in the model.
Conclusions
D insufficiency/deficiency may have a permissive role in the immune dysfunction underlying many cases of GD and that manipulating D levels could provide significant benefit in reducing autoimmune function and the risk of relapse in a safe and cost-effective manner. Prospective randomised controlled trials of the adjuvant effects of D, alongside routine ATD therapy, on recurrence of GD are required to confirm this data.

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P258

The fluctuating clinical and biochemical thyroid status of patients with oscillating TSH receptor antibody predominance

Georgina Wordsworth, Lia Anguelova & Tony Robinson
Royal United Hospital, Bath, UK.

TSH receptor antibodies (TRAb) are autoantibodies directed against the TSH receptor, predominantly located on the thyroid epithelial cell surface. Two types of TSH receptor antibody have been found to exist in patients with autoimmune thyroid disease: thyroid stimulating antibodies (TSAb) and TSH-stimulation blocking antibodies (TSBAb). It has generally been felt that patients with positive TSAbs develop Graves' hyperthyroidism and those with TSBAb antibodies develop hypothyroidism and there is no co-existent antibody state. Whilst rare, several case reports have highlighted however that a switch from TSAb to TSBAb predominance (and vice versa) can occur and consequently result in oscillation between clinical and biochemical hyper- and hypothyroidism.
We present the chronological events, including clinical history and biochemical results of 3 patients with fluctuating thyroid status and correlate this with the history of therapeutic interventions for their thyroid disease. All 3 patients had positive TRAb antibodies and similarly to other case reports in the literature, were all women and had comparable characteristics to other patients with autoimmune thyroid disease.
Studies have shown that in cases where there is a simultaneous presence of TSAb and TSBAb in vivo, the subsequent clinical state of the patient can be correlated with the relative concentrations and affinities of these antibodies at any one time. A recent review discusses the potential mechanisms involved in this immunological and clinical thyroid switching including the impact of levothyroxine, anti-thyroid drugs and physiological states such as pregnancy on thyroid status. We discuss the importance of this rare phenomenon including the need for careful patient monitoring and the implications for prognosis and options for definitive management.

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ePoster Presentations

EP1

An unusual presentation of 17alpha hydroxylase deficiency

Maura Moriarty[1], Jeannie Todd[1], Francis Lam[1], Gill Rumsby[2] & Florian Wernig[1]
[1]Imperial College Healthcare NHS Trust, London, UK; [2]University College London Hospitals, London, UK.

17alpha hydroxylase deficiency accounts for less than 1% of all patients diagnosed with congenital adrenal hyperplasia. Almost 100 mutations in the *CYP17A1* gene causing 17-hydroxylase/17,20-lyase deficiency (17OHD) have been described (OMIM 609300). CYP17A1 is expressed in both the adrenals and gonads. Hallmarks of 17OHD include hypertension, hypokalaemia, primary amenorrhoea and absence of secondary sexual characteristics. Most patients with 17OHD remain infertile.

Here we report the case of a 26 year old Afghan lady of consanguineous parents. Aged 14 she had investigations for primary amenorrhea. 17OHD was suspected, but not confirmed and she was lost to follow up. She underwent spontaneous menarche at the age of 18. Aged 24, she represented with primary infertility. She had otherwise been in good health and her menstrual cycle remained regular.

On initial examination she was normotensive with normal breast development but reduced body hair. Gonadotrophins were normal as was oestradiol. ACTH stimulation testing showed a peak cortisol of 139 nmol/L and no rise in 17-hydroxyprogesterone. DHEAS, testosterone and aldosterone were undetectable with normal renin activity. Imaging demonstrated normal pelvic viscera. 24 hour urinary steroid profile showed a decrease in cortisol metabolites, elevated corticosterone and progesterone but also some 17-hydroxyprogesterone metabolites suggesting reduced 17-hydroxylase and 17,20-lyase activities. Aldosterone metabolites were absent raising the added possibility of aldosterone synthase deficiency.

Genetic testing confirmed 17OHD with the variant, c.160_162del (g.Phe54del) known to have residual 17alpha-hydroxylase activity (37%) but more complete loss of 17,20-lyase activity (8%) (rs.121434319). Aldosterone synthase genetic testing results are pending.

She is currently undergoing IVF treatment and was commenced on 3 mg of prednisolone daily. There has been no symptomatic change since she was commenced on glucocorticoid replacement and the question arises whether she does require lifelong continuous steroid replacement or simply cover at times of stress.

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EP2

Cushing's disease detected following an adrenal incidentaloma

Shailesh Gohil, Veronica Kieffer & Miles Levy
University Hospitals of Leicester NHS Trust, Leicester, UK.

Background

Adrenal incidentalomas are classified as adrenal lesions picked up on imaging performed due to reasons other than to look at the adrenals. With cross sectional imaging becoming more frequent, the frequency of adrenal lesions being detected and referred to endocrine services is increasing and dedicated adrenal incidentaloma clinics are being set up to screen these patients for potential pathology.

Case

We present a 63 year old lady who underwent a CT colonogram due to change in her bowel habit. This picked up a 14 mm bulky left adrenal gland, described as an adenoma, and prompted referral to the nurse led, adrenal incidentaloma clinic. She had type 2 diabetes and was on 3 antihypertensives. On questioning, she complained of abdominal obesity and thin limbs with proximal myopathy. Initial screening biochemistry was requested. This showed raised urinary free cortisol (UFC) of 1136 nmol/24 hr, with post overnight dexamethasone test cortisol of 427 nmol/L. An MRI of her adrenals showed bilateral lipid rich nodules consistent with small adenomas. Hypercortisolaemia was confirmed on second UFC and her cortisol did not suppress on the low dose dexamethasone suppression test. A CRH test showed an exaggerated ACTH response adding evidence for pituitary driven Cushing's syndrome. A pituitary MRI was subsequently arranged which showed a 14 mm hypoenhancing pituitary lesion. She has been discussed in our regional pituitary MDT and has now been listed for a trans-spenoidal hypophysectomy.

Discussion

Adrenal incidentalomas are a common finding and, although the majority of these patients have benign lesions, a proportion of patients do have functioning adrenal adenomas requiring intervention. Incidental adrenal lesions leading to functional pituitary adenomas being detected are less common, as in this case. Therefore appropriate, thorough testing of adrenal incidentalomas is required to ensure pathologies are not missed and this can be done through structured adrenal incidentaloma clinics.

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EP3

Apparent Mineralocorticoid Excess due to daily consumption of liquorice - containing tea

Isolda Frizelle, Domnhal J. O'Halloran & Mohammed Sohail Anjum
Cork University Hospital, Cork, Ireland.

Apparent mineralocorticoid excess is a rare syndrome with few reported literature entries. Liquorice tea is a common dietary supplement often used as a slimming aid.

We present the case of a 50 year old woman who presented with a two week history of headache, nausea and light sensitivity. Background medical history consisted of irritable bowel syndrome, tubal ligation, thrombosis of a retinal vessel at 17 years of age and a smoker of 10 pack year.

Investigations showed a hypokalaemia of 3.2 mmol/L(normal range 3.5–5.5 mmol/L) in the setting of new hypertension. Mineralocorticoid excess was suspected. Baseline plasma aldosterone <10 pg/mL and plasma renin <2.0 pg/mL.

On further probing she admitted to drinking up to five litres daily of liquorice extract tea.

Repeat testing one month off the tea revealed plasma renin level of 5.5 pg/mL and plasma aldosterone 34 pg/mL, aldosterone renin ratio 6.2. The hypertension and hypokalaemia also resolved.

Liquorice is a known competitive inhibitor of the enzyme 11 beta dehydrogenase 2 which is responsible for conversion of active cortisol to inactive cortisone enabling aldosterone to bind to the mineralocorticoid receptor where normally it would have equal affinity for cortisol and aldosterone.

This case describes liquorice tea- induced apparent mineralocorticoid excess. The case illustrates an unusual cause of new onset hypertension. The importance of careful history taking is also highlighted as essential in correct diagnosis.

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EP4

Failure to suppress TSH in thyroid cancer – could it be Addison's disease?

George E Fowler[1], Jonathan Wadsley[2], Jonathan Webster[3] & Sabapathy P Balasubramanian[4]
[1]The Medical School, University of Sheffield, Sheffield, UK; [2]Department of Oncology, Weston Park Hospital, Sheffield, UK; [3]Department of Diabetes and Endocrinology, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [4]Sheffield Endocrine Surgical Unit, Directorate of General Surgery, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.

Background

Papillary thyroid cancer is the commonest thyroid malignancy. Surgery is first-line treatment, followed by radioiodine and long-term, high dose levothyroxine to suppress TSH.

Cortisol is known to suppress TSH secretion by the pituitary, although the mechanism remains unclear. Correspondingly, hypocortisolism may raise TSH levels.

Case Summary

A 64 year old woman presented with a right-sided thyroid nodule, normal TSH and raised TPO antibodies (141 IU/ml). On conservative management, she developed biochemical evidence of hyperthyroidism and was commenced on carbimazole. A radionuclide scan showed the right-sided nodule to be cold. To treat her hyperthyroidism and remove the nodule, she underwent a near-total thyroidectomy a year after her initial presentation. Histology showed multi-nodularity, focal lymphoid infiltrate and multifocal papillary cancer (pT1m pN0 pMx, R0). Further treatment included radioiodine ablation and high dose thyroxine for TSH suppression.

TSH remained supressed at <0.1 mIU/L for 5 years following surgery (at $\sim$250 mcg/day of thyroxine), but later started to rise. The thyroxine dose had to be increased gradually to 350 mcg/day (more than double her starting dose) to ensure a low TSH. Non-compliance to treatment was considered unlikely.

Five years later, her sister (non-medical background) suggested that she may have Addison's disease following an online search based on symptoms. Subsequent

examination demonstrated cutaneous and mucosal hyperpigmentation and a short synacthen test (basal and 30 minute cortisol of 61 and 66 respectively) confirmed the diagnosis. After commencing hydrocortisone her TSH levels suppressed using much lower doses of thyroxine (currently 225 mcg/day).

Conclusion

This case report highlights how the rare occurrence of Addison's disease can be overlooked. In patients on long-term thyroxine, an increasing T4 requirement (either for replacement or TSH suppression) should raise the suspicion of Addison's disease as a potential cause, in addition to the possibility of non-compliance.

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EP5

Adrenal TB: the great master of disguise!

Eswari Chinnasamy, C Cosgrove, N Beharry & G Bano
St George's University Hospitals NHS Foundation Trust, London, UK.

Delay in diagnosis of adrenal insufficiency is common. About 47% of patients have symptoms for over 1 year and 20% for over 5 years before diagnosis. Autoimmunity is the most common aetiology for Primary Adrenal Insufficiency (PAI) in developed countries. But up to 10–20% of PAI could be due to TB.

We present an interesting case of 42 year old Afro Caribbean male with isolated adrenal TB. He had 2 year history of nonspecific illness including reduced appetite, weight loss and intermittent fever. He was referred as an emergency due to neutropaenia. After extensive inpatient investigations, he was discharged with probable viral infection and neutropaenia related to ethnicity. He denied any exposure to TB and his sputum and bone marrow aspirates were negative for TB. His T-spot has come back as reactive. However there was no evidence of active TB at other sites and this was thought to be a latent infection and was not treated. Subsequent CT CAP for weight loss revealed significant bilateral adrenal hyperplasia with some calcifications. Further investigations confirmed PAI. This along with radiological features raised suspicion for Adrenal TB and he was started on treatment. He has now completed 6 months anti-tuberculous therapy and on follow up imaging, there is almost complete resolution of radiological abnormalities in adrenal glands. He remains on Hydrocortisone and Fludrocortisone.

High degree of clinical suspicion is necessary to diagnose adrenal TB, especially when there is no extra adrenal involvement. This should be considered in anyone with PAI in the presence of bilaterally enlarged adrenal glands. 12% of patients with adrenal TB have no evidence of active TB elsewhere. Adrenal biopsy would also be helpful in this scenario.

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EP6

Prednisolone 3 mg once daily should be the glucocorticoid replacement for hypopituitarism

Pratibha Machenahalli, Sirazum Choudhury & Karim Meeran
Imperial College Hospitals NHS foundation Trust, London, UK.

A 33 year-old male bus driver with long standing pemphigus requiring high dose prednisolone, presented with acromegaly in 2001. MRI pituitary revealed a

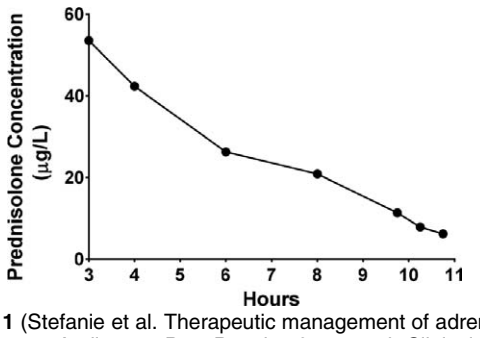

Figure 1 (Stefanie et al. Therapeutic management of adrenal insufficiency, April 2009, Best Practice & research Clinical Endocrinology & Metabolism).

Table 1

Date	Time	Time of Pred Dose	Time from Pred dose	Cortisol/ nmol/l	Prednisolone/ ug/l	Pred dose	Half life
10/05/2016	09:00	06:00	03:00	53	53.528	3	
10/05/2016	10:00	06:00	04:00	35	42.338	3	
10/05/2016	12:00	06:00	06:00	25	26.283	3	
10/05/2016	14:00	06:00	08:00	24	20.862	3	
10/05/2016	15:45	06:00	09:45	<20	11.344	3	
10/05/2016	16:15	06:00	10:15	59	7.901	3	
10/05/2016	16:45	06:00	10:45	79	6.213	3	3.01

Prednisolone 3 – 4 mg daily is an adequate replacement dose and, as it can be given once daily is more convenient than hydrocortisone, which is given thrice daily.

2×2×0.5 cm pituitary adenoma and his GH levels of 14.8–16.4 nmo/L throughout and were not suppressible with glucose. His IGF1 was 191 nmol/l (normal range: 13–64 nmol/L), Prolactin 6,557 milliunit/L, testosterone 2 nmol/L and cortisol uninterpretable as he was on prednisolone. Trans-sphenoidal hypophysectomy and external beam radiotherapy to the pituitary were undertaken in 200× with good response. He was started on levothyroxine, testosterone and the prednisolone for his pemphigus was continued. Because he remained on prednisolone, there was no opportunity or reason to check his cortisol reserve, as we presumed he would stay on prednisolone for life. In 2015 he began to respond to alternative therapies for his pemphigus that was being reviewed at another dermatological centre,were unaware of his hypopituitarism. They began to wean him off the prednisolone using a standard protocol to 5 mg, then reducing by 1 mg per month. He remained well even on 3 mg, but on 2 mg he felt very tired. When the dose was reduced to 1 mg daily, he started vomiting and was unable to go to work. Without seeking medical advice he then increased the dose and improved. He has been well since 3 mg daily and a prednisolone day curve on this dose is shown below. A SST revealed a sub-optimal response (<20, 59, 79 nmol/L).

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EP7

An unusual case of adrenal metastases

Moayed Alhelfi, Annice Mukherjee, Adam Robinson, Lili Nelson & Emma Baker
Salford Royal Foundation Trust, Salford, UK.

Section: Case history

73-year old gentleman referred from GP with a two month history of worsening dizziness, malaise, postural hypotension and general deterioration and spiking pyrexia ranging 38-40°C over 3 weeks. PMH of NSCLC T2b N0- left lower lobectomy & chemotherapy 3 years prior.

Section: Investigations and treatment

At re-presentation his CT TAP showed bilateral bulky adrenal glands but no other abnormality. The patient's bloods showed mild raised inflammatory markers, at this time he treated as sepsis of unknown origin with antibiotics and fluid.

A SST test done as suspicion of adrenal insufficiency (given his postural hypotension) revealed flat response, however steroid and fludrocortisone started with marginal symptoms improvement. Meanwhile he had been treated with several courses of antibiotics, however all micro cultures were clear (including several sets of blood cultures). The patient's CXR was normal as well as viral screen, autoimmune screen while Echocardiogram showed normal LV function and no valvular lesions. The CSF results revealed mild raised of protein the rest including PCR to TB, as well as flow cytometry/immunophenotyping all negative. He had been commenced acyclovir as meningoencephalitis, though no evidence suggested this diagnosis.

Inpatient CT-TAP showed Progressive generalized enlargement of both adrenal glands. Peri-adrenal inflammatory change.

He had CT guided Adrenal biopsy which showed malignant cells in the adrenals, poorly differentiated; these are needle cores of fibrovascular tissue and some adipose tissue, widely infiltrated by a malignant appearing tumour. Non-necrotic. Whilst an inpatient on the general medical ward, despite all supportive care progressive inexorable deterioration occurred. The patient was transferred to medical HDU as he deteriorated further. In spite of best supportive care he continues spiking fevers and died after cardiac arrest.

Section: Conclusions and points for discussion

His presentation with swinging pyrexia and malignant adrenal infiltration without necrosis or other evidence of metastatic disease or positive microbiology was difficult to explain. An atypical presentation of adrenal metastasis without

radiological or histological evidence of necrosis or sepsis was the final working diagnosis. Post Mortem report is awaited.

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EP8

Will the routine use of high dose steroids for alcoholic hepatitis result in an increased incidence of clinically significant hypocortisolism in patients with liver cirrhosis?

Priya Karia[1], Vassiliki Bravis[1,2], Victoria Salem[1,2], Shiva Radhakrishnan[1] & Dri Choa[1]
[1]Department of Diabetes and Endocrinology, St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK; [2]Division of Diabetes, Endocrinology and Metabolism, Imperial College London, London, UK.

Introduction
Recent evidence supports the use of high dose steroids for 28 days in acute alcoholic hepatitis. We present a patient with Childs Pugh C liver cirrhosis, who developed adrenal axis suppression following such treatment. We discuss the complex aetiology and biochemistry of hypocortisolism in liver disease.
Case
48 year-old female admitted with alcoholic hepatitis, treated with a non-tapering 28-day course of 40 mg prednisolone. The patient was re-admitted 4 weeks later with severe, symptomatic hyponatraemia. This resolved only following hydrocortisone replacement therapy.
Results
Serum sodium (mmol/L)
- Prior to discontinuation of prednisolone: 131
- At re-admission, 4 weeks later: 104
- Following hydrocortisone replacement: 138

Short Synacthen test (after cessation of prednisolone):
Cortisol (mmol/L)
- Basal (09:00am): 44 mmol/L
- 30-minute: 107 mmol/L
- 60-minute: 137 mmol/L (normal peak on local guidelines >450 nmol/L)

Basal ACTH <5 pg/ml
Cortisol post-hydrocortisone dose: 764 mmol/L
Serum albumin: 26 g/L
Cortisol-binding globulin (CBG): 43.2 mg/L (normal range 31.0-53.4 mg/L)
The free cortisol index (FCI) is a surrogate marker for free cortisol and is defined as total cortisol (nmol/L)/CBG (mg/L). FCI $>$ 12 represents sufficient adrenal reserve. This patient's peak, post-synacthen FCI was 9.09.
Learning points
1. A 28-day course of 40 mg prednisolone induced adrenal suppression in this patient with acute alcoholic hepatitis and liver cirrhosis.
2. Adrenal dysfunction is already prevalent in patients with liver failure. Causes are multifactorial and include pituitary suppression and poor synthetic function of steroid hormones ("hepatoadrenal syndrome").
3. Biochemical diagnosis should account for changes in circulating albumin. CBG affects the availability of free cortisol.
4. The use of high dose Prednisolone for 28 days in the treatment of alcoholic hepatitis in patients with liver cirrhosis should be used cautiously and be recognised as a risk for subsequent adrenal suppression. Hepatologists should consider adrenal axis interrogation after completion of such courses.

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EP9

Case of prolonged hypoaldosteronism after unilateral adrenalectomy for Conn's syndrome

Natasha Shrikrishna, Naing Koko, Ellen Jones, Betty Loumpardia, Steven Wong & Aye Nyunt
Glan Clwd Hospital, Denbighshire, Wales, UK.

Introduction
Unilateral adrenalectomy is an effective treatment for aldosterone producing adenoma. However, after adrenalectomy, suppression of the contralateral zona glomerolura (ZG) function can lead to transient hypotension & hyperkalaemia. We present a protracted case of post-operative adrenalectomy related hypoaldosteronism.
Case
A 54-year-old hypertensive male with confirmed primary hyperaldoseronism (PRA <0.1 nm/h, aldosterone 1050 pmol/l; PRA ratio 2200) underwent a left laparoscopic adrenalectomy following confirmatory AVS and MRI in September 2014. Postoperatively, he developed acute hypotension and acute kidney injury (AKI). After discharge, he was found to have hypoaldosteronism with a PRA level 0.1 and aldosterone levels <100. He was commenced on fludrocortisone and his AKI resolved. He remained on fludrocortisone with interval measurements of his PRA, aldosterone and U&Es.
Discussion
The incidence of post-operative hyperkalaemia is approximately 16%, with 5% exhibiting prolonged hypoaldosteronism requiring mineralocorticoid replacement therapy. Possible mechanisms underlying delayed recovery include:
1) Reduced renal perfusion following normalization of blood pressure post adrenalectomy can unmask renal impairment secondary to previous aldosteronism (via hypertension or via direct effects on fibrosis/inflammation)
2) Delayed recovery of the remaining renin angiotensin- ZG function related to elevated (primary hypoaldosteronism) or supressed (secondary hypoaldosteronism) of renin levels.

It has been recommended in 2008 potassium sparing agents should be withdrawn and antihypertensives reduced. Plasma aldosterone renin levels should be measured after the adrenalectomy and on day one postoperative. However, this is not predictive of the complications described in this case as renin levels can be suppressed or elevated. In this case, this gentleman required 15 months of fludrocortisone. Predictive factors include age >53, long duration of hypertension, previous use of NSAIDs and size of adenoma. A pragmatic postoperative monitoring approach is to measure regular U&Es, aldosterone every 3-6 months with a trial reduction/ withdrawal of fludrocortisone.

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EP10

Pediatric Cushing's Syndrome due to primary pigmented nodular adrenocortical disease

Dia Eddine Boudiaf & Farida Chentli
Department of Endocrinology and Metabolic diseases, Bab El Oued teaching Hospital, Algiers, Algeria

Introduction
Primary pigmented nodular adrenocortical disease (PPNAD) is a rare cause of ACTH-independent Cushing's syndrome in pediatric population. This entity due to genetic mutation has specific histological appearance and can be associated to Carney's complex and McCune Albright syndrome. Our aim was to report a pediatric case in order to specify clinical and biological characteristics.
Case report
A 6 year-old boy with no family or personal medical history was sent for puffiness of the face, stature delay and progressive weight gain. Clinical examination showed a short stature (–1,5 SD) with severe android obesity (BMI = 50,5), acanthosis nigricans and pubic hair (Tanner stage 3), but without any hypercatabolism feature. Blood pressure = 100/60 mmHg. There was not any manifestation of Carney's complex or McCune Albright syndrome. Biological assessment showed endogenous hypercortisolism with low ACTH and paradoxical response to dexamethasone. He had bilateral adrenalectomy and histological study pleaded for PPNAD. Research for genetic mutation was negative for PRKAR1A. The follow up under hydrocortisone and mineralocorticoid substitution showed a very good result.
Conclusion
PPNAD is a very rare cause of Cushing syndrome in children. It may be familial or isolated. It can be part of Carney's complex or McCune Albright syndrome which was not the case in our patient. Three genetic mutations can cause PPNAD: PRKAR1A, PDE11A, PDE8B. The first and most important one was negative in our patient. On the biological point this syndrome is characterized by paradoxical response to dexamethasone as in the presented case. For treatment bilateral adrenalectomy is indicated to avoid Cushing's morbidities.

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EP11

Elevated renin levels heralds adrenocortical involvement in a case of adrenoleukodystrophy

Mehjabeen Beebeejaun, Laura To, Yaqza Hussain, Matthew Craner, Frances Coyle, Emma Bingham & Jennifer Tringham
Frimley Park Hospital, Surrey, UK.

Adrenoleukodystrophy (ALD) is an X-linked, widely heterogeneous, neurodegenerative disorder of peroxisomal metabolism characterised by the

accumulation of very-long-chain fatty acids (VLCFA). A mutation in the ABCD1 gene is responsible. ALD has both a neurological and an endocrine interface as VLCFA deposit in the central and peripheral nervous system as well as the adrenal cortex and testis. ALD can present in childhood with a cerebral form or later in life as an adrenomyeloneuropathy type. ALD can also present with isolated adrenocortical failure. There is no clinical correlation between the severity of the neurological presentation and the endocrine manifestations. We describe the case of a 40 year old gentleman who presented with progressive spastic paraparesis following a road traffic accident. Neurological imaging did not reveal any structural or demyelinating abnormalities. After extensive investigations, he was noted to have elevated levels of VLCFA and genetic tests confirmed an ABCD1 gene mutation, hence confirming a diagnosis of ALD. An endocrine work-up was carried out. He described fatigue and minimal postural symptoms. On examination, he was not obviously hyperpigmented and demonstrated no postural blood pressure changes. Other tests revealed normal sodium and potassium levels, an aldosterone level of 180 pmol/L (100–800) and a renin level of 78.8 mu/L (12.9–33.7). A short synacthen test revealed a normal cortisol response to ACTH with a 30 minute cortisol of 603. This case highlights the importance of carefully screening all ALD cases for adrenocortical involvement; this will prevent catastrophic Addisonian crises in periods of stress. Elevated renin levels indicates deposition of VLCFA in the zona glomerulosa which can herald impending adrenal cortex failure further during the course of the disease; hence the need for regular adrenal reserve assessments. Likewise, male patients diagnosed with idiopathic or negative adrenal antibody Addison's disease should have VLCFA measured to exclude ALD.

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EP12

Bilateral adrenal haemorrhage secondary to non-meningococcal sepsis

Malgorzata Lubczynska, Thrasos Macriyiannis & Marie-France Kong
Leicester Royal Infirmary, Leicester, UK.

A 69 year old man presented to the hospital after he fell from a 6 foot ladder. He was previously fit and well with no co-morbidities apart from a 55 pack year smoking history. He complained of right shoulder and hip pain. CT scan revealed fractures of the left 6th rib and right superior and inferior pubic rami. In addition, there was an incidental finding of a 5.2 cm in diameter abdominal aortic aneurysm (AAA) with no radiological evidence of a leak. He was treated conservatively on an orthopaedic ward. Two weeks later he developed signs of sepsis with pyrexia, hypoxia and oliguria and went on to develop multi-organ failure and was transferred to the intensive care unit (ICU). Emergency CT scan of the abdomen showed acute bilateral adrenal haemorrhage with stable and non-bleeding AAA. Upon endocrinology consult, he was commenced on intravenous hydrocortisone. A noticeable improvement was noted on day two of ICU stay following antibiotic, glucocorticoid therapy and inotropic support. Three sets of blood cultures showed no growth after 72 hours of incubation. On day three, he was transferred back to a base ward and was subsequently discharged home on oral hydrocortisone and fludrocortisone.

When reviewed in the endocrinology clinic he reported that he had not had any hydrocortisone or fludrocortisone tablets for 6 weeks as he did not realise he had to continue taking these medications. His short Synacthen test showed a basal serum cortisol level of 231 nmol/l and peak cortisol of 283 nmol/L and baseline ACTH level of 339 ng/l (0–46). His renin level was normal. He was restarted on hydrocortisone. He subsequently underwent endovascular AAA repair in November 2015.

Acute adrenal insufficiency resulting from extensive bilateral adrenal hemorrhage caused by sepsis is uniformly fatal if unrecognized and untreated.

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EP13

Pheochromocytoma in pregnancy

Kavitha Dhevi Krishnasamy Ganapathy, Murali Ganguri, Shilpa Mahadasu & Rasha Mukhtar
James Cook University Hospitals, Middelsbrough, UK.

Introduction

Pheochromocytoma is extremely rare in pregnancy and occurs 1 in 54000 pregnancies. If undiagnosed, Maternal and fetal mortality amounts to 40–50%. Early detection and prompt treatment decreases the maternal and fetal mortality to $<5\%$ and $<15\%$ respectively. There are multiple and complex issues in managing this condition in pregnancy. We would like to present such a case with very good outcome.

Case

28-year-old woman was admitted with palpitations, hypertension, flushing and throbbing headache during her second pregnancy. She was prescribed sertraline and also a beta blocker for anxiety. Her symptoms were persistent. The suspicion of pheochromocytoma was raised, as she had paroxysmal hypertension. Serum normetadrenaline were raised at $>25{,}000$ pmol/L. MRI scan revealed a $59\times54\times58$ mm right adrenal mass. She was treated with Phenoxybenzamine and Bisoprolol. MDT (Obstetrician, endocrinologist, Endocrine surgeon, Neonatologist and Anaesthetist) decided to arrange elective LSCS and a planned adrenalectomy after the delivery after MIBG scan. She had an uneventful perioperative period and delivered a healthy baby. A month later she had her right adrenalectomy and her biochemistry normalised. She is waiting for genetic screening.

Discussion

This is a complex condition with rare occurrence. Some of the symptoms are associated with pre-eclampsia and can be present in normal pregnant women. However, the paroxysmal nature of the symptoms should raise the suspicion. Plasma metanephrines are extremely useful. If they are normal, it confidently rules out the condition whereas borderline values should be repeated. An experienced MDT team is very useful in planning the time and mode of delivery. Caesarian section (19% mortality rate) is preferred and safer than vaginal delivery (31%). There are certain medications that can precipitate 'Pheo' crisis that are routinely used during pregnancy including steroids for pre-term labour. MRI is preferred radiological investigation during pregnancy. Use of alpha blocker reduces the mortality. It is very important to prevent 'Pheo' crisis and as well as preparing the patient for tumour removal. This case highlights the importance well-co-ordinated MDT approach for the best outcome.

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EP14

Not another case of low sodium

Sobia Arshad & Denis Barnes
Tunbridge Wells Hospital, Kent, UK.

An 82 year old man was admitted to hospital with lethargy, anorexia and back pain. His past medical history included chronic lymphocytic leukaemia and hypertension. Blood tests revealed a serum sodium of 115 mmol/l and potassium of 5.4. His irbesartan was discontinued and sodium rose to 126 prior to discharge. 9 am cortisol was 408 nmol/l. He was readmitted to hospital 6 days later with hyponatraemia (116 mmol/l). A short Synacthen test was performed which showed a flat response (baseline cortisol 282 nmol/l with a 60 minute post-Synacthen level of 265). ACTH level on the baseline sample was raised at 400 pg/ml. He was commenced on hydrocortisone replacement therapy and felt much improved. A CT scan of the abdomen showed large bilateral adrenal masses (4.9×3.5 cm on the right, 9.2×6 cm on the left), small para-aortic lymph nodes and multiple hepatic metastases. A subsequent biopsy of the left adrenal mass showed features consistent with a high grade B-cell non-Hodgkin's lymphoma. The incidence of adrenal involvement in non-Hodgkin's lymphoma is estimated to be between 0.8–2%. Although autoimmune adrenalitis is the most common cause for primary adrenal insufficiency in the developed world, malignancy should be considered as an underlying cause, especially in the elderly.

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EP15

Primary pigmented nodular adrenocortical disease: a rare cause of Cushing's syndrome

Catriona Kyle[1,2] & Roland Stimson[1,2]
[1]University of Edinburgh, Edinburgh, UK, [2]NHS Lothian, Edinburgh, UK.

