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Volume 36
November 2014

42nd Meeting of the British Society for Paediatric Endocrinology and Diabetes 2014

12 – 14 November 2014, Winchester, UK

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CME Session

CME1

Endocrine tumours
J Newell-Price
Sheffield, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.36.CME1

CME2

Surgery of endocrine tumour
B Harrison
Sheffield, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.36.CME2

CME3

The late effects of treatment for childhood cancer
Nikki Davis
Southampton Children's Hospital, Southampton, UK.

As survival from childhood cancer continues to rise, attention to the quality of survivorship becomes more relevant and important. The most frequent causes of death after surviving a malignancy, are disease recurrence, development of second cancer, and then cardiovascular disease. This means that strategies aimed at assessing the risk factors and contributions to cardiovascular disease in this group, with a view to developing effective secondary prevention strategies are required. Cancer survivors have suffered from the effects of the malignancy itself which can impair growth, nutrition, and quality of life. However, cancer treatments have also exposed the survivor to short and long term toxicities from chemotherapy, glucocorticoids, surgery, and irradiation. CCLG guidelines for long term follow-up, recommend screening for long term late effects according to disease and treatment exposure. Cranial irradiation causes hypothalamic and pituitary dysfunction, which are dependent on dose, fractionation, time since irradiation, and age at irradiation dependent. These patients require monitoring of pituitary function and timely pituitary hormone replacement. More recently it has emerged that some groups of cancer survivors also suffer from obesity, abnormal body composition (increased adiposity), increased risk of metabolic syndrome, and diabetes mellitus. This can be related to the tumour itself or surgery via local effects on the hypothalamus or pituitary, GHD after pituitary irradiation, glucocorticoid use, or reduced activity and fitness. Recent research has explored these late effects in more detail and a number of exercise interventions have shown promising results in terms of metabolic and cardiovascular risk, quality of life, and physical function. Future research aims to help to inform future treatment protocols to minimize toxicity and maintain high levels or survival, whilst also developing detailed long term follow-up strategies to enhance the longevity and quality of survival.

DOI: 10.1530/endoabs.36.CME3

CME4

Female contraception and reproductive endocrinology

Abstract unavailable.

DOI: 10.1530/endoabs.36.CME4

CME5

Infertility and infertility management
N Macklon
Southampton, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.36.CME5

CME6

Trainees update
Rachel Besser[1] & Caroline Steele[2]
[1]College of Paedactrics and Child Health, London, UK; [2]Royal College of Paedactrics and Child Health, Manchester, UK.

The trainee reps (Drs C Steele and R Besser) will provide an update on their activities on behalf of the trainees in the past year including:
i) Update of the trainees' section of the BSPED website.
ii) Results of a recent survey of GRID trainees aimed to track training and for future workforce planning.
iii) Ongoing activities (such as trainees' section of the BSPED newsletter) and number of e-mail contacts for trainees.
iv) Any other issues.

DOI: 10.1530/endoabs.36.CME6

Plenary Guest Lecture

PL1

The future of the child with T1DM
E Gale
Bristol, England.

Abstract unavailable.

DOI: 10.1530/endoabs.36.PL1

Symposia 1 Controversies in Vitamin D deficiency

S1.1

Consequences of maternal vitamin D deficiency
Cyrus Cooper
University of Southampton, Southampton, UK.

Osteoporosis is a skeletal disease characterised by low bone mass and susceptibility to fracture. Preventive strategies against osteoporotic fracture can be targeted throughout the life course. Although there is evidence to suggest that peak bone mass is inherited, current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk. Evidence has begun to accrue that fracture risk might be modified by environmental influences during intrauterine or early postnatal life: i) epidemiological studies which confirm that subjects who are born light and whose growth falters in the first year of postnatal life, have significantly lower bone size and mineral content, at age 60–75 years; ii) cohort studies demonstrating that subsequent lower trajectories of childhood growth are associated with an increased risk of hip fracture among such men and women; iii) detailed physiological studies of candidate endocrine systems which might be programmed have shown that birthweight and growth in infancy alter the functional settings of the GH/IGF1 and vitamin D/PTH axes; iv) studies characterising the nutrition, body build, and lifestyle of pregnant women which relate these to the bone mass of their newborn offspring, have identified a number of important determinants of reduced fetal mineral accrual: these include maternal smoking, excessive weight bearing physical activity in late pregnancy, and low maternal fat stores. More recently, maternal vitamin D insufficiency during mid and late gestation has been associated with bone mineral content and areal BMD in the offspring at age 9 years. As a consequence, large randomised controlled trials of

vitamin D supplementation in pregnancy have been instituted and the results of these will inform public health interventions aiming to reduce the frequency of maternal vitamin D deficiency.

DOI: 10.1530/endoabs.36.S1.1

S1.2

The role of vitamin D deficiency in unexplained fractures of infancy

Zulf Mughal
Central Manchester University, Manchester, UK.

Multiple fractures, for which there is no clear explanation, raise the possibility of non-accidental injury (NAI). Vitamin D deficiency, defined as serum 25-hydroxyvitamin D (25OHD) concentrations of <50 nmol/l, is common during pregnancy and infancy.

It had been suggested by Keller & Barnes (*Pediatr Radiol* 2008 **38** 1210–1216) that subclinical vitamin D deficiency could explain some fractures that have been ascribed to NAI. Evidence from review of available literature (observational studies and series of case reports), suggests that children with clinical, biochemical and radiological evidence of rickets have increased risk of fracture. In a retrospective study, Chapman *et al* found that fractures 17.5% of infants and toddlers with rickets aged between 2 and 14 months (*Pediatr Radiol* 2010 **40**(7) 1184–1189). Fractures only occurred in those who were mobile and had severe radiological evidence of rickets. None of the fractures were considered to be characteristic of NAI. In contrast, there is no convincing evidence that subclinical vitamin D deficiency is associated with increased fracture risk in children. Schilling and colleagues found that serum 25OHD levels in 118 <2-year-old infants with fractures which were considered to have occurred accidentally (60%) or due to non-accidental injury (31%) or where the cause could not be determined with certainty (9%) were not different (*Pediatrics* 2011 **127**(5) 835–841).

In infants with multiple unexplained fractures the possibility of NAI and disorders associated with fragility fractures, e.g. osteogenesis imperfecta and florid vitamin D deficiency rickets should be considered. However, vitamin D deficiency, in the absence of biochemical & radiological evidence of rickets is not likely to be associated with increase risk of fragility fractures in young infants.

DOI: 10.1530/endoabs.36.S1.2

S1.3

Strategies for prophylaxis and treatment of vitamin D deficiency

Nick Shaw
Univeristy of Brimingham, Birmingham, UK.

Current strategies for prevention of vitamin D deficiency are primarily aimed at infants and young children to prevent rickets. In most countries this is based on recommendations to take a daily multivitamin supplement containing vitamin D often in a dose of 350–400 IU. There is variation in recommendations as to at risk groups who should receive supplementation and at what age these commence. In the UK this is currently delivered through the Healthy Start scheme with a recommended age of commencement at 6 months. The uptake of Healthy Start multivitamins is however quite poor which at best reaches 20% of the relevant age group. Some European countries advocate higher daily doses of 1000–1200 IU daily in infants up to age 18 months.

The concept of intermittent dosing to prevent vitamin D deficiency in this age group is not widely accepted with some concerns regarding vitamin D toxicity. Children with chronic disease are often at risk of vitamin D deficiency with different strategies being used to maintain acceptable vitamin D levels.

The treatment of vitamin D deficiency is again largely based on daily oral dosing for several weeks. Recommended dosage guidelines vary significantly internationally with little supporting evidence base and some variation in the threshold for defining vitamin D sufficiency. A significant issue in the UK is the use of unlicensed vitamin D preparations which are regarded as 'special products' and as such may attract significant prescribing costs. Newer licensed products are becoming available which may change this. The use of single or intermittent large doses or 'stoss therapy' although used in some countries are not routinely used although there is a reasonable evidence base for their efficacy and safety. A recent international consensus meeting on Rickets hosted by ESPE has produced recommendations on prevention and treatment of vitamin D deficiency in children.

DOI: 10.1530/endoabs.36.S1.3

Symposia 2 Recent advances in adrenal disease

S2.1

Adrenal development and adrenal insufficiency

John Archermann
UCL Institute of Child Health, London, UK.

The human adrenal gland develops from around 4 weeks post conception and undergoes rapid growth and differentiation in early fetal life. At birth, the adrenal gland consists of a mature adult type cortex capable of mineralocorticoid and glucocorticoid production, as well as a fetal zone that involutes in the first few months. Disruption of the HPA axis development can cause adrenal hypoplasia. This is classically broken down into secondary causes (ACTH insufficiency); ACTH-resistance like conditions (sometimes called familial glucocorticoid deficiency (FGD)); and defects in adrenal development itself (primary adrenal hypoplasia). Advances in molecular biology have played an important role in defining some of these conditions, leading to better understanding of phenotype and clinical evolution. The best example of this is X-linked adrenal hypoplasia, which was first reported to be due to defects in DAX1/NR0B1 20 years ago. This condition classically presents with salt-losing adrenal failure and hypogonadotropic hypogonadism, but a much greater range of presentations and features have now been described. More recently, IMAGe syndrome (Intrauterine growth restriction, Metaphyseal dysplasia, Adrenal hypoplasia and Genital anomalies) has been shown to be due to activation of the cell-cycle regulator CDKN1C, a factor where loss of function causes Beckwith–Wiedemann syndrome and hyperinsulinism. Diabetes has recently been reported in CDKN1C activation. Finally, the range of ACTH resistance-like conditions has expanded rapidly (MRAP, NNT, and MCM4), some of which have unique associated features. Establishing a specific diagnosis can be important for identifying associated features, tailoring treatment to an individual, establishing long-term prognosis, and identifying other family members at risk of adrenal insufficiency. As many of these conditions have overlapping clinical and biochemical features, genetic approaches to diagnosis are proving invaluable in many cases.

DOI: 10.1530/endoabs.36.S2.1

S2.2

Curing Addison's disease

Simon Pearce
Newcastle University, Newcastle, UK.

Addison's disease is a good therapeutic target for regenerative medicine, as adrenal cell mass and steroidogenesis have clear intrinsic plasticity, as determined by circulating ACTH concentrations. With the advent of the biological agents as disease-modifying therapy for inflammatory arthritis and their experimental use in several other autoimmune conditions including type 1 diabetes, we undertook a pilot study of immunomodulatory therapy in patients with autoimmune Addison's disease. Six newly diagnosed patients were treated with B cell depletion, leading to a drop in serum 21-hydroxylase antibodies in all and one patient had a progressive rise in serum cortisol, such that she was able to discontinue steroid replacement. In a further attempt to explore the plasticity of adrenal steroidogenesis in Addison's disease, we performed a 20-week study of high dose $ACTH_{1–24}$ (Synacthen) therapy in 13 patients with established autoimmune Addison's disease. Two of the 13 patients had significant residual adrenal function at baseline, and both had progressive rises in serum cortisol and aldosterone during ACTH therapy. Both were able to stop oral glucocorticoid and mineralocorticoid replacement during the study, but one of the patients had a progressive decline in steroidogenic function once ACTH was discontinued. The other patient remains well with good steroidogenic function and no replacement medications 36 months after ACTH was stopped. These studies highlight that residual adrenal function in patients with Addison's disease is important as a future therapeutic target, and starts to explain why spontaneous recovery of established Addison's disease has occasionally been reported.

DOI: 10.1530/endoabs.36.S2.2

Symposia 3 New developments from trials in TIDM

S3.1

New developments from trials in TIDM: findings from the DECIDE trial

John Gregory
Cardiff University, Cardiff, UK.

Objectives
There is uncertainty about the best approach to management of type 1 diabetes (T1D) in clinically well children at diagnosis. This study, investigated the impact of home and hospital management on biopsychosocial and economic outcomes.
Methods
Multi-centred randomised controlled trial. 203 newly diagnosed children aged 0–17 years from eight UK centres were randomised for treatment initiation at home ($n=101$) or in hospital ($n=102$). Primary outcome: difference in HbA1c at 2-year follow-up. Secondary outcomes: coping, anxiety, quality of life, diabetes knowledge, social activities, satisfaction, and total costs. Qualitative interviews were conducted with health professionals, parents, and children.
Results
There was no significant difference ($P=0.86$) in mean HbA1c at 2 years between home (72.1 mmol/mol) and hospital (72.6 mmol/mol), nor for most secondary outcomes. Diabetes specific resource use was similar between groups during initiation (days 0–3) but total initiation costs were significantly higher in the hospital arm due to the indirect hospital-related ('hotel') costs of children being in-patients. Post initiation NHS costs were similar between arms during the 2-year follow up. Many children/parents initially desired the home arm but in retrospect preferred whichever arm they had been randomised to. Most nurses preferred home management despite logistical challenges. Consultants had less contact with home-managed children and reported difficulties building rapport with these families. No children in the home arm were re-admitted to hospital in the first 4 days.
Conclusions
Hospital management of T1D in clinically-well children at diagnosis significantly increases NHS costs, with no difference in glycaemic control or quality of life over the first 2 years when compared to home management.

DOI: 10.1530/endoabs.36.S3.1

S3.2

How do the findings from the Hvidore study change practice?

Hilary Hoey
Royal College of Physician, Dublin, Ireland.

The Hvidoere International Study Group on Childhood Diabetes comprising of 26 paediatric diabetes centres from 23 countries (Europe, North America, Japan, and Australia) has conducted five major studies, in order to asses metabolic control and quality of life in children and young people with type 1 diabetes and determine factors influencing good metabolic control and those creating barriers. The findings of these studies have led to an internationally recognised remission parameter and the development of validated well-being and quality of life questionnaires with multiple translations. Whilst major advances in diabetes management tools including CSII and glucose sensors metabolic control in children is suboptimal with less than one-third achieving a HbA1C of <59 mmol/mol (7.5%). Empowering the child and family by education, motivation, and support is the cornerstone of good control. The diabetes management regimen should be tailored to the individual psychosocial needs of the family and should be provided by a multidisciplinary team trained in paediatric diabetes care. Psychosocial factors are often not obvious, so it is important that healthcare professionals do not make assumptions but assess them scientifically. The health care team should have a cohesive approach and target optimal glycaemic control. Continued parent involvement is important with the promotion of independent, responsible self-management. Easily accessible ongoing care and phone support is required. Children from single parent families and ethnic minority groups have poorer metabolic control, poorer parent well-being, and ethnic minority groups have a significantly lower quality of life and thus require additional resources.
The best results were obtained by physicians who were target-driven and teams and families where there was unanimity of purpose. There is a need for ongoing collaborative international research to determine the most effective treatments, education, and psychosocial intervention programmes.

DOI: 10.1530/endoabs.36.S3.2

S3.3

Prevention trials in type 1 diabetes', including an update on the ongoing TRIGR trial

M Knip
Helsinki, Finland.

Abstract unavailable.