A 34-year-old lady presented with a 3 year history of central weight gain, hypertension and secondary amenorrhoea. Initial 24-hour urinary free cortisol (UFC) was raised (536 nmol/24 hr) and subsequent overnight dexamethasone suppression test (DST) was elevated at 593 nmol/L. Low and high dose DST confirmed the diagnosis of Cushing's syndrome with a slightly unusual trend of increasing cortisol levels compared with baseline. ACTH levels were undetectable while adrenal imaging revealed 4 right adrenal nodules (7–11 mm in size) and a normal left adrenal. Metyrapone was used to normalise UFC pre-operatively and she underwent right adrenalectomy. Post-operatively, cortisol levels remained elevated at 280 nmol/L with an undetectable ACTH. Pathological examination of the excised adrenal revealed characteristics of primary pigmented nodular adrenocortical disease (PPNAD), a rare familial cause of Cushing's syndrome. No other features of Carney complex were observed in this individual. Subsequent investigation of her mother (who complained of a 10-year history of

weight gain and uncontrolled hypertension despite 3 agents) also confirmed ACTH-independent Cushing's syndrome with an increase in UFC following high dose DST. Adrenal imaging identified a 27mm left adrenal adenoma with appearances of the right adrenal reported as normal.
PPNAD is a form of micronodular adrenal hyperplasia causing ACTH-independent Cushing's syndrome. Isolated PPNAD is an autosomal dominant inherited condition often associated with germline mutations in PRKAR1A and PDE. Bilateral adrenalectomy is the treatment of choice, although imaging may not always identify the bilateral micronodular changes. An important biochemical feature of PPNAD is a paradoxical rise in cortisol post high dose DST.
Genetic testing of these patients has failed to reveal the causative mutation thus far, although further testing of alternative candidates (e.g. PRKACA) is in progress.
This case represents an extremely unusual cause of Cushing's syndrome ($<1\%$ of all cases) and highlights the importance of considering rare diagnoses before referring for surgery.

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EP16

X-linked adrenoleukodystrophy – a rare cause of Addison's disease

Claudia Matta-Coelho, Selma B. Souto & Olinda Marques
Endocrinology Department, Braga Hospital, Braga, Portugal.

X-linked adrenoleukodystrophy (X-ALD) is a metabolic disorder caused by mutations in the ABCD1 gene leading to accumulation of very long-chain fatty acids (VLCFA) in plasma and all tissues, including the white matter of the brain, the spinal cord and adrenal cortex. There is an estimated incidence of 1 in 17.000 new-borns. The clinical features are variable ranging from primary adrenal insufficiency and progressive myelopathy to cerebral demyelination.
The authors report three cases of X-ALD confirmed by determination of VLCFA levels.
Case1
X-ALD diagnosed at 28 years old with primary adrenal insufficiency. Personal medical history of epilepsy. At 44 years old, no clinical manifestations of myelopathy or physical examination abnormalities. Normal magnetic resonance (MR).
Case 2
X-ALD diagnosed at 22 years old with primary adrenal insufficiency. His mother is a carrier and there is a high suspicion of maternal uncle death due to X-ALD at 22 years old. At 32 years old, reference to sporadic headaches and vertigo. Normal MR, however myelopathy confirmed by brainstem auditory evoked potentials.
Case 3
X-ALD diagnosed at 11 years old, discontinued medical follow-up at 25. After 3 years, admitted to the emergency department due to headaches, disorientation and urinary retention. MR showed active areas of demyelination. Normal previous MR. After 2 years is in a persistent vegetative state. Family history revealed brother with X-ALD, and mother and sisters carriers.
These cases emphasize the high clinical suspicion necessary for this rare clinical entity that exhibits a variable spectrum of clinical manifestations. Therefore VLCFA determination is recommended in male patients with Addison disease, in particular if adrenocortical autoantibodies are negative.

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EP17

Please don't operate on this patient - A case of 'Adrenaline running high'

Irfan Khan[1], Faisal Hasan[2] & Kathryn Lonnen[1]
[1]Southmead Hospital, Bristol, UK; [2]Musgrove Park Hospital, Taunton, UK.

Phaeochromocytomas are rare catecholamine secreting tumours arising from the chromaffin cells of the adrenal medulla. The annual incidence is approximately 0.8 per 100,000 person-years. Most of them are sporadic but in about 25–30% of patients, they are part of a familial disorder. The classic clinical features are episodic headache, sweating and tachycardia (with or without hypertension). However, a minority of patients are asymptomatic. We present a clinical case in which a patient presented as an acute surgical emergency (posing as a diagnostic and management challenge) subsequently diagnosed as an 'asymptomatic' phaeochromocytoma.
A 49 year old lady with sickle cell trait was admitted to the hospital under the care of the surgeons with generalised abdominal pain and vomiting. Investigations showed raised inflammatory markers, anaemia and metabolic acidosis. She was given conservative treatment with fluids and analgesia for a possible diagnosis of sickle cell crisis. She became more unwell with the haemoglobin acutely dropping from 91 to 64 g/L and without any evidence of sickling on the blood film. An urgent abdominal CT scan showed a large left retroperitoneal haemorrhage which was thought to arise from an 8 cm adrenal mass. Following stabilisation with blood transfusion, the surgical team were keen to carry out emergency surgery. However after discussion with the Endocrinologist, who strongly advised against this, surgical treatment was put on hold because of the possibility of the adrenal mass being a phaechromocytoma and the potential risk of a 'Phaeo crisis'. The patient remained stable and after extensive discussion she was started on alpha blockade with Phenoxybenzamine and transferred to the regional tertiary care centre for elective surgery. Urgent sample for plasma metanephrines was sent which confirmed phaeochromocytoma (Plasma metadrenaline $>25{,}000$ - Normal <800). The patient underwent elective adrenalectomy and histology confirmed a benign phaeochromocytoma.
This case highlights the importance of taking a step back in similar situations and thinking about possible phaeochromocytoma even in the absence of typical signs and symptoms.

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EP18

Bilateral adrenal nodules and phaeochromocytoma associated with neurofibromatosis

Zeenat Banu & Ravi Menon
Colchester General Hospital, Colchester, UK.

We report two cases of unilateral and bilateral phaeochromocytoma in patients with neurofibromatosis type 1 (NF-1) respectively.
Case 1
64 year old Caucasian male with known NF-1, hypertension, depression and osteoarthritis was referred with episodic symptoms of palpitation, chest pain and breathlessness. Biochemically confirmed phaeochromocytoma with 24 hr urinary metanephrines of 18595 nmol/24 hrs. CT revealed 4.2 cm right adrenal nodule and 2 cm left adrenal nodule. Both nodules showed increased uptake with MIBG. His BP was optimised with phenoxybenzamin initially and beta blockade later and had bilateral adrenalectomy followed by hydrocortisone and fludrocortisone replacement therapy. Histology confirmed bilateral phaeochromocytomas with complete resection and no atypical features. 24 hour metanephrines on follow-up were normal.
Case 2
54 year old male with NF1 with a history of hypertension was found to have a 3.2 cm incidental left adrenal nodule while being investigated by Gastro-enterology for weight loss. 24 hr urinary metanephrines were elevated to 3000 nmol/24 hrs. MIBG was in keeping with left pheochromocytoma. There was some evidence of increased uptake of MIBG on the right side, but CT did not reveal any nodules. He was managed pre-operatively with phenoxybenzamine and propranolol and underwent left laparoscopic left adrenalectomy with good recovery. Post-surgery urinary metanephrines were negative with no evidence of recurrence. He is being kept under review for the right side side.
Discussion
Neurofibromatosis-1 also called Von Recklinghausen's disease has an autosomal dominant inheritance with complete penetrance and has an incidence of 1 in 3500. Phaeochromocytoma has been clinically identified in 0.1–5.7% of patients with NF-1 and in 20–50% of NF-1 patients with hypertension, compared to 0.1% of all hypertensive individuals. Of the individuals with NF-1 and phaeochromocytomas, 9–27% have bilateral phaeochromocytomas. Bilateral phaeochromocytomas remain a rare manifestation of. In many cases, it presents with unilateral phaeochromoctoma with the other side developing it at a later stage. Screening for phaeochromocytoma should be a part of monitoring of people with NF-1 and particular attention should be paid to those with hypertension.

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EP19

Challenging hypercalcaemia

Rahat Tauni[1,2] & Nida Ali[1]
[1]Luton and Dunstable University Hospital NHS Foundation Trust, Luton, UK; [2]University of Bedfordshire, Luton, UK.

Hypercalcaemia is one of the common cases seen in Endocrine clinics. We report another challenging case of hypercalcaemia. A 43 old Asian man was referred by GP initially in 2011 with asymptomatic hypercalcaemia of 2.87 mmol/L. His past medical history included chronic plaque psoriasis with arthropathy, hypertension, stage 3 CKD, Fatty liver with mild fibrotic change secondary to methotrexate and learning difficulties. Hypercalcamia was thought to be contributed by Dovonex

(Calcipotriene), Dovobet (Calcipotriol) and Bendroflumethiazide as calcium was nomal prior to starting Vitamin D analogues. These medications were changed and calcium levels subsequently settled to 2.62 mmol/L (PTH 1.4).
Calcium rose to 3.05 mmol/L in early 2013 and patient was symptomatic. Despite oral fluids at home, calcium further rose to 3.50 mmol/L with non suppressed PTH 3.1. 24 hour urinary Calcium 6.3 mmol. Ultrasound, SPECT MIBI and thyroid pertechnetate scan showed poorly tracer concentrated PTH adenoma. He had full neck exploration in April 2013, and 2 parathyroid glands (right inferior and left superior) were identified and removed. Biopsy revealed mild hyperplasia.
Postoperatively, calcium remained normal until February 2015 cca 2.67, proceeding to recurrent hypercalcaemia with 6 emergency admissions with vomiting, dehydration fro May 2015 to January 2016, requiring IV fluids and bisphosphonates. He was also diagnosed with severe Vitamin D deficiency (25 OH Vitamin D less than 18) and started on cholecalciferol 800 IU/day. He was also commenced on cinacalcet, but calcium and PTH levels continue to fluctuate.

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EP20

Adult presentation of hypophosphatasia due to a novel compound heterozygous Tissue Nonspecific Alkaline Phosphatase (ALPL) mutation

Catriona Farrell, Judith Strachan, Sripada Sankar, Catherine McWilliam, Faz Alipour, Paul Newey & Chris Schofield
Ninewells Hospital, Dundee, UK.

A previously well 27-year old female presented with atraumatic foot pain to the orthopaedic service and was identified to have a healing subacute metatarsal stress fracture in the right foot. In view of the unusual presentation, the patient was referred to the metabolic bone clinic for further evaluation.
On initial evaluation the patient reported no prior skeletal, joint or dental problems. However at the time of review she reported pain in her right thigh and clinical examination revealed a myopathic gait. Unexpectedly, plain x-rays revealed a stress fracture of right femoral shaft. Simultaneous biochemical analysis demonstrated undetectable serum alkaline phosphatase (ALP) activity consistent with a diagnosis of hypophosphatasia. Subsequent genetic analysis revealed a compound heterozygous *ALPL* mutation (p.Tyr101*;Ala176Thr). The patient required intra-medullary nailing of the right femoral fracture and subsequent physiotherapy. Future treatment options are limited but potential therapies include teriparatide or enzyme replacement with asfotase alfa.
Hypophosphatasia is a condition characterised by low ALP activity due to loss-of-function mutation of the *ALPL* gene, which encodes tissue non-specific ALP (TNSALP). Consequently inorganic pyrophosphate accumulates extracellularly and impairs skeletal mineralisation. It may be inherited in an autosomal dominant or recessive manner with wide ranging clinical expressivity.
Adult hypophosphatasia typically presents during middle age with loss of adult dentition, or with recurrent non-healing metatarsal fractures. The diagnosis may be made clinically on the basis of radiographic fractures coupled with low serum ALP. Genetic analysis of the *ALPL* gene can confirm the diagnosis. The treatment of adult hypophosphatasia is challenging. Teriparatide has been reported to stimulate osteoblast synthesis of TNSALP resulting in reduced pain and potential fracture healing, although benefits of such treatment appear increased if a wild type *ALPL* allele is present. Enzyme replacement therapy with asfotase alfa has been approved for paediatric onset hypophosphatasia but with limited evidence for adult use.

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EP21

Severe hypercalcaemia following Vitamin D replacement therapy in patient found to have co-existing sarcoidosis and primary hyperparathyroidism

Jodie Sabin, Jack Scannell, Jane Donald & Alison Evans
Department of Diabetes & Endocrinology, Cheltenham General Hospital, Cheltenham, UK.

Current guidance recommends replacing vitamin D in patients with mild primary hyperparathyroidism although there are reports of worsening hypercalcaemia in some patients. Vitamin D replacement has also been known to cause hypercalcaemia in patients with sarcoidosis. We present a case of a patient with co-existent sarcoidosis and primary hyperparathyroidism, who developed severe hypercalcaemia following treatment with high dose Vitamin D.
A 63 year old lady presented to hospital with symptomatic hypercalcaemia. Her admission calcium levels were 3.59 mmol/l with mild acute renal impairment (creatinine 132 umol/l, eGFR 37 ml/min). PTH level was 2.0.
Her past medical history included pulmonary hypertension secondary to chronic venous thromboembolism. Two months previously she was admitted for a fractured neck of femur and found to have Vitamin D levels $<$ 12.5 nmol/l. She was treated with high dose vitamin D replacement followed by maintenance therapy. Blood tests prior to this treatment had shown a Calcium level of 2.73 mmol/l, coincidental with a PTH of 10.6 pmol/l.
She was initially treated with IV fluids and IV pamidronate but despite this her calcium levels failed to decrease significantly. A CT scan showed mediastinal and abdominal lymphadenopathy, unchanged since a previous scan the year before. Subsequent review of her medical notes and previous investigations found that she had had a lymph node biopsy 6 months beforehand which had shown features of sarcoidosis, which her previous team had been unaware of.
Steroid treatment was commenced for sarcoid-associated hypercalcaemia and calcium levels returned to normal within 5 days of this. A parathyroid MIBI scan showed a likely parathyroid adenoma. There was biochemical evidence of primary hyperparathyroidism from 3 years before these recent clinical events suggesting she had co-existing primary hyperparathyroidism and sarcoidosis.
This case highlights the need to monitor calcium levels closely in patients with primary hyperparathyroidism or sarcoidosis who are receiving vitamin D replacement.

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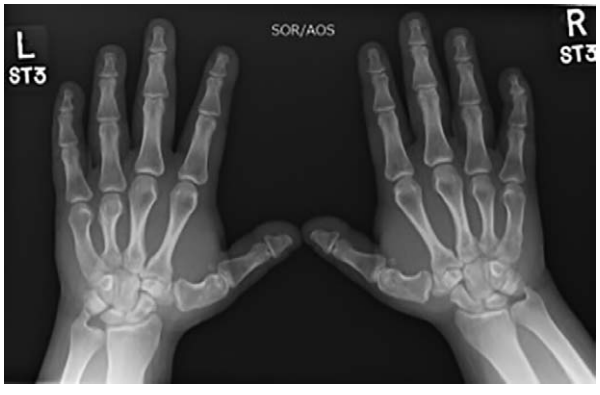
EP22

Albright hereditary osteodystrophy

Tobias Cox, Rajni Mahto, Umar Raja & Rakhi Kakad
Warwick Hospital, Warwickshire, UK.

Hypocalcaemia is a common presentation to the emergency department; patient's symptoms vary but typically report pins and needles and muscle cramps, due to neuromuscular irritability. Other important features include ECG changes (prolonged QTc) and seizures. The most common causes are hypoparathyroidism, vitamin D deficiency and chronic kidney disease.
A 25-year old male presented with symptomatic hypocalcaemia who was referred to us for follow up, after replacement.
On examination he was short of stature, a stocky build, obese for his height and clinically had shorter 4th metacarpals. He had 2 siblings on his father's side with similar body habitus. He had coexisting hypothyroidism, but was not on replacement as it was stopped aged 12.
Additionally he described a syncopal episode 6 months prior to presentation, with no features of epilepsy.
His serum calcium was 1.47 mmol/L with elevated PTH at 54 pmol/L and a phosphate of 1.78 mmol/L. He was also severely vitamin D deficient with a level of 19 nmol/l. His TSH was 10.3 mU/L suggesting subclinical hypothyroidism. A diagnosis of pseudo-hyperparathyroidism was suspected and X-rays of his hands, along with a CT head were arranged to assess his 4–5th metacarpal joints and to look for evidence of basal ganglia calcification. These investigations supported the diagnosis of Albright hereditary osteodystrophy. He was managed with calcitriol, a more active form of vitamin D, but unfortunately developed an urticarial rash. Therefore he was given alfacalcidol and sandocal; with the goal of therapy to maintain calcium levels, supress PTH to normal levels and avoid hypercalciuria. This case highlights the investigations and management of hypocalcaemia and the importance of considering more unusual causes, such as pseudo-hyperparathyroidism.



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EP23

Idiopathic Infantile Hypercalcaemia (IHH) caused by a missense mutation of 1,25-dihydroxyvitamin D_2 24-hydroxylase (*CYP24A1*)

Victoria Stokes[1], Caroline Gorvin[1], Bahram Jafar-Mohammadi[2], Fiona Ryan[3] & Rajesh Thakker[1]
[1]Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, UK; [2]Department of Clinical Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, UK; [3]Department of Paediatric Endocrinology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

Idiopathic infantile hypercalcaemia (IHH) is an autosomal recessive disorder typically presenting in the first few months of life with failure to thrive, vomiting, dehydration, and nephrocalcinosis with hypercalcaemia and low or undetectable parathyroid hormone (PTH) concentrations. IHH is caused by loss-of-function mutations of the cytochrome P450 family 24 subfamily A member 1 (*CYP24A1*) gene that encodes the 514 amino acid protein 1,25-dihydroxyvitamin D_3 24-hydroxylase which converts the active 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) to the inactive metabolite $1,24,25(OH)_3D_3$, thereby resulting in elevated $1,25(OH)_2D_3$ concentrations and hypercalcaemia. We report a case of IHH in a Caucasian female born to a non-consanguineous family. The proband was born by elective Caesarean section at 38 weeks gestation for placenta praevia and had poor feeding, lethargy, weight loss, jaundice and a baseline bradycardia shortly after birth. At 7 months old she was investigated for delayed developmental milestones and constipation and was found to have an elevated serum calcium of 3.91 mmol/l (normal range 2.12–2.62), normal phosphate of 1.27 mmol/l (normal range 0.80–1.45), elevated magnesium of 1.25 mmol/l (normal range 0.75–1.05), normal $25(OH)D_3$ of 38.0 μg/ml (normal range 7–50), elevated $1,25(OH)_2D_3$ of 127 pg/ml (normal range 20–50) and suppressed PTH concentration of <0.7 pmol/l (normal range 1.0–6.1). Other causes of hypercalcaemia including William's syndrome were excluded and she was diagnosed with IHH. She was placed on a strict low calcium and low vitamin D diet and this resulted in marked reductions in serum calcium concentrations (range $=2.54$–2.66 mmol/l) and a clinical improvement. DNA sequence analysis of the 12 coding exons and intron-exon boundaries of *CYP24A1,* using leukocyte DNA, revealed her to be homozygous for a transition of a T to C at position 1620 within exon 9, that predicted a missense Leu409Ser mutation that has been reported to severely impair *CYP24A1* function *in vitro* and cause IHH.

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EP24

An unusual case of hypercalcaemia

Grace Pink[1], Ramanand Athavale[2], Shatrughan Sah[2] & Rajni Mahto[1]
[1]Warwick Hospital, South Warwickshire NHS Foundation Trust, Warwickshire, UK; [2]University Hospital Coventry and Warwickshire, West Midlands, UK.

We present the case of a 19 year old female who presented to A&E with a three week history of nausea, vomiting and constipation. She was noted to have hypercalcaemia at 4.11 mmol/l. There was no family history of note and prior to this illness she had been fit and well with no regular medications. Investigations revealed a suppressed PTH of <0.6 pmol/L. U&E, vitamin D, TSH, serum ACE and cortisol were within normal range.

Examination revealed a suprapubic mass thought to be a distended bladder. Further investigation with USS and CT scans abdomen and pelvis revealed a 17 cm left ovarian mass. Her CA125 was markedly raised at 320 ku/l. She was transferred to the care of the gynaecology team who performed a laparotomy and left salpingo-opherectomy. Histology confirmed an ovarian small cell carcinoma of hypercalcaemic type (OSCCHT), FIGO stage 2b, later on PET scanning found to be stage 3b-4. Genetics confirmed a SMARCA4 gene inactivating mutation.

This case represents a rare presentation of hypercalcaemia in a young woman. Hypercalcaemia is an uncommon occurrence in gynaecological malignancies, occurring in around 5% of ovarian cancers. It is more common within the rarer ovarian cancer subtypes and indeed present in 66% of OSCCHT cases. This rare and aggressive tumour type affects young females, and in half of cases has extra-ovarian spread at diagnosis. First described in 1982, it has until recently has evaded cytogenetic or molecular classification. In 2014 the pathology 'enigma' was decoded by Foulkes *et al*. who identified deletion mutations in the chromatin-remodelling gene SMARCA4 (encoding BRG1). This gene has been linked to various other human cancer types (including breast, prostate, lung, pancreas and colon) and is mutated in most rhabdoid tumours.

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EP25

Association of neurofibromatosis type 1 with primary hyperparathyroidism: report of a case

Emily Austin & Andrew Bates
Heart of England Foundation Trust, Birmingham, UK.

Introduction

Neurofibromatosis Type 1 (NF1) is an autosomal dominant inherited disorder, which increases the risk of developing both benign and malignant tumours. A Swedish study conducted by Zöller et al in 1997, suggested that up to 25% of these tumours are neuroendocrine in origin, of which phaeochromocytomas were the commonest with a prevalence of 0.1–6%. The association between NF1 and primary hyperparathyroidism is described in the literature but clinically rare.

Case Report

This case is a 42-year-old gentleman known to have NF1 with disease manifestations including multiple cutaneous neurofibromas and café au lait spots. He was referred due to hypercalcaemia after presenting to his General Practitioner with abdominal discomfort.

On examination, his pulse was regular at 82/minute, and his blood pressure was 148/78-mmHg.

The diagnosis of primary hyperparathyroidism was biochemically confirmed, with corrected calcium of 2.82 mmol/L (normal range 2.2–2.6 mmol/L) and PTH 110 pg/ml (normal range 15–65pg/ml). There was no clinical suggestion of phaeochromocytoma and 24-hour urinary metanephrines were normal.

Imaging studies demonstrated a possible lesion behind the middle of the left lobe of the thyroid, which was most likely an adenoma.

The patient is now awaiting a parathyroidectomy.

Conclusion

A literature review has identified 17 other cases of hyperparathyroidism associated with Neurofibromatosis to date. The vast majority of these cases were due to a parathyroid adenoma in patients of a mean age of 45 years.

Several hypotheses have been suggested to explain the link between these conditions, one of which is that NF1 in association with primary hyperparathyroidism may be a variant of MEN2.

Given this association, and considering that patients with NF1 present at a relatively young age, it is appropriate to screen these patients for primary hyperparathyroidism, as it is likely that the majority would be candidates for parathyroidectomy.

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EP26

Osteocalcin suppression may be a useful marker of steroid exposure

Yvette Ang[1], Adam Leckey[1], Sirazum Choudhury[1], Alan Courtney[2], Tricia Tan[1] & Karim Meeran[1]
[1]Imperial College London, London, Greater London, UK; [2]Imperial College Healthcare NHS Trust, London, Greater London, UK.

Mrs. M is a 66-year-old female who has had secondary adrenal insufficiency for many years following the withdrawal of prednisolone therapy for pulmonary eosinophilia. Synacthen tests revealed complete adrenal suppression when the dose of prednisolone was weaned to 5 mg in previous years. The dose was further reduced by switching to hydrocortisone three times daily, following a 10 mg-5 mg-5 mg regimen. Occasionally, a flare of eosinophilia required restarting high-dose prednisolone, but she had become accustomed to cutting the dose as needed, and then switching to hydrocortisone. She has since developed osteoporosis.

She wanted to compare the effects of prednisolone 3 mg daily, which she had been weaned to during her most recent review, and the hydrocortisone regimen. She experienced no difference in symptoms of withdrawal between the two treatments. Carboxylated osteocalcin (Gla-OC) is an osteoblast-specific product and a marker of bone formation. Gla-OC concentrations were measured at various

Table 1

	Gla-OC (ng/ml)	
Time after morning dose (hours)	Prednisolone	Hydrocortisone
2	9.0	7.8
4	7.2	7.5
6	8.4	7.8
8	8.4	7.8
9		7.3
10		9.3

time points during the day on each treatment, accounting for the diurnal variation. There was no significant difference between the mean Gla-OC concentration measured 2, 4, 6 and 8 hours after the morning dose of prednisolone (8.25 ng/ml) and hydrocortisone (7.73 ng/ml). Gla-OC was also measured 9 and 10 hours after the morning dose of hydrocortisone (see table 1).
Suppression of bone formation may be reflected by Gla-OC levels, and such levels have the potential to be used to monitor bone formation in patients treated with glucocorticoids, guiding the choice of medication. Long-term follow-up of the patient's bone mineral density would be necessary to investigate the correlation between Gla-OC and osteoporosis.

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EP27

Maternal hypercalcaemia due to CYP24A1 loss of function mutations

Thomas Upton[1], Chris Florkowski[2], Ian Phillips[2] & Penny Hunt[1]
[1]Department of Endocrinology, Canterbury District Health Board, Christchurch, New Zealand; [2]Canterbury Health Laboratories, Christchurch, New Zealand.

Background
Significant changes in calcium metabolism occur during normal pregnancy to meet the needs of the growing fetus. These include a rise in 1,25-dihydroxyvitamin D (1,25-$(OH)D_2$ and consequent suppression of parathyroid hormone (PTH). In spite of this, maternal hypercalcaemia is very uncommon and should prompt further investigation.
Clinical case
A 24-year-old primigravida woman was referred for assessment of maternal hypercalcaemia. She was well with no history of nephrolithiasis or nephrocalcinosis. Of note, monthly cholecalciferol supplementation had been commenced just prior to the pregnancy. At 13 weeks' gestation corrected calcium was 2.9 mmol/L (2.2–2.6), PTH 0.7 pmol/L (1.6–7.0), and urine calcium:creatinine 2.09 mole ratio (0.06–0.45). 25-hydroxyvitamin D was 116 nmol/L (50–150) and 1,25-$(OH)D_2$ was significantly elevated at 380 pmol/L (65–175). Vitamin D supplementation was stopped. Hypercalcaemia persisted throughout the remainder of the pregnancy with minimal symptoms and a healthy, normocalcaemic infant was born at 38 weeks' gestation. Breast feeding was not established and maternal plasma calcium returned to the normal range at 10 days post-partum. However, hypercalciuria persisted and renal tract ultrasound showed unilateral nephrolithiasis. Analysis of the CYP24A1 gene identified a compound heterozygote state with E143Del and K351Nfs*21 mutations. Family screening and genetic counselling is now underway.
Conclusion
Hypercalcaemia in pregnancy is rare and the differential diagnosis should include an underlying disorder of 1,25-$(OH)D_2$ metabolism. Compound heterozygote or homozygous mutations in CYP24A1 may result in hypercalcaemia and hypercalciuria, particularly in states such as pregnancy, and supplemental vitamin D should be avoided. At other times, with this condition calcium may be normal although hypercalcuria often persists. Monitoring these patients for complications including nephrocalcinosis and nephrolithiasis is recommended.

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EP28

Lithium associated Hyperparathyroidism (LAH): Cinacalcet is an effective alternative treatment option

Satya V Sagi[1], Neelima Jampana[1], Jeyanthy Rajkanna[2] & Samson Oyibo[2]
[1]Department of Old Age Psychiatry, Gloucester Centre, Peterborough, UK; [2]Department of Endocrinology, Peterborough City Hospital, Peterborough, UK.

Introduction
Lithium associated hyperparathyroidism (LAH) resulting in hypercalcaemia is a known problem. Treatment options are limited in frail elderly patients with multiple co-morbidities, in whom parathyroid surgery could be dangerous. Cinacalcet, a calcimimetic agent can be an alternative option. We report a case of an elderly lady on Lithium, who was initiated on Cinacalcet for hypercalcaemia and has had to continue the Lithium for her bipolar affective disorder.
Case
A 78 year old lady was admitted with severe hypercalcaemia (serum calcium - 3.03 mmol/L, serum PTH – 10.4 pmol/L). She has bipolar affective disorder, other medical co-morbidities and has been on long term Lithium treatment. Several years ago she had severe LAH treated with three-and-a-half-gland parathyroidectomy and has had normal serum calcium levels ever since. During this admission her Lithium was stopped and hypercalcaemia responded to intravenous fluids and Bisphosphanates. During outpatient monitoring her serum calcium started rising (serum calcium – 2.81 mmol/L) over time despite stopping Lithium. After considering risks and benefits of completion of parathyroidectomy, she was commenced on Cinacalcet 30 mg once daily. Her calcium levels returned and settle back to the normal range (average serum calcium – 2.32 mol/L). Unfortunately her bipolar affective disorder had relapsed since stopping lithium therapy. With the consent of the patient and her family, we restarted lithium while continuing her Cinacalcet. Her calcium levels were monitored closely. After 10 months of treatment with the combination of Cinacalcet and Lithium, her serum calcium levels remain normal (average calcium – 2.37 mmol/L, serum PTH – 5.9 pmol/L) and her bipolar affective disorder remains in remission.
Conclusion
Treating LAH can be challenging in elderly patients with complex psychiatric and multiple medical co-morbidities. Cinacalcet appears to be an effective alternative treatment for such patients, however further studies are needed for its regular use.

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EP29

Severe hypercalcaemia in sarcoidosis: Is Vitamin D replacement safe?

Ahmed El-Laboudi, Rozana Ramli & Emma Hatfield
Imperial College Healthcare NHS Trust, London, UK.

Objective
To highlight the issue of vitamin D supplementation in patients with sarcoidosis.
Case report
We report the case of a 66-year-old lady, who presented with one week history of general weakness, drowsiness, nausea and confusion. 6-weeks prior to presentation, she underwent right-sided intra-medullary nail insertion for a traumatic femur fracture, whilst abroad. Her past medical history includes stage IV pulmonary sarcoidosis, pulmonary hypertension and vitamin D deficiency. Immediately post-operatively, she was started on calcium and vitamin D supplement including calcitriol (0.25 μg daily) and cholecalciferol (60,000 IU weekly).
On examination, she was clinically dehydrated with a blood pressure of 165/52 and sinus tachycardia of 110 beats per minute. She had bibasal crepitations on chest auscultation. Examination of neurological and GI systems was unremarkable.
Initial investigations revealed adjusted calcium of 5.35 mmol/L, Phosphate 1.33 mmol/L, creatinine 342 μmol/L, Urea 17.2 mmol/L, PTH 1.2 pmol/L. ECG showed sinus tachycardia with a cQT of 480 msec. Four months prior to presentation, 25 hydroxy-vitamin D (25(OH)D) level was 24.6 nmol/L.
Her hypercalcaemia was felt to be secondary due to Vitamin D toxicity on the background of sarcoidosis. She was admitted to HDU, where she was treated with aggressive fluid resuscitation, increased dose of glucocorticoids, Calcitonin and diuretics, with subsequent clinical and biochemical improvement. The result of 25(OH)D level came back raised at 390 nmol/L.
Discussion
Stimulation of 1 α-hydroxylase enzyme in patients with sarcoidosis can result in adequate 1,25(OH)2D3 levels with insufficient 25(OH)D. Therefore, pharmacological vitamin D supplementation in patients diagnosed with vitamin D deficiency, based on 25(OH)D measurement, can increase the risk of hypercalcaemia secondary to vitamin D toxicity.
This case highlights the importance of practising caution when prescribing vitamin D particularly in patients with a background of granulomatous diseases. Measurement of active form of vitamin D in those patients should be considered.

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EP30

Hypercalcaemia induced psychosis due to primary hyperparathyroidism in pregnancy

Alice Thomas, Kirun Gunganah, Girish Rayanagoudar, Eliot Williams, Philippa Hanson, Williams Drake, Daniel Berney, Laila Parvanta, Simon Kirwin & Karl Metcalfe
Barts Health NHS Trust, London, UK.

Background
Primary hyperparathyroidism is the third most common endocrine condition in pregnancy after thyroid disease and diabetes. Untreated hypercalcaemia due to

primary hyperparathyroidism increases the risk of miscarriage, intrauterine death and preterm labour. Pharmacological and surgical limitations in pregnancy often make diagnosing and managing this condition challenging. We report a complex case of hypercalcaemia-induced -psychosis due to primary hyperparathyroidism in pregnancy.