DOI: 10.1530/endoabs.36.S3.3

Debate: Children with diabetes should be managed centrally or locally

D1.1

Children with diabetes should be managed centrally

Peter Hindmarsh
University College London, London, UK.

Paediatric diabetes is essentially a hospital based service with opportunities for care delivery in settings such as the home, school and community based organisations. The delivery of care (as defined in part by HbA1c) varies throughout the UK. Factors influencing this include varying staffing levels and skill sets along with social deprivation and ethnic diversity and attaining a standard of equitable care is a major challenge. The fundamental issue is not whether care is delivered centrally or not but whether that care is of value to the patient. This means moving from a supply driven health care system organised around what physicians do to a patient-centred system organised around what patients need. To achieve this organisation into integrated practice units (IPU) of about 500 patients is a proven way to improve outcomes. An IPU is patient centric and results driven, focused on best way to deliver care using interdisciplinary groups, manages information, integrates decisions, and ensures continuity, is responsible for the whole cycle of care even if other entities are involved and the staff work exclusively in diabetes. The benefits for the patient are a partnership of excellence serving them, care delivered using state-of-art facilities and technologies, expertise always available when needed by the patient or their family, continuity of care and scale that allows development of dedicated teams rather than part time practitioners with shorter wait times and convenient booked appointments. For the clinical service common management allows for unified process of care, shared staff training developing skilled teams, strong governance, efficient division of labour, more rapid evolution and deployment of effective techniques and care plans. The scale allows for richer feedback and support, better flexibility, and efficiencies in scheduling. Finally for commissioners there are economies of scale in terms of best practice tariff and procurement, high patient value a rapidly responsive system to needs of patients and families with rapid implementation of advances in clinical management.

DOI: 10.1530/endoabs.36.D1.1

D1.2

Children with diabetes should be managed locally

Neil Hopper
Sunderland, UK.

Paediatric diabetes is a common, chronic, largely self managed disease. The problems children and young people deal with are complex and wide-ranging in scope. The key to success lies in close, personalised support and education for families facing this condition by an MDT who knows them well and is familiar with the local environment.
I will put the case that this is best delivered in the UK by properly trained, resourced and accountable local teams, supported by regional and national networks.

DOI: 10.1530/endoabs.36.D1.2

Diabetes Professionals Session

DP1

Paediatric obesity and type 2 diabetes

Nikki Davis
Southampton Children's Hospital, Southampton, UK.

Paediatric obesity, metabolic syndrome, and type 2 diabetes are on the rise worldwide and in the UK, and specialist services to address these complex and difficult problems are still in development. The definitions of obesity, diabetes and prediabetes in childhood and adolescence are not globally agreed and are affected by cultural and racial differences. In addition effective screening depends on the local availability of resources and the local population. The natural history of childhood obesity, insulin resistance, prediabetes and diabetes is becoming clearer and the associated co-morbidities are becoming better defined and described though certainly there are knowledge gaps in these areas which need to be addressed. In the UK, NICE guidance sets out the basic requirements for management of paediatric obesity but these recommendations are not being universally achieved. We will discuss the barriers to effective management of obesity and T2DM including joining up services between primary, secondary and tertiary care, multi-disciplinary working, the obesogenic environment, lack of ring-fenced resources, child protection concerns, cost-effectiveness and the modern problem of information overload. We will discuss the effective assessment and management of paediatric obesity, pre-diabetes and T2DM including the roles of diet, exercise, behavioral change, medication, bariatric procedures, and child protection procedures. Various new drugs and technologies are in development to manage obesity, and T2DM although these will only be helpful in addition to the strategies already discussed. Obesity and T2DM in childhood and adolescence can be successfully managed at the secondary and tertiary care level but this requires specialist multidisciplinary service development, and political and cultural change is also required to turn the tide. Some clinical cases will be presented to illustrate the successful factors in management.

DOI: 10.1530/endoabs.36.DP1

DP2

Type 2 diabetes

Sarah Ehtisham
Central Manchester University, Manchester, UK.

Over the last 20 years, the phenomenon of type 2 diabetes in childhood has been increasingly recognised. National Audit data shows that in the UK there remains a relatively low prevalence of childhood type 2 diabetes, whilst the incidence has increased sharply in other parts of the world.
This presentation aims to cover the pathogenesis of type 2 diabetes, its presentation, investigation, diagnosis and management, with a discussion of some of the newer treatments available. Long-term outcome data is now emerging and demonstrates a high risk of complications and comorbidities.

DOI: 10.1530/endoabs.36.DP2

DP3

Hypoglycaemia in type 1 diabetes mellitus

Peter Hindmarsh
University College London, London, UK.

Hypoglycaemia is the main factor limiting the use of intensive insulin regimens. The frequency is 0.1 – 0.3 episodes/person per day for symptomatic episodes and 1/year for severe ones. There is also an estimated mortality of 2–4% of people with type 1 diabetes mellitus (T1DM). Severe hypoglycaemia increases in frequency with duration of insulin treatment. The symptoms and signs of hypoglycaemia can be separated into those due to neuroglycopenia (cognitive impairment, seizures, coma) and neurogenic (adrenergic and cholinergic). The risk factors for development of hypoglycaemia relate to a relative or absolute excess of insulin e.g. exercise or missed meals. Recurrent hypoglycaemia is associated with the development of hypoglycaemia associated autonomic failure (HAAF). T1DM is also associated with the loss of glucagon secretion because the close interaction between the α and β cells is lost. Loss of glucagon coupled with HAAF which attenuates the catecholamine response to hypoglycaemia are the two major components to hypoglycaemia unawareness in T1DM. Recurrent hypoglycaemia leads to unawareness through HAAF. The mechanism of how HAAF develops ranges from altered neurotransmitter function, through perturbations in lactate metabolism to changes in cerebral neural networks. Selective serotonin-reuptake inhibitors increase the counter-regulatory response to hypoglycaemia. This would certainly reduce recurrent hypoglycaemic episodes. However, hypoglycaemia would still remain a risk as the loss of the glucagon response is independent of HAAF. Currently the best approaches to minimising hypoglycaemia are to better match insulin with carbohydrate and develop better exercise algorithms. In meta-analysis glucose sensing improves hypoglycaemia risk. The artificial and bionic pancreas projects will assist further in reducing hypoglycaemia risk while in the longer term cell based therapies are more likely to remove hypoglycaemia risk from the lives of patients with T1DM.

DOI: 10.1530/endoabs.36.DP3

DP4

National Audit Data highlight persistent sub-optimal control among increasing numbers of people living with diabetes with severe consequences for the individual and the NHS

Katherine Barnard
Southampton, UK.

Despite advances in therapies and healthcare, the prevalence of diabetes has reached epidemic proportions with increasing numbers of children and their families affected.
The psychological and psychosocial challenges facing families in living with the burden of diabetes are immense and have a direct and detrimental impact on their ability to achieve optimal glycaemic control. A paradigm shift away from a purely medical model to a greater emphasis on psychosocial aspects of diabetes has been advocated for several years to improve outcomes however a vision of what that actually looks like in routine clinical practice remains opaque.
This presentation will cover some of the challenges faced by children with diabetes and their families, the underlying reasons for these challenges and the consequences. Furthermore, it will present an alternative model of care that encompasses the psychosocial aspects of diabetes and ongoing research to implementation in routine care.

DOI: 10.1530/endoabs.36.DP4

DP5

School care plans

S Singleton
Blackpool, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.36.DP5

DP6

Fat and Protein counting: what's the evidence?

Francesca Annan
Alder Hey Children's Hospital, Liverpool, UK.

Fat and protein 'counting' is now being advocated as part of intensive diabetes management for patients on insulin pump therapy in addition to carbohydrate counting and insulin adjustment.
This presentation will review the current evidence and practical strategies that may be used to improve post meal glycaemic excursions.

DOI: 10.1530/endoabs.36.DP6

DP7

BPT
F Cambell
Oxford, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.36.DP7

Endocrine Nurse Session

EN1

Genetics: back to basics
Jessica Williams
Wessex Cinical Genetics Service, Southampton, UK.

The evolution of molecular genetics has altered our understanding of many endocrine conditions. Some conditions have clear inheritance patterns and others have a more complex genetic influence.
Whilst genetic disorders have previously been considered to represent a small minority of the clinical workload, it is now apparent that many clinical conditions have some genetic influence.
The purpose of this session is to re-familiarise some of the key concepts of genetics. This will include inheritance patterns, genetic testing, understanding genetic risk, and the implications for families when a diagnosis of a genetic condition is made.

DOI: 10.1530/endoabs.36.EN1

EN2

Breathe-easy – the significance of respiratory assessment in Prader–Willi syndrome
Hazel Evans
University of Southampton, Southampton, UK.

Prader–Willi syndrome is a complex genetic disorder. The characteristics of hypotonia put children at increased risk of respiratory problems during childhood. These range from an increased propensity to respiratory infection to problems during sleep of central and obstructive sleep apnoea. Obesity a common finding in children with Prader–Willi syndrome has the tendency to exacerbate these increased risks. There are often concerns around the use of GH in children with Prader–Willi syndrome and the effect that this has on the risks for obstructive sleep apnoea.
This presentation aims to provide an overview of respiratory problems including the patterns of sleep disordered breathing in children with Prader–Willi syndrome and the treatments available. The rationale behind screening children for sleep disordered breathing will be discussed as well as the integration of sleep studies into current consensus guidelines. Respiratory management of the severely hypotonic Prader–Willi infant will be presented.

DOI: 10.1530/endoabs.36.EN2

EN3

Sleep easy: the practicalities of sleep study
J Dingle-Gavlak
Southampton, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.36.EN3

EN4

Patient experience

Abstract unavailable.

DOI: 10.1530/endoabs.36.EN4

EN5

Home grown: PENS vs homecare GH start
C Davies
Cardiff, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.36.EN5

Oral Communications

Oral communications 1

OC1.1

Paediatric pituitary adenomas: rare, complex, and by no means benign

Hoong-Wei Gan[1], Chloe Bulwer[1], Owase Jeelani[2], Marta Korbonits[3] & Helen Spoudeas[2]
[1]University College London Institute of Child Health, London, UK; [2]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [3]William Harvey Research Institute, Queen Mary University of London, London, UK.

Introduction
Pituitary adenomas (PAs) account for <3% of all paediatric supratentorial tumours. Despite being benign, they can cause significant tumour- and treatment-related neuroendocrine and visual morbidity. Patients may be the index case for syndromes such as multiple endocrine neoplasia type 1 (MEN1).
Case report
Patient R was referred at 11.9 years with longstanding headaches and bilateral visual deterioration to the point of near-blindness. MRI revealed a large supra-intrasellar tumour causing third ventricular compression. Emergency debulking was initially scheduled for a suspected craniopharyngioma to preserve remaining vision. However, pre-treatment biochemistry revealed severe hyperprolactinaemia (PRL 23723 mU/l) alongside GH and TSH deficiencies. Surgery was deferred in favour of cabergoline therapy with an initial brisk response (PRL nadir 1993 mU/l) after a dose of 250 μg/week.
Unfortunately, despite escalating doses to 7 mg/week, his tumour demonstrated continued biochemical escape with radiological progression, requiring two partial resections (histology confirming a macroprolactinoma) and adjuvant proton beam radiotherapy. He suffered a post-operative stroke following his second operation and is now completely blind.
Initial questioning revealed only one paternal first cousin and one maternal first half-cousin (both once removed) with macroprolactinomas (i.e. no common ancestor). Patient R was positive for a functionally deleterious heterozygous *MEN1* splicing mutation (c.784-9G>A). After multiple consultations, a history of multiple relatives with prolactinomas, hyperparathyroidism, and gastrinomas was revealed (the latter in a maternal grandaunt with a confirmed diagnosis of MEN1) within an inter-generationally multiply consanguineous family, with other members requiring screening.
Conclusions
This case demonstrates: i) the importance of excluding PAs by pre-treatment biochemistry as management differs from other suprasellar tumours, (ii) the difficulties in prioritising disease control against preservation of neuroendocrine and visual function without a clear evidence base, and (iii) the crucial need for a careful family history and universal genetic testing to identify the need for screening of relatives.

DOI: 10.1530/endoabs.36.OC1.1

OC1.2

Functional adrenal tumour as a cause of virilised infant

Rebecca Poole, Victoria Howard, Wendy Watts & Tafadzwa Makaya
Oxford University, Oxford, UK.

Introduction
Childhood adrenocortical tumours (ACT) are extremely rare (world wide incidence: 0.3/million per year). Most affected are young girls – female:male 2:1, peak age at diagnosis – 3.5 years.
Case report
A 2.5-year-old girl presented with a 4-month history of greasy hair, acne, and weight gain especially around face and upper shoulders. She had irritability, daytime lethargy, and night-time sleep disturbance. She later developed pubic hair. On examination she was virilised:pubic hair stage II, enlarged labia majora and clitoris, acne over the nose, cheeks and scalp-line; and cushingoid: weight 91st centile, height 2nd – 9th centile; with moon facies and a buffalo hump. Abdominal examination and BP were unremarkable.
An ultrasound scan revealed a 6 cm mass in the right adrenal gland. MRI showed no calcification, invasion of adjacent structures, or evidence of distant metastases. Further investigations confirmed a functional ACT: serum androstenedione >35 nmol/l, DHEAS >27.1 nmol/l, testosterone 5.5 nmol/l, and cortisol 850 nmol/l.
Following a right adrenolectomy, histology confirmed an adrenocortical adenoma weighing 105 g, measuring 7×6×6 cm. Clinical genetics review showed insufficient family history to warrant p53 gene testing; however the patient had a medical history of large birth-weight, an unusual appearance to umbilicus: enlarged base, small supra-umbilical hernia and one side of abdomen more prominent than the other. More recently mother had noted asymmetry of the leg and foot. Therefore testing for Beckwith–Wiedemann syndrome was recommended. She remains on hydrocortisone cover and a Synacthen test is planned for the future.
Conclusions
Typical presentation of ACTs is with syndromes of hormone excess, usually virilisation. Cushing's is present in 1/3 cases but ACTs are usually inefficient at producing cortisol. While is it rare, ACT should be considered in any child presenting with premature virilisation. Genetics review is always recommended: 80% of children with sporadic ACT have atypical p53 germline mutations. ACT is also associated with isolated hemi-hypertorphy and Beckwith–Wiedemann syndrome.

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Oral communications 2

OC2.1

Unilateral gynecomastia: an unusual presentation of Peutz Jegher's syndrome

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Background
Peutz Jegher's syndrome is a rare condition with substantial cancer risk. Testicular cancer risk is 9%, the commonest being pre-pubertal large cell Sertoli cell tumour (LCST) which usually presents with bilateral gynecomastia. Here we present a case of Peutz Jegher's syndrome with LCST who presented with unilateral gynecomastia.
Case
A 5-year-old boy was referred to our endocrine service with unilateral gynecomastia. He had right sided gynecomastia (stage 4 with a disc of 4.5 cm) with bilateral testicular enlargement (4–5 ml) and no evidence of pubic hair or penile growth. He also had dark pigmentation of the buccal mucosa of the lips and cheeks. His testosterone was 0.4 nmol/l, with oestrogen of 44 pmol/l. LH-releasing hormone (LHRH) stimulation test showed a pre-pubertal response with peak LH of 1.9 I.U/l and FSH of 0.3 I.U/l. Ultrasound scan (USS) of the breast was normal and Doppler USS of the testes showed bilateral enlarged testicles with speckled appearance suggestive of Sertoli cell tumour. The rest of his investigations were normal except high levels of Inhibin B (295.5 ng/l). The clinical picture was suggestive of Peutz Jegher's syndrome. Endoscopy revealed several benign gastric and duodenal polyps. His testicular biopsy confirmed intratubular LCST without evidence of malignancy. Genetic tests revealed mutations in the *STH11* gene confirming the diagnosis.
In view of the advanced bone age and progression of gynecomastia he was started on letrazole with good effect. He continues to have regular reviews with testicular USS to monitor the Sertoli cell tumour and endoscopy for the polyps.
Conclusion
Peutz Jegher's syndrome must be considered in all cases of pre-pubertal gynecomastia which can rarely be unilateral as in our case. Aromatase inhibitors like letrazole are efficient in controlling clinical symptoms. In view of 27% reported risk of malignant transformation of the LCST, regular surveillance has been recommended.

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OC2.2

Isodicentric chromosome Y mosaicism in a female patient: an indication for gonadectomy

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Introduction
Patients presenting with isodicentric chromosome Y (idicY) formation in a mosaic karyotype can present with phenotypic features ranging from mixed gonadal dysgenesis, to females with stigmata of Turner's syndrome. The presence of the *SRY* gene increases the risk of germ-cell tumours.
Case report
A 12-year-old prepubertal girl was referred for evaluation of extreme short stature (height 122 cm; −4.58 SDS; weight 26.7 kg; and −3.3 SDS). No significant past medical history of note. General examination was normal. Investigations revealed elevated gonadotropins (FSH 81.3 IU/l and LH 15.5 IU/l) indicating ovarian failure and a low IGF1 (86 ng/ml). Her blood karyotype was 45,F(26)/46,X,i(Y)(p11.3)(3).ish i(Y)(p11.3)(SHOX+, SRY+) confirming a female karyotype with two cell lines, the majority cell line showing monosomy X and an idicY with the

breakpoint at p11.3. Ultrasound couldn't identify gonadal tissue on the right and 0.19 ml gonadal tissue on the left. The presence of isochromosome Y (SRY+) raised the possibility of mixed gonadal dysgenesis with an associated risk of germ-cell tumour which led to bilateral gonadectomy. Biopsy revealed ovarian stroma and absence of oocytes, bilateral focal areas of Wolffian structures and minute foci of gonadoblastoma confirming mixed gonadal dysgenesis. She had shown a brilliant response (height velocity 8.43 cm/year; 6.53 SDS) to GH treatment (1.4 mg/m^2 per day for 1.25 years) and will soon be commenced on estrogen therapy for pubertal induction.

Discussion

IdicY is normally unstable during cell division; most patients reported are chromosomal mosaics, generally including a 45,X cell line. As in our case, patients reported with a high proportion of 45,X cells and idic(Y)p breakpoints at Yp11.2 or 11.3 resulting in a deletion of the distal Yq are usually phenotypically female. The presence of SRY in idicY mosaicism can result in the early presentation of gonadoblastoma requiring early gonadectomy.

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Oral communications 3

OC3.1

The Scottish audit of atypical genitalia: first year results

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Introduction

The early management of atypical genitalia has been highlighted as being of critical importance by the UK-DSD guidance in 2011.

Objectives

To estimate the incidence of atypical genitalia requiring early specialist input in neonates and its clinical presentation and management.

Method

Prospective audit through the Scottish DSD network and the Scottish Paediatric Endocrine Group, between June 2013 and June 2014. Monthly emails were sent to senior clinician members to notify newborns $\geq$37 weeks gestation with atypical genitalia requiring specialist input in the previous calendar month and aged $<$4 weeks at presentation. Notified newborns were followed to 3 months age. Average monthly response rate was 72%. Cross-verification through regional genetics laboratories in Scotland was performed using karyotype as a marker to identify newborns with suspected DSD.

Results

24 newborns were reported, of whom 15 were true positives. In addition, two cases were identified through cytogenetic laboratories. Amongst the nine false positives, four were born at gestation $<$37 weeks. The incidence of atypical genitalia requiring specialist input within the first month of birth, in term newborns in Scotland was 3/10 000. Of the 16 cases completed follow up, 10 (63%) presented within 24 h. Age at sex assignment ranged from birth to 4 days and 11 (69%) had sex assignment at birth. All continued to have same sex at 3 months. 9 (56%) were assigned male sex with XY karyotype. Of the seven girls, three were XY. A neonatologist, surgeon or endocrinologist was involved in 14 (87%), 13 (81%), and 11 (69%) of infants, respectively. Communication and provision of information was mainly through face-to-face discussion.

Conclusions

Atypical genitalia requiring specialist input and investigations within first month of life is a rare occurrence affecting one term newborn in every 3400 born in Scotland. Electronic targeted surveillance of members of closely collaborating clinical networks can be beneficial for auditing the management of rare conditions.

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OC3.2

Vertebral fracture assessment in a paediatric population using dual-energy X-ray absorptiometry

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Background

Vertebral Fractures (VF) are recognized as an important aspect of bone health in children and adolescents. The clinical utility of vertebral fracture assessment (VFA) using dual-energy X-ray absorptiometry (DXA) has not been evaluated in the paediatric population.

Method

VFA was performed independently by two non-radiologist observers, in 165 patients (77M/88F) as part of their investigation for low bone mineral density. Lateral thoracolumbar X-ray images (LXR) were obtained in 20/165 patients. The median age of the patients was 13.4 years (3.6, 18). Lateral DXA images of the spine from T6 to L4 were obtained using Lunar Prodigy DXA device. The diagnosis of VF was performed according to Genant's semi-quantitative classification.

Results

Interobserver agreement in vertebral readability using VFA was 94% (κ, 0.73 (95% CI, 0.68, 0.73)). The vertebrae not readable by both observers were 287/1815 (16%) and 266/287 (93%) were located between T6 and T9. Conversely, 1134/1155 (98%) of vertebrae from T10 through L4 were adequately visualised ($P<0.0001$). Among the 1528 vertebrae visualised by both observers, 72 (4.7%) in 45 (27%) patients and 84 (5.5%) in 48 (29%) patients were classified as VF by observer 1 and by observer 2, respectively. Interobserver per-vertebra agreement for the presence of VF was 99% (κ, 0.85 (95% CI, 0.79, 0.91)). Interobserver per-patient agreement was 91% (κ, 0.78 (95% CI, 0.66, 0.87)). The two observers had in common 67 (4.5%) VF in 39 (24%) patients and 18 (27%) of them were classified as moderate or severe. The anatomical distribution of VF was biphasic, with peaks located on T9 (odds ratio, 2.1 (1.1, 4.2)) and L4 (odds ratio, 1.7 (1.0, 3.4)). Among those who underwent both LXR and VFA, 24 (11%) VF in 6 (30%) patients and 20 (9%) VF in 5 (25%) patients were identified by LXR and VFA, respectively. Per-vertebra agreement was 95% (κ, 0.79 (95% CI, 0.62, 0.92)) and per-patient agreement was 95% (κ, 0.88 (95% CI, 0.58, 1.0)). Specificity of VFA was 98.4% per-vertebra and 100% per-patient.

Conclusion

VFA reaches an excellent level of agreement between observers and a high level of specificity in identifying VF in paediatric population. The readability of vertebrae from T6 to T9 is suboptimal and interpretation at this level should be exercised with caution.

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OC3.3

An analysis of meta-data from three UK centres on the sequelae of paediatric craniopharyngiomas over four decades

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Background

The optimal management of paediatric craniopharyngiomas has been debated for years. Radical surgery aimed at complete resection (CR) was the approach for several decades, with higher reported rates of tumour control compared with incomplete resection (IR). The shift towards conservative surgery with adjuvant radiotherapy (DXT), aimed at reducing post-operative morbidities, especially hypothalamic and visual, has not been systematically studied.

Aims

To review the sequelae of different management strategies in paediatric craniopharyngioma at three tertiary centres over four decades.

Methods

Meta-data from 185 patients was extracted and retrospectively reviewed from three UK tertiary centres. The analysis was undertaken over two time periods: 1973–2000 (study A) and 1998–2011 (study B).

Results

100 patients from study A and 85 patients from study B either had CR (A – 35% and B – 19%), partial resection (PR: A – 49% and B – 46%) or limited surgery (LS, e.g. cyst decompression: A – 16% and B – 34%). CR without DXT was associated with a lower tumour recurrence rate than IR (PR+LS) with DXT in study A (OR=0.43) but in study B recurrence rates were higher (OR=1.62). 28 patients (28%) in study A received DXT (with nine recurrences) and 53 (62%) in study B (with 14 recurrences) (OR=0.56 for recurrence with DXT vs no DXT). The rates of gonadotrophin deficiency ($P<0.001$), diabetes insipidus ($P=0.04$), and panhypopituitarism ($P=0.001$) were lower in study B than in A. However, post-operative hypothalamic ($P=0.1$) and visual ($P=0.3$) morbidity rates remained unchanged. In fact, the proportion of patients with post-operative BMI SDS $>+2.0$ was higher in study B (49%) than in A (36%).

Conclusion
These metadata show that changing from CR towards more conservative surgery with DXT has improved tumour recurrence and hormone deficiencies. However, visual and hypothalamic morbidities remain a significant challenge. New approaches to managing craniopharyngioma (e.g. proton radiotherapy and in future, novel molecular pathway targeted therapies) are required to improve outcomes.

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OC3.4

Standard population screening for diabetes mellitus has low sensitivity in identifying diabetes in adult survivors of childhood bone marrow transplantation with total body irradiation

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Background
Adult survivors of childhood leukaemia treated with bone marrow transplantation and total body irradiation (BMT/TBI) have an increased risk of diabetes mellitus (DM) disproportionate to their level of adiposity or other recognised risk factors. Post prandial hyperglycaemia due to reduced β-cell reserve after irradiation will be missed by fasting glucose (FG) levels. However, the UK National Institute of Clinical Excellence (NICE) screening guidelines recommend the use of fasting glucose (FG) >7 mmol/l and/or HbA1c >48 mmol/mmol (6.5%) for the diagnosis of DM and FG 5.5–6.9 mmol/l or HbA1c 42–47 mmol/mmol to indicate high risk.
Objective
To evaluate sensitivity of the UK national screening criteria in the diagnosis of DM in survivors of childhood BMT/TBI.
Method
Subjects: 37(M = 19) BMT/TBI survivors from a single UK centre 2006–2013, mean age (s.d.) 18.9 (3.1) years treated for acute lymphoblastic leukaemia ($n=31$) and acute myeloid leukaemia ($n=6$) by BMT/TBI at 7.9 (3.8) years of age. Outcome measures: demographic and treatment details, results of OGTT and HbA1c, prevalence of hypertension ($>130/85$), hypertriglycerides (>1.7 mol/l), and reduced HDL ($M<1.03$, $F<1.29$ mmol/l).
Results
OGTT results revealed 6 (16.2%) with DM (120 min glucose >11.1 mmol/l), 13 (37.1%) with impaired glucose tolerance (120 min glucose 7.8–11.1 mmol/l) and 2 (5%) with impaired FG (>7 mmol/l). NICE screening criteria for DM with FG (>7 mmol/l) or HbA1c (>48 mmol/mmol) identify 2/6 (33%) patients with DM. The lower cut-offs recommended for higher risk patients with FG >5.5 mmol/l and HbA1c >42 mmol/mmol identify 3/6 (50%) and 2/6 (33%) with DM respectively. In addition, only 1/13 (7.7%) with impaired glucose tolerance had a FG of >5.5 mmol/l and none had HbA1c >42 mmol/mmol. BMT/TBI survivors had a high prevalence of hypertension (16%), hypertriglyceridaemia (62%) and reduced HDL (35%).
Conclusions
There is a high prevalence of abnormal glucose tolerance and metabolic abnormalities in BMT/TBI survivors. Standard screening criteria under NICE with FG and HbA1c will miss 67% of those with DM and therefore do not identify those at risk. Screening of DM in BMT/TBI survivors requires standard OGTTs although the optimal frequency needs ongoing evaluation.

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OC3.5

Statistical prediction of HRpQCT microstructural trabecular parameters using 1.5T skeletal MRI

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Background
High resolution peripheral quantitative computed tomography (HRpQCT) can accurately determine three-dimensional *in-vivo* skeletal microstructure. However, HRpQCT is limited to the ultradistal radius and tibia (9 mm) imaging. MRI may be an alternative approach to cortical and trabecular bone analysis; to date there is limited information regarding the accurate quantification of trabecular bone.
Method
Ninety-three 13–16 years-old underwent ultra-distal HRpQCT and skeletal MRI (sMRI). Participants underwent 2/6 sMRI sequences (T1, T2, T2*, gradient-echo, fiesta, and ultrashort-time echo). sMRI sequences were delineated into cortical and trabecular compartments using segmentation software. Owing to the varying number of MRI slices available (one to four per subject), and the geometrical variation in trabecular area between participants, we calculated a number of image descriptors from trabecular signal intensities to obtain the same level of information for each case. Image descriptors included statistical measures (mean, s.d., entropy), geometrical measures (e.g. primitive emphasis primitive uniformity), and textural measures (e.g. homogeneity, contrast, and fractal dimension). Kernel partial least squares was used to find an optimal non-linear predictor model from the data relating sMRI to HRpQCT parameters.
Results
Leave-one-out cross-validation experiments were carried out to assess the mean prediction accuracy of HRpQCT from sMRI. To this end, the data used for testing the predictive model was removed from the construction of the statistical predictive model itself. We then calculated the relative errors of the predictions in percentage, i.e. error = (prediction − measurement) × 100/measurement. sMRI predicted trabecular number, spacing, and thickness to within 7.52, 9.51, and 7.43% of HRpQCT respectively.
Conclusions
Using the established predictive model, 1.5T sMRI can predict trabecular number, spacing, and thickness to within 10% of the values derived from HRpQCT. There was little variation in the predictive value between sMRI sequences. This study demonstrates the future potential of clinical MRI in assessing trabecular bone.