Case

A 32-year-old pregnant lady presented at 8 weeks gestation with nausea and vomiting. She was initially diagnosed with hyperemesis gravidarum and was treated with intravenous fluids. She was incidentally found to have an elevated calcium level of 3.12 mmol/L. Primary hyperparathyroidism was confirmed biochemically (Calcium 3.12 mmo/L, Phosphate 0.6 mmol/L, PTH post Vitamin D replacement 14.6 mmo/L (1.6 to 6.9), Urine calcium excretion index $>$ 0.01). An US parathyroid showed a 3.7 cm parathyroid adenoma inferior to the left lobe of the thyroid and foetal US scan confirmed a viable pregnancy.

Her hypercalcaemia remained refractory to aggressive fluid replacement. A trial of Cinacalcet was successful in improving her calcium levels but was discontinued due to adverse reactions including worsening nausea and generalised myalgia. Throughout the first trimester, her calcium level remained above 3.0 mmol/L.

At 13 weeks gestation, she became anxious, confused and developed a thought block. Our psychiatry team diagnosed her with hypercalcaemia-induced-psychosis. She was started on Olanzapine with subsequent improvement in her symptoms. Once in the second trimester, at 18 weeks gestation, she had a successful and uneventful parathyroidectomy. Post-operatively, her calcium level normalised (2.43 mmol/L) and her mental health improved with resolution of thought disorder and return to a euthymic mood. Her Olanzapine dose was halved and is being weaned off.

Conclusion

This is a case of hypercalcaemia-induced-psychosis due to primary hyperparathyroidism in pregnancy successfully treated with parathyroidectomy in the second trimester. Our patient is currently in her third trimester, remains normocalcaemic and has satisfactory follow-up foetal growth scans.

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EP31

Hypercalcaemia due to Pelvic Sarcoidosis

Julia Burkert, Jane Evans & Nicola Neary
St George's University Hospitals NHS Foundations Trust, London, UK.

A 51-year-old lady presented as an emergency with disabling, recurrent hypercalcaemia in July and August, 2015 with a peak corrected calcium of 3.94 mmol/l (normal range 2.2–2.6). She had been diagnosed with a stage 1A endometrial cancer, treated with hysterectomy and bilateral salpingo-oophorectomy in April 2014. Significant pelvic and left groin lymphadenopathy was noted, and was found to be enlarging on surveillance CT of July 2015. She was also found to have a left kidney lesion, biopsy of which in February 2015 showed a low grade neoplasm consistent with a renal oncocytoma.

The initial concern was that her hypercalcaemia was due to malignancy. PTH was appropriately suppressed and a myeloma screen was negative. However, PTH-rp was undetectable and careful review of the histology from the hysterectomy of 2014 revealed abundant non-caseating granulomata in nine lymph nodes resected, but without evidence of malignancy. There was no evidence of pulmonary sarcoidosis on the CT of July 2015. At MDT, it was agreed that there was sufficient evidence to make a diagnosis of pelvic sarcoidosis. This diagnosis was later supported by elevated pre-treatment serum ACE of 113U/l (16-85) and 1,25 OH(2) vitamin D of 253 pmol/l (43–143).

The patient was started on Prednisolone 35 mg daily (0.5 mg/kg). Six weeks later, she was back at work. The serum calcium had fallen into the normal range and a CT scan showed reduction in the size of the pelvic and groin lymph nodes. Over the next five months, Prednisolone was successfully withdrawn, without further elevation of serum calcium.

In the literature, undiagnosed sarcoidosis has been reported to delay the correct staging, prognosis and management of a newly diagnosed cancer. This case illustrates the importance of considering extra-pulmonary sarcoidosis as a cause of hypercalcaemia, especially in the context of concurrent malignancy.

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EP32

Normocalcemic tetany after parathyroidectomy for hyperparathyroidism

Umaira Aziz, Ritwika Mallik, Swarupini Ponnampalam & Ali Rathore
Southend University Hospital, Westcliff on Sea, Essex, UK.

Introduction

Hypocalcaemia is a frequent complication after thyroid and parathyroid surgery. We report a case of tetany occurred in a patient with normal serum levels of calcium, magnesium and phosphate after parathyroidectomy for hyperparathyroidism.

Case History

55 year old Caucasian male was referred by general physician with three month history of fatigue, loss of appetite, intermittent constipation and abdominal pain. Systemic examination unremarkable. His investigations were keeping with primary hyperparathyroidism with adjusted ca raised at 3.3 mmol/l. He also had vitamin D deficiency which was treated with loading dose of oral cholecalciferol. A right inferior parathyroid adenoma was identified on concordant imaging and isotope scan. He underwent parathyroidectomy in the local hospital. He presented to accident emergency twice within days of surgery with severe spasms of the hands and legs. On clinical examination, trousseau sign was positive.

Investigations and results

His calcium levels were normal at 2.3 mmol/l. Magnesium and phosphate levels were also normal at 0.82 mmol/l and 0.96 mmol/l respectively.

Conclusion

Our patient presented with usual symptoms and signs of hypocalcemia but normal serum levels of calcium and magnesium. We propose that our case represents normocalcemic tetany, which has been rarely reported in post-parathyroidectomy patients. The likely underlying mechanism appears to be neuronal excitability due to sudden reduction in serum calcium levels after long standing marked hypercalcemia.

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EP33

Can parathyroid carcinoma be predicted preoperatively?

Adnan Agha, Kerrie Anne Aldridge & Sofia Salahuddin
Queen Elizabeth Hospital, Birmingham, UK.

Introduction

Parathyroid carcinoma (PTHCa) is a rare malignant tumour which, although associated with higher calcium and parathyroid hormone (PTH) levels at presentation and younger age group, can only be diagnosed on histological basis. Recent studies have shown a logarithmic formula (using Calcium, PTH and age) can predict PTHCa if it scores more than 5%, with a sensitivity and specificity of 100% and 30% respectively. We describe a case where application of similar formula helped predict parathyroid carcinoma preoperatively.

Case

A 43 years old man presented with new onset worsening lethargy, thirst and constipation over last 2 weeks. History was not suggestive of any previous medical problems or exogenous supplements. On examination, a soft mass was palpable in the left anterior triangle of the neck with no other pertinent clinical findings. His initial investigations showed corrected calcium level 4.74 mmol/L. PTH 35.2 pmol/L, Urea 9.5 mmol/L and Creatinine 206 umol/L. He was treated with aggressive intravenous hydration and zolendronate which improved his calcium levels to 2.79 mmol/L with normalization of renal function. His neck ultrasound showed 4.2$\times$6.7 cm cystic parathyroid mass and he was referred for surgical removal.

Discussion

Early detection of PTHCa and differentiating it from parathyroid adenoma affects the surgical technique, waiting time as well as long-term patient outcome and applying the non-invasive formula by Karakas et al. can help aid in the preoperative diagnosis of PTHCa.

Reference

Karakas E, Müller HH, Lyadov VK, et al. Development of a Formula to Predict Parathyroid Carcinoma in Patients with Primary Hyperparathyroidism. World J Surg; 2012 36:2605–11.

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EP34

A pain in the neck (or is it in the neck?)

Rodica Chelmenciuc & Raj Tanday
King George Hospital, London, UK.

We present the case of a 50 year old with primary hyperparathyroidism and 2 unsuccessful surgeries. Initially presenting in 2012 we question whether further surgical attempts to cure her should be made.
She was found to have hypercalcaemia since 2009 with levels 2.60–2.80 mmol/l with PTH 21.9–28.9 pmol/l, vitamin D 9 nmol/l, ACE 37.8 iu/L, normal protein electrophoresis, creatinine 84 umol/l, phosphate 1.06 mmol/l, TSH 0.86 mU/l, Hb 142 g/l, and CCR of 0.027 confirming primary hyperparathyroidism. USS renal tract shows no calculi or calcinosis. DEXA showed osteopenia with T score –1.0 at the femoral neck. She was given vitamin D and felt should receive surgical treatment given her young age.
Imaging with SESTAMIBI showed increased uptake in the anterior mediastinum and right midpole but MRI demonstrated no obvious lesion. She had neck exploration in summer 2014 finding no convincing adenoma and histologically normal parathyroid tissue. She remained hypercalcaemic and repeat imaging in December 2014 showed concordance at the right midpole but subsequent exploration was difficult due to scarring. Histology showed benign reactive lymph nodes, fat and no parathyroid tissue.
She was admitted with a DVT in September 2015 and found to have worsening hypercalcamia and was symptomatic on the ward with levels over 3 mmol/l. She was given iv hydration and bisphosphonate. Other medical history includes 2 previous DVTs and hypertension. She is currently taking candesartan, atenolol, lercanidipine and rivoroxaban. There is no family history of hypercalcaemia or thromboembolism. She is Pakistani, tee total and a nonsmoker.
She is currently well with no symptoms and serum calcium of around 2.60 mmol/l. She is aware that the condition will cause her bone density to decline and she risks symptomatic hypercalcaemia again without treatment but not keen for surgery. How shall we proceed?

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EP35

An interesting case of 'skyrocketing hypercalcaemia'

Irfan Khan[1], Jawad Bashir[1] & Fong Chau[1]
[1]Southmead Hospital, Bristol, UK; [2]Singleton Hospital, Swansea, UK.

Disorders of calcium metabolism are common in Sarcoidosis. The frequency of hypercalciuria and hypercalcaemia has been reported as 30–50% and 10–20% respectively. The underlying mechanism is enhanced PTH independent extra-renal production of 1,25-Dihydroxy Vitamin D (Calcitriol) which increase absorption of Calcium from the gut causing hypercalcaemia.
A 79 year old lady was admitted with fever, cough and night sweats and was treated for pneumonia. Initial investigations showed raised WBC, acute kidney injury (on background of CKD) and anaemia. As a part of geriatric assessment, the following results were obtained: severely low 25-OH vitamin D level (14 nmol/L), normal Calcium (2.42 mmol/L) and normal PTH (2.7 pmol/L). She received only one dose of 25,000IU Vitamin D (as part of weekly replacement regime). Two days later, Calcium was 2.69 and AKI slightly worsened. Combination of AKI, anaemia and hypercalcaemia triggered investigations for multiple myeloma which came back negative. Over the next few days, there was further deterioration in the AKI and the repeat Calcium level went sharply up to 4.0mmol/L despite fluid resuscitation. Digging into the past medical history, this lady had a previous history of active sarcoidosis 43 years ago requiring high dose steroids for a few months.
Further investigations showed elevated serum ACE level (88, Normal 8–50). HRCT did not show any changes of pulmonary sarcoidosis or hilar lymphadenopathy. Repeat 25-OH Vitamin D was 26, PTH was suppressed (1.3) and 1,25 Dihydroxy Vitamin D level is still awaited. She was empirically treated with high dose Prednisolone and the Calcium level came down to normal range over the next 2 weeks.
This is an interesting case of acute severe hypercalcaemia where the cause is not entirely clear. We think that the likely cause of severe hypercalcaemia in this lady is extra-renal activation (1-alpha hydroxylation) of exogenous 25-OH vitamin D3 secondary to sarcoidosis, though we do not have convincing evidence for relapse of acute sarcoidosis.

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EP36

Periodic episodes of weakness over 7 years

Jolyon Dales, Pradeep Vasudevan & Marie-France Kong
University Hospitals of Leicester, Leicester, UK.

A 24-year-old traffic warden was initially referred to the neurology department with episodes of "funny turns" over the past 7 years. Without warning she would become dizzy and lightheaded with blurring of vision and weak legs. These symptoms would resolve after ingesting something sweet but the relief of her symptoms was not immediate. The episodes could happen at any time of the day but never first thing in the morning and could happen several times a week. She reported that sometimes she gets spasms in her neck and arms, flopping of her head as well as weakness of her legs. She had gained 10 kg over the past year. There was a family history of multiple sclerosis. A MRI of her spine was normal. The neurologist felt that her symptoms were due to hypoglycaemia and she was referred for further investigations. Fasting blood sugars were normal and blood sugars during an attack were also normal. Urea and electrolytes, thyroid function test and creatine kinase were normal. On a subsequent clinic visit she was accompanied by her father who mentioned that the patient's mother was investigated for similar symptoms when she was 20 years old and several members of her family were also affected with similar symptoms. It transpired that her mother was diagnosed with hyperkalaemic periodic paralysis (PP). The patient was referred to a geneticist. The result of her genetic testing is awaited.
Hyperkalaemic PP is a rare disorder, with an estimated prevalence of 1:200,000. It follows autosomal dominant inheritance with nearly complete penetrance. The cause of hyperkalaemic PP is a change in a gene that regulates the production of a protein (SCN4A) in the sodium channel of skeletal muscle. Dietary modifications to prevent attacks include avoiding foods rich in potassium and avoiding carbohydrate loading.

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EP37

Spurious hypoglycaemia caused by an IgM paraprotein

Annie Armston[1], Nadia Zarif[1] & Daryl Meeking[2]
[1]UHSNFT, Hampshire, UK; [2]QAH, Hampshire, UK.

Mrs IP is a 79 year old lady with a past medical history of spleenic marginal zone lymphoma, diagnosed in 2007 and treated with chemotherapy. She has suffered two relapses but despite her diagnosis had remained generally quite fit and healthy until the recent issues. An IgM paraprotein was identified in the patient's serum an December 2014.
In April 2015 Mrs IP presented to her GP complaining of cramping symptoms overnight, especially marked in her hands, weight loss, fatigue, poor appetite with night sweats on and off over the past few months. Blood tests revealed an elevated ALP and a random glucose of 1.5 mmol/L. At this point she had an urgent referral to the Endocrine team where similar results for the plasma glucose were obtained, HbA1c was 33 mmol/L with a lymphocytosis. On examination there were no lumps anywhere and radiologically there was no sign of relapse. LDH was 563 U/L, ESR just above normal at 37 mm/h, cortisol 288 nmol/L, IGF-1 80 ug/L, insulin 32.1 U/L, C-peptide 1433 pmol/L (the latter two were non-fasting samples) and magnesium 0.84 mmol/L. Importantly there was a failure to demonstrate Whipple's triad as the patient was asymptomatic at the time of the documented hypoglycaemia. Glucose, measured on the Radiometer ABL 800 Flex analyser, was 7.0 mmol/L in comparison with 0.6 mmol/L obtained by the hexokinase method on the Beckman Coulter AU 8500. Examination of the blank and reaction OD in the glucose measuring cuvette of the Beckman-Coulter AU revealed interference in the blank measurement typical of that observed with a paraproteinaemia.

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EP38

Hypokalaemic periodic paralysis

Vikram Aarella[1], Anjan Lenkalapally[1], Ramya Parasa[1], Mahesh Cheryala[2] & Bhavani Merugu[3]
[1]Nottingham University Hospitals, Nottingham, UK; [2]Royal Derby Hospital, Derby, UK; [3]Sherwood Forest Hospitals, Mansfield, UK.

Introduction
Hypokalaemic periodic paralysis is a medical emergency when patients present with acute onset paraparesis usually noticed in the mornings secondary to low

serum potassium levels with a prevalence of 1 in100,000. The symptoms resolve promptly with correction of potassium. The patient experiences motor symptoms while the sensation is preserved and can be differentiated from acute inflammatory demyelinating polyneuropathy with preserved ocular, bulbar or respiratory involvement.

Case report

A 23 yr old man presented with generalised weakness of few hours duration. He woke up in the morning to find that he was unable to move his arms and legs. There was no respiratory distress. He experienced diarrhoea about twice a day for 2 days which was about 3 days prior to his presentation. Neurological examination revealed reduced power 2/5 in all the limbs with hypotonia, hyporeflexia in all the joints and down going plantars. There was no sensory deficit. The respiratory rate was 16/m and BP 136/75.

Bloods showed low potassium of 2.0 with normal sodium and other electrolytes. Blood gas showed an acidotic picture with a pH of 7.28 and HCO3 of 19. ECG showed sinus tachycardia of 105/m.

A spirometry could not be performed. The symptoms improved following IV administration of KCL.

Discussion

The mechanism is due to activation of Na/K/ATPase pump leading to influx of potassium into the cells thus causing reduced serum potassium levels. Androgens activate the pump too, hence the condition is seen more commonly in men than women.

ECG changes in HPP include the changes usually seen in hypokalaemia which are prolonged PR interval, T wave flattening or inversion with ST depression, appearance of U waves and QT prolongation.

Treatment includes potassium supplemation intravenously not faster than 10 mmol/hr to avoid rebound hyperkalaemia. Prompt treatment is mandatory as severe dyselectrolytaemia can cause asystole and cardiac arrest. Patients should be warned to avoid trigger factors and maintain adequate hydration.

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EP39

A young person with recurrent severe hypokalaemia - familial, iatrogenic or just unknown?

Muhammad Shafqat, Navya Basavaraju, Srinivasa Rangan, Prashant Singh & Probal Moulik
Department of Endocrinology, Royal Shrewsbury Hospital, Shrewsbury, Shropshire, UK.

A 26-year-old female presented with 5-year history of episodic muscle weakness, abdominal cramps and facial paresthesia. She had 2 hospital admissions elsewhere within 6months with severe hypokalaemia (1.9 mmol/L). She was started on Lamotrigine for epilepsy 7 years ago and changed to Levetiracetam in October 2010 following further seizures. She is now seizure-free for over 5 years. Her potassium levels before and after Levetiracetam are shown in Table 1.

Table 1

Dates	Potassium levels (mmol/L)
18/04/2008	3.9
04/10/2010	4.3
30/10/2010	3.5
30/07/2011	2.8

Table 2

Serum	Result
Sodium	135 mmol/L (133–146)
Potassium	2.8 mmol/L (3.5–5.3)
Chloride	91 mmol/L (95–108)
Bicarbonate	38 mmol/L (22–30)
Magnesium	0.76 mmol/L (0.70–1.0)
Aldosterone	130 pmol/L
Renin	238 mU/L (9.8–33.7)
Aldosterone/renin ratio	0.5 pmol/mU (0–70)
Urine Analysis	
Sodium	170 mmol/L
Potassium	82 mmol/L
Chloride	21 mmol/L
Diuretic & laxative screen	Negative

She had an uneventful childhood. She had no osmotic or urinary symptoms, denied diuretic, laxative, excessive alcohol/liquorice ingestion. No relevant family history. Her body mass index is 22.3, blood pressure 103/55mmHg. Physical examination was unremarkable. Biochemical evaluation is in Table 2: Genetic screen results are awaited.

In this case with normotensive hypokalemic alkalosis, differential diagnoses are Bartter syndrome (negative family history, normal aldosterone), Gitelman syndrome (no family history, normal magnesium), diuretic use (negative urine screen), laxative abuse (history), normotensive primary hyperaldosteronism (normal aldosterone). Given the sequence of results, most likely cause of severe hypokalaemia is Levetiracetam. She declined temporary withdrawal of Levetiracetam due to risk of seizure recurrence affecting driving and job. She remains on spironolactone and potassium supplements.

Our literature search yielded only two case-reports of Levetiracetam-induced hypokalaemia involving 3 patients all of whom had additional hypomagnesaemia. To our knowledge, this is the only report of Levetiracetam-induced severe life-threatening isolated hypokalaemia. Levitracetam is increasingly used for epilepsy and further studies on the prevalence of life threatening electrolyte imbalance are required to guide biochemical surveillance.

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EP40

Insulinoma misdiagnosed as alcohol induced hypoglycaemia

Khaled Tofeec, Michelle Howarth & Prasanna Rao-Balakrishna
Central Manchester Foundation Trust, Manchester, UK.

A 48 years old male presented with an acute episode of dizziness, weakness, diaphoresis, palpitations, and shakiness. Hypoglycaemia was confirmed with a CBG of 1.6 mmol/L. His symptoms resolved on treatment with Hypostop gel and 10% dextrose. He had an otherwise unremarkable physical examination. In view of his history of consumption of a bottle of vodka daily a diagnosis of alcohol induced hypoglycaemia was made on discharge. A year later he was found being agitated and aggressive in a shopping centre requiring restraint by police. This was followed by collapse with a CBG of 0.6 mmol/L. He reported having had similar symptoms, of lesser severity, for approximately 2-yr duration, which continued despite his cutting down drinking to 1 pint beer weekly. Whipple's triad was positive. Endogenous hyperinsulinemic hypoglycaemia was suspected. Insulin level 55 pmol/L (reference range 12–150),C-peptide level 850 pmol/L (reference range 350–1800), Betahydroxybutyrate $<$ 100 umol/L, VBG 2.0 mmol/L; insulin antibodies and sulphonylureas screen were negative. Diazoxide and continuous dextrose infusion were initiated as he had recurrent hypoglycaemic episodes with seizures. Ultrasound showed fatty liver. CT abdomen revealed left adrenal incidentaloma which proved non-functional. MRI pancreas and Octreotide scan were normal. Endoscopic ultrasound suggested 11X13 mm hypo-echoic mass in the pancreatic head which could be an insulinoma or an inflammatory lesion. So as to obtain a more definitive evidence of insulinoma an intra-arterial calcium stimulation test was performed which revealed positive rises in the hepatic vein insulin when gastroduodenal and superior mesenteric arteries (supplying the head of pancreas) were injected. Although a Redo-endoscopic ultrasound with FNA was non-diagnostic; a repeat MRI pancreas revealed a 10 mm lesion in the uncinate process. Enucleation of the tumour with occlusion of small vascular feeding branches was successful. The frozen section sample confirmed well differentiation neuroendocrine tumour. The patient was discharged in good health with safe glucose levels.

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EP41

A rare case of Diabetic ketoacidosis (DKA) in a patient with genetically confirmed maturity onset diabetes of young (MODY)

Hannah Mcquade, Sajjad Ahmad & Stanaway Stephen
Wrexham Maelor Hospital, Wrexham, North Wales, UK.

Maturity Onset Diabetes of the Young (MODY) accounts for upto 2% of all patients with diabetes. Hepatocyte Nuclear Factor 1 alpha (HNF1-A) MODY is the most common subtype accounting for 30–70% of all MODY cases. Typically, it presents in young adults below the age of 45, frequently $<$ 25 with autosomal

dominant family history of diabetes, absence of autoimmune markers and insulin resistance and c-peptide positivity.
DKA is a rare complication of MODY particularly in situations of non-compliance. We describe a case of DKA in a genetically confirmed HNF1-A MODY patient presented to our hospital.
A 26-year-old female was admitted with severe vomiting. She had a background history of HNF1- alpha MODY diagnosed at the age of 15 when she was found to have hyperglycaemia during pregnancy. She was on Gliclazide 40mg daily but stopped taking it about a year ago. Her pH was 6.96, blood glucose of 31.4 mmol/L and blood Ketones of 5.8 mmol/L. This was consistent with DKA which was successfully treated. There was no evidence of sepsis. Her HbA1c was high at 101mmol/mol suggesting poor glycaemic control. She had uneventful recovery and was discharged home on Gliclazide with appropriate follow up arranged.
The presence of DKA was previously considered an exclusion criterion for MODY according to the International Society for Paediatrics and Adolescent Diabetes (IPSAD) 2009 guidelines. It is presumed that patients with MODY do not develop DKA due to the presence of residual insulin production that prevents ketogenesis. However, this was withdrawn in the 2014 update due to several case reports of DKA in confirmed MODY patients. The majority of patients with genetically proven MODY are initially incorrectly diagnosed as Type 1 or Type 2 diabetes. Exclusion of DKA from the diagnostic criteria will lead to further misdiagnosis which will have implications for the patient and family members. MODY should be included in the differential diagnosis of patients presenting with DKA particularly if there are other features to suspect. This should of course be balanced with the limitation of resources for carrying out genetic testing.

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EP42

Birds of a feather flock together: Maternally inherited diabetes and Deafness AND Mitochondrial encephalopathy lactic acidosis and stroke like episodes

Adnan Agha, Yousuf Ansari, Hammad Bajwa & Jonathan Webber
University Hospitals Birmingham, West Midlands, UK.

Introduction
The mutation at m. 3243 adenine to guanine (A>G) in mitochondrial encoded transfer-RNA Leucine 1 (MTTL1) gene is the single most prevalent disease-causing mitochondrial DNA (MtDNA) mutation, with carrier status of 1:400 in our general population. The distinct disease phenotype is dependent on the level of heteroplasmy of wild-type vs mutation-type mtDNA in the specific target tissues, ranging from Maternally inherited diabetes and Deafness (MIDD) to mitochondrial encephalopathy lactic acidosis and stroke like episodes (MELAS). However, current studies have shown MELAS/MIDD overlap to be present (6%) but not without posing diagnostic dilemmas as current clinical criteria are based on classical features of one or the other with the likelihood of missing conditions with overlapping features.[4]
Case
A 33-year-old female with a background of MELAS and type 1 diabetes mellitus, admitted because of symptomatic uncontrolled capillary blood glucose levels and despite optimization of her insulin it was felt that she was unable to follow instructions. Further examination revealed sensorineural deafness and in light of previous genetic testing a diagnosis of MIDD was made. Her mother was also found to have m. 3243 A>G mutation with classical MIDD features.
Discussion
The case highlights the importance of recognizing patients with three of more clinical features of either MIDD or MELAS without the classical presentation and the need for genetic testing in these patients as well as in those with either classical MIDD or MELAS or overlap syndrome or with maternal history of m. 3243 A>G mutation.

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EP43

Navigating troubled waters: Hyperglycaemic Hyperosmolar State precipitated by Nephrogenic Diabetes Insipidus

Parizad Avari, Aditi Sharma, Suhaniya Samarasinghe & Quirinius Barnor
Watford General Hospital, West Hertfordshire Hospitals NHS Trust, Watford, UK.

Hyperglycaemic hyperosmolar state (HHS) is a common medical presentation, typically occurring in older patients with Type 2 diabetes mellitus. Mortality rates have been reported to be up to 60%. Precipitating factors include dehydration, sepsis, cardiovascular disease and drugs. Here, we describe a rare case of HHS, likely to have been precipitated following the development of lithium-induced nephrogenic diabetes insipidus (DI).
A 62-year-old female presented with lethargy, confusion and reduced mobility. Her past medical history included bipolar disorder treated with lithium for more than 10 years. She was noted to be persistently hypernatraemic with sodium >170 mmol/L despite intravenous fluids. However on day ten of admission, her blood glucose was noted to be 25 mmol/L with serum osmolality of 398 mmol/L. She was reviewed by the endocrinology team and deemed to be in HHS. Treatment was commenced with a fixed rate insulin infusion and 0.9% saline. CT head excluded intracranial pathology. Over the forthcoming few days in the Intensive Care Unit, despite a fall in blood glucose, her plasma sodium remained persistently elevated despite intravenous fluids. She remained polyuric with an increasing plasma osmolality and a reduced urine osmolality. This prompted the consideration of nephrogenic DI as a concomitant pathology. Overnight water deprivation confirmed the diagnosis of DI. Amiloride with hydrochlorothiazide was started as treatment for nephrogenic DI, and a subsequent improvement was observed with falling serum osmolalities and plasma sodium. Her plasma glucose concentrations remained stable on oral anti-hyperglycaemic agents.
Our case illustrates HHS, associated with severe and life-threatening water depletion and hypernatraemia, to be the presenting feature of nephrogenic DI. Following recovery from hyperglycaemia, a persistent polyuric and hyperosmolar state should prompt consideration of DI. It is rare for the two conditions to co-exist; however it is an important differential to consider, so that appropriate therapy is initiated promptly.

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EP44

A case of reversible elevation in liver enzymes in a patient with poorly controlled type 1 diabetes

Nneka Obisi[1], Adam Al-Hakim[1], Hassan Kahal[1,2] & Belinda Allan[1]
[1]Department of Diabetes and Endocrinology, Hull Royal Infirmary, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK; [2]Warwick Medical School, University of Warwick, Coventry, UK.

Introduction
Hyperglycaemia induced elevation in alanine aminotransferase (ALT) in people with type 1 diabetes has been well described in children but is a less recognised complication in adults.
Case
An 18 year old slim girl was admitted to hospital with diabetic ketoacidosis (DKA). She had type 1 diabetes for 16 years and recurrent hospital admissions with DKA. Her HbA1C was 126 mmol/mol. After correction of her DKA and restarting her normal insulin regimen she became hyperglycaemic again likely secondary to non-compliance or poor insulin injection technique. Her hyperglycaemia was accompanied by a rise in ALT at 1122 iU/L (5–45), and alkaline phosphatase at 163 iU/L (30–125). Other liver function test including albumin, bilirubin and prothrombin time were normal.
Physical examination revealed mild hepatomegaly and right upper quadrant tenderness, abdominal ultrasound scan showed fatty infiltration and coarse liver texture. Her liver screening was negative including auto antibodies, alpha 1 anti-trypsin, ferritin, caeruloplasmin, and viral hepatitis screening. With supervised insulin therapy and better glycaemic control, her ALT levels decreased within a few days to 149 iU/L, and subsequently to 24 iU/L.
Discussion
The pathogenesis of hyperglycaemia induced elevation in ALT levels is not fully understood but is probably related to glycogen accumulation in the hepatocytes. Literature review suggests that the prognosis is good with complete normalisation of ALT levels on correction of hyperglycaemia.
Conclusions
Sudden elevation in liver transaminase levels in people with type 1 diabetes could be related to poor glycaemic control and is potentially reversible by correction of hyperglycaemia.

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EP45

An Unusual Cause of Hypoglycaemia

Steven Law, Tríona O'Shea, Penelope Hyatt, Anukul Garg & Chidambaram Nethaji
North Middlesex University Hospital, London, UK.

An 84 year old female with a known history of chronic kidney disease (stage IV) and benign lung tumour presented to the Emergency Department with collapse. She had suffered recurrent collapse over the previous 2 years. Of note she reported significant weight gain during this period. She was diagnosed with symptomatic hypoglycaemia (venous blood glucose 2.8 mmol/l). She was admitted to the ward and found to have recurrent hypoglycaemia both when fasting and post-prandial.
Investigations
Capillary blood glucose 2.5 mmol/L, venous glucose 3.2 mmol/L. Cortisol 413 nmol/L, insulin <1.0 mU/L, C-Peptide 122 pmol/l. IGF1 4.2 nmol/L, creatinine 296 umol/L. CXR: Large left lower lobe mass, consistent with known spindle cell lung fibroma. Given this, non-islet cell tumour hypoglycaemia was suspected and IGF2 levels were measured at 236.4 nmol/l. IGF2:IGF1 was 31.1, consistent with non-islet cell tumour hypoglycaemia.
Management
She was commenced empirically on prednisolone, and dose titrated down to the lowest effective dose. At 10 mg/day she suffered no hypoglycaemia. Given her disabling symptoms a multidisciplinary decision was taken to proceed with surgical resection of the tumour. She underwent a complete resection, and has made a good recovery functionally.
Follow-up: She reports no further hypoglycaemic events despite weaning for corticosteroid therapy. Histology confirmed a benign spindle cell lung fibroma. Repeat IGF2 measurement confirmed that secretion had ceased.
Discussion
Non-islet cell tumour hypoglycaemia is a rare entity, which has been described in other patients with pleural fibromas. It should be considered in patients with benign lung mass. Corticosteroid therapy is an effective means of symptom control, but surgery is curative.

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EP46

Management of Thyrotoxicosis with Chronic Neutropenia; Case Report

Nida Pasha, Kathryn Hodson, M Vidarthyi, Nemanja Stojanovic & Frederick Nkonge
Queens Hospital, Romford, UK.