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OC3.6

A novel non-invasive short Synacthen test

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Introduction
The short Synacthen test (SST) is a popular diagnostic investigation for adrenal insufficiency (AI). Cannulation and blood sampling are required making it invasive, time-consuming and resource-intensive. Salivary cortisol is a well-established alternative to serum sampling. We have developed a non-invasive alternative to the 1 μg SST, using a novel formulation of Synacthen (with a nasal drug enhancer, chitosan) given nasally and utilising saliva to measure the cortisol response.
Methods
We undertook a pharmacokinetic dose escalation study with five doses of nasal Synacthen (tetracosactide): 25, 100, and 100 mcg with chitosan, 500 and 500 μg with chitosan, administered to 12 healthy adult males on different occasions and compared them to a 1 μg i.v. test. During each 3-h visit, 15-paired blood and saliva samples were taken and measurements of plasma Synacthen, serum cortisol and salivary cortisol and cortisone made. Volunteers were dexamethasone suppressed enabling measurement of Synacthen on an ACTH RIA.
Results
The 25 and 100 μg doses showed minimal absorption. Addition of the chitosan improved bioavailability and cortisol response but dose escalation increased the absorption of nasal Synacthen more than the chitosan. The 100 μg with chitosan and 500 μg formulations showed a comparable cortisol response to the 1 μg i.v. dose. Nasal administration of the 500 μg Synacthen with chitosan formulation resulted in the highest bioavailability and was the only dose in which all volunteers attained a peak serum cortisol of more than 500 nmol/l. Salivary cortisol and cortisone samples had a close and reliable relationship with serum samples. Salivary cortisone was the more sensitive marker of adrenocortical response at lower values.
Conclusions
Synacthen is absorbed nasally and appears safe and well tolerated. Nasally administered 500 μg Synacthen with chitosan and salivary cortisol or perhaps cortisone sampling at 60, 75, and 90 min may provide a useful alternative to the low-dose SST.

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OC3.7

Patterns of gene expression in pre-pubertal children are associated with the severity of their GH deficiency

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Background
GH deficiency (GHD) has a spectrum of severity as characterised by GH stimulation tests; the cut-off level for GHD has been a long standing contentious issue. An independent biological correlate of severity would be valuable.
Objectives
To identify patterns of gene expression (GE) that correlate with severity in GHD.
Methods
Pre-pubertal children with GHD ($n=72$) were enrolled from the PREDICT study (NCT00256126). GHD severity was defined using two standard GH stimulation tests with peak GH levels (pGH) <10 μg/l (range 0.2–9.3 μg/l). Whole blood GE was determined prior to treatment using Affymetrix U133v2 microarrays. GE was correlated with pGH using rank regression (gender, ethnicity, age, and BMI as co-variates]. Models of GHD severity based on network clusters were generated, which were then used to investigate mechanistic relationships (Moduland algorithm and causal network analysis (CNA) (Ingenuity Pathway Analysis software]). Associated biological functions were determined with the hypergeometric test.
Results
Rank regression identified 1631 genes that were correlated with pGH: 619 positively ($R>+0.28$) and 1012 negatively related ($R<-0.28$) ($P<0.05$). These genes were causally associated with pathways related to 'failure of growth' ($P<2.4\times10^{-3}$). Sub-clusters of similar gene expression patterns could be recognised in GHD children with pGH >7 μg/l (borderline GHD) and pGH <2 μg/l (very severe GHD) and to a lesser extent for pGH $\geq2-\leq5$ μg/l (severe GHD) and $>5-\leq7$ μg/l (moderate GHD). In the model of negatively correlated GE, functional clusters were causally related to the cyclin binding gene, *CUL3* and in the model of positively correlated GE to the cyclin dependent kinase gene, *CDK9* with both clusters causally associated with genes related to body size ($P<2.8\times10^{-3}$).
Conclusions
This study has demonstrated a relationship between gene expression patterns and pGH; this could provide biological correlates and mechanisms for the range of severity of childhood GHD.

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OC3.8

Trends in off-label prescription of GH: results from the National GH Audit

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Introduction
National Institute of Health and Care Excellence (NICE) has provided guidance for the use of human recombinant GH in the treatment of growth failure in children. An ongoing National GH Audit was established in 2013 by BSPED to maintain a central database and gather information regarding trends in prescribing and facilitate future long-term follow up. This part of the audit looked at the trends of off label prescribing of GH.
Method
Data were collected from 79 centres across the UK who prescribed GH therapy for children <16 years of age. The data were collected on a quarterly basis and collated centrally for a year. Data collected included indication for starting GH, age, sex, GH dose, and ongoing prescriptions (GP/hospital).
Results
Of the total 816 children who were commenced on GH in 2013, 11% (93) were for off label indications. Boys (58%) were more likely to receive GH treatment for indications outside NICE recommendations. Short stature (24%) was the most common indication followed by syndromic or genetic causes of extreme short stature (18%) and Noonan's syndrome (10%). Majority of the off label prescriptions were from England (80%) followed by Scotland (19%) with none reported from Northern Ireland. In England most of the off label prescriptions were from Merseyside (37%), followed by Central Manchester (16%), North East England (11%), and West Midlands (9%). 57 (60%) of these prescriptions were funded by the hospital and the remainder (40%) by clinical commissioning groups.
Conclusion
A significant number of prescriptions for GH therapy in children are outside NICE recommendations. Long-term follow up is essential to establish the actual benefit and effects of GH in this cohort of patients.

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OC3.9

Physiological dose reverse rhythm testosterone treatment abolishes the development of permanent gynaecomastia in adolescents with 47,XXY Klinefelter syndrome

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Introduction
Gynaecomastia (GM) is common in boys with Klinefelter syndrome (KS) during adolescence. It develops due to the relatively higher diurnal oestradiol–testosterone ratio in early to mid puberty. The physiological mid-late pubertal rise in testosterone causes the GM to disappear in chromosomally normal boys, but it persists in boys with KS if this rise in testosterone is blunted.
Aim
As a previous longitudinal RCT of testosterone in boys with KS identified by birth screening had found no persistence of GM in treated boys, we examined the effect of routine testosterone supplementation in boys with KS ascertained antenatally or clinically on the persistence of GM. Testosterone was administered each morning, in reverse rhythm, in order to counterbalance the usual rapid decline of testosterone concentrations in the afternoon/evening in the physiological diurnal rhythm of normal puberty, which is known to be more marked in boys with KS.
Methods
The presence of GM was routinely ascertained in boys with KS consecutively referred to and followed up in a specialist multidisciplinary KS Clinic. 29 of the boys were over 11 years. Once puberty had started and GM identified and recorded using Tanner breast staging and measurement of cross sectional disc diameter, either oral testosterone undecanoate (TU; Restandol) 40 mg or transdermal testosterone (Tostran) 20 mg was commenced each morning.
Results
Eight out of the 29 boys developed GM. Two did not comply with the treatment and the GM persisted. In the remaining six, GM stages B2–B3 with breast discs diameter range 1–3 cm appeared at mean age 12.8 years (range 11.4–14.2 years) and at puberty stages G2–G3. Only one had a high BMI ($+3$ S.D.). GM resolved completely within a mean of 1.1 years on treatment (range 0.2–1.9 years). Physiological testosterone replacement was continued. Transient recurrence in one boy was ablated with a physiological TU dose increase. No major adverse effects were noted.
Conclusion
Reverse rhythm testosterone, using a morning administration regimen started at the onset of GM and then given continuously in physiological dose increments, abolishes the development of permanent GM in adolescent boys with KS.

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Oral Communications 4

OC4.1

Utility of basal LH in comparison to the GnRH test for identifying central precocious puberty in girls

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Background
Harrington *et al.*[1] suggest that basal LH of ≥0.3 IU/l as measured by ICMA (Immulite 2500) has 100% specificity and 90.5% sensitivity in identifying progressive central precocious puberty (CPP).
Aims
To examine the utility of basal LH measured with the DELFIA assay for identifying CPP in girls.
Methods
All girls under age 9 years (median 7.3 years) investigated for precocious puberty with a GnRH test from 2010 to 2012 were studied retrospectively. The diagnosis of CPP was made by a consultant endocrinologist from reviewing follow-up clinical and growth data, ultrasound appearances of the uterus and ovaries, and biochemical results. Basal LH (IU/l) and results of the GnRH test were compared between girls diagnosed with and without CPP.

Results
Of the 77 girls, 21 were diagnosed with CPP having developed signs of precocious puberty at $\leq$8 years of age. Compared to girls without CPP, those with CPP had higher basal LH (median 0.5 vs 0.09, $P<0.001$), peak LH (13.0 vs 2.65, $P<0.001$), basal FSH (3.1 vs 1.2, $P<0.001$), and ratio of peak LH:FSH (1.1 vs 0.26, $P<0.001$). Peak FSH did not differ between the two groups (12.0 vs 9.9, $P=0.2$). As a cut-off for CPP, peak LH $\geq$5 IU/l gave 90.5% sensitivity and 82.1% specificity. A cut-off for basal LH of $\geq$0.3 IU/l gave 66.7% sensitivity and 91.1% specificity, suggesting lower sensitivity than the ICMA assay. Basal LH of $\geq$0.1 IU/l gave 85.7% sensitivity and 78.6% specificity.
Conclusion
Although basal LH alone may be useful as an initial screening test in identifying girls with CPP, the sensitivity and specificity for a cut-off of $\geq$0.3 IU/l varies according to the assay used. The limitations of assay-specific diagnostic cut-offs to differentiate girls with CPP from those without CPP need to be recognised.
Reference
1. Harrington J *et al. Arch. Dis. Child.* 2014 **99** 15–20.
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OC4.2

Validation of a Food Frequency Questionnaire for rapid assessment of daily dietary calcium intake in children

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Introduction and aims
Adequate dietary calcium (Ca) intake is important for maintenance of bone health. In a clinical setting we employ a simple Food Frequency Questionnaire (FFQ) for rapid assessment of dietary Ca intake. In this study we have validated our FFQ using a 3-day food diary (3FD) in children presenting to our metabolic bone and endocrine clinics.
Methods
Dietary Ca intake values estimated using the FFQ were compared to those estimated by the 3FD in the same children. Daily dietary Ca intake values from 3FDs were calculated using the Microdiet Software (Downlee Systems Ltd, UK).
Results
FFQ data was obtained from 74 children out of which 32 children (age 1–17 years) completed a 3FD. Mean daily Ca intakes ($\pm$S.D.) were 875$\pm$580 and 878$\pm$329 mg, estimated by FFQ and 3FD respectively. There was a significant positive correlation between dietary Ca estimated by 3FD and FFQ ($r=0.69$; $P<0.01$). The degree of agreement between the two methods was assessed using a Bland–Altman plot. The majority of data points fell within $\pm$1.96S.D. of the mean, indicating a good level of agreement between the two methods. The FFQ had a specificity of 93% in identifying children who consumed inadequate amount of dietary Ca based on UK's Reference Nutrient Intake (RNI) for their respective age group. The FFQ had a sensitivity of 78% in identifying children whose dietary Ca intake exceeded RNI.
Conclusions
Results of this study suggest that our FFQ is useful for rapid assessment of children's daily dietary Ca intake.
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OC4.3

A role for delta-like homologue 1 in a secretory placental population and implications for fetal growth

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Background
Delta-like homologue 1 (DLK1) encodes a transmembrane protein, which may also be secreted into the circulation. Levels are known to rise in maternal serum during late gestation and our genetic studies in the mouse have shown that this DLK1 arises from the conceptus. The cell population that secretes DLK1 into the maternal circulation has not been identified. In humans DLK1 has been shown to be differentially expressed in intrauterine growth restricted (IUGR) when compared with normal placentas suggesting a role in intrauterine growth.
Objective and hypothesis
We hypothesise that maternal serum levels of DLK1 derived from the conceptus may reflect indices of fetal and placental growth. Our objective is to find the source population of DLK1-secreting cells in the placenta, and assess if maternal circulating DLK1 correlates with fetal growth parameters.
Methods
45 women from our Obstetric Department were followed up prospectively. Measurements of fetal growth parameters, maternal serum samples (for DLK1 ELISA) and clinical data were collected at 20, 28, 34, and 38 weeks gestation. DLK1 immunohistochemistry was carried out on placental samples.
Results
We localised DLK1 expression to cell populations within the placental villi including the fetal endothelium and trophoblast compartments. Maternal DLK1 levels rise during gestation and fall post-delivery. Furthermore there was a positive correlation between DLK1 levels from $\sim$32 weeks and birth weight. DLK1 serum levels were also lower in our IUGR population.
Conclusion
Fetal endothelium and trophoblast cell types of the placenta express DLK1 and may be responsible for its secretion into the maternal circulation. DLK1 levels positively correlate with normal fetal growth in the 3rd trimester and low DLK1 levels are associated with poor fetal growth. DLK1 may be a novel endocrine marker of human fetal growth.
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OC4.4

Expression of Sonic hedgehog signalling components in the developing human adrenal cortex

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Introduction
The Sonic hedgehog (Shh) pathway is an evolutionarily conserved signalling pathway, playing an essential role during embryonic development. Murine studies have shown the importance of Shh in the growth of the adrenocortical primordium. Shh expression has previously been described in relatively undifferentiated sub-capsular cells in the developing rodent adrenal, however the organisation of the human foetal adrenal (HFA) is unique. This novel study aimed to describe the developmental expression patterns of Shh and its pathway components in the early developing HFA.
Methods
The expression of *Shh*, and pathway components, *Patched-1* (Ptch-1) and *Gli1,* was demonstrated in H295R cells, primary HFA cells, and HFA tissue using PCR. Quantitative real-time PCR (qPCR) was performed on HFA tissue cDNA from a range of gestational ages to explore the temporal relative expression of *Shh* and pathway components. The spatial expression of Shh-expressing and receiving cells was determined using non-radioactive *in situ* hybridisation.
Results
Shh and Shh signalling pathway components were shown to be expressed in the developing human adrenal. Relative *Shh* expression in the HFA cortex was seen to decrease in the first trimester with increasing gestation. Cells expressing *Shh* and *Gli1* were seen to localise at the periphery of the adrenal gland and in the overlying capsular mesenchyme.
Conclusion
These studies reveal that the Shh pathway is active during HFA development. For the first time it is demonstrated that components of the Shh signalling pathway are expressed in the first trimester human foetal adrenal at mRNA level, and expression appears to be regulated in a spatio-temporal manner. This research furthers our understanding of the molecular mechanisms governing adrenal development. The function of Shh signalling in human adrenal development is unknown but is hypothesised to exhibit similarly crucial roles demonstrated in previous animal studies.
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OC4.5

Adiposity differs by fracture site in children with upper limb fractures

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Background
Children who are overweight and obese have a higher incidence of fracture, but it is unknown if this varies by fracture site. Indeed, obesity in adult women protects against forearm fracture, but increases the risk of humeral fractures. We aimed to determine if adiposity differed by fracture site in children with upper limb fractures.
Methods
Children aged 3–18 years were recruited within 60 days of fracture. Height, weight, waist circumference and triceps and subscapular skinfold thicknesses were measured. Fat percentage was calculated using the Slaughter equation and overweight/obesity defined using the International Obesity Taskforce definitions based on BMI *z*-score. Fractures were classified using the ICD10 into hand (phalanges, metacarpals, and/or carpals), forearm (radius and/or ulna), and upper arm (humerus and/or clavicle).
Results
401 children (67.6% males) participated. 34.2, 50.6, and 15.2% had fractures of the hand, forearm, and upper arm respectively. Median age was similar in children with forearm (10.8 years) and upper arm fractures (9.8 years, $P=0.30$), but both groups were younger than those with hand fractures (13.4 years, $P<0.001$ for both).
21.1, 28.0, and 19.0% of children with hand, forearm and upper arm fractures were overweight/obese ($P=0.21$) and a waist circumference $\geq$90th centile was present in 37.1, 44.4, and 19.6% of each group respectively ($P=0.008$).
After adjustment for age and sex, children with upper arm fractures had lower weight *z*-score (0.29 ± 1.23 vs 0.70 ± 1.08, $P=0.047$), BMI *z*-score (0.16 ± 1.23 vs 0.68 ± 1.05, $P=0.004$) and %fat *z*-score (-0.27 ± 0.76 vs 0.22 ± 0.82, $P=0.004$) than children with forearm fractures. Weight, BMI, and %fat *z*-scores were similar in children with hand and forearm or hand and upper arm fractures.
Conclusion
Adiposity was greater in children with forearm than upper arm fractures. Further studies are needed to determine whether higher adiposity increases forearm fracture risk or is protective against upper arm fracture.

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OC4.6

Evaluating dipeptidyl peptidase-4 expression in patients with diffuse and focal congenital hyperinsulinism.

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Background
Congenital hyperinsulinism (CHI) is the commonest cause of persistent hypoglycaemia and is due to the unregulated secretion of insulin from the pancreatic beta-cells. The role of gut hormones and dipeptidyl peptidase-4 (DPP-4) is currently unknown in patients with CHI.
Aims
To evaluate the expression pattern of DPP-4 in focal and diffuse CHI.
Method
Using intra-operative formalin-fixed paraffin embedded (FFPE) pancreatic sections; the localisation of DPP-4 in alpha-, beta- and delta-cells was carried out in patients with either diffuse CHI (DCHI) or focal CHI (FCHI) with tissue sections taken from around the focal lesion being used as controls. Additionally, using the proliferative marker, Ki67, we attempted to identify the islet-cells that were proliferating.
Results
We identified expression of DPP-4 with insulin, glucagon and somatostatin in their respective cell subtypes. Both DCHI and FCHI sections showed an increase in Ki67 expression. In comparison to control tissue, DCHI showed an increase in beta-cell DPP-4 expression. However, this was absent in the focal lesions.
Conclusion
In conclusion, this is the first study to show that DPP-4 expression profiles are histologically different in DCHI and FCHI patients. Therefore, DPP-4 might have a role in the pathophysiology of DCHI and this knowledge might be useful for potential therapeutic applications.

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OC4.7

Pitfalls in the diagnosis of neonatal adrenal insufficiency

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Introduction
Adrenal insufficiency is rare in the neonatal period and if unrecognised may cause life-threatening circulatory collapse. The initial investigations taken at the time of presentation, and prior to the institution of hydrocortisone, are a key step in the diagnostic pathway, and aid the clinician to distinguish adrenal insufficiency from mineralocorticoid resistance or renal tubulopathy. A cortisol measurement at the time of illness is useful to evaluate the adrenal glucocorticoid reserve. Here, we present four cases of neonates presenting with an adrenal crisis where the cortisol result was misleading and could have caused delayed diagnosis or lead to inappropriate discontinuation of hydrocortisone.
Case series
Four male term babies presented with a salt-wasting crisis during the neonatal period. The diagnosis of congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency was subsequently confirmed in each. The table shows the initial biochemical results at presentation and the cortisol assay used. 17-OHP results were available >24 h after presentation.
Conclusion
Assay interference from cross-reactivity with adrenal fetal zone steroids is likely to have caused the apparent elevated cortisol measurements. The use of tandem mass spectrometry may address this issue, although new reference ranges will need to be established with this technology. In the interim, the clinician should rely on clinical suspicion and the results of all of the investigations taken at the time of presentation to inform the subsequent management.

Case	Age at presentation (days)	Na (135–144 mmol/l)	K (3.5–5.0 mmol/l)	Cortisol (nmol/l)	17-OHP (nmol/l)	Cortisol assay
1	16	116	10.4	624	>200	CBIA
2	17	111	9.2	498	>800	CBIA
3	27	108	10.0	687	>2000	OSSA
4	12	110	7.2	882	44[a]	OSSA

CBIA, competitive binding immunoenzymatic assay; OSSA, one-site sandwich assay.
[a]Sample taken following hydrocortisone commenced.

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OC4.8

Recombinant human GH in paediatric inflammatory bowel disease: short term effects on bone biomarkers and long term effects on bone and lean mass

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Background
Recombinant human GH (rhGH) may improve bone mass in paediatric inflammatory bowel disease (IBD).
Objective
To investigate rhGH on bone and body composition in paediatric IBD.
Method
Bone biomarkers were evaluated in 12 children, 11CD (10M), median age 14.4 year (8.9, 16.2) who received rhGH (0.067 mg/kg per day) as part of a 6

months RCT. Eight received rhGH for 24 months and had DXA evaluation. Results were reported as median (range).
Results
Markers of osteoblastic function, P1NP and RANKL, increased significantly at T+6: PINP 204 μg/l (21, 250) at T+0 to 240 μg/l(174, 250) at T+6 ($P=0.01$), RANKL 0.35 pmo/l (0.1, 0.7) at T+0 to 0.56 pmol/l (0.2, 1.2) at T+6 ($P=0.04$). Markers of osteoclastic function, urinary CTX, also increased from 6625 mg/l (1800, 8780) at T+0 to 9575 mg/l (5450, 9900) at T+6 ($P=0.01$). There were no changes in CRP, ESR, TNFα, IL1β, IL6, and interferon over the 6 months. Percentage change in P1NP was negatively associated with percentage change in IL6 ($r=0.60$, $P=0.03$). LS BMD for bone age SDS was −1.7 (−2.2, −0.2) at T+0, −1.5 (−2.2, −0.2) at T+6 (vs T+0, $P=1.0$), −1.5(−1.9, 0.2) at T+12 (vs T+0, $P=0.09$), and −1.9 (−2.4, 0.1) at T+24 (vs T+0, $P=0.86$). There were no significant differences in LS BMD for height SDS and BMC for bone area SDS over the 24 months. Lean mass for height centile was 28 (0.0, 87) at T+0, 39.5 (7, 56) at T+6 (vs T+0, $P=0.80$), 33 (8, 88) at T+12 (vs T+0, $P=0.08$), and 25 (11, 58) at T+24 (vs T+0, $P=0.80$).
Conclusion
Short term treatment with rhGH in paediatric IBD was associated with increase in bone turnover but did not lead to improvement in bone mass and body composition in the long term.
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OC4.9

Neurodevelopmental phenotypes in children with early and late presenting congenital hyperinsulinism
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Introduction
Adverse neurodevelopmental outcomes have been recognised in children with hypoglycaemia due to early and late presenting congenital hyperinsulinism (CHI). The Vineland Adaptive Behaviour Scales II (VABS-II) is a standardised measure used to assess parent reported adaptive behaviour. The test measures five domains; motor, communication, daily living skills (DLS), socialisation, and maladaptive behaviour. We have used VABS-II to identify specific neurodevelopmental phenotypes in both early and late CHI.
Methods
A cohort of 42 children (29 males, 69%) with CHI treated either medically or surgically, was selected at age >1.5 years for VABS-II testing. Total VABS-II and sub-domain scores except behaviour were converted to SDS using normative data. The Social Communication Questionnaire (SCQ) was used to screen for neurodevelopmental difficulties associated with an autism spectrum disorder (ASD). Those presenting before age 1 month were early-CHI and those after 1 month were late-CHI.
Results
In our cohort, 27 (64%) children presented early, while 15 (36%) presented later (median (range) age 1.0 (0.3; 3.5) years). VABS-II–SDS was low in the whole cohort (−1.0 (−3.6; +2.3)) and was negatively correlated with age ($R=-0.3$, $P=0.05$). While all VABS-II domain SDS showed declining trends with increasing age at presentation, DLS–SDS showed the strongest correlation ($P=0.04$, $R^2=0.2$), when adjusted for gender. In contrast, behaviour scores tended to be higher in early than late CHI (18 (13; 24) vs 16 (10; 22), $P=0.1$), particularly for internalising behaviours ($P=0.02$), suggesting maladaptive behaviour in early presenters. SCQ scores were also higher in early CHI (5.5 (1; 31) vs 3.0 (0; 18), $P=0.04$), although there was no difference in ASD-at risk scores (4 (20%) vs 1 (9%), $P=0.4$). ASD was diagnosed in one child, each from early and late CHI.
Conclusion
VABS-II psychometric testing shows differential neurodevelopmental phenotypes in early and late CHI, suggesting that the pattern of hypoglycaemic neuronal injury is dependent on the age at presentation.
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OC4.10

Impact of prematurity on timing of puberty
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Background
It is well recognised that prematurity predisposes to metabolic syndrome. However the impact of prematurity on the timing of puberty is not fully understood.
Aim
To determine whether prematurity, has an impact on the timing of onset of puberty.
Methods
Longitudinal data on growth and puberty were collected on all preterm infants and 50 term controls born at the Jessops Hospital, Sheffield in 1994. Data included height, weight, head circumference measured at birth, 1, 2, and 5 years; hormone levels including insulin:glucose (I:G ratio), androgens, cortisol, HOMA-IR, and leptin at 5 years and Tanner stage 2 penile size and pubic hair in boys; breast stage 2 and menarche in girls.
Results
A total of 132 children, 65 females and 67 males were studied. Thirty-six (36/65) females reported their age at onset of menarche and 56 (56/67) males reported their Tanner stage 2. Girls born <34 weeks ($n=20$) reached menarche (mean 12.59 years) about 6 months earlier than girls born >34 weeks ($n=16$) (mean 13.07 years). There was a significant positive correlation between gestational age ($P=0.043$), birth weight ($P=0.014$), and catch up in weight ($P=0.00$) and length ($P=0.002$) to onset of menarche in girls. Also a significant association between I:G ratio ($P=0.025$), HOMA-IR ($P=0.049$), cortisone to cortisol ratio ($P=0.018$), and onset of puberty. However, no significant correlations to pubertal onset were found in boys, suggesting that prematurity and pubertal programming may affect the males differently. Mean age of pubertal onset in males across both groups' was 10.9 years.
Conclusion
Prematurity and low birth weight is a cause of early onset of puberty in girls with strong links to catch up weight and length. However these correlations are not applicable in males suggesting that there might be different pathways involved for premature boys.
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Oral Communications 5

OC5.1

Congenital adrenal hyperplasia: a survey on the current practice in UK
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Introduction
Congenital adrenal hyperplasia (CAH) varies significantly in clinical presentation and progression causing challenges in management. The ultimate goal of treatment is to achieve normal growth and development while avoiding adrenal crisis and hyperandrogenism.
Aim
Our aim was to ascertain the current practice in the UK on CAH management in children and compare these with the endocrine society recommendations.
Methods
An online survey with ten questions was emailed to the British Society of Paediatric Endocrinology (BSPED) members asking for one response from each centre regarding CAH management.
Results
The survey was completed by 35 out of 92 centres (38% response rate). Tertiary paediatric endocrine centres constituted 63% (22/35) of centres, while 23% (8/35) were district general hospitals (DGHs) providing tertiary endocrine services. The number of patients per centre varied from 15 to 120 amongst the tertiary centres to 5–30 patients in the DGHs. The hydrocortisone dose ranged from 6 to 20 mg/m^2 per day with 71% (25/35) of centres using 10–15 mg/m^2 per day. The fludrocortisone dose ranged from 50 to 300 μg/day with 60% (21/35) using 50–150 μg/day. The frequency of clinical reviews was contentious and centres felt it varied depending on the child's age and clinical status. Reviews were done 3–4 monthly in 68% (24/35) and 6 monthly in 31% (11/35) centres. The frequency of investigations including 17- hydroxyprogesterone (66% 3–6 monthly; 34% yearly), Testosterone/DHEAS (37% 6 monthly; 51% yearly), renin/aldosterone (31% 6 monthly; 69% yearly), and bone age (83% yearly, 6% 2 yearly) varied significantly among centres. Genetic counselling was provided at

diagnosis in 69% of centres while surgical (66%) and psychology (80%) input were primarily on an as required basis.
Conclusion
Our survey highlights the diversity in UK in managing children with CAH as compared to the recommendations of the Endocrine Society Guidelines. It demonstrates inconsistent involvement of other specialists which is an essential part of this multifaceted condition.

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OC5.2

The impact of receiving a diagnosis of congenital hypothyroidism on families

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Background
Congenital hypothyroidism (CHT) may be viewed as a relatively easy condition to diagnose and treat. However, for the parents who are contacted with the neonatal screening results the news can be devastating. The quality of information provided at diagnosis is variable, and there are few support groups they can turn to. Many seek information online before meeting a paediatrician.
Methods
The British Thyroid Foundation in conjunction with our regional service, organised a family education day, followed by a nationwide web-based questionnaire to ascertain the views of families regarding their experiences. Questions included how and by whom the diagnosis was made, when treatment was initiated and what information they were given at the time.
Results
One hundred people responded to the questionnaire. Seventy percent said they were first given the diagnosis by a doctor, and 70% were seen at the local hospital on the same or next day, although 18% were seen later than 4 days after diagnosis. Seventy percent felt that the doctor clearly explained the diagnosis and its implications, 38% were given comprehensive written information and 4% were given information about support groups. Ninety-three percent of families would have valued being put in touch with other parents of children with CHT. Common responses to free text questions were feelings of isolation, shock and fear for the future, and a lack of information and coordinated follow up. Positive points included receiving reassurance about the long-term outlook and spending time with a knowledgeable professional.
Conclusion
Whilst we inform our patients and families about rare and complex medical diagnoses, perhaps we underestimate the need for equivalent input into what we may consider to be a relatively simple condition. We clearly need to provide more written information and support to our patients with congenital hypothyroidism at the time of diagnosis.

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OC5.3

Does treatment with GnRH analogues affect BMI in children with precocious or early puberty?

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Background
Treatment of precocious puberty with GnRH analogues is well established. But there are concerns about weight gain in patients on this treatment. There have been conflicting reports about the effect of GnRH analogues on weight.
Aims
To assess the change in BMI in children treated with GnRH analogues within a UK Endocrine Service and to analyse the patient/parent experience of the treatment.
Methods
A retrospective study along with a questionnaire survey of patient/parent experience of the treatment was conducted. Data were collected from patients with precocious puberty on GnRH analogues for at least 2 years. Baseline BMI was compared with BMI at 2 years of treatment. An anonymised questionnaire survey assessed patient's experience of treatment, associated side effects, and overall satisfaction of the service.
Results
10% of children were overweight (BMI SDS between 2 and 3) prior to treatment, while 21% were overweight at 2 years of treatment ($n=19$). BMI SDS showed an increasing trend (0.78–0.91) but was not statistically significant ($P=0.379$). 92% of patients were either satisfied or very satisfied with the service. 70% of patients did not report any side effects ($n=14$). 30% of patients perceived weight gain which resulted in low self-esteem.
Conclusion
Our study showed an increasing trend in the BMI of children treated with GnRH analogues for precocious/early puberty though this was not statistically significant. This is in agreement with the recent joint consensus statement (2009) by the (European Society of Paediatric Endocrinology) ESPE and (Lawson Wilkins Paediatric Endocrine Society) LWES on GnRH analogues. Along with the joint consensus statement, this study on a UK regional patient population will enable us to give more reassurance to our patients.