The new patient with Thyrotoxicosis and neutropenia is not uncommon and requires focussed deliberations on avoidance of iatrogenic neutropenic injury and raises a clinical dilemma when treating patients with pre-existing neutropenia.
There is a paucity of published experience on the safety of Carbimazole and Propylthiouracil in defined neutropenic Thyrotoxic patient's preparation for definitive ablative RAI therapy or thyroidectomy.
53 year old female was referred for an urgent endocrine review with a diagnosis of thyrotoxicosis. The presenting symptoms developing over the few months included palpitations, lethargy and 6 kg weight loss.
She had a longstanding chronic neutropenia, documented as a cyclical neutropenia under regular Haematology review and was on long term Penicillin- V.
She had had a very low frequency of septic episodes in the past.
The laboratory presentation: Haemoglobin 136, white blood cell count 2.3, neutrophils 0.4, FT4 74.1; TSH 0.01, elevated TPO and normal TSH receptor antibody.
The anti-thyroid drugs considered Propylthiouracil and Carbimazole and known associated risk of neutropenia; often idiosyncratic required a multidisciplinary team focus and discussion with Haematology, Nuclear medicine and Endocrinology.
The preferred treatment option was radioactive iodine thyroid ablation after restoring euthyroidism with brief, closely monitored Carbimazole and Propranolol therapy.
The patient was informed in detail about potential issues and dilemmas in her management and consented to treatment. Regular blood tests revealed a stable neutrophil count; she remained well throughout her treatment with a persistently low neutrophil count.
She had a single ablative Radioiodine therapy dose and remains well with a stable neutropenia on Thyroxine replacement.
This case highlights the importance and potential dilemmas and the need to individualise the management in cases of patients with Thyrotoxicosis who present with thyrotoxicosis and neutropenia (ethnic variant, benign, immunosuppression or autoimmune).

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EP47

Hyperosmolar Hyperglycaemic state following Diazoxide therapy for Insulinoma

Arshiya Tabasum, Peter Taylor, Thomas Dacruz, Katherine Kang, Mina Wenike-Briggs, Katie Jenkins & Hemanth Bolusani
University Hospital of Wales, Cardiff, UK.

A 67-year-old lady was admitted through her General Practitioner with a history of reduced oral intake & unresponsiveness. She was diagnosed to have an insulinoma in 2012 and has been on diazoxide 75 mg thrice daily as she was deemed to be unfit for any surgical intervention. On clinical examination, she was pyrexial, tachycardic, hypoxic and had an initial GCS of 3. She was noted to have shingles on her chest & right basal coarse crackles.
On admission her blood glucose was surprisingly found to be elevated at 44 mmol/L considering her past diagnosis of an insulinoma. She was clinically dry with a sodium of 162 mmol/L, Urea of 32 mmol/L, Creatinine of 162 umol/L and a Serum osmolality of 408 mmol/kg. She had a positive varicella zoster (VZ) PCR and a CTPA confirmed a right lower lobe consolidation. Her HbA1c was 39 mmol/mol.
The above clinical & investigation findings supported a diagnosis of Hyperosmolar hyperglycemia state (HHS) triggered by pneumonia & VZ infection. She was given IV fluids, IV antibiotics, variable rate IV insulin infusion & IV acyclovir. Her Diazoxide was stopped on admission.
Diazoxide was believed to be a potential agent precipitating HHS in our patient through its inhibitory effect on pancreatic insulin release & subsequent uninhibited glycogenolysis. In our patient, the effect was likely to have been amplified by sepsis triggering adrenocortical and catecholamine release potentiating further glycogenolysis. She recovered well in the next 48 hours and was discharged home. Unfortunately she was re-admitted again few days later and died in hospital due to bronchopneumonia.
To our knowledge this is a first case report of this kind where HHS has developed as a complication of diazoxide therapy for insulinoma. This case warns the possibilities and dangers of diazoxide therapy and highlights the importance of monitoring blood glucose & ketones particularly during intercurrent illnesses.

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EP48

Resistant Hypertension – A Fourth Cause?

Katherine Powell & Khin Swe Myint
Norfolk and Norwich University Hospital, Norwich, Norfolk, UK.

Background
Resistant Hypertension is defined as uncontrolled high BP despite treatment with at least three antihypertensive agents. The underlying cause is usually found to be phaeochromocytoma, Conn's or renal artery stenosis (RAS). We would like to present two cases with difficult control of hypertension which did not fall into these categories.
Case 1
History: 68 year old gentleman presented 2012 with >10 year history of hypertension. BP 200/100. Medical history: strokes, obstructive sleep apnoea, LVH, T2 DM, cervical spondylosis, psoriasis, partial sightedness. Drug treatment: 15 different medications, including 4 antihypertensives.
Investigations: USS kidneys ruled out RAS, normal urine metanephrines and plasma renin measurements excluded phaeochromocytoma and Conn's respectively. 24 hr BP excluded white coat syndrome. Renal denervation offered but declined. After 3 years of monitoring and medication adjustment, with no improvement in BP, a urine screen showed that no antihypertensive medications were present.
Outcome: Patient admitted hiding tablets as he could not cope with amount of medication. Hypertension medications reviewed and reduced to 2 which he now takes. July 2015 BP 130/78.
Case 2
History: 47 year old gentleman admitted 2013 with resistant hypertension. BP 168/90. Medical history: glomerulonephritis, IHD with recurrent angina, CVA with post stroke seizures, intracranial bleed. Drug treatment: 16 different medications, including 7 antihypertensives.
Investigations: Cushings, phaeochromocytoma excluded with normal UFC's and urine metanephrines respectively. MRI kidneys showed no significant narrowing. Unmeasurable aldosterone excluded Conn's. 24 hr BP excluded white coat syndrome. After 3 years with no improvement, urine screen sent for analysis which showed the only drug detected was hydralazine.
Outcome: Patient confirmed he was hiding tablets as he didn't want any major side effects. Medication reviewed. All antihypertensives stopped except amlodipine 10 mg. BP 120/85.

Conclusion
The issue of adherence should be considered if all other causes of resistant hypertension have been excluded. Urine screen sent for analysis using mass spectrometry is not a quantitative assay, but will confirm compliance. This needs to be handled very tactfully to continue to engage the patient.

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EP49

A case of Euglycaemic Diabetic Ketoacidosis in a patient treated with Canagliflozin

Katherine Hodson, Nida Pasha, Edel Casey, Gangani Yakandawala & Nemanja Stojanovic
Queen's Hospital, Romford, London, UK.

Canagliflozin is an oral hypoglycemic agent from the novel class of Sodium Glucose co-Transporter 2 (SGLT2) inhibitors, used in the treatment of patients with Type 2 Diabetes Mellitus (T2DM). Although effective in treatment of hyperglycemia, these medications have been linked to development of diabetic ketoacidosis (DKA) in patients with T2DM. We describe the case of a patient with T2DM, who presented with severe metabolic acidosis while taking Canagliflozin.
SGLT-2 Inhibitors prevent glucose resorption from urine, leading to increased urinary glucose clearance and subsequent improvement of glycaemic control. Nonetheless, in May 2015, the FDA published a safety warning for this class of drugs, reporting over 20 cases of DKA in patients taking the medication.
We report the case of a 43-year-old Caucasian male with T2DM who presented with vomiting, dehydration, fatigue, and abdominal pain. He had been prescribed Canagliflozin four months earlier. The patient was found to have a severe metabolic acidosis, with high urinary ketones but normal blood glucose levels. He was haemodynamically stable at presentation, and remained so throughout admission. Treatment with intravenous insulin, fluids and sodium bicarbonate resolved the acidosis, and canagliflozin was stopped.
It is important for clinicians and patients to be aware of the potential risk of euglycaemic DKA in patients taking SGLT2 inhibitors. Acute illness, dehydration and relative insulinopenia may be predisposing factors. Whether supplying patients prescribed with these medications with ketone meters could help prevent DKAs, or lead to earlier admissions, merits further research.

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EP50

Acute Disseminated Encephalomyelitis (ADEM) secondary to severe diabetic ketoacidosis

Anne DeBray, Karthik Munichoodappa, Amar Puttanna & Parijat De
City and Sandwell NHS Trust, Birmingham, UK.

A 20 year old female with a 3 year history of type 1 diabetes presented to the emergency department unresponsive and was diagnosed with severe diabetic ketoacidosis (DKA). She had no other past medical history and was on a basal bolus regime of insulin only. GCS was 7, pH 6.7, HCO3 3.5 mmol/l, ketones 3 + on urinalysis and blood glucose of 43 mmol/l.
She was commenced on fixed rate insulin infusion and IV fluids however also noted to have unequal pupils. She was subsequently intubated and a computed tomography (CT) scan of the head revealed no cerebral oedema or other abnormalities.
Electrolytes remained normal with no evidence of infection and a lumbar puncture was negative for encephalitis and meningitis. The patient remained drowsy and intermittently agitated despite improvement in biochemistry. A repeat CT head was organised revealing several new low attenuation areas in sub-cortical white matter. Subsequent magnetic resonance imaging (MRI) confirmed multiple sub-cortical and deep white matter lesions in keeping with acute disseminated encephalomyelitis (ADEM) and discussion in neurology MDT confirmed the diagnosis.
The episode of DKA resolved with the patient improving clinically, becoming more alert and cognitively intact. A repeat MRI showed improvement in the lesions. The patient recovered fully and was discharged back to her home awaiting a repeat MRI scan and further neurology review in clinic.
ADEM is a rare immune mediated neurological condition that tends to occur following an infection or spontaneously. This is the first known case of ADEM developing secondary to DKA and highlights this unusual presentation in an adult.

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EP51

Spontaneous hypoglycaemia in a nondiabetic man with end stage renal disease caused by repaglinide or endogenous hyperinsulinaemia: An enigma entangled

Rahat Ali Tauni[1,2], Shiu-Ching Soo[1] & Ritwik Banerjee[1]
[1]Luton and Dunstable University Hospitals NHS Foundation Trust, Luton, UK; [2]University of Bedfordshire, Luton, UK.

A 56 year old man was admitted from psychiatry ward after episode of symptomatic hypoglycaemia with capillary blood glucose of 2.5 mmol/L. His background included CKD on thrice weekly haemodialysis, IHD, stroke, hypertension and paranoid psychosis but not diabetes. He denied taking hypoglycaemics, his oral intake was normal and weight was stable. He had another symptomatic hypoglycamia after 22 hours with venous glucose of 1.5 mmol/L, Insulin 320 mU/L (3.0–17.0) and C-peptide 7935 pmol/L (260–650 pmol/L). Full sulphonylurea screen was negative, and further screening using high performance liquid chromatography (HPLC) to exclude inadvertent drug intake detected metformin but no other hypoglycaemics. A relative had diabetes treated with metformin and repaglinide. He and his family denied drug dipensing error or mix up of tablets. CT abdomen and MRI pancreas showed lobulation of pancreatic head, but no foci of contrast enhancement. Patient did not comply with further investigations including prolonged supervised fast. He was managed conservatively and was discharged with glucometer, PRN dextrogel and glucagon. He did not have any hypoglycaemic episodes during his outpatient follow up for 8 months.
The cause of his hypoglycaemia remains unknown. Exogenous hypoglycaemia induced by repaglinide remains a possibility, supported by psychiatric background, family history of metformin and repaglinide intake, detection of metformin by HPLC, technical limitation of HPLC to detect some drugs and the fact that he did not have further hypoglycaemia. Endogenous hyperinsulinaemia can not be excluded due to non-compliance. Hypoglycaemia due to sulphonylureas and repaglinide should always be considered with high insulin and non suppressed C-peptide levels. Repaglinide is primarily excreted in bile but clearance is reduced in renal impairment and prolonged monitoring of glucose is needed. Where cause of hypoglycaemia is not identified, careful counselling for symptoms and prompt treatment of hypoglycaemia, blood glucose monitoring and long term follow up are essential.

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EP52

Adrenal carcinoma, a rare incidental finding: case presentation

Ana Maria Hilma[1], Adriana Gogoi[2], Simona Jercalau[2] & Corin Badiu[2,3]
[1]Elias Emergency University Clinic Hospital, Bucharest, Romania; [2]National Institute of Endocrinology "C.I.Parhon", Bucharest, Romania; [3]"C.Davila" University of Medicine and Pharmacy, Bucharest, Romania.

Adrenal carcinoma is a very rare malignancy accounting for 0.05–0.2% of all cancers, with an incidence 0.5–2/10^6.
We present the case of a 60 year old woman with impaired fasting glucose and hypertension, who was incidentally diagnosed, after a non-enhanced abdominal CT, with a right adrenal tumor of 4.5/6 cm. The mass was described as having smooth borders, and a heterogeneous aspect including solid parts, necrotic areas and 1 microcalcification. Laboratory findings revealed a low-normal ACTH (8.2 pg/mL, nv: 7.2–63.3), normal morning serum cortizol (13.4 μg/dl, nv: 3.7–19.4) with insufficient suppresion after the over night and the two-day low dose dexamethasone tests (3.3/2.7 ug/dl). The DHEA-S was low (15.9 ug/dl nv: 29,7–182) and testosterone normal. We excluded a pheocromocytoma: normal CgA, plasmatic metanephrines and normetanephrines. The patient also presented chronic autoimune thyroiditis with hypothyroidism and a slightly high CEA, probably due to the hypothyroidism. She was given 50 ug LT4/day.The MRI exam showed a T2 hyperintense mixed right adrenal tumor, with apparent diffusion coefficient (ADC) and heterogeneous enhancement seen with administration of gadolinium- both specific for benign structures.The patient was operated. The histopathology exam showed an adrenal carcinoma (**pT3NxMx**) with a Weiss Score of 4 and IHC was positive for Vimentin, inhibin, sinaptofizin, Chromogranin. Ki-67 was 5–10%. Postoperatory, the patient did not present adrenal insufficiency and was reffered to the Oncology ward for initiation of Mitotan therapy.
Conclusions
The DWI/ADC MRI sequences- have no diagnostic utility in differentiating between lipid-rich and lipid-poor adenomas and between benign and malignant nodules and should not be used for this purpose. Malignant nodules may have MRI contrast enhancement suggestive for benign tumors. The best tool for

differentiating between benign and malignant nodules remains enhanced CT by comparing the attenuation value before and after contrast administration.

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EP53

Common Features of Giant Prolactinoma and Paranasal Neuroendocrine Carcinoma-Case Report

Adriana Gogoi[1], Lidia Radomir[1], Ana Maria Hilma[2], Cristina Stancu[1], Maria Picu[4], Simona Jercalau[1] & Corin Badiu[1,2]
[1]"CI Parhon" National Institute of Endocrinology, Bucharest, Romania; [2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [3]Elias" Emergency University Clinic Hospital, Bucharest, Romania; [4]"C.M.I. dr Maria Picu", Craiova, Romania.

Giant prolactinoma it's a very rare tumor that due to its massive extension into surrounding structures can present more often with neurological complications such as visual defects, cranial nerve paresis or even hydrocephalus, unlike the classic prolactinoma presentation with amenorrhea, infertility and galactorrhea. On CT/MRI exams it can present as aggressive skull base tumor and its immunohistochemistry (IHC) may have common features with neuroendocrine neoplasms.

We present the case of a patient with giant prolactinoma first misdiagnosed as a paranasal sinus neuroendocrine carcinoma (PSNEC).

A 43 y.o. woman was diagnosed with a large destructive tumor of the skull base measuring 7.6 cm in the clinical context of diplopia, facial paresthesia and right retroocular pain. CT scan revealed sella turcica involvement, bilateral cavernous sinus, right sphenoid sinus and right nasal cavity extension, and compressive mass effect on the right temporal lobe and brainstem. She was known with secondary amenorrhea since 27 y.o.

She underwent a biopsy and the pathology and IHC evaluation pleaded for PSNEC. IHC was diffuse positive for synaptophysin and CD 56, focally positive for chromogranin, negative for S-100 and ki 67 was positive in aprox 8% of the cells. Prolactin was not performed.

Awaiting a decision on surgery vs radiation therapy, endocrine assessment revealed a very high prolactin 34.311 ng/ml (ref 4.79–23.3 ng/ml), low gonadotropins, a normal pituitary function in rest, and slightly elevated plasma CgA, ENS and 5-HIIA.

Reviewing the diagnosis, IHC staining was repeated and it was strongly positive for prolactin.

Therapeutic decision involved 2 mg/week cabergoline and after 2 months prolactin is 192 ng/ml with evident clinical improvement reported by the patient. Imaging evaluation is in pending.

Conclusion

Evaluation of large skull base tumors must include full pituitary hormonal profile due to the giant prolactinoma's atypical presentation and its common IHC features with neuroendocrine neoplasms.

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EP54

A rare case of type 2 diabetes for 35 years on metformin who developed insulinoma and diazoxide induced renal failure

Muhammad Alam, Adnan Agha, Hammad Bajwa & Brian Mtemrerwa
University Hospital Birmingham, Birmingham, UK.

Background

Insulinoma in a pre existing patient of type diabetes is extremely rare presentation.

Methods

We are presenting a a rare case of insulinoma in a pre existing case of type 2 diabetes. A 73 years old patient with type 2 diabetes for 35 years presented to endocrine clinic with hypoglycaemic symptoms ultimatley diagnosed with insulinoma and patient developed renal failure with diazoxide treatment.

Result

A 73 years old chinese lady who presented to endocrine clinic with symptoms of hypoglycaemia for 12 months. She was a type diabetic patient for 35 years and using metformin.

Her metformin was stopped by her doctor but still she was getting hypoglycaemic symtoms.She use to take four bottles of lucozade a day to treat her symptoms.

She was started on 72 hours fasting test and she developed hypoglycaemic episode with 6 hours of starting fast. Her biochemical profile was consistent with insulinoma.An ultrasound abdomen showed possible mass in distal pancreas which was confirmed by CT abdomen. She was started on diazoxide and in few days she developed vasodilation and diazoxide toxicity.She went to renal failure secondary to diazoxide and transferred to ITU for haemofilteration. Her diazoxide was stopped and she was started on octreotide.

She had distal pancreatectomy and histology was consistent with well differentiated neuroendocrine tumour, grade 1 with ki67 index 4%.

Conclusion

In case of dramatic improvement in diabetes control and hypoglycaemias in a long standing type 2 diabeteic patient, one should always consider the possibility of insulinoma.

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EP55

Pituicytoma - Lessons from anabolic steroid abuse?

Amber Khan, Malcolm Littley & Jonathan Lim
Royal Blackburn Hospital, Blackburn, UK.

A 34 year old male, previously healthy nightclub doorman presented with 2 years of reduced libido, fatigue, hot flushes and reduced beard growth. He had fathered three healthy children. He admitted to previous use of veterinary anabolic steroids up until 2 years ago. He had normal secondary sexual characteristics, no features of pituitary hypersecretion, normal visual fields but reduced testicular volumes (8 ml).

Biochemical investigation showed growth hormone, gonadotrophin and corticotrophin deficiency. Serum prolactin and thyrotrophin reserve were normal. Urinary screening for anabolic steroids was negative. Treatment with Hydrocortisone and subsequently testosterone was commenced. Magnetic resonance imaging showed a 15 mm lesion (hyperintense on T2 weighted studies) arising from the hypothalamic region. Biopsy demonstrated a pituicytoma with positive staining for S100 and Epithelial Membrane Antigen. Unfortunately, the patient died as a result of haemorrhage from the tumour after the biopsy.

This case demonstrates the importance of undertaking full assessment of pituitary function in hypogonadal patients, even when there is an apparently obvious cause. Subsequent imaging and biopsy revealed an unusual type of hypothalamic-pituitary tumour.

Some anabolic steroids can be extremely long acting, particularly those normally used in veterinary practice. This may confound accurate diagnosis. Anabolic steroids have been reported to be mitogenic in both human and animal models. Affected tissues include bone, bone marrow, pancreas and liver. There is some evidence that this may be mediated through the androgen receptor and induction of growth factors. We were unable to find previous reports of pituitary or other intracranial tumours in association with anabolic steroid use.

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EP56

An Unusual case of a para-sellar mass

Ramesh Kumar, Ashutosh Surya, Anthony Dixon & David Watson
Wrexham Maelor Hospital, Wrexham, UK.

A 36 year-old female presented with increasing headaches over the previous 8 months. She had seen in the neurology clinic recently and treated for migraines and cluster headache. She also had a history of depression. She had prodromal aura of visual disturbance including blurred vision and photophobia.

She was admitted following sudden onset of stabbing pain over the left eye along with nausea. All these symptoms were classic of her usual migraines. On admission to hospital there was no focal neurological deficit but she was noted to have palpable lymph nodes in her right groin and neck. A full body CT scan revealed widespread enlargement of lymph glands, enlarged spleen, along with an abnormal enhancing focus with soft tissue nodularity in the para-sellar and suprasellar region.

MRI of brain showed enlargement on the pituitary gland with displacement of the pituitary stalk. There was also an abnormal soft tissue focus in the right para-sellar region encroaching upon the sella. There was no evidence of involvement elsewhere in the brain. Baseline and dynamic pituitary function testing was normal.

Lymph node excision biopsy confirmed Hodgkin's lymphoma of the nodular sclerosing type. Lumbar puncture was normal and bone marrow biopsy and trephine showed no evidence of lymphoma. She was diagnosed with stage IIIB Hodgkins lymphoma. The nature of the para-sellar mass was uncertain as cranial involvement in Hodgkin's lymphoma usually occurs in the terminal phase of the disease.
The patient underwent chemotherapy with the ABVD regimen. A repeat MRI of the brain and pituitary after 2-months of chemotherapy showed a dramatic change with almost complete resolution of the para-sellar mass and normalization of the pituitary size. Repeated interval MRIs have been normal and the patient has remained in remission from her Hodgkin's Lymphoma.
This case illustrates an unusual presentation of a para-sellar mass due to Hodgkin's lymphoma and it's response to chemotherapy.

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EP57

Co-existent macro-prolactinoma, raised free T4 and right sided facial nerve palsy

Shailesh Gohil, Ragini Bhake, Narendra Reddy & Miles Levy
University Hospitals of Leicester NHS Trust, Leicester, UK.

Background
Pituitary adenomas commonly present with palsies involving the cranial nerves in the cavernous sinus. It is unusual, however, for other cranial nerve palsies to co-present and to have biochemical results that do not fit with the clinical picture.
Case
A 47 year old man was admitted with 3 days of headache, vomiting, right sided facial paraesthesia and facial droop. He had no symptoms suggestive of endocrine disturbance. Neurological examination revealed right lower motor neurone facial nerve palsy. Admission CT scan showed a pituitary macroadenoma and soft tissue in the right middle ear and mastoid air cells. Pituitary profile showed prolactin: 95570 miu/L, testosterone: 0.8 nmol/L, LH: 1 iu/L, FSH: 1.1 iu/L. Thyroid function showed fT4: 118.9 pmol/L and TSH: 3.2 miu/L. These suggested a macroprolactinoma with co-secretion of TSH leading to raised fT4. Dedicated pituitary and neck MRIs showed a 40 mm $\times$ 32 mm $\times$ 47 mm pituitary mass and soft tissue in the right middle ear and facial nerve canal, separate from the pituitary lesion. Formal visual testing revealed bitemporal hemianopia.
Cabergoline was started. No treatment for the high fT4 was started due to the absence of symptoms and simply re-testing using a different assay was arranged. These returned normal and repeat TFTs using our lab following discharge also returned normal, suggesting assay interference. With cabergoline, serum prolactin reduced significantly and his macroadenoma also shrunk. ENT advice was sought for the middle ear lesion and facial nerve palsy, and this was managed separately.
Discussion
It is thought that low molecular weight heparin caused assay interference through displacement of T4 from its binding site on proteins (e.g. thyroglobulin) during the assay whilst he was an inpatient. This leads to falsely raised fT4, normal TSH and a clinically euthyroid patient. It is therefore important to think of assay interference when investigations are discordant with clinical symptoms.

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EP58

Endocrine Dysfunction in Diamond Blackfan Anaemia

Maria Rita Talla[1], Louisa McIlwaine[2], Maurizio Panarelli[2] & Kate Hughes[1]
[1]Department of Diabetes & Endocrinology, Glasgow Royal Infirmary, Glasgow, UK; [2]Department of Haematology, Glasgow Royal Infirmary, Glasgow, UK; [3]Department of Biochemistry, Glasgow Royal Infirmary, Glasgow, UK.

Introduction
Diamond Blackfan anaemia (DBA) is a rare disorder of red blood cell aplasia characterized by normocytic or macrocytic anaemia and reticulocytopaenia. Short stature, of multifactorial aetiology, is often present. Some patients are glucocorticoid-responsive, while others remain transfusion-dependent leading to iron overload.
Case Report
Asymmetrical growth restriction was present at birth. Aged ten weeks, severe anaemia developed. Bone marrow aspirate was in keeping with DBA. Initial treatment was transfusion and high-dose prednisolone. Relapse occurred at age of 4 years. Steroids were recommenced with no response, resulting in transfusion-dependence and a requirement for iron chelation therapy.
Growth hormone therapy was administered for 10 years, achieving a final height of 139 cm ($<$0.4th centile). Menarche was attained age 15 with subsequent oligomenorrhoea. Gonadotrophins were elevated (LH 18.7 U/L, FSH 8.1 U/L) with detectable oestradiol (163 pmol/L). Ultrasound of pelvis was normal as were androgens. Growth hormone remained detectable (1.0 ug/L) with low IGF-1 61 ug/L (96–417). The remainder of pituitary and adrenal function was normal. Glucose was 4.8 mmol/L. PTH was 7.8 pmol/L (1.6–7.5) and vitamin D 48 nmol/L ($>$50). DEXA demonstrates osteoporosis. Cardiac and liver MRI demonstrated no significant iron overload.
Discussion
Over half of DBA patients have one or more endocrinopathies including adrenal insufficiency, hypogonadism, hypothyroidism, growth hormone dysfunction, diabetes mellitus and diabetes insipidus. Osteoporosis, osteopenia and parathyroid disease have also been described.
Although endocrinopathies in DBA have been reported, there are no specific DBA endocrine guidelines on screening. Regular assessments of growth and puberty are recommended. Growth hormone therapy should be considered as indicated. Delayed puberty should be investigated. Surveillance should continue into adulthood for secondary gonadal failure. Patients should be monitored for glucose intolerance, in addition to screening for adrenal and pituitary dysfunction in those on chronic glucocorticoid therapy or iron overload. Measurement of bone mineral density is also recommended.

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EP59

New onset Sarcoidosis following treatment of Cushing's Disease

Ross Andrew Cairns & Lesley Hall
Wishaw General Hospital, Wishaw, North Lanarkshire, UK.

We report the case of a 47-year-old woman with a 5-year history of weight gain, resistant hypertension and uncontrolled type 2 diabetes. She complained of oligomenorrhoea, depression and had a strikingly Cushingoid appearance and so underwent evaluation for Cushing's Disease.
Investigations revealed elevated 24-hour urine free cortisol (UFC) collections on 2 occasions: 540 nmols/24h and 624 nmols/24h. Overnight dexamethasone suppression testing (ODST) showed elevated 9 am cortisol concentrations of 671 nmol/L and 790 nmol/L. Cortisol failed to suppress following a 2-day low dose dexamethasone suppression test (LDDST)- post LDDST cortisol 125 nmol/L. Following a high dose dexamethasone suppression test (HDDST) the cortisol did suppress to 43 nmol/L. ACTH was high at 7 mU/L and then 5 mU/L at 9 am on 2 occasions.
3T MRI of pituitary revealed a left sided inferoposterior microadenoma. Bilateral inferior petrosal sinus sampling (BIPSS) was unsuccessful. CT Thorax revealed no ectopic source of ACTH secretion.
Transphenoidal left sided hemi-hypophysectomy was performed and pathology confirmed a pituitary microadenoma with positive immunostaining for ACTH. Day 3 postoperative serum cortisol was $<$30 nmol/l and replacement Hydrocortisone was commenced.
The patient was frequently readmitted to hospital with systemic illnesses of unclear aetiology and complained of myalgia, arthralgia, lethargy and breathlessness with no evidence of sepsis or overt hypocortisolism. CT Thorax was repeated, owing to breathlessness and a normal CXR, and showed new bilateral mediastinal and hilar lymphadenopthy. Serum ACE was elevated. Epitheloid granulomas in keeping with sarcoidosis were demonstrated on hilar biopsy.
The unveiling of a steroid responsive disease post treatment for CD is rare. Sarcoidosis has been reported as a sequel with dermatological signs but here were absent with only a generalised systemic illness with hilar and mediastinal lymphadenopathy seen. The convalescent period following treatment for CD can be stormy and consideration must occasionally be given to unusual diagnoses.

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EP60

Extra-pancreatic, extra-intestinal pancreatic polypeptide secreting tumour presenting as a case of diarrhoea

Ehtasham Ahmad & Stonny Joseph
Queen Elizabeth the Queen Mother Hospital, Margate, UK.

Pancreatic Neuroendocrine tumours, P-NETs, comprise 2–3% of all pancreatic tumours. Usually classified as functional or non-functional based on whether these secrete biologically active amines, causing specific syndromes or not. Even non-functional P-NETs in majority of cases secrete substances, not associated

with any specific syndrome, like Chromogranin A and Chromogranin B and Pancreatic Polypeptide (PP). An estimated 2% of all the neuroendocrine tumours secrete Pancreatic Polypeptide exclusively and are sometimes called PPomas. This is a rare group of NETs and in almost all the reported cases, the source, usually a tumour, was originating from the pancreas.
The case we describe is unique as the source of excess PP is neither coming from the pancreas nor the intestine. This 65-year old gentleman with background of type 2 DM presented initially with a few weeks' history of explosive diarrhoea with no flushing, pruritus or other symptoms usually associated with carcinoid syndrome. CT scan showed a soft tissue mass with calcifications close to the mesentery at the level of the lower poles of kidneys. A full biochemical profile for work up of neuroendocrine tumour was carried out showing raised Chromogranin A (364 pmol/l) and B (282 pmol/l) and PP levels (>500 pmol/l) with rest of profile unremarkable (Gastrin 6 pmol/l, Glucagon 25 pmol/l, Somatostatin 51 pmol/l, VIP 10 pmol/l and 24 hour urine 5HIAA 67 umol/24 hour). The mass was confirmed as somatostatin avid lesion with no uptake elsewhere on Octreotide scan. Patient was referred to neuroendocrine oncologist for further management.
A thorough literature search has not shown previously reported extra-pancreatic PPoma causing diarrhoea. Usually PPomas are considered silent but we believe this is no longer true and can arise even from outside pancreas. This case highlights that we should continue to have a high index suspicion of a functional NET even if GUT hormones and 5HIAA are normal.
Keywords: PPoma; Extra-pancreatic; Extra-intestinal

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EP61

A rare case of Follicular Stimulating Hormone (FSH) secreting pituitary adenoma in male

Punith Kempegowda, John Ayuk & Andrew Toogood
Queen Elizabeth Hospital Birmingham, Birmingham, UK.

A 61-year-old man presented to his primary care service with complains of frequent hot flushes, dizziness and headache. Following initial screening, an incidental pituitary lesion was diagnosed on computed tomography (CT) scan and hence was referred to specialist review. Further detailed history revealed similar presentation with dizziness and hot flushes two and a half years ago. He was then diagnosed with essential hypertension after a negative work-up for Cushing disease. He did not have any other co-morbidities and no family history of endocrinopathy.
Clinical examination was essentially unremarkable with intact visual fields. Pituitary function test results showed unusually high follicular stimulating hormone (FSH) (>200 IU/L) and moderately raised prolactin (700 mU/L). Serum testosterone was normal (7.3 nmol/L). Magnetic resonance imaging (MRI) scan showed large pituitary adenoma with right cavernous sinus involvement.
Following multi-disciplinary team discussion, the patient underwent elective trans-sphenoidal debulking resection of pituitary adenoma due to concerns about the size of the tumour and uncertainty of the nature of lesion. Histopathology confirmed the tumour to be a FSH secreting pituitary adenoma. Patient had residual adenoma despite the surgery and his FSH remained high (187.5 IU/L) post-surgery. The patient was then trialled with octreotide. Although the first trial of subcutaneous octreotide failed to lower FSH (>200I U/L), we saw good response with continued monthly treatment. His FSH levels normalised (11.2 IU/L) and his residual rumour shrunk. On his latest follow-up, patient continues to enjoy the period of symptom resolution and good health.
On reviewing the literature, we found limited reports of FSH secreting pituitary adenoma with fewer reports of successful resolution. We hereby report one such case which showed good response to treatment with octreotide.
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EP62

Protienurea, oedema, murmur and skin rash – an interesting case of gut carcinoids

Khwaja Nizamuddin, Sajjad Ahmad, Rajesh Thaman & David Glover
Wrexham Maelor Hosital, Wrexham, UK.

A 52 years old man was referred to the renal clinic for persistent proteinurea and leg swelling with suspicion of nephrotic syndrome. He had a history of Hypertension and chronic depression and was taking olanzapine, venlafaxine, Ramipril.He also had diarrhoea of 5–6 stools per day over the last 6 months. He was getting short of breath and had lost weight. On examination he had erythematous rash over the face, limbs and abdomen which he mentioned was exacerbated by stress intermittently. He had a palpable liver of 3–4 cm and there was evidence of lower limb and peri-orbital swelling. The initial suspicion was that he has membranous glomerulonephritis associated with underlying malignancy. His abdominal US showed grossly enlarged and irregular liver containing multiple lesions of varying echotextures which were confirmed on CT along with a well defined lesion in the small bowel mesentry.Liver biopsy confirmed neuroendocrine tumour showing strong positive staining for CD56, chromogranin, NSE and synaptophysin. Ki67 shows 3% of the cells with positivity. Echo showed right sided heart involvement with severe tricuspid regurgitation and pulmonary stenosis. Repeat echo one week later showed new finding of aortic regurgitation suggesting left heart involvement.
24 hours Urinary 5-HIAA was significantly raised at 1384 micromole. A diagnosis of carcinoids syndrome was made.
Carcinoids are slow growing neuroendocrine tumours originating from enterochromaffin cells. Metastasis to the liver manifest as carcinoids syndrome via 5-HIAA and typically cause diarrhoea, flushing, wheeze and right sided cardiac involvement.
Apart from the typical features of carcinoids syndrome our case highlighted some unusual features like possible membranous GN and severe right sided cardiac involvement extending to the left side due to excessive amines load.
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EP63

Carney Complex-a 30 year journey

Gideon Mlawa[1,2], Dora Affam[2] & Marek Oshodi[1]
[1]Queens Hospital, London, UK; [2]Darent Valey Hospital, Kent, UK.

Background
Carney complex is rare multiple endocrine neoplasia syndrome affecting adrenal, pituitary and thyroid glands. It's associated with other non-endocrine tumours such as cardiac, skin, mucosal or breast myxomas, testicular tumours, melanotic shwanomas and abnormal pigmentation (spotty skin pigmentation (freckles).
Case
We present the case of a 54 year old lady, who was referred for echocardiography in December 2014 following an episode of paroxysmal atrial fibrillation. Echocardiography revealed a large mobile left atrial mass (Myxoma). She underwent urgent surgical excision of the Atrial myxoma on the same day. Cardiothoracic surgery was complicated by postoperative fast Atrial Fibrillation that was successfully chemically cardioverted with intravenous Amiodarone She was discharged 7 days later. She presented to hospital 2 months later with cardiac sounding chest pain and breathlessness.
Findings
Chest clear, ECG sinus rhythm, troponin negative. Reviewed by the Cardiologist who arranged outpatient follow up. She was noted to have pigmented freckles, coarse facial features and large hands. Medications included Cabergoline 250 mcg weekly, hydrocortisone 15 mg am 5 mg midday and 5 mg evenings, levothyroxine 125 mcg od. Background Acromegaly treated by transphenoidal surgery in 1979, Goitre requiring partial thyroidectomy and hypothyroidism.
Discussion
It's an autosomal dominantly inherited condition due to an inactivating mutation of PRKARI alpha on the long arm of chromosome 17q2. This mutation is found in about 50% of the families The commonest endocrine manifestation is primary pigmented nodular adrenocortical disease causing Cushing's syndrome. Others include Large cell calcifying Sertoli cell tumours, growth hormone and prolactin secreting pituitary adenomas, thyroid adenomas and ovarian cysts.
Conclusion
Arriving at a unifying diagnosis can be difficult and is often delayed as demonstrated in this case report. Patients with Carney's Complex should have an annual symptoms review as well as blood tests for IGF1, prolactin and thyroid function, Echocardiography, Pituitary MRI, Thyroid and testicular/ovarian ultrasound.
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EP64

A case of anterior hypopituitarism as the initial presentation in pituitary metastasis from breast cancer

Vindya Gunawardena, Madeline Candelario-Cosme & Howard Lilienfeld
Moffitt Cancer Center, Tampa, Florida, USA.

Pituitary metastasis has been reported in about 6–8% of the breast cancer patients. Diabetes insipidus is the most common initial presentation in metastatic lesions of the pituitary. Anterior pituitary lobe lacks a direct blood supply and involvement usually is due to spread from the posterior lobe. We present a case of a 68-year-old female with known stage IV breast cancer with bone metastasis on trastuzumab, lapatinib and anastrozole who presented with hypotension, lethargy and nausea. Patient had a MRI of the brain that showed abnormal enhancement with intravenous contrast of the anterior pituitary gland and infundibulum. Laboratory work was suggestive of hypopituitarism. Patient was on steroid and thyroid replacement with improvement in symptoms. Patient did not have clinical or laboratory signs of diabetes insipidus. Pituitary biopsy was done that was indicative of metastatic adenocarcinoma of breast origin, with no adenoma or hypophysitis reported. Molecular pathology displayed ER positive, PR negative, HERs/neu positive which was consistent with her molecular pathology from breast biopsy. Further genetic tumor marker testing indicated three PIK3ca variants, pE78Q, pG118D, pD155N. These mutations are reported in squamous cell carcinoma, colorectal cancer, breast cancer, lung cancer and glioma. Patient was also positive for stop codon TP53 variant, pQ331. Germline variants of TP53 has been associated with Li-Fraumeni syndrome and Somatic TP53 variants are seen in various malignancies. Following the biopsy, patient developed increased urination and was hypernatremic to 150 mmol/L and was diagnosed with diabetes insipidus secondary to surgery. Desmopression 0.1mg twice a day was started and sodium level and increased urination improved. Patient is currently undergoing radiation treatment for the pituitary lesion. As diabetes insipidus is the more common presentation in pituitary metastasis, the above case represents an uncommon presentation in a rare form of breast metastasis.

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EP65

Pituitary apoplexy precipitated by head trauma in a Nigerian: A case report

Bolanle Okunowo & Morgan Eghosa
Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria.

Background
Pituitary apoplexy is a neuroendocrine emergency, commonest cause is pituitary adenoma. It can occur with or without precipitating factors. Commonest precipitating factor is hypertension. Post traumatic pituitary apoplexy due to tumour infarction is not common.
Case report
58 year old Nigerian painter presented with loss of consciousness, sudden headache, weakness in upper and lower limbs following fall from 3 meters high ladder while painting a house.
He had six months preceding history of poor vision in his right eye.
He was not hypertensive or diabetic. His social and family history was unremarkable. Also married with children.
Pulse rate was 93 bpm and blood pressure was 155/103 mmHg. He had laceration on the occipital region. His GCS was 10 (eye opening 3, verbal response 3 and motor response 4), power in all limbs was 4. Pupils were sluggishly reactive, no light perception on the right eye and 20 cm visual acuity on the left eye. Non-contrast brain CT scan showed pituitary fossa haemorrhage and haemorrhagic sellar/suprasellar mass suggestive of apoplectic pituitary macroadenoma.
On admission, he developed slurred speech and persistent hypoglycaemia. Hormonal profile showed low basal cortisol (99 nmol/L), low ACTH (0.5 pmol/L), low LH (0.9 u/L) and thyroid function test (TFT) suggestive of secondary hypothyroidism. Serum electrolytes & renal function were essentially normal. Assessment of Hypopituitarism secondary to post-traumatic pituitary apoplexy with C5 quadriparesis was made.
He was commenced on intramuscular hydrocortisone 100 mg every 6 hours. Repeat basal cortisol and RBG level were normal. Later switched to oral prednisolone 5 mg am, 2.5 mg pm and tabs Levo-thyronine 50 ug daily after discontinuation of hydrocortisone.
Further management was hampered by severe financial constraint and he was lost to follow up.
Conclusion
Pituitary apoplexy could be precipitated by head trauma with or without pituitary tumour. High index of suspicion is needed to avoid missed diagnosis.

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EP66

Vanishing insulin requirements in patient with type 1 diabetes

Dinesh Nagi & Ravikumar Bachuwar
Pinderfield Hospital, Mid Yorkshire NHS Trust, Wakefield, UK.

We describe a case of 31 year young lady with Type 1 Diabetes, who started experiencing reduction in insulin requirement and hypoglycaemia episodes due to an endocrine disorder following Pregnancy. She presented with recurrent episodes of documented hypoglycaemia and amenorrhea following successful pregnancy. Her basal insulin requirements fell from 36 units to 24 units per day and she required little if any insulin as bolus (0.5 unit for every 10 gm). She did not breast feed. She denied any headaches and visual symptoms. Further questioning revealed a difficult labour with forceps delivery and intrapartum haemorrhage needing blood transfusion. She was clinically hypothyroid with slow relaxing ankle jerks. Her Blood pressure lying and standing was 123/88 mm hg and 135/84 and weight 81.45 kg. She was not pigmented and had no features of Addison's disease. Her Visual fields were normal and had no other signs of endocrinopathies. Further investigations showed abnormal pituitary function as evidenced by TSH 0.92 mu/L, Ft4 <3.0 pmol/lit, 10 am cortisol 173 nmol/l, GH <0.05 ug/L, IGF-1 <3.2 nmol/l, FSH 4.6 iu/l, LH 2.9 iu/L, oestradiol 35 pmol/l. Short synacthen test showed baseline cortisol of 71 nmol/l, 30 min 233 nmol/l. MRI showed empty sella confirming likely diagnosis of sheehans syndrome. She was commenced on levothyroxine and hydrocortisone. We will explore growth hormone and fertility issues in future.
Conclusion
We would like to take this opportunity to discuss and remind ourselves Sheehans syndrome a possible reason for diminishing insulin requirements in postpartum patients with Type 1 Diabetes. Is it vanishingly rare.

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EP67

Ectopic somatotroph adenomas

Farida Chentli
Deparment of Endocrinology and Metabolic Diseases, Bab El Oued Teaching Hospital, Algiers, Algeria.

Introduction
Ectopic somatotroph adenomas are very rare and their mechanism is still debated. Our aim was to report 2 cases: One was located in the clivus and the other one in the supra sella area.
Case 1
A woman aged 45 years old, treated for post surgical hypothyroidism, was diagnosed as acromegaly by the family doctor. Growth hormone (GH) = 44 ng/ml, IGF1 = 504 ng/ml (150–350). Prolactin (PRL) = 37 ng/ml. The rest of pituitary function was normal. Cerebral MRI showed a tumor measuring 16×14mm located in the clivus with pituitary empty sella.
Case 2
A young woman aged 24 consulted for secondary amenorrhea. Clinical examination argued for acromegaly. Hormonal assessment confirmed the diagnosis as GH = 76 ng/ml, IGF1 = 563 ng/ml (105–217), PRL = 15 ng/ml. The rest of pituitary function was normal. MRI showed an intra and supra sella tumor measuring $24 \times 19 \times 16$ mm without cavernous system invasion. She was operated on, but the resection was partial as the post operative tumor height was 12 mm. Immunohistochemical study argued for pure somatotroph adenoma. Then after she was treated by somatostatin analogues with a good result as only a 6 mm tumor located in the infundibular area, near the chiasm, persisted. The diagnosis of ectopic pituitary adenoma was made in retrospect.
Conclusion
The two somatotroph adenomas are considered as ectopic: One in the clivus and the other in the infundibular area: the last one was diagnosed retrospectively after tumor shrinkage under somatostatin analogues.

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EP68

Panhypopituitarism secondary to compression by bilateral "kissing" internal carotid artery aneurysms

Harriet Daultrey[1] & Andy Smith[2]
[1]Brighton and Sussex University Hospital, Sussex, UK; [2]Brighton and Sussex University Hospital, Sussex, UK.

We describe a 91 year old woman who presented to hospital with transient loss of consciousness resulting in facial trauma. In the preceding 6 weeks she described 2 similar episodes of loss of consciousness and general malaise. She had a past medical history of pulmonary hypertension secondary to recurrent pulmonary emboli. Relevant medication included furosemide 20 mg od and life-long warfarin.

On examination she had significant orbitofrontal bruising and was noted to be hypotensive with a drop in systolic blood pressure of 50 mmHg on standing. Routine investigations revealed a hypontonic hyponatraemia of 126 mmol/L with a normal serum potassium and urea concentration.

CT brain revealed no intracranial haemorrhage however a mass in the region of the pituitary fossa extending into the suprasellar region was noted. Pituitary function tests performed at 9 am where as follows: cortisol 145 (171–536) nmol/L, LH $<$0.1 (2.4–13) iu/L, FSH $<$1.0 (3.5–13) iu/L, Prolactin 6312 (102–496) miu/L, TSH 1.46 (0.3–4.2) mu/L, FT4 7.2 (12–22) pmol/L, FT3 3.0 (3.1–6.8) pmol/L. MRI/MRA revealed bilateral, large (25 mm), partially thrombosed, cavernous carotid aneurysms encroaching on the pituitary fossa. The aneursyms were abutting in the midline such that it was not possible to delineate with certainty the pituitary in between.

The patient was commenced on replacement dose hydrocortisone with rapid resolution of her hyponatraemia and improvement in her constitutional symptoms. Levothyroxine was subsequently added and titrated appropriately. A conservative approach was taken with respect to the carotid aneurysms and she continues to be followed up in endocrine clinic. Her quality of life has significantly improved on hormone replacement allowing her independence to return.

Carotid aneurysms are a rare cause of panhypopituitarism accounting for an estimated 0.17% of cases however the majority of cases are caused by unilateral aneurysms rather than bilateral ones seen in this case.

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EP69

Cushing's Syndrome secondary to ACTH-producing prostate adenocarcinoma: A case report

Marcello Scopazzini[1], Josh Pomroy[1], Emma Hatfield[1,2] & Rozana Ramli[1]
[1]Imperial College Healthcare NHS Trusts, London, UK; [2]Imperial College London, London, UK.

A 67 year-old man, with metastatic prostate cancer diagnosed in July 2015, presented with a two-week history of lethargy, intermittent confusion, facial flushing, and increased thirst. Other medical history included well-controlled hypertension on irbesartan monotherapy, and paroxysmal atrial fibrillation. On examination, he was flushed and lethargic, but had no other features of Cushing's Syndrome. His pulse was 66 bpm and BP 179/78. There was no evidence of hypovolaemia or infection.

Bloods revealed potassium 2.1 mmol/l, chloride 97 mmol/L, bicarbonate 43 mmol/L and glucose 18.1 mmol/L. His ECG showed a long QTc and widespread T wave inversion. Other routine bloods were unremarkable. Two random cortisol levels 12 hours apart were 1601 nmol/L and 1785 nmol/L, with ACTH of 301 nmol/L. Following an overnight 1mg dexamethasone suppression test, the morning cortisol failed to suppress (1741 nmol/L).

He was managed as prostate cancer associated with ectopic ACTH secretion and Cushing's Syndrome. He was commenced on metyrapone with ketoconazole subsequently added, IV and oral potassium replacement and gliclazide.

The case was reviewed at the local neuroendocrine tumour and prostate cancer MDTs. Review of histology from August 2015 showed prostatic adenocarcinoma with neuroendocrine differentiation. The original biopsy was negative when subsequently stained for ACTH. His prognosis was poor and therefore he was managed medically; oncology administered emergency chemotherapy, followed by further palliative chemotherapy. Cortisol levels have subsequently been maintained within normal range on low-dose metyrapone.

An extended literature search revealed one other case with a similar presentation to our patient (Alwani RA et al. 2009). Treatment modalities are limited, as definitive treatment is surgical. There is limited evidence that medical therapy is effective in lengthening survival of affected individuals.

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EP70

Rare source of catecholamine secretion in two cases

Yasmeen Khalid, Eswari Chinnasamy, Jonny Vlahos, Katie Snape & Gul Bano
St Georges Hospital, London, UK.

Pheochromocytomas account for increased catecholamine secretion in about 90% of cases. Less than 5% of Less head and neck paragangliomas (PGs) secrete catecholamines. As in all extra-adrenal catecholamine secreting paragangliomas (CSPs) they produce predominantly norepinephrine and little epinephrine secretion. About 25% of PGs are familial and have mutations involving RET,VHL, SDHB, SDHC or SDHD and other newly described genes.

We present two cases of carotid body tumours (CBT) with systemic manifestations and increased catecholamine secretion.

Case 1

A 44 year old gentleman presented with dizziness, headache, facial flushing and blackouts while coughing. He had no significant past medical history and he was not on any medications. There was no family history of note. He had elevated Plasma normetadrenaline (1736 pmol/L) and 3 methoxytyramine levels (290 pmol/L). The adrenal CT scan was normal. Examination of his neck revealed a painless 6 cm right neck swelling. MRI scan showed a 4.0$\times$2.2$\times$ 6.2 cm contrast enhancing lesion between the internal and external carotid artery. This neck lesion was MIBG, Octreotide avid and his adrenals were normal. Genetic tests confirmed that he had SDHB mutation. He has been managed with medical therapy so far and his symptoms have improved.

Case 2

A 43 year old lady presented with 6 month history of light headedness and pre-syncope usually when lying flat or on extension of her neck. Her mother had renal cell carcinoma. A duplex scan confirmed bilateral carotid body tumours measuring 3.2 (right side) and 1.6 cm (left side). 24 hour urine levels for metadrenaline (2.14 umol), normetadrenaline (5.21 umol) and 3 methoxytyramine (5.03 umol) were elevated. CT and FDG PET scan confirmed bilateral carotid body. Right CBT was MIBG avid and she had surgery after α and β blockade. Genetic tests confirmed that she had SDHD mutation. We will discuss the management of these tumours, particularly optimization of medical therapy prior to the surgery.

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EP71

Morvan's syndrome: could insulin like growth factor- 1 be a marker?

Simon Edeghere, Duncan Browne & Brendan McLean
Royal Cornwall Hospital, Truro, UK.

Morvan's syndrome is a rare autoimmune disease characterised by peripheral nerve hyper excitability, central nervous system symptoms and autonomic dysfunction which can mimic other endocrine presentations with symptoms including hyperhidrosis, weight loss, neuromyotonia and insomnia. Morvan's is associated with malignancy, in particular thymomas, suggesting a paraneoplastic aetiology. This case is the first to associate Morvan's with renal carcinoma and proposes insulin like growth factor 1 (IgF1) as a marker of disease activity.

A 52 year old man presented with non-specific symptoms including weight loss, hyperhidrosis and paraesthesia. He was extensively investigated and a CT scan revealed an incidental 5.4$\times$5.1 cm left renal mass which was confirmed to be renal cell carcinoma following a curative nephrectomy. His symptoms persisted three months following surgery and a phaeochromocytoma, carcinoid tumor, thyrotoxicosis and Cushing's syndrome were excluded. Furthermore, he had a normal positron emission tomographic scan that ruled out metastatic spread or a secondary malignancy. Interestingly, his IgF1 was found to be elevated at 103 nmol/L (normal range 8–39 nmol/L) which was confirmed on subsequent testing (although he had a normal oral glucose tolerance test excluding acromegaly). Voltage gated potassium antibodies (diagnostic of Morvan's) were positive at 843 pM (normal $<$100 pM) confirming Morvan's syndrome. He received an immunoglobulin infusion and high dose prednisolone and his symptoms improved significantly with a stepwise improvement in his IgF1 to 91 nmol/L then presently 42 nmol/L.

This case report is significant because it is the first case of Morvan's syndrome. with renal cell carcinoma and not a thymoma and proposes IgF1 as a marker of disease as the patient's levels progressively improved with treatment and resolution of symptoms. Furthermore, voltage gated potassium channel antibodies should be considered in unexplained autonomic symptoms associated with malignancy and further research into the association of raised IgF1 with Morvan's disease activity is indicated.

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EP72

A case of pituitary hypophysitis following treatment with ipilimumab

Fizzah Iqbal, Nidhi Choudhary & Daniel Flanagan
Plymouth Hospitals NHS Trust, Plymouth, Devon, UK.

Case

We present an interesting case of pituitary hypophysitis following ipilimumab therapy. A 66 year old lady previously diagnosed with left ocular melanoma in 2006 was under oncology follow up, when routine surveillance scan showed recurrence in segment six of the liver. She underwent laparoscopy and was found to have multiple liver metastases following which she was commenced on ipilimumab. Four weeks after completing her second cycle of ipilimumab, she developed severe headaches. MRI showed diffuse hypophysitis of the pituitary stalk and enhancement. She was found to have a random cortisol of 64 nmol/L and a low TSH of 0.05 miu/L with a FT4 of 7.7 pmol/L. Her FSH and LH were also low at 3.3 and 0.8 iu/L respectively. She did not have any visual field defect on formal testing of the right eye. She was started on dexamethasone 8 mg bd and soon after her headaches improved. At 6 weeks, her TSH, FSH and LH were all improved. She did not report any symptoms suggestive of diabetes insipidus. Follow up MRI at 3 months showed considerable improvement in pituitary and infundibular size. She was not recommenced on ipilimumab.

Insulin stress test at six months confirmed persisting hypocortisolism with a peak cortisol of 307 nmol/L only. Several months later, she developed progressive metastatic disease and passed away.

Discussion

Pituitary hypophysitis due to monoclonal antibodies, although rare has been reported before. In some cases the acute hypophysitis may resolve over a period of time with return of pituitary function to normal. In others, hypopituitarism persists as was the case in our patient. With the increasing use of biological therapy in management of advanced cancers clinicians need to be aware of this serious complication.

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EP73

Somatostatin analogue use to treat visual field loss in acromegaly newly diagnosed in pregnancy

Isolda Frizelle & D.J. O'Halloran
Cork University Hospital, Cork, Ireland.

Acromegaly in pregnancy is rare. There is limited literature on the use of medical therapy to treat this condition. We report for the first time somatostatin analogue use in a woman presenting with newly diagnosed Acromegaly in pregnancy to treat visual field loss.

This is the case of a 32 year old woman with a background of anxiety, depression, asthma and smokes. The patient underwent brain imaging for recurrent headache at 11 weeks gestation. At this time a pituitary mass was noted. She was referred to our endocrinology department and was found to be clinically acromegalic at 13/40 gestation. At this time visual field loss was found on visual field testing. MRI showed $3.2 \times 2.7 \times 2.8$ cm mass with significant compression of the infundibulum and optic chiasm. Our patient opted for medical therapy and was initiated on 100 micrograms tds Octreotide subcutaneously. Visual fields completely recovered on repeat visual field testing after 2 weeks.

Gestational diabetes evolved which improved on somatostatin therapy. Our patient remained normotensive throughout pregnancy.

At 24/40 gestation there was further deterioration in visual fields, at which point we uptitrated Octreotide dose to 150 micrograms tds. This once again allowed return of visual fields to normal within 2 weeks. (Images available)

Foetal growth continued along the 50th centile throughout pregnancy.

An elective caesarean section was planned at 34/40. Foetal weight was 3.2 Kg at birth with an APGAR score of 9.

This patient currently continues on 200 micrograms tds octreotide.

She is menstruating regularly post partum. Her basal labs post partum showed normal thyroid function and prolactin. Random GH was 9.81 ug/L and IGF-1 was 460 ug/L. HbA1c is 40 mmol/mol.

This is the first case we are aware of where octreotide was used to treat visual field deficit in the setting of Acromegaly newly diagnosed in pregnancy.

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EP74

Hypopituitarism secondary to carotid artery aneurysm complicating a new presentation of hepatocellular carcinoma

Lavanta Farouk, Janine Makaronidis & Anukul Garg
North Middlesex Hospital, London, UK.

An 82 year old gentleman was admitted with lethargy, shortness of breath and weight loss of 26% total body weight over a two-year period. His past medical history included hypertension, pulmonary fibrosis, thalassaemia trait and unexplained thrombocytopenia.

He had previously been investigated for weight loss with a CT thorax/abdomen/pelvis in 2014 which demonstrated no evidence of malignancy and FDG PET had shown no disease.

On admission he was cachectic. He was anaemic - haemoglobin 69 g/L and thrombocytopenic - platelets 115. His thyroid function tests demonstrated a TSH of 0.86 mU/L and free T4 of 7.6 pmol/L; cortisol was 276 nmol/L. CT thorax/abdomen/pelvis showed appearances consistent with portal vein thrombosis and an ill-defined 25 mm high density area in the right lobe of the liver suspicious of hepatocellular carcinoma (HCC). Alpha-fetoprotein was significantly elevated at $>30{,}000$ KU/L. Ferritin was mildly raised at 673 ng/ml. Therapeutic dose low molecular weight heparin was commenced as well as hydrocortisone and levothyroxine replacement. MRI liver with contrast demonstrated liver cirrhosis with splenomegaly, ascites with extensive portal vein thrombosis. The adrenal glands appeared normal.

In view of discordant thyroid function, a detailed anterior pituitary profile was requested, which revealed - prolactin 8127 mU/L, ACTH 25 ng/L, LH 0.2 U/L, FSH 1.5 U/L, testosterone less than 0.3 nmol/L, IGF-1 2.7 nmol/L (NR 6–36). MRI pituitary scan demonstrated a 26×29 mm partially thrombosed aneurysm of the right internal carotid artery. CT angiography confirmed a partially thrombosed giant aneurysm from the cavernous segment of the right internal carotid artery extending into and expanding the pituitary fossa with no evidence of pituitary apoplexy. His case was discussed at the Neurovascular MDT and the decision was for conservative management with anticoagulation in view of the expected poor prognosis from HCC.

This is an interesting case of hypopituitarism secondary to carotid artery aneurysm complicating a new presentation of HCC.

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EP75

The challenges to diagnose and differentiate TSHoma from thyroid hormone resistance: a case report

Khaliq Hamdan[1], Olympia Koulouri[2], Mark Gurnell[2], Krishna Chatterjee[2] & Penelope Owen[1]
[1]Cwm Taf University Health Board (NHS), Llantrisant, UK; [2]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.

TSHoma is rare, with an incidence of 1 per million, and $<1\%$ of all pituitary tumours. We reported a case involving a 49-year-old female who was first referred to our endocrine unit in 2006 with excessive lethargy and abnormal TFT's. She was thought to have thyroid hormone resistance for several years until 2015 when she reported having persistent symptoms and further investigation suggested an alternative diagnosis.

Results

Ft4 = 41.6 pmol/l, TSH = 4.6 mU/l, alpha subunit <0.3 IU/l (normal <1 IU/l), SHBG = 147 nmol/l (normal range 18–114 nmol/l) and sequencing of thyroid hormone receptor β gene showed no abnormalities. Her prolactin was 893mU/l. She complained of excess thirst and high production of dilute urine. Her urine osmolality was 278 mOsm/kg following water deprivation, and post-desmopressin urine osmolality showed a partial urine concentration (607 mOsm/kg). MRI pituitary scan revealed 2 small foci of enhancing lesion (3 mm) consistent with microadenoma.

Diagnosing TSHoma

Patient went on to have a TRH test which showed basal TSH of 1.59 mU/l rising to 2.54 mU/l after 60 minutes. A Methione-PET scan (protocol by Dr Gurnell, Cambridge) showed changes consistent with TSHoma. Octreotide (100 mcg) suppression test demonstrated a reduction in TSH from 1.89 to 0.93 mU/l, five hours after administration.

Management of TSHoma

Sandostatin LAR 20 mg once monthly was initiated which showed normalization of TFT's (ft4 22.4 pmol/l, ft3 5.1 pmol/l and TSH 0.08 mU/l). However, patient reported probable Sandostatin-related side effects (diarrhoea and abdominal cramps). She underwent transphenoidal pituitary surgery that resulted in stabilization of TFT, however she developed hypoadrenalism post-operatively and was started on steroid therapy.

Conclusion
Biochemical and dynamic tests are required to diagnose TSHoma. PET scan can be useful in definitive localisation of pituitary lesion. Treatments are directed at treating the symptoms secondary to elevated thyroid hormones, however deciding between medical and surgical options require careful consideration of fitness for surgery, co-morbidities and therapeutic complications.

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EP76

Acromegaly gigantism with dilated cardiomyopathy and heart thrombus

Farida Chentli, Amina Laloui, Dia-Eddine Boudiaf & Said Azzoug
Department of Endocrinology and Metabolic Diseases, Algiers, Algeria.

Dilated cardiomyopathy with congestive heart failure (CHF) is a very rare complication of growth hormone excess due to (GH)-secreting pituitary adenoma; It occurs in nearly 3% of acromegaly. Our aim was to report a case with CHF, large right auricular thrombus, and pulmonary embolism.
Case report
A man aged 41, was known as an acromegaly gigantism due to a large pituitary somatotroph adenoma. That one was operated on twice but the tumor persisted and GH = 79 ng/ml; As somatostatin analogues were not available, radiotherapy was proposed but was refused, and then the patient was lost in sight for 13 years. He consulted again in 2015 for heart failure. Heart echosonography showed a dilated cardiomyopathy with severe left ventricular dysfunction (ejection fraction = 25%, shortening fraction = 15%) and a right auricular thrombus. The patient was admitted in intensive care unit but he died of pulmonary embolism.
Conclusion
Although it is rare, heart complication of GH excess can be fatal even in young people as in our case. Therefore, it is mandatory to treat aggressively every acromegaly on due time.

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EP77

A patient who presented unresponsive and unseated from the sella

Kathryn Stammers & Andrew Solomon
East and North Hertfordshire NHS Trust, Hertfordshire, UK.

Case History-A 74 year old female patient presented to the emergency department following a witnessed seizure and profound hypoglycaemia (BM 1.1 mmol/l) with an initial GCS of 7/15. Collateral history described 4 days' feeling unwell with reduced oral intake and multiple recent 'vacant episodes'. An urgent CT head was unremarkable. Past medical history included hypothyroidism of several years' duration on T4 50 mcg [3 months' prior to admission, TSH was 2.25 mIU/l]. Observations demonstrated a temperature of 38.9 degrees, tachycardic and hypotensive. On examination of the chest, crepitations were heard on the left; Chest X-Ray showed opacity of the left lower zone. Blood tests revealed hyponatraemia [128 nmol/l] and raised CRP. The patient was treated for a community-acquired pneumonia, commencing with intravenous [i/v] fluids and antibiotics. The seizures were initially thought to be precipitated by severe hypoglycaemia due to systemic illness. Endocrine consultation however suggested the possibility of hypocortisolaemia and i/v hydrocortisone was initiated, with prompt clinical improvement. Pituitary blood tests were requested with the following results; LH 5.6 u/l [16–75 u/l], FSH 19.9 u/l [21–140 u/l], Prolactin 487 [59–619 mU/l] and IGF-1 15 [6–36 nmol/l]. A short synacthen test response was highly insufficient, with 60′ cortisol of 143 nmol/l [> 550 nmol/l] and an unrecordable ACTH of < 5 ng/l. An MRI scan of the pituitary provided clear evidence of an Empty Sella. Testing for adrenal cortex antibodies was negative. The patient has been maintained on hydrocortisone and thyroxine replacement therapy and is now well. Case Discussion-Hypoglycaemic seizures are an acute, uncommon, presenting feature of Empty Sella Syndrome [ESS]. This case highlights the diagnostic challenges and difficulties in managing such patients. It emphasises that in all patients presenting with severe hypoglycaemia who are not taking any hypoglycaemic-inducing agents, that ESS is a key differential diagnosis to be considered.

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EP78

Heterogeneous presentation of giant prolactinoma

Lidia Radomir[1], Adriana Gogoi[1], Simona Jercalau[1] & Corin Badiu[1,2]
[1]C. I. Parhon National Institute of Endocrinology, Bucharest, Romania; [2]University of Medicine and Pharmacy Carol Davila, Bucharest, Romania.