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Oral Communications 6

OC6.1

Exploring variation in treatment targets across paediatric diabetes units in England and Wales

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Background
Achievement of treatment targets in children and young people (CYP) with diabetes represents an important intermediary step between delivery of care and 'hard' outcomes such as complications. Funnel plots have been proposed as a useful tool for visualising variation in performance indicators across centers and distinguishing between common-cause (centers lying within the control limits) and special-cause variation (centers lying outside the control limits exhibiting more variation than expected).
Methods
Aggregate data collected from Paediatric Diabetes Units (PDUs) across England and Wales in 2011–2012 as part of the National Paediatric Diabetes Audit (NPDA) were analysed. Percentage of CYP who achieved the NICE recommended HbA1c level of $<7.5\%$ was used as an outcome and performance indicator of diabetes control. Each PDU outcome was plotted against PDU size and the 95 and 99.8% control limits around the mean calculated using the binomial distribution. The relationship between PDU size and outcome was also examined.
Results
Of the 169 PDUs included in the analysis, 42 (24.9%) lay outside the 95% control limits and 13 (7.7%) fell outside the 99.8% limits. The coefficient for the regression of the PDU size (per 100 patients) on the percentage of CYP with HbA1c $<7.5\%$ was 1.2 (95% CI from -0.6 to 3.1%, $P=0.19$).
Discussion
The percentage of CYP achieving the glycaemic target HbA1c $<7.5\%$ varied considerably across PDUs with one in four units exhibiting more variation than expected by chance. There was a non-significant trend for larger PDUs to achieve greater numbers reaching this performance indicator. Further work on individual-level data is needed to examine the extent to which the observed variation is warranted, i.e. due to differences in the sociodemographic and ethnicity profile of the populations served by different clinics, or unwarranted and potentially attributed to how local services organize and deliver diabetes care.
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OC6.2

The diabetic pregnancy and offspring adiposity in infancy and childhood: a meta-analysis

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Introduction
Offspring of mothers with diabetes have greater risk of adverse metabolic outcome in later life. Increased adiposity is a plausible mediator. We performed a

meta-analysis of studies examining adiposity in infants and children in relation to maternal diabetes.
Methods
Citations were identified in PubMed and authors contacted for additional data. Fat free mass, fat mass, body fat %, and skinfold thickness were compared in offspring of mothers with and without diabetes. Random effects analysis was used.
Results
23 studies examining 20 000 infants and 14 studies of 16 000 children were included. The majority of studies examined newborn infants within 72 h and the mean (S.D.) age of children was 8.1 (3.7) years.
Infants of mothers with diabetes had higher fat mass (83 g (49, 117); $P<0.00001$), body fat % (2.2% (1.1, 3.2); $P<0.0001$), triceps (0.52 mm (0.37, 0.68)), and subscapular skinfold thickness (0.81 mm (0.56, 1.05); $P<0.00001$) than infants of mothers without diabetes, but high study heterogeneity was apparent. Fat free mass was similar (−11 g (−99, 77); $P=0.81$).
Children of mothers with diabetes had higher fat mass (1.69 kg (0.96, 2.43); $P<0.00001$), fat free mass (0.58 kg (0.10, 1.06); $P=0.02$), body fat % (2.3% (1.0, 3.7); $P=0.0008$), triceps (1.2 mm (0.3, 2.2); $P=0.01$), and subscapular skinfold thickness (1.6 mm (0.6, 2.6); $P=0.001$) than children of mothers without diabetes. Similar results were seen in the subgroup analysis of maternal gestational diabetes but insufficient data of types 1 and 2 diabetes were provided.
Conclusion
Infants and children of mothers with diabetes appear to have greater adiposity than offspring of mothers without diabetes, displaying 20–30% greater fat mass. Persistence or amplification of adiposity in adult life may explain the increased risk of type 2 diabetes in offspring of mothers with diabetes.

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OC6.3

Comparison of breath acetone, with blood glucose and blood ketones in children and adolescents with type 1 diabetes

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Aims
Studies have suggested that breath gases, including acetone, may be related to simultaneous blood glucose (BG) and blood ketone levels in adults with types 2 and 1 diabetes. We aimed to study these relationships in children and young people with type 1 diabetes to assess the efficacy of a simple breath test as a non-invasive means of diabetes monitoring.
Methods
Gases were collected in breath bags and measurements were compared with capillary BG and ketone levels taken at the same time on a single visit to a routine hospital clinic in 113 subjects (59 males, age 7 years 11 months–18 years 3 months) with type 1 diabetes. Gases were also collected at the same time as a capillary blood ketone level in five young people admitted as inpatients with poor BG control or in diabetic ketoacidosis, in order to assess the correlation at higher ketone levels for comparison.
Results
A significant relationship was found between blood β-hydroxybutyrate level and breath acetone (Spearman's rank correlation $\rho=0.364$, $P<0.0001$) in the clinic measurements. These patients were well-controlled and this relationship was apparent over the low concentrations of the blood ketones seen (0–0.4 mmol/l). A weak positive relationship was found between blood glucose and breath acetone ($\rho=0.16$, $P=0.1$). Young people presenting in DKA or with poor BG control had elevated levels of both blood ketones and breath acetone, with the latter having increased in some cases to over 100 parts/million. However there was no direct correlation.
Conclusions
Single breath measurements of acetone do not provide a good measure of blood glucose levels in this cohort. However within the limited range of blood ketones observed in well-controlled patients in a clinic, breath acetone levels were found to increase with blood β-hydroxybutyrate levels. Young people being treated for DKA had very high levels of breath acetone, although the changing situation during treatment may mean that there is a time-lag between blood and breath. This might suggest a potential to develop breath gas analysis to provide an alternative to blood testing for ketone measurement, for example to assist with the diagnosis of type 1 diabetes or the prevention of diabetic ketoacidosis.

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OC6.4

The role of the AMPK pathway in mediating the effects of metformin on mesenchymal stem cell differentiation

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Introduction
Insulin sensitising agents are reported to have a diverse range of effects on bone with metformin exerting positive effects and thiazolidinenediones (TZDs) exerting negative effects. 5′AMP-activated protein kinase (AMPK) plays a critical role in cellular energy homeostasis. It is widely expressed in the body and can be activated by metformin.
Aim
We investigated the role of AMPK pathway in mediating the effects of metformin on the osteoblast and adipocyte differentiation of mesenchymal stem cells (MSCs).
Methods
Confluent murine MSCs (C3H10T1/2) were treated with 500 μM metformin and 100 μM A769662 (AMPK activator) respectively, in an adipogenic-inducing environment (the TZD, pioglitazone 10 μM) for five days. Cells were harvested and nuclear extracts prepared. Nuclear extracts were separated by SDS–PAGE and immunoblotted with primary antibodies to peroxisome proliferator-activated receptor gamma (PPARγ; marker for adipogenesis) and runt-related transcription factor 2 (Runx2; marker for osteogenesis). Immunoblots were scanned using a Licor fluorescent reader. Adipogenesis was also quantified histochemically by fixing with 10% formalin followed by staining neutral lipids with Oil Red O.
Results
MSCs treated with pioglitazone for 5 days demonstrated marked adipogenic phenotype with accumulation of lipid-rich vacuoles that stained positively with Oil Red O. Pioglitazone induced a significant ($P<0.01$) increase in PPARγ1 and PPARγ2 expression compared to diluent control, as determined by western blotting. In the presence of pioglitazone, metformin suppressed PPARγ expression ($P<0.001$) to basal diluent levels, as did the AMPK activator, A769662 ($P<0.01$), which suggests that metformin acts through the AMPK pathway, at least to a degree, to suppress adipogenesis in MSCs. Runx2 expression was unaffected by treatment with either metformin or A769662, suggesting that AMPK is not involved in the induction of osteogenesis in these cells.
Conclusion
Metformin appears to exert its bone protective effects on MSCs by reducing adipogenesis, through activation of AMPK signalling, with no direct effect on osteogenesis.

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OC6.5

Capillary beta-hydroxybutyrate levels reliably predicts clinical severity in established diabetes but not in first presentations of type 1 diabetes in children

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Background
Near-patient capillary beta-hydroxybutyrate (BOHB) meters have been available for several years but evidence as to their clinical utility and reliability in children is still growing. Anecdotal evidence suggests that patients may have a significantly high level of capillary ketones but look clinically well, little evidence is available as to the kind of levels of blood ketones that paediatric patients can clinically compensate for. There is a move towards home blood ketone testing but there is uncertainty about the impact on services.
Methods
A retrospective case note review was conducted to investigate near-patient BOHB testing in paediatric patients who presented at two district general services with established or new diagnosis of type 1 diabetes over 2 years. Data on clinical impression at presentation, paediatric early warning score (PEWS), blood parameters and treatment were collected and statistically analysed.
Results
14/47 patients presenting as first episode of type 1 diabetes were assessed as clinically well (PEWS = 0 or 1) and found to have a significant blood ketone level (> 3 mmol/l). Eight of these were non-acidotic as defined by capillary blood gas. When compared with the patients in established diabetes who were assessed as

clinically well, with blood ketones >3 mmol/l where none had normal capillary gases, a significant difference was found ($P=0.01684$).
These ketotic patients, with or without acidosis, were treated with either i.v. or s.c. insulin. No significant difference in time to resolution of BOHB in these two groups was found (12.1 vs 9.3 h, $P=0.402$).
Conclusion
This evidence suggests that diabetic ketosis is common at the initial presentation of diabetes in clinically well children who may not be acidotic. Capillary BOHB is a better predictor of biochemical severity in established diabetes. This outcome supports the provision of home-ketone equipment in established diabetes but also provides insight into first presentations of type 1 diabetes in children.

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OC6.6

Comparison of type 1 diabetic control before and 5 years after transfer to adult services: audit of the 2008 cohort from the Royal Hospital of Sick Children (RHSC), Glasgow

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Background
Within the NHS Greater Glasgow and Clyde (GGC), many children with type 1 diabetes mellitus (T1DM) are looked after at the RHSC until the age of 16 years, after which they are transferred to their local adult diabetes services. This is the first longitudinal audit within the GGC looking at the changes in diabetic control of the patient pre-and post-transfer.
Method
A cohort of 75 patients referred onto the adult diabetes service from RHSC in 2008 was identified, of which 58 patients were eligible for inclusion in the audit. Glycaemic control, assessed by HbA1c and complication data at the time of transfer (2008) were collected from the Magistral database, and compared with the latest (2013) results available from the SCI-Diabetes database. Parameters of interest included HbA1c, retinopathy, microalbuminuria, and neuropathy.
Results
The average HbA1c value changed from 73 mmol/mol in 2008 to 86 mmol/mol ($P<0.001$; paired sample tests). Patients in the extremely high risk category (of developing complications) increased from 23 (39.7%) to 37 (63%). Background diabetic retinopathy rose from 4 (6.9%) to 19 (32.8%) patients, of which 5 (8.6%) now have maculopathy. The number of people with microalbuminuria also increased from 0 to 8 (13.8%). 4 (6.9%) patients are currently at increased risk foot ulceration due to impaired sensory nerve function or absent pulses. The average attendance rate also dropped from 3.6 to 2.3 visits/18 months ($P<0.001$; paired sample tests).
Conclusion
Patient's glycaemic control appears to deteriorate in the 2008 cohort 5 years on from transfer to the adult services with significant increase in microvascular complications.

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Oral communications 7

OC7.1

Additional professional support for paediatric patients with diabetes mellitus: are we targeting the right patients?

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Introduction
Outcomes of the National Paediatric Diabetes Audit have shown that patients of Black ethnic origin have poorer glycaemic control. Additional professional contacts mandated by the Best Practice Tariff aim to improve glycaemic control in paediatric patients with diabetes mellitus, but do not allow for differing needs.
Aim
To evaluate whether additional professional support for paediatric diabetic patients are targeted at those with worst glycaemic control in an ethnically diverse inner-city population.
Methods
This audit of three neighbouring London Paediatric Diabetes Centres collected data prospectively from 1/4/13 to 31/3/14 of patients aged <19 years diagnosed with type 1 diabetes for >1 year including: HbA1c, gender, age of and time from diagnosis, current age, ethnicity, townsend deprivation index, and number of additional professional contacts outside routine follow-up. Statistical analysis (significance <5%) by odds ratios, ANOVA (*post hoc* Tukey's test), Student's *t*-test, and Spearman's correlations.
Results
There were 275 (M=133) patients of median (range) age 14.5 (3.6–19.7) years, HbA1c 73 (35–132) mmol/mmol from the following ethnic groups: White (63.6%), Asian (11.6%), Black (9.8%), mixed (4%), others (11%). Median HbA1c showed no gender differences ($P=0.14$) and correlated with time from diagnosis ($P<0.001$), current age ($P=0.012$), and number of admissions ($P=0.001$). Patients with poor HbA1c (>80 mmol/mmol) had significantly higher deprivation scores (1.61 (3.4) vs 0.68 (3.4), $P=0.032$). Although mean deprivations scores were higher in the Black ($P<0.001$), Asian ($P<0.001$), and other ($P<0.001$) compared with White ethnic groups, there were no differences in mean HbA1c or prevalence of poor HbA1c (>80 mmol/mmol). Median number of additional professional contacts made were 17 (0–112) and correlated negatively with factors of poorer glycaemic control: time from diagnosis ($P=0.034$), current age ($P<0.001$), and deprivation scores ($P=0.027$). There were no differences in the number of contacts between patients with or without poor HbA1c (>80 mmol/mmol; $P=0.2$).
Conclusion
In this ethnically diverse population, deprivation regardless of ethnicity is associated with poor glycaemic control. Additional patient contacts are not targeting those with the greatest needs. Local and population demands should be considered during resource allocation.