Giant prolactinomas are rare pituitary tumors, defined as adenomas greater than 4 cm, with extrasellar extension, presenting with PRL levels > 1000 ng/dl. Dopamine agonists (DA) are the first-line treatment. Most (90%) of giant prolactinomas occur in men.
We describe two cases of giant prolactinoma. A 17 years man presented with frontal headache, gradual visual deficit, nausea and dizziness. MRI demonstrated a sellar tumor of 6.4 cm with extrasellar extension, compressing the right optic nerve and optic chiasm. Laboratory testing revealed an elevated PRL (19093 ng/ml), hypogonadotropic hypogonadism, secondary hypothyroidism and adrenal insufficiency. Perimetry detected right side temporal quadrantanopsia and left side temporal hemianopsia. Treatment with cabergoline 2 mg/week resulted in PRL decrease by 88% after two months, later up-titrated to 4.5 mg/week during the follow-up. Most recent CT scan, after five years of cabergoline, revealed marked reduction in tumor size to less than 4 cm and PRL normalization (13.78 ng/ml) but persistent central hypothyroidism.
The second patient, a 27 year-old man, presented for headache, recurrent posterior epistaxis and decreased libido in the last 6 months. CT scan showed an intra- and perisellar extensive tumor measuring 6.0 cm. Laboratory evaluations showed PRL levels of 31398 ng/ml and central hypogonadism. The other pituitary tests and visual field examination were normal. Cabergoline 2 mg/week was started, resulting in 80% reduction of PRL in the first 48 hours.
Despite the similar size and PRL values, giant prolactinomas in men can have a heterogeneous profile at diagnosis, from the classical visual field deficiency and pituitary failure to normal visual field and almost normal pituitary function. Correct diagnosis is capital to ensuring appropriate treatment. Lifelong follow-up is usually needed.

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EP79

Pseudoacromegaly - a differential diagnostic problem for acromegaly

Rupert Spencer[1], Per Dahlqvist[2], Mary N. Dang[1], Gudmundur Johannsson[2] & Márta Korbonits[1]
[1]Centre for Endocrinology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, EC1M 6BQ, London, UK; [2]Department of Endocrinology, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Grona straket 8, Sahlgrenska University Hospital, SE-413 45, Gothenburg, Sweden.

Introduction
Acromegaly is usually not a difficult condition to diagnose if the possibility of this diagnosis has been raised. However, there are a few conditions presenting with some aspects of acromegaly or gigantism but without growth hormone excess. Such cases are described as 'pseudoacromegaly' (acromegaloidism).
Methods
A female patient was first investigated for GH excess at 10 y for tall stature since infancy (over 97th percentile). Height and weight was +3SD, bone-age 15y with full set of permanent teeth except wisdom teeth. Typical acromegalic features, large hands/feet (shoe size 43EU/UK9), large jaw, tongue, hoarse deep voice and headache. Her performance in school was below average with difficulties in concentration and learning. Pubertal development was corresponding to her chronological age. No clinical features of Sotos syndrome was found. Normal sella Xray and GGT and insulin-arginine-TRH-LHRH test. Ethinyloestradiol & medroxyprogesterone was given for 2 y which successfully stopped further height increase (171 cm and 78.4 kg). Although her growth rate plateaued, coarsening of the facial features and acral enlargement led to investigations for acromegaly on at least four occasions during her life-time with negative results. At 52 y weight gain, sweating, sleep apnoea, headaches, joint pain and enlarged tongue led to reassessment with normal GH axis. Genetic testing was performed with a macrocephaly/overgrowth syndrome panel including CUL4B, EZH2, GLI3, NSD1, PTEN and UPF3B.
Results
A heterozygous mutation was identified in the NSD1 (c.6605G > C; p.Cys2202Ser) gene known to cause Sotos syndrome. This variant has not been previously described but mutations affecting the same cysteine residue have been identified in other patients with Sotos syndrome. DNA samples from her parents found no mutation suggesting that the mutation had occurred *de novo*.

Conclusion
There are a number of conditions which can mimic the clinical manifestations of acromegaly or gigantism, like Sotos syndrome, which can be recognised with careful clinical assessment.

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EP80

Glioma in an AIP mutation carrier patient

Shiv Datta[1], Mary N. Dang[1], Atik Baborie[2] & Márta Korbonits[1]
[1]Centre for Endocrinology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, EC1M 6BQ, London, UK; [2]The Walton Centre for Neurology and Neurosurgery, L9 7LJ, Liverpool, UK.

Introduction
Around 15–20% of patients suffering from familial isolated pituitary adenoma (FIPA) possess heterozygous germline mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene. AIP carriers are predisposed to pituitary adenomas with a penetrance of approximately 20%. No other tumours have been observed in subjects with *AIP* mutations, hence the name "isolated". *AIP* is acting as a tumour suppressor gene in the pituitary and loss of heterozygosity (LOH) has been identified in most pituitary adenoma samples from *AIP* mutation-positive patients. The purpose of this study was to investigate whether LOH played a role in a patient with *AIP* mutation with an incidental finding of a glioma.
Case report
A 52 y old male was screened for *AIP* mutation as his brother, who suffers from young-onset, somatostatin analogue resistant acromegaly, was found to be a carrier (p.R304*). The patient underwent clinical screening: while no abnormalities were found in his pituitary hormones and his pituitary was normal size on MRI, an incidental finding of a glioma was identified in the right frontal lobe. Following four years of observation, while he was asymptomatic, he was operated due to gradual increase of tumour size.
Methods
DNA was extracted from blood and from the glioma sample carefully avoiding normal tissue. PCR amplification and sequencing of the region (exon 6) possessing the *AIP* mutation was performed.
Results
Sequence analysis revealed a heterozygous state both in the blood as well as in the glioma-derived DNA, indicating lack of "loss of heterozygosity" in the glioma.
Conclusion
The sequencing result supports, although does not prove, that the *AIP* mutation is unlikely to play a role in the pathogenesis of the glioma. This supports clinical observations and similar studies in meningioma (Guaraldi, Pituitary, 2012), showing that *AIP* mutations do not predispose to tumours outside the pituitary gland.

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EP81

Retroperitoneal fibrosis presenting with panhypopituitarism

Maria Rita Talla[1], Kate Hughes[1], Lucy McGeoch[2], James Boyle[1], Russell Drummond[1] & David Carty[1]
[1]Department of Diabetes & Endocrinology, Glasgow Royal Infirmary, Glasgow, UK; [2]Department of Rheumatology, Glasgow Royal Infirmary, Glasgow, UK.

A 68-year-old gentleman with hypertension and diet-controlled type 2 diabetes presented in September 2015 with weight loss, fatigue, low libido and cold intolerance.
Blood results demonstrated secondary hypothyroidism (TSH 0.59 mU/l (reference 0.35–5.00), free T4 8.3 pmol/l (ref 9.0–21.0)), hypogonadotrophic hypogonadism (testosterone 1.0 nmol/l (ref 10.0–36.0), FSH 1.5, LH 1.1) and a modestly elevated prolactin (795 mU/l (ref <400)). Short synacthen test revealed baseline cortisol of 87 nmol/l rising to 376 nmol/l after 30 minutes. Serum angiotensin converting enzyme and ferritin were normal. MRI pituitary with contrast revealed normal appearances of the pituitary gland.
The working diagnosis was panhypopituitarism of unclear aetiology. He was treated with oral hydrocortisone, levothyroxine and Testogel, with good symptomatic improvement.
Six weeks later, he re-presented with a swollen left leg. Doppler ultrasound excluded DVT. To exclude underlying malignancy, CT thorax, abdomen and pelvis was performed. This confirmed extensive inflammatory-looking tissue within the abdomen and pelvis, involving the left ureter and iliac vessels resulting in hydroureteronephrosis. Radiological appearances and subsequent biopsy were in keeping with retroperitoneal fibrosis. Serum IgG4 levels are pending.
He has been commenced on high-dose oral prednisolone and awaits repeat imaging.
Immunoglobulin G4-related disease is a collection of disorders characterized by tissue infiltration with IgG4-positive plasma cells and CD4+T lymphocytes, accompanied by fibrosis. It may affect one or more organs, and in this case manifests as retroperitoneal fibrosis and hypophysitis. Lymphadenopathy is often present, alongside weight loss in those with multiorgan disease.
Retroperitoneal fibrosis has been associated with hypopituitarism in a number of case reports; the relationship is poorly understood but the underlying pituitary disease is thought to be related to hypophysitis.
Diagnosis is based on characteristic histopathological features on biopsy. Serum levels of IgG4 are elevated in 60–70% of patients. Most patients respond well to glucocorticoid treatment.

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EP82

Pituitary atrophy: a rare cause of pan hypopituitarism

Manish Shrikrishna Kushe, Vinod Joseph, Chinnadorai Rajeswaran & Suresha Muniyappa
Dewsbury District Hospital, Wakefield, West Yorkshire, UK.

Introduction
Idiopathic Pituitary atrophy is rare cause of pan hypopituitarism. Various hypotheses were proposed to identify aetiology of idiopathic pituitary atrophy. Still definite cause is not known. There are very few reported cases of pituitary atrophy. We present a case of pituitary atrophy that required complete replacement of pan hypopituirsm to alleviate her symptoms.
Case report
About 64 year lady was referred for evaluation of hyponatraemia and tiredness. She was known have Asthma, Hypothyroidism, osteoporosis and auditory hallucinations. Investigation revealed adrenal insufficiency with basal cortisol of 106 mmol per litre going up to 166. Her tiredness did not improve despite of adequate thyroxine and steroid replacement. There was no postural hypotension and serum sodium was normal. Pituitary profile revealed normal prolactin but hypogonadotropic hypogonadism and low IGF1. (IGF1-6.9, normal range= 10–28.4) MRI Pituitary showed pituitary atrophy with no mass or empty Sella. Surprisingly there was no evidence of pituitary atrophy in computerised Tomography of head done a year back. She had glucagon stimulation test instead of insulin tolerance test due to her age. Test showed impaired growth hormone and cortisol response with peak Growth Hormone level of 0.1 mcg/l (normal response 7 mcg/l). Her AGHDA (Assessment of GH Deficiency in Adults) score was high at 25. She was started on Growth Hormone replacement according to NICE guidelines. She has shown good response to treatment. Her AGHDA score improved.
Discussion and Conclusion
Diagnosis of Growth hormone deficiency can be challenging in advanced age group patients. However it is quite rewarding to see symptom improvement due to full replacement of pan hypopituitarism including growth hormone. We still don't have better understanding of underlying mechanism for pituitary atrophy which is a rare cause of pan hypopituitarism.

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EP83

Sweaty arms and legs: is it acromegaly?

Chong Lim, Maura Moriarty, Shakunthala Narayanaswamy & Jeannie Todd
Hammersmith Hospital, London, UK.

About 19 year-old, female, presented with sweating in both arms for many years. The sweating has progressively got worse over the last several years. Occasionally, her feet and lower back can also be affected. They do not tend to

occur particularly at night and have no association with alcohol, meals or fasting. Her periods are regular. She does not have any associated symptoms such as headache and visual disturbance.
She has no significant family history. She is a student, who is a non-smoker and consumes alcohol at weekends.
On examination, her hands and feet were sweaty. BP 125/70 mmHg. No prognathism and no other features to suggest acromegaly. She had no skin tags, goitre or macroglossia.
Results
IGF-1 level – 75.6 nmol/l (ref: 35–62), oral glucose tolerance test (OGTT) – nadir growth hormone of 0.06 µg/l, MRI Pituitary - the pituitary gland is enlarged with a convex upper margin and the optic chiasm is not involved. There is an area of slight hypo enhancement within the right side of the gland.
Her case was discussed at the local pituitary MDT. The likely diagnosis is acromegaly, but since there was no clear surgical target lesion on pituitary gland, she was offered somatostatin analogues to alleviate her symptoms and we plan to perform an interval pituitary MRI scan.
This is a rare case of likely acromegaly with discordant results. Dimaraki et al (2002) reported that serial plasma IGF-1 measurements could uncover cases of acromegaly (13% cases) despite a suppressed nadir growth hormone level following a glucose challenge. Therefore, IGF-1 alone may be adequately used to diagnose acromegaly and not to be misled by a negative gold standard OGTT. It is important to diagnose acromegaly early in these patients to bring about improvements in the morbidity and mortality associated with elevated IGF-1 and acromegaly.

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EP84

Delayed diagnosis in a case of insulinoma due to hypoglycaemia unawareness

Vinod Joseph, Manish Kushe, Chinnadorai Rajeswaran & Suresha Muniyappa
Dewsbury District Hospital, Dewsbury, Wakefield, West Yorkshire, UK.

Introduction
Insulinoma is a neuroendocrine tumour derived from the pancreatic islet cells producing excessive amounts of insulin. It can be seen at every age but mostly seen in females above age 50 years old. Because of nonspecific symptoms 20% of cases are misdiagnosed primarily. Major symptoms and signs are related to hypoglycaemia and become significant due to exercise and fasting. This case reveals the diagnostic difficulty due to hypoglycaemia unawareness.
Case report
Mrs. X, 50 years fit and well lady had unexplained falls twice in two years since 2012. First one was in gym while she was exercising. Second episode was a year later, unwitnessed fall with incontinence of urine without tongue bite. She was investigated by cardiologist and neurologist. All investigations including postural BP, ECG, 24 cardiac tape, tilt test, MRI head and EEG were normal. She also lost her driving licence. General practitioner found hypoglycaemia of 2.2 on her routine blood test. Hence he referred her to endocrinology clinic after 27 months since her first episode of symptoms. She was then given a glucometer and diary to check her blood glucose. She was found to have regular hypoglycaemia every day without being aware of it. She was investigated for hypoglycaemia with mixed meal test, which showed Glucose of 2.1 mmol per litre, Insulin-63 pmol per litre and C-peptide-317 pmol per Litre, Anti-insulin antibodies negative. CT abdomen/pelvis confirmed 13 mm hypervascular lesion in the pancreas. She had surgery, partial pancreatectomy. Her blood glucose improved after surgery and she felt very well.
Conclusion
The diagnosis of insulinoma could be delayed due to a variety of non-specific symptoms. Insulinoma is a rare neuroendocrine tumor, usually benign, but can be life-threatening in causing hypoglycemic accidents. Our patient had hypoglycaemia unawareness.

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EP85

Spontaneous resolution of primary amenorrhoea in a patient with mosaic Turner's Syndrome

Yaasir Mamoojee[1], Phil Jones[1], Jane Stewart[2], Meena Choudhary[2] & Richard Quinton[1]
[1]Department of Endocrinology, Newcastle-upon-Tyne Hospitals, Newcastle upon tyne, UK; [2]Newcastle Fertility Centre at Life, Newcastle-upon-Tyne Hospitals, Newcastle upon tyne, UK

Turner's syndrome (TS) results from a genetic abnormality in phenotypical female individuals where the second X chromosome is either absent or present in a mosaic form. The most obvious consequences are short stature and primary amenorrhoea, although there are often dysmorphic features as well as cardiovascular and genitourinary complications. 90% of TS patients experience primary amenorrhoea with subsequent infertility. Spontaneous recovery of ovarian function in patients with TS has not been previously described in the literature as per our knowledge.
We describe a 26-year-old female with mosaic TS who developed primary amenorrhoea at 21 years of age. Of note she had a history of Graves' thyroid disease in childhood treated with a total thyroidectomy. Her serum estradiol level was undetectable and corresponding FSH level was 101 IU/L. She was started on hormone replacement therapy (HRT).
She later elected to have fertility treatment and two in-vitro fertilization (IVF) attempts, using donated eggs from her sister, were unsuccessful. During her second IVF attempt she was noted to have some underlying ovarian activity. She was thus advised to stop her HRT. Her AMH was detectable at 8.3 pmol/l and she subsequently had 2 menstrual cycles, the last one being ovulatory with day 21 progesterone level of 113 nmol/l. She later conceived naturally.
Although her previously-documented ovarian insufficiency was ascribed to TS, her past history of autoimmune Graves' thyroid disease may explain a propensity to autoimmune ovarian insufficiency, which unlike that arising directly from TS, is known to remit and relapse. In TS patients with ovarian insufficiency and other underlying autoimmune diseases, consideration should be given to possible recovery of ovarian function prior to attempting fertility treatment due to the possibility of autoimmune ovarian insufficiency being a confounding aetiology.

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EP86

Central autonomization of peripheral precocious puberty

Belazzouz Abderahmen Youssouf

Introduction
The precocious puberty defines itself by the appearance of secondary sexual characters before the age of 9 years at the boy.
We bring back the case of a precocious pseudo puberty iso sexual having evolved towards a central precocious puberty revealed by in an advance of secondary bony age in a delay of diagnosis.
Observation
It is about a child masculine sex of 6-year-old and 11 month without personal.
ATCD, accepted for reappraisal of a precocious pseudo puberty linked to a bilateral testicular increase of measuring volume between 6–8 ml a stadium of Tanner G2P3, associate in d ' other signs of hyper androgénie such as of the acne, a husky voice, a wingspan android, a staturale advance (3DS) and weight with BMI in 24 kg/m^2 as well as bony age of 13 years and 1/2 is. This in spite of a treatment freinateur by Déxaméthasone 0.25 mg/j, Acetate of cyprotérone 25 mg/j, hydrocortisone 10 mg/j.
On biological plan: ACTH: 44 pg/ml 17 (oh) p: 0.55 ng/ml.
FSH: 2.34 LH: 1.94 mui/ml Testo: 1.72 nmol/l (0.1–1.12).
Scrotal ultrasound scan confirmed the increase of volume of the 2 testicles in 30 mm (6 ml) while eliminating the presence of surrénaliennes testicular inclusions.
Conclusion
The precocious pseudo puberty by block in 21 hydroxylase virilisante pure secondary form in a mutation I172N which represents 33% of classical forms, can autonomiser especially in case of diagnostic delay and as a result, an advance of bony age by leading a central ripening of Gonadostat can trigger off a central puberty.
This motivated a treatment of our patient by Décapeptyl 1ampoule/month.

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EP87

Thionamide in a Neutropenic Thyrotoxic patient- Culprit or Cure

P Kumar
ABMU LHB, Wales, UK.

A 59 yr old man was admitted with sweating, tremors and generalized weakness. Blood tests showed FT4 > 100 pmol/l, FT3 > 50 pmol/l, TSH < 0.01 mU/l, neutrophils 0.6×10^9 /l Past medical history included recurrent hyperthyroidism, type 2 diabetes mellitus, and neutropenia of 'unknown' origin(under investigation by haematology). Carbimazole 20 mg BD was started 2 days prior to admission by his general practitioner.

The neutrophil count 4 months prior to initiation of carbimazole was 1.0. Treatment with high dose carbimazole was continued under close observation, in spite of the neutropaenia. Intravenous steroids and oral propranolol were administered too. Over the subsequent days, the neutrophil count rose to 2.8×10^9 /l (on day 5) and his symptoms improved significantly. The patient was discharged home a week later, with an outpatient referral for radioiodine ablation. Thionamides are known to cause reversible neutropenia in 0.2%–0.5% of cases, usually in first three months although it can occur anytime. The mechanism is immune mediated destruction of circulating neutrophils by drug-dependent or drug-induced antibodies. Thyrotoxicosis itself lowers the neutrophil count in 5%–16% of patients believed to be predominantly via a humoral mechanism. Neutrophil count tends to improve as the thyrotoxicosis subsides, as shown in a retrospective series in the literature (N Aggarwal et al. BES 2014).In another recent prospective series, a third of neutropenic patients coming to a haematology clinic were found to be hyperthyroid. Our case is unique, as the patient was already known to have borderline neutropenia for several years. After the initiation of Carbimazole, the neutrophil count dropped further, to their lowest recorded level in his case. An analysis of the neutrophil count in relation to the thyroid status over the past decade showed our patient's neutrophils improved when he was euthyroid with or without carbimazole. A decision was therefore taken to continue carbimazole (under close monitoring) to good result. Other treatment options (potassium iodide) were considered and reserved as an alternative if neutropenia failed to improve.

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EP88

Abstract unavailable.

EP89

An unusual cause of thyrotoxicosis

Ramesh Kumar, Ashutosh Surya & Anthony Dixon
Wrexham Maelor Hospital, Wrexham, UK.

A 24 years old veterinary nurse presented to the cardiology outpatient clinic with palpitations, breathlessness and lethargy. There was no history of weight loss. She had a past history of bulimia. She was clinically euthyroid. ECG demonstrated sinus tachycardia with heart rate of 120 bpm. Thyroid functions test (TFT) done by GP was normal. She was initially treated with beta-blockers.

She was subsequently admitted to hospital a month later with palpitations, breathlessness and intermittent chest pain. She was tremulous, had a small goitre but no eye sign. Repeat TFT at this time were as follows: FT3 > 46, FT4 > 75 and TSH 0.01. She was started on carbimazole 5 mg tds and propranolol 80 mg bd and referred to the endocrine clinic as an outpatient.

In clinic six weeks later, her FT4 remained greater than 75. The patient admitted that she was omitting carbimazole on occasions and the dose was increased to 60 mg od.

After a further six weeks FT4 remained markedly elevated at 155, with undetectable TSH. Anti-TPO and anti-TSH receptor antibodies were negative. US scan of her neck showed normal size and echotexture of the thyroid gland.

There was a suspicion of factitious thyrotoxicosis and that she was taking thyroxine surreptitiously. A thyroid uptake scan showed no uptake of technetium. Although a negative thyroid uptake scan can occur in thyroiditis, the prolonged period of thyrotoxicosis suggested a diagnosis of factitious thyrotoxicosis.

This case illustrates the importance of physicians correlating biochemical findings with clinical features and considering other causes of thyrotoxicosis when patients fail to respond to treatment

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EP90

Thyroid dysfunction caused by three different Tyrosine Kinase inhibitors (TKI)

Siva Sivappriyan, Viktoria Clarke, Jesse Kumar & Supriya Joshi
Maidstone Hospital, Maidstone, UK.

Tyrosine kinase inhibitors (TKIs) are relatively new therapy drugs used for the treatment of metastatic cancers including Renal cell carcinoma (RCC), gastrointestinal stromal tumours, thyroid and neuroendocrine tumours. They block vascular endothelial growth factor and other growth factors Thyroid dysfunction is often a side effect of this treatment. A close monitoring of thyroid hormone levels is a necessity.

We have a case of a 69-year-old lady with RCC diagnosed in 2001 and she was treated with three different types of TKIs: Sunitinib (2010–2012), Pazopanib (2012–2016) and Axitinib (2016). She developed hypothyroidism in 2010 was started on replacement treatment. Despite no changes in the dose she developed profound clinical and biochemical hypothyroidism after (TSH 26 mU/l and normal T4 15 pmol/l) after initiation of Axitinib. Her symptoms included tiredness and hair thinning and body aches.

This was initially picked up by the biochemistry department and was later communicated to the oncologists by the endocrinologists through MDT discussion. And her thyroxine dose was increased.

Discussion

This case illustrates the lack of awareness among clinicians about the significance of thyroid dysfunction related to TKI despite this being common. Also we could prove different degrees of thyroid dysfunction with different TKIs in the same patient, Axitinib being the potent agent followed by Sunitinib and Pazopanib. The research evidence in this area is scarce and there are no National guidelines about how to treat this. Also a MDT approach is required as in this case to improve the patient outcome.

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EP91

Papillary thyroid cancer within an auto-immune goitre: two birds with one stone

Emma Bremner, Veronica Kieffer, FJ Uddin & Miles Levy
University Hospitals of Leicester, Leicester, UK.

Clinical presentation

This 32 year old lady was referred with a history of weight loss, sweating, tremor and anxiety and biochemical hyperthyroidism; fT4 41 pmols/l (9.00–25.00 pmols/l) TSH < 0.05 miu/l (0.30–5.00 miu/l); strongly positive TPO antibodies (1600 IU/ml.). She was toxic clinically, had subtle left sided proptosis and a palpable left sided thyroid nodule. She was started on carbimazole 20 mg and the initial differential diagnosis was between Grave's disease and a toxic thyroid nodule.

Further investigation

A technetium uptake scan surprisingly showed a cold nodule correlating clinically with the palpable nodule. Fine needle aspiration (FNA) was initially non-diagnostic but repeat FNA demonstrated papillary thyroid cancer. By the time of the FNA, her hyperthyroidism had gone into remission. On discussion with the patient, it was decided she would undergo a total thyroidectomy rather than hemi-thyroidectomy, both to definitely treat her auto-immune hyperthyroidism as well as remove the malignant nodule.

Learning points

This young lady presented with auto-immune hyperthyroidism and a malignant thyroid lesion. The lesson here is that that all thyroid nodule nodules require investigation even in the context of hyperthyroidism, as dual pathology may exist. The other interesting aspect of this case was to recommend a total thyroidectomy both to remove the lesion and definitively cure her hyperthyroidism, thereby killing two birds with one stone.

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EP92

A case of uncontrolled thyrotoxicosis and congestive heart failure due to Graves' disease

Clement Aransiola & Michael Olamoyegun
LAUTECH Teaching Hospital, Ogbomoso, Oyo, Nigeria.

Introduction
Graves' disease is the commonest cause of thyrotoxicosis. If left untreated myriad of complications, chief among which are cardiac related morbidity and mortality might supervene.
Case presentation
A 31-year-old man presented to the endocrine clinic of LAUTECH Teaching Hospital, Ogbomoso, Nigeria 19 months ago with features suggestive of hyperthyroidism and a diagnosis of thyrotoxicosis secondary to Graves' disease was made. He was commenced on carbimazole and propranolol tablets. He has defaulted follow-up care until 14 months later when he presented at the emergency unit with a 10 month history of progressive bilateral swelling of the legs and 2 week history of worsening dyspnoea accompanied by other features of congestive heart failure; and tell tail signs of unabated thyrotoxicosis. He has not been compliant with carbimazole. On examination he was conscious but in respiratory distress and afebrile with temperature of 36.4°C. Other findings include: chemosis, exolphthalmos, lid lag, goitre and bilateral pitting pedal oedema. Cardiovascular system examination revealed a pulse of 108/min regular and of normal volume. His blood pressure was 160/100 mmHg, has distended neck veins, apex beat was not displaced and heart sounds were S1S2S3 and no murmurs. Significant findings in other systems included a right pleural effusion and ascites. He was stabilized on supplemental oxygen, intravenous lasix; carbimazole and propranolol were recommenced. Antimicrosomal antibody titre was 615.65 IU\ml (reference range is 0–35). His latest TFTs results of 13/05/2016: free T3-18.83 pmol/l (reference range is 3.1–6.8) free T4-22.03 pmol/l (reference range is 12–22), and TSH-0.005 uUI/ml (reference range is 0.270–4.20). He is presently out of failure and has been continued on carbimazole to await definitive treatment once euthyroid.
Conclusion
Graves'disease can be complicated by congestive heart failure which is reversible with the use of antithyroid drugs, and diuretics at the acute phase.

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EP93

A different cause of thyrotoxicosis: Alemtuzumab induced thyrotoxicosis

Fareha Bawa, Dhanya Kalathil & Sid McNulty
St Helens and Knowsley NHS Trust, Liverpool, UK.

30 years old female with history of sinusitis, anxiety states, diagnosed with relapsing multiple sclerosis from May 2005, initially had abnormal sensation and weakness of left side of body with MRI finding of demyelinating lesion in the cervical cord, treated with i/v methyl prednisolone with good recovery. Unfortunately had multiple relapses, therefore treated with two doses of Alemtuzumab since June 2012, presented with shakiness and a rash in her neck in July 2012. Clinical examination showed a BMI of 24.5, no exophthalmos and no pretibial myxoedema but tremulous sweaty hands.
Her thyroid function test showed a tsh of less than 0.05, free t4 of 35 and t3 of 14.7. Was started on carbimazole 20 mg daily by her neurologist and was referred to endocrinology clinic. Her Thyroid receptor antibodies were more than 400 and thyroperoxidase antibodies were more than 1300. After 18 months treatment with carbimazole, was observed with thyroid function tests and had a relapse of thyrotoxicosis in November 2013, she was restarted back on carbimazole. Had a second relapse in September 2015 and received radio iodine due to two relapses, subsequently required thyroxine replacement.
Alemtuzumab is an anti-monoclonal CD52 antibody which is used in relapsing and remitting multiple sclerosis (as Lemtrada), B cell chronic lymphocytic leukaemia, kidney, bone marrow and islet cell transplant (as campath).
Despite the proven efficacy in reducing the relapses and disability in multiple sclerosis, Auto immune disease remains at significant risk. The adverse effect could be due to secondary auto immune disease through suppression of suppressor T lymphocytes. It particularly affects the thyroid gland in up to 20 to 30 percent of patients treated with alemtuzumab.
This case highlights the need for physicians using alemtuzumab to be vigilant on presentations of thyrotoxicosis, which could be subtle clinical presentation and to request thyroid function at the earliest and treat.

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EP94

A case of severe hypercalcaemia caused by hyperthyroidism with concomitant adrenal insufficiency

Jodie Sabin, Hannah Coakley & Alison Evans
Department of Diabetes & Endocrinology, Cheltenham General Hospital, Cheltenham, UK.

Hypercalcaemia is a recognised feature of hyperthyroidism due to accelerated bone turnover caused by thyroid hormone. When present, it is generally mild, usually with levels < 3.00 mmol/l. We present a case of a 19 year old male with thyrotoxicosis, who had severe hypercalcaemia and was also found to have possible co-existent adrenal insufficiency at the same time.
He presented with a 4 month history of weight loss, anxiety, tremors and palpitations. Blood tests revealed fT4 > 95.0 pmol/l, fT3 > 30 pmol/l and TSH < 0.05 mIU/l. He also had a Calcium level of 3.21 mmol/l and was admitted to hospital for IV fluids, carbimazole and propranolol. After 24 hours, his calcium levels rose to 3.53 mmol/l, co-incidental with a PTH of < 0.7 indicating that the significant hypercalcaemia was likely due to severe thyrotoxicosis. He received IV pamidronate treatment.
Two days into his admission he developed pyrexia, tachycardia, hypertension and increased agitation. This was managed as a thyrotoxic crisis with Propylthiouracil, iodine solution and hydrocortisone resulting in significant clinical improvement within 48 hours.
A cortisol level had been checked prior to steroid treatment and was found to be 117 mmol/l. A short synacthen test demonstrated adrenal insufficiency, with 0 minute cortisol level of 195 mmol/l and 30 minute cortisol of 247 mmol/l. He also developed rebound hypocalcaemia, necessitating calcium supplementation.
Within one month, his clinical symptoms and thyroid function have improved significantly. He has stopped calcium supplementation and remains normocalcaemic. He continues on hydrocortisone treatment. Once he is euthyroid, a repeat short synacthen test will be performed to establish whether this was relative adrenal insufficiency caused by severe hyperthyroidism or whether he has co-existent primary adrenal insufficiency.
This case highlights the need to consider thyrotoxicosis with concomitant adrenal insufficiency as a cause for severe hypercalcaemia, along with the management of a thyrotoxic crisis.

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EP95

Thyrotoxicosis resistant to treatment: Graves' disease or Factitious thyrotoxicosis: A Puzzle

Dinesh Nagi[1], Simon Holems[1] & Richard Jenkins[2]
[1]Diabetes and Endocrine Unit, Mid Yorkshire NHS Trust, Pinderfields Hospital, Wakefield, West Yorkshire, UK; [2]Trust HQ, Barnsley Hospital NHS Foundation Trust, Barnsley, South Yorkshire, UK.

We describe an interesting case of a man who poses a significant ongoing management challenge. He presented with mild biochemical evidence of T3 thyrotoxicosis (FT3, 8.2, FT4 13.6, TSH 0.02). Carbimazole 20 mg was started and despite increasing dosage, he deteriorated significantly. He was concordant with medication. His TBII and thyroid auto-antibodies were negative. A Tc uptake scan showed reduced uptake. Prednisolone was added, thinking that he may have thyroiditis. Despite continued treatment with Carbimazole and 60 mg of prednisolone, he failed to respond, and underwent thyroidectomy. After a very a short period of euthyroidism post-surgery, he became thyrotoxic and asked as to why this was the case. A re-think of the diagnosis raised doubts about factitious thyrotoxicosis. A radioiodine uptake scan showed no uptake in the thyroid bed or any ectopic thyroid tissue. Review of thyroid histology showed no features of Grave's disease. We felt that he may be taking exogenous thyroid hormones. He continues to be thyrotoxic and subsequently developed hypogonadism with a suppressed FSH/LH, consistent with exogenous administration of anabolic steroids. The patient denies taking any exogenous medication either known or unknown to him, and continues under endocrine follow-up. We feel that this case is likely to represent a case of severe factitious thyrotoxicosis, on the basis of a poor initial response to high dosage of Carbimazole and Prednisolone; lack of biomarkers of autoimmune thyroid disease. No evidence of Graves' disease or other thyroid pathology on review of histology. A negative RAI uptake scan post-surgery and an undetectable thyroglobulin; Continuing thyrotoxicosis despite having no thyroid tissue.
Conclusions
Factitious thyrotoxicosis is rare in men and this case demonstrates some of the clinical features and challenges of management. This diagnosis needs to be

considered when clinical judgment and investigations do not conform to known causes of thyrotoxicosis.

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EP96

Acute confusion in a cyclist

Angeliki Giannopoulou, Sian Hancock, Senthil Kumar, Akhila Mallipedhi & Sam Rice
Hywel Dda University Health Board, Llanelli Wales, UK.

A 46-year-old male was brought to the hospital by his uncle as he was found to be acutely confused and agitated 'talking rubbish' and giggling inappropriately. Last time he was seen well was 3 days ago. He was a cyclist who lived alone and his past medical history included Graves' disease and AF. He was on propranolol, carbimazole and warfarin. A month ago he needed admission to a different hospital after falling off his bike. At that time he also developed confusion and had undergone CT and MRI of his brain which were normal. An LP and EEG had excluded herpes encephalitis and the symptoms eventually had been attributed to opioid analgesics. On this admission, he was apyrexial, tachycardic, overtly confused and incoherent. He had prominent exopthalmos and fine tremor in both arms with brisk reflexes. The rest of the examination was unremarkable. There was mild leukocytosis and septic screen and CT head were normal. His TSH was 0.01 mU/l (0.27–4.2 mU/L) and fT4 was 43.2 pmol/l (11.0–25.0 pmol/L).This was felt not to be high enough to cause his psychotic presentation and it was queried whether his current symptoms could be related to psychiatric illness. The day after he was referred to the endocrine team because of the deranged TFTs and the advice given was to increase the carbimazole and check his anti TPO antibodies which came back >600 U/ml (<34.0 U/ml) The diagnosis of Hashimoto's encephalopathy was made and the patient improved dramatically after having 20 mg of prednisolone OD. His TFTs a few weeks after were within range and as he was not a candidate for radioactive iodine, in view of his active ophthalmopathy, he had a partial thyroidectomy. He made a good recovery and currently is on thyroxine replacement and weaning dose of steroids.

TFTs are some of the basic tests we do when we are investigating confusion but this case illustrates that when a patient has already a background of thyroid disease it is advisable that we check specifically his antibody status. When other aetiologies have been excluded then remarkably raised anti TPO antibodies can provide the diagnosis of Hashimoto's encephalopathy. It is a rare condition mostly associated with autoimmune thyroiditis and as it is highly responsive to steroids, an impressive reversal of the presenting symptoms can be expected.

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EP97

Graves' disease with fluctuating thyroid status and hypothyroidism with positive anti-TSH receptor antibody levels – distinctive autoimmune side-effects following alemtuzumab therapy for multiple sclerosis

Nadia Pariani[1], Mark Willis[3], Ilaria Muller[4], Sarah Healy[3], Taha Nasser[3], Joanne Jones[2], V. Krishna K. Chatterjee[1], Colin Dayan[4], Neil Robertson[3], Alasdair Coles[2] & Carla Moran[1]
[1]Wellcome-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK; [2]Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK; [3]Department of Neurology, University Hospital Wales, Cardiff, UK; [4]Institute of Molecular & Experimental Medicine, Cardiff University, Cardiff, UK.

Alemtuzumab, a highly effective, newly-licensed, treatment for multiple sclerosis (MS), is notably associated with Graves' disease (GD), which reportedly has an indolent course.

Methods

Case record review of patients who developed thyroid dysfunction (TD) after alemtuzumab treatment in Cambridge & Cardiff, to determine type, frequency and course of TD.

Results

41.8% (104/249; 81F, 23M) of alemtuzumab-treated patients developed TD, mainly GD (69%). Mean age was 37.7 years. Mean TD onset was 23 months (range 2–107 months) post alemtuzumab; most (88.5%) occurred within 3 years of the last dose.

We focused further analysis on the 74 cases with follow up data (median 5 years; range 5–198 months) post TD. 52 (70%) of these developed GD; nine of whom (17%) showed fluctuating thyroid status (seven transitioning from hypo to hyperthyroidism and two vice versa). 29 GD patients completed a course of anti-thyroid drug (ATD) therapy, with 48% (14/29) relapsing and 52% (15/29) in remission after drug withdrawal; eight patients had definitive treatment before the end of course of medical treatment mainly because of difficult control of thyroid function on ATD treatment. Three cases of thyroiditis, seven cases of anti-TPO antibody positive hypothyroidism, two seronegative hypothyroidism were identified; in 10 cases, hypothyroidism with positive TRAB was recorded. Seven of 62 (11.3%) TRAb+ patients had signs of Graves' ophthalmopathy (GO); two with severe GO.

Conclusion

Post-alemtuzumab TD occurred more frequently then previously described. GD was the most common cause of TD, with post therapy relapse rate not lower than conventional GD. Fluctuating thyroid status in alemtuzumab-induced GD (17% of cases), together with an unexpectedly high occurrence of TRAB+ hypothyroidism, suggests that both stimulating and blocking anti-TSH receptor antibodies develop in this context. We aim to investigate this hypothesis by checking the TRAb bioactivity in those patients with fluctuating thyroid status.

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EP98

Thyrotoxic periodic paralysis, and a high carbohyrdate diet; an unusual presentation in a Caucasian male

Rahat Ali Tauni[1,2], Rameez Arif[1] & Shiu-Ching Soo[1]
[1]Luton and Dunstable University Hospital, Luton, UK; [2]University of Bedfordshire, Luton, UK.

A 54 year old Caucasian male presented with progressive muscle weakness leading to complete paralysis in upper and lower limbs evident on examination. Initial venous gas analysis showed potassium of 2.1 mmol/l, and ECG showed U waves with prolonged QTc. A diagnosis of hypokalaemic periodic paralysis was made, and intravenous potassium administered. The paralysis gradually resolved over the next 3–4 h, as repeat serum potassium level rose to 4.0 mmol/l. He described 6 month history of episodic weakness happening almost daily after exercise, and resolved spontaneously with rest. He exercised strenuously as a professional body builder and consumed unusually high calorific and high glycemic index foods. Further assessment revealed a history of tremor, weight loss, sweating, and family history of thyroid disease. He had tremors and lid lag. Biochemistry confirmed Graves' thyrotoxicosis with fT4 of 58 pmol/l, suppressed TSH, and elevated TRAb 19.3 U/l. He was advised on low carbohydrate and low glycemic index diet, and commenced on propranolol and carbimazole. He noticed instant improvement in weakness, and had no further paralysis for a week in hospital.

Thyrotoxic periodic paralysis (TPP) is most commonly seen in Asian men. Although familial hypokalaemic periodic paralysis can be seen in Caucasians, TPP, as in this case, is exeptionally rare in Caucasian men. TPP is a complex disorder, leading to muscle paralysis through variety of mechanisms. Treatment with antithyroid drugs, beta blockers and dietary modifications can lead to immediate relief of symptoms. Intravenous potassium in acute setting is essential to prevent potentially life threatening cardiac arrythmias. Raising physician awareness about early detection of thyrotoxicosis in all patients of periodic paralysis may improve patient outcomes. This case also demonstrates that unusually high carbohydrate diet can often precipitate paralysis, and physicians should consider patients dietary habits in establishing diagnosis and formulating management plan.

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EP99

Vomiting as harbinger for Graves' disease

Emanuela Bejinariu, Ritwik Banerjee & Shiu-Ching Soo
Luton and Dunstable University Hospital, Luton, UK.

Introduction

Isolated vomiting is a rare often forgotten presentation of Graves's disease and can lead to delayed diagnosis. Multiple case reports quote vomiting in thyrotoxicosis co-presenting with Addisonian crisis, diabetic ketoacidosis or with abnormal liver function and jaundice. Another common association is hyperemesis gravidarum. Vomiting in paraneoplastic hyperthyroidism occurs through a similar mechanism of beta-HCG secretion, mainly related to germ-line tumours. We present a case of severe prolonged vomiting caused by Graves's disease.

Case presentation
A 46 years old postmenopausal woman of Afrocaribbean origin presented with unremitting vomiting and dramatic 38 kg weight loss over 3 months. She reported tiredness, headaches and anxiety. Her heart rate was 91/min sinus rhythm, BP 115/80, temperature 37.2°C. She had no palpable thyroid nor thyroid eye signs. Thyroid function tests showed suppressed TSH < 0.01 mU/l and elevated fT4 86.9 pmol/l.
Further investigations and progress
Thyroid uptake scan and TSH-receptor antibodies confirmed Graves's disease. Her liver function tests were normal. Gastroscopy and CT body imaging were normal. Beta-HCG was negative. The patient required a prolonged two weeks admission for managing her unremitting vomiting during which Propylthiouracil and Propranolol were administered via nasogastric tube. Vomiting was refractory to antiemetics but improved alongside amelioration of hyperthyroidism with antithyroid medication. There was no further recurrence at follow up.
Conclusion
The pathophysiology of thyrotoxicosis-associated vomiting is related to the thyrotoxic adrenergic effect on peristalsis, while high oestrogen levels in hyperthyroidism in both sexes have also been quoted. Previous case reports have no Graves's thyroid eye signs making early diagnosis challenging. Typically such vomiting fails to respond to usual antiemetics, but responds to antithyroid medications. Glucocorticoids are also useful adjuncts in bringing symptoms under control.
Recommendations
Increased awareness of vomiting as presentation of thyrotoxicosis is necessary in order to avoid a delayed diagnosis. Ruling out alternative aetiologies is also important. Rare paraneoplastic thyrotoxic conditions may present as such.

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EP100

Sole metastatic spread from a renal cell carcinoma presenting as a goitre 6 years following renal cell carcinoma

Rachel Livingstone & Russell Drummond
Department of Diabetes, Endocrinology and Clinical Pharmacology, Glasgow Royal Infirmary, Glasgow, UK.

Metastatic disease to the thyroid is rare, accounting for 2–3% of thyroid malignancy. The most common malignancy to metastasise to thyroid is renal cell carcinoma (48.1%), followed by colorectal (10.4%) and lung (8.3%). Clinically, clear cell renal cell carcinoma (CCRCC) can present with thyroid metastases years or decades later. Several studies have shown that thyroid gland abnormalities, including nodular goitre or thyroiditis, are more likely to harbour metastases.
A 68 year old lady with no past medical history was found to have an incidental grade 2, pT1b clear cell carcinoma of the kidney during investigation of back pain with MRI spine. Staging investigations demonstrated no macroscopically visible distant metastases. It did however demonstrate the presence of a multi-nodular goitre. She underwent total nephrectomy and remained well.
Five years later she was referred to ENT with haemoptysis. No cause was found, but once again CT demonstrated multi-nodular goitre. Simultaneously she was referred to endocrinology with subclinical thyrotoxicosis (TSH <0.01, fT4 21.1). Antibody testing was negative and uptake scan normal. Ultrasound revealed a left goitre composing of multiple colloid nodules and several hypoechoic nodules. FNA on two separate occasions (THY3a, THY1) failed to yield definitive diagnostic material, and she underwent diagnostic left hemithyroidectomy.
The pathology showed nodular thyroid hyperplasia with numerous metastatic deposits of CCRCC. The pathology was positive for CD10, and negative for thyroglobulin.
The patient has now undergone completion thyroidectomy, and at this moment has no evidence of ongoing disease or requirement for systemic therapy.
This case highlights that metastatic renal cell carcinoma to the thyroid should be considered in any patient with a history of malignancy and thyroid abnormalities, regardless of the duration since the primary diagnosis. Prognosis is favorable following thyroidectomy in the absence of other metastases.

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EP101

The curious case of thyroid dysfunction and the monoclonal antibody

Faisal Hasan[1], Irfan Khan[2] & A.P. Lambert[1]
[1]Musgrove Park Hospital, Taunton, UK; [2]Southmead Hospital, Bristol, UK.

Alemtuzumab is the first humanised monoclonal antibody. It is used in haematological malignancies. It is associated with secondary autoimmune adverse effects including Grave's disease, hypothyroidism, Goodpasture's disease and ITP. We present a case where there was a drastic change in the thyroid biochemistry in a short span of few weeks- from raging free hormone levels to profound hypothyroidism.
A 46 year old man was found to have abnormal thyroid function tests on routine monitoring 2 years after his last Alemtuzumab infusion. He did not have any symptoms of thyroid disease. There were no signs of Grave's disease. His previous thyroid tests had been completely normal. There was no history of thyroid or other autoimmune disease in the family.
His had positive anti-TPO and TSH Receptor antibodies. He was started on 20 mg of Carbimazole with which his thyroid chemistry improved and the drug was tapered to 5 mg.
Five weeks later, he went to his GP feeling generally unwell. At this point he had a repeat thyroid test which showed his TSH had jumped from 0.15 to 75.8, along with low free hormone levels (previously normal). He was started on 50 μg of L-thyroxine, and this had to be gradually increased.
This case offers a fascinating illustration of rapid change in thyroid function resulting from an autoimmune process. The mechanism of the thyroid dysfunction is thought to be due to lymphopenia, which results in production of self-reactive T-cells. Literature review shows a spectrum of thyroid disorders can occur-thyrotoxicosis, hypothyroidism, Grave's disease and subclinical hyperthyroidism. Interestingly, he did not have any symptoms despite the initial high free hormone levels. This lends weight to the recommendation of monitoring thyroid function 3 monthly following Alemtuzumab treatment and this should be done for at least 4 years since the last infusion.

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EP102

Thyrotoxic periodic paralysis in a Nigerian male

Artemis Vogazianou[1,2], Triona O'Shea[1], Penny Hyatt[1], Chidambaram Nethaji[1] & Anukul Garg[1]
[1]North Middlesex University Hospital, London, UK; [2]University College London Hospital, London, UK.

Introduction
Periodic paralysis is a rare condition characterized by muscle weakness in the presence of triggers including cold, heat, high carbohydrate meals or physical activity. It is classically described in the presence of profound hypokalaemia; when this occurs in conjunction with thyrotoxicosis it is termed thyrotoxic periodic paralysis.
Case history
A 30-year old Nigerian man presented with a 3 h history of inability to move, on a background of recurrent similar episodes over the preceding 2 years. He had associated severe muscle cramps in his upper and lower limbs. On examination he had a profound proximal myopathy. He had a moderately and diffusely enlarged goitre with a loud bruit. There was no retrosternal extension, palpable nodules or neck lymphadenopathy. He had a sinus tachycardia and was tremulous.
Biochemistry
Serum potassium 2.0 mmol/l (3.5–5.5), TSH < 0.01 mU/l (0.35–5.5), fT4 72.7 pmol/l (10.0–22.7), CK 2047 u/l (<170). Subsequently TSH-receptor antibodies were found to be elevated at 28.17 U/l (0–0.4).
Treatment
He was treated with intravenous potassium replacement with rapid resolution of his paralysis. He was commenced on Propranolol and Carbimazole as treatment for his thyrotoxicosis. On discharge his potassium was 5.0 mmol/l without additional supplementation. He is now euthyroid, and has had no further episodes of paralysis.
Discussion
Thyrotoxic periodic paralysis (TPP) is a rare complication of hyperthyroidism which is predominantly seen in Asian patients. It is likely due to increased sodium–potassium adenosine triphosphate pump activity (NaK-ATPase), with rapid intracellular shift of potassium into muscles. This may be due to the direct effects of excess thyroid hormone, or indirectly due to sympathetic overactivity. This case provides a rare example of TPP in an Afro-Carribean male and demonstrates the need to consider the diagnosis in any patients presenting with hypokalaemia and weakness.

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EP103

Thyrotoxicosis with ocular myasthenia – A case report

Meghana Patel & Narayana Prasad Pothina
Department of Endocrinology & Diabetes, Scunthorpe General Hospital, Scunthorpe, UK.

Background
Graves' disease with ocular myasthenia are autoimmune disorders with their association being rare but well documented. There is overlap of ocular clinical features in both these conditions which can pose a significant clinical challenge. The diagnosis is necessary for both therapeutic and prognostic reasons.
Case presentation
A 35 year old lady presented with diplopia on downward gaze for 4 weeks. There is history of unintentional weight loss, variable mood, fatigue and palpitations. She is haemodynamically stable with mild tremor in both hands and no palpable goitre on neck examination. She has vertical diplopia with mild right eye proptosis, lid lag and bilateral ptosis. Systemic examination is unremarkable. Investigations revealed hyperthyroidism with TSH <0.01 mU/l (0.27–4.2); Free T4 63.2 pmol/l (12–22); Free T3 21.61 pmol/l (3.1–6.8); TPO antibodies 117 IU/ml (0–34); Thyrotropin receptor antibodies 11.9 U/l (1–1.8). She is treated with carbimazole for graves thyrotoxicosis. Due to ptosis MRI orbits was done which excluded thyroid eye disease. Tensilon test and single fibre electromyography were done which confirmed ocular myasthenia. CT thorax has excluded any thymoma. She is treated with pyridostigmine with improvement of diplopia.
Discussion
Autoimmune thyroid disease is present in 5–7.5% of myasthenia patients but myasthenia is present in only 0.2% of patients with thyrotoxicosis. The reason for this association is unknown though many postulated theories are present. They both have similar neuromuscular involvement which can be challenging for the physician. Ptosis is generally seen in myasthenia in contrast to thyroid ophthalmopathy. In our patient this is the giveaway sign which warranted us to investigate further to confirm the diagnosis of myasthenia in coexistent graves thyrotoxicosis.
Conclusion
The main objective of this case is to consider myasthenia in presence of ptosis or orbicularis oculi paresis in patients with thyroid eye disease.

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EP104

An unusual case of resistance to thyroid hormone behaving as TSH-secreting pituitary adenoma (TSHoma)

Sajjad Ahmad & Anthony Dixon
Wrexham Maelor Hospital, Wrexham, North Wales, UK.

A 74 years old man was referred to endocrine clinic with abnormal TFTs with raised free T4 (39.7 pmol/l; NR: 7.0–17 pmol/l), raised FT3 (7.3 pmol/l; NR: 3.5–6.5 pmol/l) and normal TSH (1.9 mU/ml; NR: 0.35–5.5 mU/ml) which were done on routine testing by his GP. PMH included COPD and B12 deficiency. He had no symptoms suggestive of thyrotoxicosis and was clinically euthyroid. Investigations were arranged to exclude the three possibilities of assay interference, Resistance to Thyroid Hormone and TSHoma. Assay interference was excluded with negative anti-heterophil antibodies and the similar TFT results using several different assays. Further investigations showed elevated SHBG (84 nmol/l, NR: 12–78) and alpha-subunit (3.72 IU/l, NR: <1.00) which favoured TSHoma. CT pituitary surprisingly showed an empty sella. The rest of the pituitary profile including prolactin, LH, FSH, IGF-1 and testosterone were normal. Specialist centre at Cambridge agreed with possible diagnosis of TSHoma. On their advice a TRH stimulation test and an octreotide suppression test was performed. On the TRH stimulation the TSH risen from 1.86 mU/l at baseline to 8.20 mU/l at 20 min and 7.58 mU/l at 60 min. This was a brisk response but still within the fold rise for TSHoma The octreotide suppression test showed a reduction of TSH, FT4 and FT3 from 3.12 mU/l, 45.5 pmol/l and 6.5 pmol/l at baseline to 0.93 mU/l, 36.3 pmol/l and 5.1 mU/l at 300 min respectively. He was commenced on Lanreotide 90 mg monthly. After two injections there was no biochemical improvement in his TSH or FT4 and he developed side-effects. At this stage genetic testing was considered and this confirmed THR beta-gene mutation consistent with RTH.
Both RTH and TSHoma are rare conditions which can be completely asymptomatic. None of the biochemical tests are entirely pathognomonic but a combination of tests can be suggestive of either. A high SHBG and alpha-subunits favours TSHoma together with blunted TSH response to TRH and good response to octreotide. This case was unusual in that RTH behaved biochemically as a TSHoma. Genetic testing for RTH is not always positive with 10–15% of cases having no demonstrable mutation on the TR beta-gene. Therefore, physicians need to be cautious in the interpretation and be aware of the limitations of these tests in differentiating between RTH and TSHoma.

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EP105

Normal neurodevelopment of children from a mother treated with only Liothyronine (T3) during pregnancy – a case report

Sidrah Khan & Trevor Wheatley
Princess Royal Hospiatal, Haywards Heath, UK.

Untreated hypothyroidism in pregnancy is associated with severe neurodevelopmental delay. Based on rodent experiments, maternal T3 is said not cross the placenta and to have little if any role in fetal brain development.
Case report
A 36-year-old female with known hypothyroidism treated only with liothyronine (T3) 20 μg TDS. attended the antenatal clinic. It was suggested that she changed to treatment with levothyroxine (T4) or a combination of T3 and T4. However, she decided to continue on T3 only. Her booking thyroid function tests (TFTs) showed free T4 of 0.6, free T3 6.4 pmol/l and TSH 0.06 μ/l. In the second pregnancy the free T4 was 1.1, free T3 5.4 pmol/l and TSH 0.1 μ/l. Serial growth scans were normal throughout both pregnancies. Her first baby was forceps delivery with birth weight of 3065 g. Second baby was spontaneous vaginal delivery at term, with birth weight of 3685 g. Both children were euthyroid and were breast fed. Both children had normal physical and neurodevelopment as evidenced by normal growth scans during pregnancies, normal growth charts in the first years of life achieving all milestones for age and excellent school performances. Both siblings are currently progressing well in primary school.
Conclusion
We were not able to identify any case where liothyronine was administered solely in all three trimesters. This case has shown normal neurodevelopment in both siblings. Maternal serum T3 concentrations were maintained within reference range while her serum T4 concentrations were very low i.e <2 pmol/l in both pregnancies. These pregnancies seem to challenge current dogma re thyroid hormone treatment during pregnancy.

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EP106

A challenging case of thyroid storm

Azmi Mohammed, Ashwin Joshi & Nimantha De-Alwis
Sunderland Royal Hospital Foundation Trust, Sunderland, UK.

Thyroid storm is a rare complication of thyrotoxicosis, life-threatening if not managed appropriately.
We report a 43-year-old woman who presented to emergency services with shortness of breath, palpitations and weight loss. She was pale, cachectic, in atrial fibrillation and had signs of decompensated heart failure. Investigations showed: WBCs: 3.2×109/l, neutrophils 2.1×109/l, Hb 53 g/l, platelet 233, TSH <0.02 mIU/l, FT4 64 (10–25 pmol/l), FT3 19 (2.8–7 pmol/l) and Thyroid stimulating antibody >40 U/l confirming a diagnosis of Grave's disease. Chest X-ray showed bilateral pleural effusions, ECG confirmed atrial fibrillation with rate of 130/min. Echocardiogram demonstrated moderate LVSD with mild mitral and tricuspid regurgitations. Due to initial suspicion of wet beri-beri, she was treated with diuretics, blood transfusion, thiamine then commenced on Digoxin & betablocker for rate control.
Following endocrinology review, carbimazole 30 mg once daily was commenced. On day 3, she became hypotensive, WBC dropped to 2.7 and neutrophils to 1.7. Carbimazole was switched to Propylthiouracil due to agranulocytosis. At that point FT4 was 30 pmol/l. Patient declined OGD hence was not anti-coagulated due to undiagnosed iron deficiency anaemia pending outpatient CT angiogram.

Learning points:
1. Thyroid storm diagnosis needs high index of suspicion since symptoms may resemble any high cardiac output state e.g. severe sepsis or anaemia and it might be precipitated by them.
2. Both thyroid storm and sepsis can cause leucopoenia, however, vigilance and observation for rare complications of antithyroid drugs including agranulocytosis needs to be considered.
3. There is a solid evidence to suggest that patients with untreated overt thyroid dysfunction are at increased risk of cardiac dysfunction. Persistent sub-clinical thyroid dysfunction is associated with the development of Heart failure.
4. Pernicious anaemia is commonly reported with hyperthyroidism, although there are some reports of microcytic anaemia; however its severity in this case suggests a coexisting aetiology.

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EP107

Case of pre-tibial myxedema with features of medium-vessel vasculitis on biopsy

Akinyele Akinlade & Ehiage Anaba
General Hospital Odan, Lagos, Lagos, Nigeria.

26-year-old female lawyer who was first diagnosed to have Grave's disease in our Endocrinology clinic, when she presented with palpitations, protruding eye balls, progressive weight loss good appetite, heat intolerance and a small goiter and confirmatory TFT results. She was controlled with (and maintained on) 10 mg of carbimazole. She also had flesh-colored swellings, with areas of hyperpigmention and induration on her shins, as well as hyperpigmented patches on her ankles. The lesions were diagnosed as pre-tibial myxedema. She had a punch biopsy of the lesion, a year after she had been on carbimazole, because of her increasing concern about the lesions. Histology report showed a macroscopic specimen consisting of negroid skin tissue while histologic section shows the dermis having widespread collagen tissue, indicating increased ground substance; the vessels in the subcutis show swollen endothelial walls and perivascular lymphocytic infiltrates. The epidermis was normal. Conclusion was that of pre-tibial myxedema with vasculitis of medium vessels.
She had no other features of systemic vascilitis or connective tissue disease. Serum pANCA was done and was negative confirming the vasculitis was unrelated to carbimazole use. Her connective tissue disease or ENA screen showed no evidence of connective tissue disease.

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EP108

Transient thyrotoxicosis following external beam radiotherapy to the neck

Ritwika Mallik, Swarupini Ponnampalam & James Ahlquist
Southend Hospital, Westcliff on Sea, UK.

Hypothyroidism is a recognised late complication of radiotherapy to the neck. However, radiation-induced thyrotoxicosis is not generally considered, and may not be diagnosed. We report a case of transient thyrotoxicosis following radiotherapy to the neck.
A 71-year-old man with supraglottic squamous cell carcinoma was treated with 65Gy radiotherapy, delivered by volumetric arc therapy in 38 fractions. During radiotherapy he became confused. Three days after completing radiotherapy a blood test revealed thyrotoxicosis: TSH <0.01 mU/l, fT_4 36.5 pmol/l, fT_3 10.1 pmol/l. On examination he had fine tremor, increased sweating and tenderness over the anterior neck. There were no signs of thyroid eye disease. There was no past history or family history of thyroid disease. Radiation-induced thyroiditis was suspected, and thionamide treatment was not given. Four days later fT_4 had fallen to 24.8 pmol/l. TPO antibody and TSH-receptor antibody were negative. After 6 weeks thyroid function had returned to normal, TSH 3.05 mU/l, fT_4 12.5 pmol/l. A thyroid uptake scan was planned but was not performed.
It is well recognised that radiotherapy to the neck may lead to late hypothyroidism. However, radiation-induced thyrotoxicosis may not be generally recognised. There have been isolated reports of thyrotoxicosis due to Graves' disease developing years after neck radiotherapy. In this case, the early development of transient thyrotoxicosis indicates the diagnosis of radiation-associated thyroiditis.
In an oncology setting the clinical features of tachycardia and sweating may be mistaken for acute illness such as sepsis, and thyrotoxicosis may not be diagnosed. We suggest that if thyrotoxicosis develops soon after neck radiotherapy, thyroiditis should be suspected, treatment with thionamides should not be given, and thyroid status should be monitored closely for resolution and progression to hypothyroidism. Awareness of this condition by endocrinologists and oncologists will help avoid inappropriate treatment and will ensure appropriate monitoring and follow-up.

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EP109

The night when a floppy Chinese lad almost died due to his thyroid

Jawad Bashir[1], David Price[1], Irfan Khan[2] & Tamar Saeed[3]
[1]Morriston Hospital, Swansea, UK; [2]Musgrove Park Hospital, Somerset, UK; [3]Royal Berkshire Hospital, Reading, UK.

Thyrotoxic period paralysis is a rare endocrine emergency associated with hyperthyroidism that needs urgent treatment. We present a case of a 19-year-old Chinese student who was admitted with progressive weakness in his lower limbs developing overnight. He was resident at the students' hostel and went to sleep after ignoring mild leg weakness overnight but could not even get up from his bed in the morning. Luckily his friend called the ambulance and brought him in hospital.
At the time of admission he was found to be completely flaccid with a power of 1 out of 5 (on MRC scale) in all four limbs. The pattern of rapidly ascending flaccid paralysis with preserved cognition raised the suspicion of Guillain-Barre syndrome. But his potassium was 1.7 mmol/l and ECG was showing junctional tachycardia with long QTc (630 ms) which led to the differentials of hypokalaemic periodic paralysis. There had been a similar self-resolving milder episode of leg weakness three months ago. The thyroid functions showed overt thyrotoxicosis (TSH <0.01 mU/l, $FT_4 > 100$ pmol/l, $FT_3 = 35.8$ pmol/l) despite the patient being clinically eu-thyroid (with the exception of tachycardia). The patient was kept on cardiac monitoring and treated by correction of hypokalaemia along with commencement of propranolol and carbimazole. There was complete recovery of the neurological deficit within 4 h.
This case reminds the importance of a rare presentation of thyrotoxicosis in southeast Asian people which can be life threatening as a result of the arrhythmogenic potential of combination of profound hypokalaemia with severe thyrotoxicosis. These people are candidates for definitive treatment of their thyrotoxicosis in form either radio-iodine or thyroidectomy.

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EP110

A case of undetectable thyroid hormones

Samantha Hayes[1], Lucy Hawkins[1], David Halsall[2] & Supriya Joshi[1]
[1]Maidstone and Tunbridge Wells Hospitals NHS Trust, Maidstone, UK; [2]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.

Positive interference in free thyroxine (fT_4) and free triiodothyronine (fT_3) immunoassays is well known, however we report a rare case of negative interference in the Roche fT_4 and fT_3 immunoassays in a 3-year-old girl with undetectable fT_4 and fT_3.
She presented with increasing tiredness, abdominal pain, pain in her lower limbs and constipation. Examination was unremarkable. Thyroid function tests (TFTs) of TSH 1.5 mU/l (0.85–6.50), fT_4 <3.0 pmol/l (12.1–22.0) and fT_3 <1.5 pmol/l (3.0–9.1) were confirmed on a repeat specimen using the Roche method. Prolactin, Insulin like growth factor 1 (IGF1) and synacthen test were within respective reference intervals. An MRI of her brain was normal.
Idiopathic isolated central hypothyroidism is rare. In view of this, her TFTs were re-analysed by three different methods, all of which reported the following normal results: Centaur Method TSH, 2.25 mU/l; fT_4, 14.8 pmol/l (10.3–22.7); fT_3, 5.8 pmol/l (3.5–6.5), Abbott method: fT_4, 18 pmol/l (9–19), Perkin Elmer Auto-DELFIA method, TSH, 2.68 mU/l (0.40–4.0); fT_4, 12.7 pmol/l (9.0–20.0). FT_4 was also estimated from a total T_4 measurement of 159 nmol/l (69.0–141.0) and a TBG concentration of 28.5 µg/ml (14.0–31.0) using published values for the binding constant of T_4 to TBG; this returned a value for fT_4 of 15.0 pmol/l.
This case emphasizes the need for vigilance in interpreting extremely unusual immunoassay results, even if clinically plausible.

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EP111

Off legs in a 30 year old: a Grave concern?

Ming-May Chung, Anne Yingchol de Bray, Amar Puttana & Parijat De
Sandwell and West Birmingham NHS Trust, Birmingham, UK.

A 30-year-old man of Asian descent presented to the emergency department with recurrent episodes of sudden onset limb weakness and difficulty walking over a period of 3 years. Each episode resolved within 2–3 h and he had fully normal mobility in between episodes. He denied any visual, bulbar symptoms or other focal neurology.

He had a 9 year history of Graves' disease for which he had recently discontinued carbimazole therapy in preparation for radio-iodine treatment. He had been extensively investigated for these episodes of weakness, as an outpatient by the neurology team, with normal head and whole spine magnetic resonance imaging and nerve conduction studies.