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OC7.2

Urinary vitamin E metabolites as a biomarker of oxidative stress in type 1 diabetes

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Background
Oxidative stress has been implicated in the development and progression of complications in type 1 diabetes (T1DM). Vitamin E (α-tocopherol) undergoes β-oxidation of its chomanol ring and the resulting metabolite α-TLHQ has been proposed as a potential biomarker of oxidative stress. HbA1c relates in T1DM to microvascular complications predominantly although the end-points are late in disease development. The oxidative stress process may act independently of HbA1c and oxidative stress markers may be useful predictors of early vascular damage.
Objective and hypotheses
We aimed to measure the levels of vitamin E metabolites in T1DM and see whether they were elevated when compared with age-matched controls and to relate the measures to HbA1c, mode of insulin therapy and duration of diabetes.
Method
We developed a new assay using triple quadrupole tandem mass spectrometry to measure vitamin E metabolites α-TLHQ-SO3 and α-TLHQ-glucuronide. Urine samples were analysed from 133 children with T1DM and 88 age-matched controls. All subjects had normal renal function.
Results
Both vitamin E metabolites were significantly higher in T1DM compared to controls: mean α-TLHQ-SO3 (nmol/mmol creatinine) 3.09 ± 0.39 T1DM vs 1.96 ± 0.33 controls ($P=0.04$); mean α-TLHQ-glucuronide (nmol/mmol creatinine) 76.63 ± 5.65 T1DM vs 47.87 ± 2.16 controls ($P<0.0001$). No statistically significant differences were seen with HbA1c level, mode of insulin therapy, duration of diabetes or use of continuous glucose monitors.
Conclusion
These results demonstrate that urinary α-TLHQ, a biomarker of oxidative stress, is elevated in T1DM. Further work is required to validate these results and analyse variation with other parameters of diabetic control.

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OC7.3

Do diabetes teams give consistent advice on self-management and does it relate to glycaemic control? Yorkshire and Humber Paediatric Diabetes network survey

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Objectives
Glycaemic targets set by diabetes teams appear to have an impact on glycaemic control. Our objective was to identify if there is consensus between and within teams in our network on glycaemic targets and whether this correlates with HbA1c outcomes.
Methods
An online survey was sent to all network members requesting an independent response on the diabetes self-management advice given to families. Three patient groups were considered: children <5 and >5 years on multiple daily injections and insulin pump therapy (CSSI). Correlation between team consensus on target HbA1c and the actual clinic mean HbA1c was investigated using Spearman's correlation.
Results
Nineteen teams (19/20; 95%) responded with a 51% (55/108) response rate from the individual members. The response rates within teams varied from 14 to 100%. Respondents included specialist nurses (40%), dieticians (24%), senior doctors (29%), and junior doctors (7%). A target HbA1c of $\leq$58 mmol/mol (7.5%) was recommended by 78% (43/55) of the members for children <5 years, but by 96% (53/55) for children >5 years and CSSI group. Within individual teams, consistency in the HbA1c target was demonstrated in 54% (<5 years), 85% (>5 years), and 85% (CSII). Pre-meal blood glucose target of 4–7 mmol/l was advised by 34% (19/55), 49% (27/55), and 51% (28/55) of the members for the respective groups. The maximum variation was seen in <5 years group and pre-bed targets. The Spearman's ρ was -0.3 indicating a small negative correlation between teams with no consensus and mean HbA1c which was not significant ($P=0.37$).
Conclusion
There was poor consensus between and within teams on various self-management targets especially for <5 years group and pre-bed targets. There was no significant correlation with glycaemic control, probably due to the small number of teams. We believe this survey emphasises the importance of teams having agreed written targets.

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OC7.4

Hyperosmolar hyperglycaemic state: an unusual presentation of type 2 diabetes mellitus in children

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Background
Hyperosmolar hyperglycaemic state (HHS) is a life-threatening condition that can be the initial presentation of type 2 diabetes mellitus. This condition is characterized by severe hyperglycaemia, a high serum osmolality and dehydration without accumulation of ketoacids. We report two patients who presented with mixed features of HHS and DKA.
Case 1
An 11-year-old Afro-Caribbean boy with severe developmental delay presented with a 4-week history of polyuria, polydipsia, and drowsiness. Investigations showed severe hyperglycaemia (blood glucose 100 mmol/l), hyperosmolar dehydration (corrected Na 197 mmol/l) metabolic acidosis (pH 7.04, base excess -15.4 mmol/l) and renal failure (urea 40 mmol/l and creatinine 310 μmol/l). HbA1c was 9.8% with blood ketones of 5.4 mmol/l. The patient's clinical course was complicated by multiorgan failure and rhabdomyolysis requiring ventilation, inotropes, and haemofiltration. He was rehydrated and required i.v. insulin for 2 weeks. GAD and insulin antibodies were negative. There was a strong family history of type 2 DM. His HbA1c normalised (5.4%) 5 weeks later. His diabetes remains diet controlled.
Case 2
17-year-old girl with Wolf–Hirschhorn syndrome presented in an obtunded state. She had a 2-week history of polyuria, polydipsia and sudden deterioration with drowsiness and agitation. Investigations showed blood glucose >40 mmol/l, corrected Na 187 mmol/l, metabolic acidosis (pH 7.20, base excess -10.4 mmol/l), and renal failure (urea 30 mmol/l and creatinine 163 μmol/l). HbA1c was 10.5% with moderate ketonuria (3+). She required high dependency care and received i.v. insulin for 2 days and her hypernatraemic dehydration resolved slowly over the next 3 days. Her antibodies were negative. She was discharged 2 weeks on dietary treatment alone.
Conclusion
Children with type 2 diabetes can present with features of HHS and DKA. Learning difficulties and co-morbidities may lead to a delay in presentation and more severe illness. HHS can result in profound hyperglycaemia, hypernatraemia, and severe dehydration and may require intensive care.

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OC7.5

The relationship of vibration perception threshold with metabolic control and duration of disease in British children with type 1 diabetes

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Introduction
Type 1 diabetes affects a large number of children and adolescents, and its incidence is on the rise worldwide. The most devastating and important consequence of diabetes is its role in the development of long-term microvascular complications. This study aimed to study the role of the non-invasive vibration perception threshold (VPT) test in detecting subclinical peripheral neuropathy, and its correlation with metabolic control and duration of disease in British children with type 1 diabetes.
Methods
This prospective study was carried out in the paediatrics outpatients department of a secondary care centre with a specialist diabetes team. Children over the age of 18 and those with obvious neurological or foot disease were excluded. The patients had HbA1c and BMI measured, and the duration of diagnosis to the clinic appointment was calculated. The VPT measurements were taken by applying a probe to the big toes of the patients' feet and recording the lowest value when the patient reported a vibratory sensation. Statistical analyses were performed between the variables to determine significant correlations.
Results
90 patients were identified, and 70 patients (32 males and 38 females) met the inclusion criteria. The median HbA1c was 8.0%, median BMI 18.8, and mean duration of disease 4.6 years (S.D. – 2.57 years). The mean VPT in the left and right toe were 2.71 (S.D. – 1.13) and 2.87 (S.D. – 1.19) respectively. VPT was significantly correlated to age and height, but not to HbA1c and disease duration. HbA1c was significantly correlated with age, disease duration and BMI ($P<0.05$).
Conclusions
This was the first study carried out in the UK within a paediatric cohort. Although no clinically important correlations could be demonstrated, VPT could still be used in a clinical setting to introduce the discussion to promote adequate glycaemic control and foot care.

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Poster Presentations

P1

A rare cause of iatrogenic Cushing's syndrome

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Introduction
Cushing's syndrome in childhood usually results from exogenous steroids, which can potentially cause adrenal suppression and leave the patient at risk of adrenal crisis. Classically this occurs secondary to oral glucocorticoid medication, but there are also frequent reports resulting from high dose topical steroids. Prolonged intranasal or inhaled steroids have also been implicated, however cases resulting from the prolonged use of ocular steroids are extremely rare.
Case report
We present the case of an 8-year-old boy with Peters Plus syndrome who developed Cushing's syndrome and severe adrenal suppression secondary to prolonged ocular steroids given almost continuously over at least 4 years. He had bilateral congenital glaucoma, requiring multiple ophthalmic surgical procedures, including repeat corneal transplants. These dexamethasone eye drops had been given up to every 30 min, but mainly two to four times daily. On a short synacthen test he only achieved a peak cortisol level of <10 (at 0, 30, and 60 min) showing severe adrenal suppression.
Impacts on clinical practice
To date there have only been two previous reports of children developing Cushing's syndrome and two others with adrenal insuffiicency following ocular steroids.Exact mechanism is uncertain, as a study has confirmed that despite frequent dosing, the penetration of dexamethasone into the vitreous is negligible, concentration in the aqueous humor and systemic uptake is low. Possible mechanisms proposed include absorbtion through the nasal mucosa when correct instillation technique including punctal occlusion is not practised, which may reduce the steroid amount reaching the nasal mucosa. Although rare, clinicans should be aware that prolonged ocular steroids can lead to Cushing's syndrome and/or adrenal suppression (potentially occult). Its recognition is vital in order to institute appropriate management and prevent the life threatening possibility of adrenal crisis.

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P2

A unique case of a child with two inherited salt-losing conditions

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Salt-losing conditions can be challenging to manage well in infancy and early childhood. We describe a child with both salt-wasting 21-hydroxylase deficiency (SW21OHD) and cystic fibrosis (CF).
A male infant, JW, birth weight 3.5 kg, presented with a salt-wasting crisis on day 9 of life with hyponatraemia, hyperkalaemia, and weight loss of 415 g. Serum 17-hydroxyprogesterone (17OHP) was >1000 nmol/l and a diagnosis of SW21OHD was made. Neonatal screening confirmed the co-existence of CF (pancreatic sufficient). JW was established on treatment with hydrocortisone (HC) (13 mg/m^2 per day) fludrocortisone (FC) (300 μg/day), salt supplements 4 mmol/kg per day and flucloxacillin.
Throughout infancy, measurements of serum Na^+, K^+, and systolic BP were within normal limits. However, plasma renin activity (PRA) was elevated, particularly following the introduction of proprietary low-salt weaning foods. This was associated with poor weight gain, reaching a nadir of 7.5 kg (-2.3 SDS) at 0.9 years. FC dose was increased to 400 μg/day but with little beneficial effect. Salt supplementation was increased gradually, reaching a maximum daily salt intake of 11 mmol/kg per day at 2 years of age. FC dose was decreased gradually to 200 μg/day in view of its potential growth suppressing effects. At 3.9 years, JW's weight had increased to 15.6 kg (-0.3 SDS), height 98.1 cm (-0.8 SDS), height velocity 6.6 cm/year, PRA within normal limits.
This case highlights a number of important issues: i) The importance of providing adequate salt in babies with salt-wasting conditions to allow optimal growth. ii) The importance of continuing to monitor salt intake during weaning. iii) The relationship between salt intake, FC dose and PRA and their relative roles in the optimal management of SW21OHD. iv) The possible role of salt depletion in growth failure in infants and children with cystic fibrosis.

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P3

Aldosterone synthase deficiency due to a novel mutation in *CYP11B2*

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Background
CYP11B2 encodes a steroid 11/18-β-hydroxylase that functions in mitochondria in the zonaglomerulosa of the adrenal cortex to synthesize the mineralocorticoid aldosterone. The enzyme catalyzes three necessary reactions: 11-β-hydroxylation of 11-deoxycorticosterone (11-DOC) to corticosterone, 18-hydroxylation of corticosterone to 18-hydroxycorticosterone (18-OHB); and 18-oxidation of 18-hydroxycorticosterone to aldosterone. Aldosterone synthase (*CYP11B2*) deficiency is an autosomal recessive disorder associated with a defect in aldosterone biosynthesis. The clinical presentation and severity of the condition varies with age. Newborns exhibit salt wasting in the first few weeks of life with failure to gain weight. Adults may present with hyperkalaemia and postural hypotension.
Case
We report the case of an infant who presented with failure to thrive and poor feeding. At 3 months of age, his weight was 3.02 kg (-4.3 SDS), having gained just 100 g since birth. Biochemistry revealed hyponatraemia (Na^+124 mmol/l), hyperkalaemia (K^+6.3 mmol/l), and raised urea (9.7 mmol/l). After correcting the hyperkalemia, he was investigated thoroughly. The plasma renin activity (PRA) was 12 nmol/l per h; slightly elevated. Cortisol was normal and aldosterone measured 470 pmol/l (NR 100–800 pmol/l). Raised urinary corticosterone metabolites were detected suggesting an aldosterone synthesis defect, thus fludrocortisone was initiated. As the response was suboptimal and diagnosis remained unclear, he was admitted into a controlled environment and fludrocortisone withheld. The subsequent PRA was found to be raised at 100 nmol/l per h strongly supporting the diagnosis of an aldosterone biosynthetic defect. Genetic analysis revealed compound heterozygosity for a novel *CYP11B2* mutation: (c.1471C>T (p.Pro491Ser)) and a previously reported mutation (c.541C>T (p.Arg181Trp)). He responded to recommencement of fludrocortisone, sodium supplementation and dietetic support with good catch-up growth and normal development.
Conclusion
Although rare, aldosterone synthase deficiency should be suspected in infants presenting with salt-wasting. Long-term prognosis is good once fludrocortisone is commenced. If uncorrected, the resulting hypotension, hyponatraemia, and hyperkalaemia may prove devastating.

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P4

cDNA analysis reveals *NNT* pseudoexon activation in two siblings with familial glucocorticoid deficiency

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Aberrant pseudoexon inclusion is rarely recognised as a cause of human disease. Here we report two novel, compound heterozygous mutations in nicotinamide nucleotide transhydrogenase (*NNT*), one of which activates a pseudoexon, as the cause of familial glucocorticoid deficiency in two siblings. Whole-exome sequencing identified a single novel, heterozygous variant (R71X) in both affected individuals. Follow-up cDNA analysis identified the pseudoexon inclusion (p.P998_D999ins23) and Sanger sequencing of genomic DNA identified a 4 bp duplication responsible for its' activation. The variants segregated with the disease, R71X was inherited from the mother, P998_D999ins23 from the father and an unaffected sibling had inherited only the R71X variant. Neither variant has been annotated in any SNP or mutation databases and both will lead to premature truncation and presumably an inactive protein. The mutation resulting in pseudoexon inclusion could provide a potential target for antisense oligonucleotide therapy. Detection of such events in disease is hampered since introns, because of their frequently large size, are often excluded from mutational analyses, and it is often impossible/impractical to perform cDNA analysis.

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P5

Cerebral oedema: a rare presentation of Addison's disease

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Introduction
Cerebral oedema has rarely been reported in adrenal insufficiency. We report a case of decompensated cerebral oedema due to autoimmune adrenalitis.
Case report
A 12-year-old boy presented to hospital with a 1 day history of headache, fever up to 39.9 °C, confusion, diarrhoea, and vomiting. He had a left-sided ptosis, reduced conscious level (Glasgow coma scale 8/15) and was hypertensive (blood pressure 134/90 mmHg). He required intubation and 4 days of mechanical ventilation with inotropic support. A CT scan confirmed the presence of raised intracranial pressure with slit like ventricles. Initial investigations confirmed features of sepsis with hyponatraemia (sodium 128 mmol/l, potassium 5 mmol/l, pH 7.3, BE −8, CRP 305.5 mg/l, WCC 15, and neutrophils 10). The presence of pigmentation with persistent hyponatraemia and catecholamine-refractory shock led to a synacthen test which confirmed adrenal failure (30 min peak cortisol 19 nmol/l), with a modestly elevated ACTH of 63 ng/l (N10–50). He was commenced on i.v. hydrocortisone treatment with rapid improvement; this was later switched to oral medication.
Further discussion with the family confirmed a 6-month history of salt craving and progressive skin pigmentation that had been attributed to the summer weather.
There was a strong family history of autoimmunity, with systemic lupus erythematosus in the mother, hypothyroidism in the father, and type 1 diabetes in the paternal step daughter.
Convalescence sampling confirmed autoimmune adrenalitis (adrenal antibody positive and thyroid antibody negative), and further elevation of ACTH (>1250 ng/l). Mild hyponatraemia persisted on hydrocortisone, and an elevated plasma renin (33 nmol/l per h; NR 2.8–4.5) confirmed mineralocorticoid deficiency. Fludrocortisone was therefore commenced with consequent biochemical and clinical improvement.
Conclusions
Cerebral oedema is a rare life-threatening feature of Addison's disease. Earlier detection of chronic glucocorticoid and mineralocorticoid deficiency in our patient may have prevented the acute decompensation. Addison's disease should be considered in any patient with unexplained cerebral oedema.