Upon further questioning, the patient stated that these episodes coincided with instances when his thyroid state was not fully controlled and most commonly first thing in the morning. On examination, he was found to have reduced power in all four limbs with the proximal lower limbs most affected. No other abnormal neurology was elicited.

Routine blood tests on this admission identified that the patient was hypokalaemic and thyrotoxic with serum potassium 2.1 mmol/l, phosphate 0.44 mmol/l, free thyroxine (FT_4) 44 pmol/l and free tri-iodothyronine (FT_3) 40.4 pmol/l. ECG showed sinus tachycardia. A diagnosis of thyrotoxic periodic paralysis was made and he was treated with oral and intravenous potassium replacement, propranolol and carbimazole and discharged the next day when his serum potassium levels returned to normal.

This case highlights this lesser considered feature of thyrotoxicosis and is a reminder that an atypical presentation can delay diagnosis, which can be frustrating for the patient and the clinician. This patient was seen by neurologists and had multiple admissions before the correct diagnosis was considered. Careful attention to the patient's description of their illness as well as comorbidities may aid earlier diagnosis.

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EP112

A lady with psycho-affective symptoms due to Hashimoto's encephalopathy

Jawad Bashir[1], David Price[1], Irfan Khan[2] & Tamar Saeed[3]
[1]Morriston Hospital, Swansea, UK; [2]Musgrove Park Hospital, Somerset, UK; [3]Royal Berkshire Hospital, Reading, UK.

Hashimoto's encephalopathy (HE) is a very rare neuropsychiatric condition associated with autoimmune thyroid disorders which shows a remarkable response to steroid therapy and hence is also called steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT).

We report a case of 44 year old lady presenting twice with psycho-affective symptoms but not receiving the diagnosis on first presentation. She initially presented with 3 weeks history of low moods, lethargy, apathy and increased somnolence. All the initial investigations including blood cultures, virology screen, CT brain and CSF analysis were reported as normal. She had a past medical history of well controlled hypothyroidism and epilepsy but no psychiatric problems. She was labelled as being depressed and was discharged after referral to psychiatry team.

Two weeks later she re-presented with worsening symptoms of low mood, confusion and paranoid behaviour. Multiple Blood cultures, drug toxicology screen and virology screen were normal. CSF analysis (Glucose = 4.3 mmol/l; Protein = 0.26 g/l; no xanthochromia) were all reported as normal. Neurology investigations for rare encephalopathies (anti VGCC antibodies, anti VGKC antibodies, anti NMDA antibodies) were also normal. It was only after excluding all the metabolic and infective encephalopathies, the final diagnosis of Hashimoto's encephalopathy was reached. Her anti-TPO antibodies were raised. The MRI brain and EEG findings also supported the diagnosis. She was started on high dose of steroids. There was immediate improvement in neuropsychiatric symptoms but she still continues to have emotional lability.

Hashimoto's encephalopathy (HE) is a diagnosis of exclusion which is often missed but if considered after ruling out other causes in such presentations, it shows dramatic response to steroids. This case illustrates that HE can present with psychiatric symptoms in patients with long standing well- controlled hypothyroidism.

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EP113

A big price for a little mistake: similar presentations but diverse management of thyroid storm

Mawara Iftikhar & Anna Crown
Royal Sussex County Hospital, Brighton, UK.

Introduction

Thyroid storm is a rare endocrine emergency associated with the reported mortality rate ranging from 10 to 20%. We discussed the management of two cases of thyroid storm with different outcomes. It also showed the successful use of ECMO in the management of severe hyperthyroidism related cardiomyopathy and circulatory collapse.

Case History 1

A 36 years old female with known history of Graves' disease, presented with palpitations and shortness of breath. She had pyrexia of 38 °C. She was in atrial fibrillation and acute left ventricular failure. Thyroid function tests showed TSH level of 0.01 mU/l, fT_4 level > 100 pmol/l and fT3 level of 35 pmol/l, suggestive of clinical diagnosis of thyroid storm. The identified precipitating factors were non-compliance towards medication and job related stress. She was successfully managed in coronary care unit with standard medical therapy and was booked for definitive therapy with radioactive iodine.

Case History 2

Another 53 years old female with known Grave's disease and poorly compliant to medical therapy also presented with shortness of breath and palpitations. She was quite unwell due to atrial fibrillation resulting in heart failure, renal failure and liver failure. Thyroid function tests were grossly deranged. Due to multi-organ dysfunction she was transferred to intensive care unit requiring invasive ventilatory support, and inotropic support. Medical and supportive therapy failed to stabilize her, prompting transfer to a regional centre for VA-ECMO support and requiring emergency thyroidectomy and tracheostomy. Her surgery was complicated by vocal cord paralysis needing long-term rehabilitation.

Discussion and learning points

- Early recognition, prompt level 1 and multi-disciplinary care can be crucial to reduce thyroid storm related mortality.
- The ECMO can successfully be used in endocrine emergencies causing cardiorespiratory collapse due to reversible aetiology.
- Potential consequences of poor compliance of patients of Graves' disease towards medical therapy can help to delineate the importance of early definitive therapy.

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EP114

Thymic hyperplasia in Graves' disease: case presentation and review of current literature

Alex Lewis & Kelly Cheer
Pennine Acute Hospitals NHS Trust, Manchester, UK.

A 37-year-old Nigerian lady was referred to the endocrinology clinic with worsening dyspnoea, weight loss, poor sleep and palpitations over the preceding few months. She had a past history of depression treated with citalopram. She was clinically and biochemically thyrotoxic with a TSH < 0.01 μ/l [0.4–5] and free T_4 49.3 pmol/l [9–19]. TSH receptor antibodies were positive. She was commenced on carbimazole 40 mg once daily and propranolol 40 mg twice daily. After 2 months of therapy her free T_4 had improved to 23.4 pmol/l and her therapy was altered accordingly.

Despite significant improvement in her thyroid function, she experienced ongoing dyspnoea, nocturnal sweating and cough. Her general practitioner referred her to the respiratory clinic, where she described occasional haemoptysis after prolonged coughing. Induced sputum testing for Acid–Alcohol Fast Bacilli was negative. A CT scan showed a diffuse soft tissue mass in the anterior and prevascular mediastinum but importantly no lymphadenopathy was evident in her thorax, abdomen or pelvis. Acetylcholine receptor antibodies were negative. She was diagnosed as having thymic hyperplasia as a result of Graves' thyrotoxicosis. The thymic hyperplasia reduced significantly in volume on interval scans after optimal medical management of her thyrotoxicosis, and we were able to reassure her without the need for invasive investigations such as mediastinoscopy or thymic biopsy.

This case reminds us that thyrotoxicosis is a possible cause of dyspnoea. Thymic hyperplasia associated with Graves' disease is rare, but has been reported in the literature. Routine assessment for thymic hyperplasia is not recommended but with increasing use of CT scanning, may be identified as an incidental finding.

This case highlights the need to be aware of Graves' disease as a cause for thymic hyperplasia and invasive management is not necessarily required, assuming there are no features concerning for myasthenia gravis or underlying malignancy.

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EP115

Could a stitch in time save nine?

Rodicaj Chelmenciuc, Grace Cooper & Raj Tanday
King George Hospital, London, UK.

We present the case of a 55 year old woman with Graves' disease currently in remission but previous agranulocytosis with carbimazole therapy.

She has a past medical history of Sjogrens syndrome on no medication. There is a family history of type 1 diabetes and thyroid disease in several members. She is Caucasian, a non smoker and drinks no alcohol. She is a primary school teacher.

In December 2014 she presented to her GP with palpitations, breathlessness, weight loss and tiredness. She had a fT_4 of 22.6 pmol/l and fully suppressed TSH. She was given beta blocker and 20 mg of carbimazole. One month later, on this dose, she had resolution of symptoms and weight gain but developed fever and sore throat. Blood tests revealed Hb 126 g/l, WCC 2.7×10^9/l, Plt 348×10^9/l, neutrophils 0.3×10^9/l, creatinine 84 μmol/l, ALP 208 IU/l, ALT 37 IU/l, bilirubin 9 μmol/l, TSH 0.07 mU/l, fT_4 8.6 pmol/l. She was treated as a neutropenic sepsis. Carbimazole was discontinued. She was cultured given i.v. fluids, antibiotics and GCSF. She was nursed in a side room and made a good improvement after 5 days. Her cultures were negative and she was discharged.

In clinic review, March 2015 she continues to feel well with no symptoms of relapse. She has no palpable goitre and no eye signs. She is biochemically euthyroid with fT_4 13.3 pmol/l, fT_3 4.2 pmol/l, TSH 0.11 mU/l. TSH receptor antibodies are positive at 1.34 u/ml confirming Graves. Subsequent ultrasound shows 2 left sided nodules 22×9 mm and 3 mm. Both show peripheral and moderate increased vascularity. There is no microcalcification or lymphadenopathy. An uptake scan shows normal uptake levels in keeping with a well controlled multinodular goitre.

In our MDT we felt that relapse is likely and treatment with thionamide drugs is contraindicated. We consider whether we should wait for relapse or prophylactically treat with radioiodine or surgery.

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EP116

Can myxedema coma be managed in a ward? A complicated case of myxedema with peg feeding

Fareha Najeeb Mohideen Bawa & Yahya Mahgoub
St Helens and Knowsley NHS Trust, Liverpool, UK.

61 years old female with multiple comorbidities such as ckd-3, Trans abdominal hysterectomy and oophorectomy for endometrial cancer, complicated by entero-cutaneous fistula, ileal conduit and cholecystectomy.

She presented with generally unwell, nausea, vomiting, confusion.

On Examination she was bradycardic, low gcs, hypotensive and hypothermic.

The metabolic causes for confusion was excluded, anion gap was normal and myxedema coma was suspected and started on i/v triiodothyronine. She was reviewed by critical care and deemed unsuitable for critical care due to multiple comorbidities.

The investigations were as follows,

Tsh >120, free $T_4-2.3$, free T_3 <1, cortisol-920, wcc-9.8, na-141, k-3.5, creatinine-243, TPO Antibody- >1300. Abg showed –ph-70.4, hco3-12, po2-6.26, pco2-6.26.

Patient improved with i/v thyroxine (T_4) and and started on oral T_4 with a dose of 1.7 μg/kg as divided doses due to previous bowel surgery and short bowel. Her tft improved and patient was discharged for follow up in endocrine clinic.

Myxedema coma has high mortality if not treated promptly. Although patient should be managed in a ITU settings ideally, supportive measures are of paramount importance in the treatment of life threatening illness.

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Featured Clinical Cases

Featured Clinical Cases

CC1

Life threatening cardiac arrhythmias following treatment of newly diagnosed Addison's disease

J Rochester[1], ED Aflorei[1], A Roberts[2] & A Wilton[1]
[1]Department of Endocrinology, Ysbyty Gwynedd, Bangor, UK;
[2]Department of Anaesthesia, Ysbyty Gwynedd, Bangor, UK.

A 36 year old man presented with collapse following weakness and vomiting for 2 weeks and 7 kg weight loss over 6 months. Thyroxine 50 mcg OD had been commenced 2 months earlier for hypothyroidism (Free T4 9.4 pmol/l, TSH 8.4 mU/l and anti-TPO antibodies 103.1 IU/mL). Examination found cachexia (weight 53.6 Kg), vitiligo, sinus tachycardia 110 bpm and BP 90/66 mmHg. Investigations: sodium 115 mmol/l, potassium 4.4 mmol/l, urea 9.9 mmol/l, creatinine 81 μmol/l, cortisol 137 nmol/l, aldosterone <100 pmol/l and ACTH 1337 ng/l. Short synacthen test: Cortisol 0 min 137, 30 min 136 and 60 min 142 nmol/l. Adrenal autoantibodies positive. Treatment with intravenous hydrocortisone followed by oral hydrocortisone (10, 5, 5 mg) and fludrocortisone (100 mcg OD) resulted in clinical improvement and normalisation of electrolytes. Shortly before discharge at 6 days he sustained a cardiac arrest with polymorphic ventricular tachycardia, ventricular tachycardia and ventricular fibrillation requiring DC cardioversion 27 times. The admission ECG showed long QTc (530 ms), which was absent 7 years earlier and post arrest. Whilst long QT intervals are common in glucocorticoid deficiency we are aware of only 5 reports of associated ventricular arrhythmias, all of which occurred before treatment. Glucocorticoid deficiency decreases glucocorticoid inducible kinase-1 (SGK1) which controls expression of the hERG gene (human ether-a-go-go related gene). This in turn encodes the alpha subunit of the rapidly activating delayed rectifier potassium channel (I_{Kr}) which mediates cardiac repolarisation. Hence there is delayed repolarisation with consequent long QT in Addison's disease. This case demonstrates that life threatening arrhythmias can occur following treatment for Addison's disease as well as before treatment. Why this occurs in only a minority of cases is unknown. The patient made a remarkable recovery from his experience.

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CC2

More than just Diabetes Insipidus

Xilin Wu & Alan Choo-Kang
Basildon and Thurrock University Hospitals NHS Foundation Trust, Essex, UK.

A 54-year-old gentleman presented with increased urinary frequency, urgency and nocturia. His GP treated him for benign prostatic hypertrophy with tamsulosin. When this failed to alleviate his symptoms he was referred to urology. Investigations revealed he was drinking in excess of 6 litres of fluid per day, hence he was referred to endocrinology.

Aside from a 6-month history of polyuria and polydipsia, there was no history of previous head injury, headaches and no signs of any visual field defects. Investigations revealed normal fasting glucose and basal pituitary function, preserved U&Es (Na144) but high serum osmolality: 300 mosm/kg (275–295 mosm/kg) and low urine osmolality 147 mosm/kg. MRI showed appearances compatible with lymphocytic hypophysitis. A water deprivation test confirmed partial cranial diabetes insipidus (CDI). He was started on desmopressin with good effect.

Meanwhile this gentleman was being investigated elsewhere for chest pain. A CT chest revealed mediastinal, para-aortic and para-iliac lymphadenopathy. Investigations for sarcoidosis were inconclusive. Incidentally, a suspicious lesion in his left kidney and retroperitoneal fibrosis were also noted on CT. A renal biopsy performed showed evidence of interstitial nephritis. Given the host of problems this man had accumulated the question of a unifying diagnosis: immunoglobulin G4-related (IgG4-related) disease was proposed. This was confirmed with raised plasma IgG4-levels and IgG4 positive staining on renal biopsy. He subsequently developed renal failure and secondary hypogonadism. This responded well to steroid and testosterone treatment respectively. He remains on desmopressin.

Discussion

IgG4-related disease is an immune-mediated condition which can affect almost every organ system. CDI is a rare feature of this disease and even more uncommonly the presenting symptom. First reported in the literature in 2007, recent studies suggest its prevalence has been underestimated. It is therefore important to consider this multisystem disease when diagnosing CDI as this has implications on management, especially if there is multi-organ involvement.

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CC3

Tremelimumab-induced Graves' disease

Earn H Gan[1,2], Ruth Plummer[1,2], Simon Pearce[1,2] & Petros Perros[1,2]
[1]Newcastle University, Newcasle, UK; [2]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK.

Ipilimumab and tremelimumab are monoclonal antibodies directed against the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and have been used as the immunotherapies against immune checkpoints that suppress T cell activation. These anti-CTLA4 antibody-based therapies are effective in treating various cancers including metastatic melanoma. However, a few immune-related adverse events including hypophysitis and transient thyroiditis have been reported. We reported the first case of tremelimumab-induced Graves' thyrotoxicosis.

A 55-year old man who was diagnosed with metastatic melanoma was enrolled into a phase II trial of anti-CTLA4 monoclonal antibody following a relapse of metastatic nodal and lung diseases. He completed 8 cycles of Tremelimumab in 2 years followed by 6-monthly Tremelimumab treatment with good response. However, the patient started to lose weight despite good appetite within a 6-month duration, after having intermittent Tremelimumab for 8 years. He has no personal or family history of thyroid or autoimmune diseases. He was clinically euthryoid and no goitre was palpable. There were no signs suggesting Graves' ophthalmopathy. His serum TSH was suppressed with raised free thyroid free T3 13.0 pmol/l and free T4 27.6 pmol/l. Thyroid peroxidase antibodies (TPO) were elevated at >600 kU/l with raised thyrotropin receptor antibody (TRAB) at 5.0 IU/l. These results are consistent with Graves' disease. He was then started on carbimazole 40 mg daily as part of the block and replace therapy. Further Tremelimumab therapy was deferred until he was rendered biochemically euthyroid.

The mechanistic profile of anti-CTLA4 induced thyroid dysfunction and the long-term endocrine safety of this therapeutic approach remains unclear. It is important to monitor thyroid functions in patients receiving anti-CTLA4 therapies as their effects on endocrine systems could be more latent or prolonged than the data from the current clinical trials suggests.

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CC4

Asymptomatic elevated PTH level due to immunoassay interference resulting from Macro-PTH: a case report

Paul Prodan, Eka Nandoshvili, Craig Webster & Jayadave Shakher
Heart of England NHS Foundation Trust, Birmingham, UK.

Introduction

Immunoassays are important tools in the diagnosis and management of disease; however, they are not free from interference by cross-reacting substances. Discordant clinical evidence and laboratory results raised suspicion of interference in a patient with persistently raised parathyroid hormone.

Case Presentation

Case description: A 56-year-old Caucasian female previously diagnosed with hypothyroidism consistently demonstrated elevated PTH levels with normal renal function, calcium and vitamin D concentrations. There was no clinical evidence of hyperparathyroidism and imaging of thyroid and parathyroid showed no evidence of pathology.

Results

The PTH levels were persistently elevated as measured by 2 different methods. (Roche and Abbott). PTH concentrations increased on dilution (base sample 28.5 pmol/l, 1:2 dilution 47 pmol/l). After treatment of the sample with polyethylene glycol (PEG) the PTH concentration decreased to 10.2 pmol/l. On dilution of the PEG treated sample, the diluted concentration was 12.1 pmol/l, demonstrating an appropriate response to dilution. These results indicated the presence of a Macro-PTH.

Conclusion

Macro-PTH is PTH bound to an immunoglobulin molecule, which prevents its clearance by the kidneys and thus increased half-life. These molecules are usually

ROCHE PTH Reference range: (1.6 – 7.2 pmol/l)		ABBOTT PTH Reference range: (1.6 – 7.2 pmol/l)	
Oct 2012	122.5 pmol/l	Jan 2016	126.9 pmol/l
Dec 2012	195.8 pmol/l		
Feb 2013	143.7 pmol/l		
July 2013	165.6 pmol/l		

not biologically active. Interference should be sought when there is lack of clinical correlation with immunoassay hormone levels.

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CC5

A case report of a symptomatic osteopoikilosis patient caused by novel mutation in LEMD3

Khaled Tofeec[1], Handrean Soran[1], Zulf Mughal[2] & Peter Selby[1]
[1]Central Manchester Foundation Trust, Manchester, UK; [2]Royal Manchester Children's Hospital, Manchester, UK.

17 years lady presented with a fall onto her left knee, following which she continued to have severe persistent pain and occasionally her knee gave away with intermittent "locking". A referral to metabolic bone disease clinic was made as the left knee X-ray showed discreet spherical areas of increased radiological density with normal CT and MRI scans of the left knee. Physical examination was unremarkable. Her brother was under investigation for lumps under skin. Morphology of the spots noticed on X-ray was identical to those seen in osteopoikilosis. Moreover, the relative clinical and laboratory tests such as FBC, ESR, CRP, rheumatoid factor, serum electrolytes, LFT, TFT, Vitamin D, tumour markers, alkaline phosphatase, ANA, and anti-DS-DNA were negative for any type of arthritis, infection or osteoblastic bone metastases which were in the differential diagnosis. Bone densitometry was normal and skeletal survey to determine the extent of this generalised bone disorder revealed extensive changes representing osteopoikilosis throughout the skeleton involving the hands, feet, humerus, ulna and radius, femur, tibia and fibula, changes also present within the pelvis and in the sacrum. LEMD3 heterozygous gene mutation was positive. Subsequently she developed a lump over the lateral aspect of right scapula which increased in size and causing discomfort particularly at night. MRI and CT scans of the right scapula were unremarkable apart from a bony mass. She underwent surgical removal of the bone lump (Although the risk of malignant transformation of osteopoikilosis is rare) which confirmed to be osteochondroma. Her brother has been diagnosed to be suffering from Buschke-Ollendorff syndrome, which can be associated with both osteopoikilosis and melorheostosis. Despite the fact that osteopoikilosis is a very rare asymptomatic condition that most physicians are not familiar with, it is valuable to take it into consideration, particularly when diagnostic issues on bone radiography occur and severe pain at the adjacent joints co-exists.

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CC6

Vitamin D-Dependent Rickets Type I caused by a Novel Frameshift Mutation of the 25-hydroxyvitamin D1-alpha-hydroxylase gene (*CYP27B1*)

Victoria Stokes[1], Caroline Gorvin[1], Brian Shine[2] & Rajesh Thakker[1]
[1]Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, UK; [2]Oxford University Hospitals NHS Foundation Trust, Oxford, UK.

Vitamin D-dependent rickets type-1 (VDDR1) is an autosomal recessive disorder characterised by onset of rickets by 2 years of age, accompanied by poor growth and hypotonia, muscle weakness, seizures, hypocalcaemia with secondary hyperparathyroidism, hypophosphataemia and normal plasma 25-hydroxyvitamin D ($25(OH_2)D$) concentration that distinguishes VDDR1 from vitamin D deficient rickets. VDDR1 is caused by loss-of-function mutations of the 25-hydroxyvitamin D 1-alpha-hydroxylase gene, also referred to as cytochrome P450 family 27 subfamily-B member-1 (*CYP27B1*), and this explains the occurrence of low plasma $1,25(OH_2)D$ concentrations, despite the normal 25(OH)D and elevated parathyroid hormone (PTH) concentrations. To date, 46 *CYP27B1* mutations have been identified in VDDR1 patients and ~75% of these are missense, ~15% are small deletions or insertions, and ~10% are nonsense mutations. We report a consanguineous family, originating from the Indian subcontinent, in which two siblings have VDDR1 due to a novel homozygous *CYP27B1* mutation (Phe80fsX157). The proband, at 21 months of age presented with bilateral pes plano valgus and flexion deformity of the knees in association with hypocalcaemia, and his sister presented at 6 weeks of age with a hypocalcaemic seizure. Treatment with calcitriol (i.e. $1,25(OH)_2D$) restored normocalcaemia. DNA sequence analysis, using leukocyte DNA, of the *CYP27B1* nine coding exons, and intron-exon boundaries, identified a novel homozygous 1 bp deletion of a T at codon 80 in exon 2 of the *CYP27B1* gene. This mutation predicts a frameshift with 77 missense amino acids, followed by a premature stop codon at amino acid 157. Such a mutation, in which 351 amino acids are lost is likely deleterious. Thus, the VDDR1 in this family is due to a novel, frame-shifting *CYP27B1* mutation.

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CC7

Spurious diagnosis of phaeochromocytoma due to drug induced symptoms and abnormal investigation results

R Preece, J Rochester, E.D Aflorei & A Wilton
Department of Endocrinology, Ysbyty Gwynedd, Bangor, UK.

A 70 year old female was referred with a putative diagnosis of phaeochromocytoma. She was awaiting hiatus hernia surgery; the diagnosis was based on a history of hypertension and a persistent sinus tachycardia of 110 bpm. Investigations had shown modest elevation of 24 hour normetadrenaline at 4.71 to 4.98 micromol/24 hr (<4.4) on 3 occasions and plasma normetadrenaline of 2398 and 2504 pmol/l (<1180). Review of her medical records confirmed that the onset of tachycardia coincided with commencing treatment with nortriptyline 6 years earlier for symptoms of irritable bowel syndrome. She was also taking bisoprolol 7.5 mg OD, ramipril 5 mg OD and ivabradine 7.5 mg BD at time of investigation. Further in hospital investigation off nortriptyline, bisoprolol and ramipril (known to elevate noradrenaline levels) revealed plasma normetadrenaline 1261.3 and 1658.7 pmol/l (supine) rising to 1735.7 and 2503.7 pmol/l (sitting). The tachycardia resolved off these drugs. Suspicion that ivabradine was causing spurious results lead to repeat investigation off treatment. Results were plasma normetadrenaline 1170 pmol/l supine and 1470 pmol/l sitting (a physiological response). A clonidine test resulted in normal suppression of plasma normetadrenaline to 618.3 pmol/l. The ivabradine effect was confirmed by restarting 7.5 mg BD with repeat investigations showing plama normetadrenaline 1730.9 pmol/l (sitting) and 1498.8, 1600.2 and 1621.4 pmol/l (supine) at 30, 60 and 120 minutes respectively. We concluded that the clinical suspicion of phaeochromocytoma based on tachycardia was due to a drug effect (nortriptyline) as were abnormal biochemical results (nortriptyline, bisoprolol, ramipril and ivabradine). The effect of the latter has not been described previously and our report will alert investigators to the problem. She underwent uncomplicated surgery.

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CC8

Diffuse Idiopathic Pulmonary Neuroendocrine cell hyperplasia (DIPNECH): two unusual cases of cyclical ectopic adrenocorticotrophic hormone secretion

Sarah N Ali, Maura Moriarty, Lisa Yang, Jonathan Anderson & Jeannie F Todd
Imperial College Healthcare NHS Trust, London, UK.

We present two uncommon cases of cyclical ectopic ACTH-dependent Cushing's syndrome due to diffuse idiopathic pulmonary neuroendocrine tumour (DIPNECH).

Case 1

62 yr lady presented with rapid onset of muscle weakness, diabetes and hypokalaemia. Random cortisol:1710 nmol/l, ACTH level:610 ng/l. LDDST: failure to suppress cortisol levels. Imaging: normal pituitary gland and bilateral adrenal hyperplasia, consistent with ACTH dependent Cushing's syndrome. She was commenced on Metyrapone. Inferior Petrosal Sinus Sampling (IPSS) was planned and Metryapone withdrawn, however 2/52 off Metyrapone, cortisol and ACTH had normalised, consistent with spontaneous resolution of Cushing's syndrome. IPSS was postponed. 2/12 later, she again relapsed and Metyrapone was restarted. IPSS confirmed ectopic ACTH source. CT chest showed a right lower lobe nodule, with increased uptake on 68-Gallium DOTATATE PET/CT scan. Prior to resection, she again cycled out of Cushing's syndrome and therefore, given a Block and replace regime of Metyrapone/HC whilst undergoing Rt lobectomy. Histology showed Carcinoid tumour with evidence of DIPNECH. Post-operatively, she is in remission, requiring continued HC replacement.

Case 2

33 yr lady presented with a short history of weight gain, abdominal striae, proximal myopathy and secondary amenorrhoea. Of note, she reported a previous episode with similar symptoms one year earlier which subsided spontaneously after a few weeks. Random cortisol:4000 nmol/l, ACTH:98 ng/l. LDDST: failure to suppress cortisol levels. IPSS showed no central:peripheral ACTH gradient, representing ectopic ACTH source. CT chest showed multiple pulmonary

nodules, a dominant RLL nodule larger since 2006. 68-Gallium DOTATATE PET/CT scan was normal. Metyrapone was commenced. One week later, Metyrapone was stopped due to low cortisol levels. Off Metyrapone, cortisol levels remained low with concomitant reduction of ACTH levels, indicating another spontaneous remission of Cushing's syndrome. Histology from an excision biopsy of the RLL nodule revealed tumourlets with a typical carcinoid appearance and a background of DIPNECH. Post-operatively, she is clinically in remission.

Conclusion

DIPNECH is a rare disorder consisting of nodular proliferation of airway neuroendocrine cells and has rarely been associated with ectopic ACTH production, with only one case reported in the literature.

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CC9

Successful treatment of primary aldosteronism with partial adrenalectomy, facilitated by the use of ^{11}C-Metomidate PET/CT

Waiel Bashari[1], Andrew Powlson[1], Olympia Koulouri[1], Denis Quill[2], Morris Brown[1], Heok Cheow[1], Michael Conall Dennedy[2] & Mark Gurnell[1]
[1]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [2]National University of Ireland & Galway University Hospital, Galway, Ireland.

Background

Primary aldosteronism (PA) is responsible for 5-10% of all cases of HTN. The current gold standard test for determining the side of aldosterone hypersecretion is adrenal vein sampling (AVS). ^{11}C-Metomidate PET/CT (METO-PET) has recently emerged as a potential non-invasive alternative to AVS. As ^{11}C-Metomidate is concentrated within 'hyperfunctioning' nodules, METO-PET potentially not only identifies the side, but the exact site of aldosterone hypersecretion, thus allowing more targeted surgical intervention.

Case report

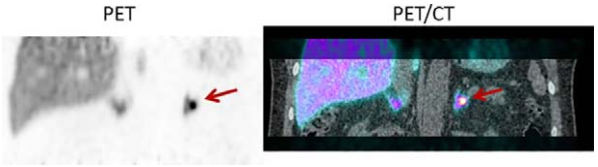
A 45-year-old man was found to have HTN and hypokalaemia after sustaining a myocardial infarction. He required four anti-hypertensive agents to achieve BP control. His aldosterone was elevated with a suppressed renin, and aldosterone did not adequately decrease following saline suppression, confirming the diagnosis of PA. Adrenal CT and MRI did not convincingly show a lesion. He underwent AVS, but the result was inconclusive (right adrenal vein not cannulated). METO-PET revealed increased tracer uptake in a subcentimeter nodule on the left adrenal (Figure 1).

Treatment

He underwent a posterior retroperitoneoscopic procedure, during which the lateral limb of the left adrenal was removed, leaving the rest of the gland *in situ*. Histology confirmed the presence of a small Conn's adenoma. The patient is normotensive post-surgery, on no antihypertensive medications, with normal biochemistry.

Conclusion

This case highlights the ability of METO-PET to not only lateralize, but actually localize the site of aldosterone hypersecretion. This allows selective removal of a Conn's adenoma with sparing of the adjacent normal adrenal gland.



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CC10

ACTH-dependent Cushing's syndrome unmasked following transphenoidal surgery for Acromegaly – the rare coexistence of dual endocrinopathies

Parizad Avari, Aditi Sharma, Quirinius Barnor, Thomas Galliford, Arla Ogilvie & Chantal Kong
Watford General Hospital, Watford, West Hertfordshire, UK.

Coexistence of Acromegaly with Cushing's syndrome in the same individual is rare. We herein describe a case of a 59-year-old woman, whose hypercortisolism was unmasked following transphenoidal surgery for Acromegaly.

She presented to the Endocrine Clinic in 2006 with acromegalic features and MRI revealing a pituitary macroadenoma $20\times18\times18$ mm. Repeat dynamic evaluation showed inadequate GH suppression (initially normal), raising the possibility of early rumbling Acromegaly. 0900 hrs serum cortisol was 287 nmol/l. She was started on Cabergoline, later switched to Lanreotide but underwent transphenoidal surgery in 2015 due to evolving visual defects. Histology revealed a sparsely granulated somatotroph adenoma, ACTH negative with Ki67 $<1\%$. Postoperative serum cortisol was noted >1000 nmol/l on discharge.

A month later, she attended outpatients with typical Cushingoid facies, new onset diabetes mellitus, hypertension with severe hypokalaemic alkalosis and significant proximal myopathy and was admitted acutely. Random serum cortisol >2000 nmol/l, with failure to suppress on overnight, low and high dose dexamethasone suppression. ACTH was elevated at 118 ng/l. She was initiated on Metyrapone and Octreotide with clinical improvement a few days later. Repeat MRI pituitary revealed significant residual pituitary tumour burden with new bilateral avid adrenal hyperplasia on FDG-PET (normal 6months earlier), with persistent incidental non FDG-avid lung and thyroid lesions. She unfortunately became septic whilst awaiting transfer to the local tertiary centre and died from a stroke.

This case highlights the rare coexistence of two endocrine pathologies with Cushing's syndrome being unmasked following discontinuation of Lanreotide and the importance therewith of close endocrine surveillance in postoperative pituitary patients in the acute, medium and long-term phases. Prompt early management of active Cushing's is imperative to minimize significant morbidity and mortality. The true source of her excess ACTH causing hypercortisolism (pituitary or ectopic) remains a discussion point as post-mortem findings were inconclusive.

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