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P6

Comparing clinical practice with consensus guidelines for the investigation and management of British children with congenital adrenal hyperplasia

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Introduction
Congenital adrenal hyperplasia (CAH) is a rare condition affecting steroid-hormone synthesis. We reviewed the investigation and management of children with CAH against current international guidelines and explored variation by region and specialty of responsible clinician.
Methods
Active national surveillance of new diagnoses of CAH in children under age 16 years and resident in Great Britain, undertaken prospectively from 2007 to 2009.
Results
Surveillance identified 144 children newly diagnosed with CAH, of whom 137 (82 diagnosed aged <1 year) were followed-up after 12 months. 108 (79%) children were referred for, or under, specialist care (endocrinologist; paediatrician with endocrinology special interest (PESI)). 85 (62%) children were referred, including to geneticists ($n=75$), psychological/counselling services ($n=27$), and surgeons ($n=17$). Serum 17-hydroxyprogesterone was measured in 132 (96%) children. Of 82 infants diagnosed aged <1 year, 60% had urinary steroid analysis, 49% DNA analysis and 22% a Synacthen stimulation test; of 55 older children, 82% had urinary steroid analysis, 55% DNA analysis, and 62% synacthen stimulation. At follow-up, 82 (100%) infants were taking hydrocortisone, 77 (94%) fludrocortisone, and 38 (46%) sodium supplements. Of 55 older children, 49 (89%) were taking hydrocortisone, one prednisolone and 11 (20%) fludrocortisone. 17 children on steroid-replacement therapy experienced 37 adrenal crises (ten associated with intercurrent illness). Of 30 severely virilised girls (Prader score ≥3), six had genital surgery; eight less virilised girls also underwent surgery. There was little variation by specialty or region, but general paediatricians were significantly less likely to request DNA analysis.
Conclusions
Our surveillance study confirms that international consensus clinical practice guidelines for managing children with CAH (European Society of Paediatric Endocrinology/Lawrence Wilkins Pediatric Endocrine Society, 2002; The Endocrine Society, 2010) are largely followed in the UK. Although current guidance recommends multidisciplinary and specialist care approaches, few families were referred for counselling and one-fifth were not under endocrinologist/PESI care.

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P7

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency in a regional cohort 1994–2004: characterisation and genotype–phenotype analysis

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Congenital adrenal hyperplasia (CAH) has an estimated prevalence of one in 10 000–20 000 live births. Patients are described as salt wasting (SW), simple virilising (SV), or non-classical (NC). The CAH genotype is usually compound heterozygous.
Aims
To characterise the cohort of CAH patients presenting to a regional centre 1994–2014, to quantify the allelic frequency of CYP21A2 mutations and to examine genotype–phenotype associations.
Method
Retrospective notes review. Genotype according to mutational analyses performed at diagnosis using pyrosequencing, fluorescent PCR, and multiplex ligation-dependent probe amplification (MLPA). Phenotype determined by clinical presentation, age of presentation, 17-OHP levels, plasma renin, urinary steroid profile, and Synacthen tests.
Results
Using the regional endocrine database, 74 patients were identified (four had declined mutational analysis). Only four were non-Caucasian. 28 had a known family history. 48 presented within the first year of age. SW: total 47 (64%); 54% female; 85% presented <30 days. SV and NC: total 26 (36%); eight on glucocorticoid only and two on no long-term medication. The most common mutations in our cohort were the CYP21A2 chimeric deletion/conversion encompassing exons 1–3, c.290-13C>G, c.515T>A; p.Ile172Asn and c.841G>T; p.Val281Leu. Two SW patients were identified with the rarer mutations g.2578 C>T (p.Pro453Ser) and exon 6 cluster (p.Ile236Asn, pVal237Glu, and pMet239Lys). c.290-13C>G and c.515T>A; p.Ile172Asn were most common in SW patients, despite usually being associated with the SV form. c.841G>T; p.Val281Leu was associated with SV CAH, especially milder disease.
Conclusions
We characterise a cohort of CAH patients from a defined region of the UK with a relatively static population. Our work supports previous findings that a small number of mutations are commonly associated with CAH, while indicating a need to reconsider some established genotype–phenotype correlations. We report interesting rarer mutations. Improved understanding of genotype-phenotype correlation will have implications for management, genetic counselling, and prenatal diagnosis.

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P8

Do babies born to mothers taking antenatal prednisolone require screening for adrenal suppression?

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Background
Limited evidence exists regarding the effect of antenatal prednisolone (ANP) on neonatal adrenal function. Our regional neonatal unit screens these babies by measuring three random serum cortisol levels 8 h apart on day 3 of life. Adrenal function is considered adequate if two cortisol levels are >100 nmol/l. Those with inadequate random cortisol levels undergo a low-dose Synacthen test (LDST). Our survey of UK tertiary Paediatric Endocrinology centres revealed that only one other unit screens for adrenal suppression in these babies, using LDST.
Objectives
i) To identify the proportion of neonates born to mothers on ANP with adrenal suppression.
ii) To determine the relationship between ANP and neonatal cortisol.
Methods
Neonates who had screening cortisols performed between Jan 2008 and Feb 2013 were retrospectively reviewed. The relationship between ANP and neonatal cortisol was investigated using Spearman's correlation.
Results
Thirty-nine neonates potentially affected by ANP were screened. Inadequate random cortisol levels were identified in 15% babies (6/39); all subsequently had a normal LDST. Two babies (5%) had three cortisol levels <100 nmol/l and were empirically commenced on hydrocortisone before LDST. All had normal adrenal function when re-tested with LDST at 3 months of age. The mean dose of ANP was 16.2 ± 2.7 mg/day. The highest of the three random cortisol levels did not correlate with ANP dose (Spearman's ρ 0.166; $P=0.36$).
Assessing specificity and sensitivity of our screening test was not possible.
Conclusion
In our small cohort we did not detect any newborn with adrenal suppression secondary to ANP. The day three cortisol levels did not correlate with the dose of ANP. Studies suggest that prednisolone has limited transfer across the placenta. Larger scale studies are required to determine the necessity of screening these neonates for adrenal suppression using serial random cortisol levels or LDST.

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P9

Functional adrenal tumour as a cause of virilised infant

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Introduction
Childhood adrenocortical tumours (ACT) are extremely rare (worldwide incidence: 0.3/million per year). Most affected are young girls – female:male 2:1, peak age at diagnosis -3.5 years.
Case report
A 2.5-year-old-girl presented with a 4-month history of greasy hair, acne, weight gain, especially around face and upper shoulders. She had irritability, daytime lethargy and night-time sleep disturbance. She later developed pubic hair. On examination she was virilised: pubic hair stage II, enlarged labia majora and clitoris, acne over the nose, cheeks and scalp-line; and cushingoid: weight 91st centile, height 2nd–9th centile; with moon facies and a buffalo hump. Abdominal examination and BP were unremarkable.
An ultrasound scan revealed a 6 cm mass in the right adrenal gland. MRI showed no calcification, invasion of adjacent structures, or evidence of distant metastases. Further investigations confirmed a functional ACT: serum androstenedione >35 nmol/l, DHEAS >27.1 nmol/l, testosterone 5.5 nmol/l, cortisol 850 nmol/l.
Following a right adrenolectomy, histology confirmed an adrenocortical adenoma weighing 105 g, measuring $7 \times 6 \times 6$ cm. Clinical genetics review showed insufficient family history to warrant p53 gene testing; however the patient had a medical history of large birth-weight, an unusual appearance to umbilicus: enlarged base, small supra-umbilical hernia and one side of abdomen more prominent than the other. More recently mother had noted asymmetry of the leg and foot. Therefore testing for Beckwith–Wiedemann syndrome was recommended. She remains on hydrocortisone cover and a synacthen test is planned for the future.
Conclusion
Typical presentation of ACTs is with syndromes of hormone excess, usually virilisation. Cushing's is present in 1/3 cases but ACTs are usually inefficient at producing cortisol. While is it rare, ACT should be considered in any child presenting with premature virilisation. Genetics review is always recommended: 80% of children with sporadic ACT have atypical p53 germline mutations. ACT is also associated with isolated hemi-hypertorphy and Beckwith–Wiedemann syndrome.

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P10

Severe hyponatraemia and pseudohypoaldosteronism secondary to infantile atopic dermatitis

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Introduction
Atopic dermatitis can cause significant exudative fluid loss from a large body surface area in an infant leading to severe hyponatraemia.
Case report
A 5-month-old boy was referred to the paediatric team from dermatology with severe cradle cap, eczema and fever. He also had faltering growth (weight: 4.95 kg, well below 0.4th centile) and moderate developmental delay. On examination, he had severe infected eczema over a large area of the scalp. Initial blood tests showed sodium: 120 mmol/l, potassium: 5.7 mmol/l and albumin: 21 g/l. Urinary sodium was <10 mmol/l ruling out renal sodium loss. He had markedly raised plasma aldosterone and renin levels at 36 100 pmol/l (reference range: 100–450) and 18 pmol/l (reference range: 1.1–2.7) respectively. However, serum ACTH, cortisol and thyroid function tests were normal. His total IgE was markedly elevated at 9800 u/ml and specific IgE to cow's milk was highly positive (class 5). Other immunoglobulins were normal and coeliac screen was negative. His cradle cap improved gradually with oral antibiotics, topical steroid therapy, emollients and cow's milk avoidance. Hyponatraemia was initially corrected with sodium chloride supplementation. His plasma sodium improved to normal range within 2 weeks and sodium supplements could be stopped within 4 weeks of initial presentation. Blood tests repeated 2 months later showed decreasing levels of serum aldosterone levels. At his clinic visit 4 months later, he showed normal biochemistry, good improvement in growth parameters and developmental milestones.
Conclusion
Severe infantile atopic dermatitis can result in significant electrolyte abnormalities such as hyponatraemia and hyperkalaemia leading to pseudohypoaldosteronism. This could affect developmental progress and growth parameters. Rigorous treatment with topical steroid therapy and emollient creams to prevent exudative fluid loss along with temporary sodium supplementation may be required to correct electrolyte imbalance. It is important to consider severe infantile eczema as one of differential diagnoses of pseudohypoaldosteronism.

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P11

The accuracy of 24-h urinary free cortisol as a screening test in the diagnosis of Cushing's syndrome in children

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Background
Endogenous Cushing's syndrome (CS) in children remains a challenge to diagnose and exclude. 24-h urinary free cortisol (UFC) measurements are a convenient, non-invasive test for paediatric patients.
Objective
To assess the screening accuracy of 24-h UFC measurements in paediatric patients referred to our centre for evaluation of possible CS.
Methods
A retrospective review of children referred to our centre between 1982 and 2014 was undertaken. The series included 62 children: 34 cases of Cushing's disease (CD), eight bilateral micronodular adrenocortical disease, two ectopic ACTH secondary to bronchial carcinoid tumours and 18 controls (CS was excluded).
Results
All but three CS patients had elevated 24-h UFC measurements: mean 1380 nmol/24 h by immunoassay (normal range 40–340 nmol/l) and 767 nmol/24 h by LCMS assay (normal range <124 nmol/l). Mean values were 904 nmol/24 h for CS, 1132 nmol/24 h for adrenocortical disease, and 2244 nmol/24 h for ectopic tumours. Mean 24 h UFC values were significantly higher in males compared to females with CD (1088 nmol/24 h vs 635 nmol/24 h, respectively; $P=0.004$). In contrast, there was no difference in UFC levels between males and females in the control group (104 nmol/24 h and 119 nmol/24 h, respectively). The sensitivity and specificity for 24 h UFC measurements in the diagnosis of paediatric CS were both 93%. The false positive rate was 7% (2/27), and so was the false negative rate (3/44). Overall, the diagnostic accuracy (AUC) for 24 h UFC measurements was excellent (0.97, 95% CI 0.901–0.996).
Conclusions
24-h UFC measurements have high diagnostic accuracy for CS in children and may be more sensitive as a diagnostic test for CS in paediatric compared to adult patients. Additionally, this test is widely available and can be performed at home. Interestingly, UFC concentrations were significantly higher in male compared to female CD patients.

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P12

Varied clinical presentations of six patients with mutations in CYP11A1 encoding the cholesterol side-chain cleavage enzyme, P450scc

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Mutations in *CYP11A1*, like those in *STAR* cause lipoid congenital adrenal hyperplasia manifesting with adrenal and gonadal insufficiencies along with derangements of the renin/angiotensin system. Increased adrenal size is usually a feature of *STAR* but not of *CYP11A1* mutation. Milder forms presenting without all of these features have also been described. We present six patients from four families with *CYP11A1* mutations discovered by whole exome sequencing. The mutations were as follows; two sisters had a homozygous A359V mutation, two siblings had compound heterozygous mutations I279Yfs*9;*122Rext*68, one patient was compound heterozygous for Q395K and R120Q and one was compound heterozygous for E314K and an exon 5/intron 5 splice site mutation. The presentation varied between cases, ranging from a patient with neonatal salt wasting/adrenal crisis and large adrenals to a pair of non-pigmented sisters aged 2 and 4y on glucocorticoid replacement alone. Whole exome sequencing revealed the nature of the underlying defects in all patients to be mutation(s) in CYP11A1, the gene encoding the first enzyme in the steroidogenic pathway, converting cholesterol into pregnenolone. These cases emphasize the utility of whole exome sequencing as a tool for improved diagnosis and therefore patient management in the endocrine clinic.

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P13

Development of a premature adrenarche management guideline

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Introduction/aims
Adrenarche, the gradual increase in adrenal androgen secretion resulting in clinical features of pubic hair, axillary hair, body odour and acne, is independent from gonadotrophin-dependent central puberty. It is important that children presenting with these features are not unnecessarily investigated, whilst ensuring significant pathology is not overlooked.
There is variation in practice in management of adrenarche. We identified current practice across Scotland using contacts from the Scottish Paediatric Endocrine Group (SPEG) and developed a guideline to standardise management approach.
Methods
A questionnaire containing four clinic scenarios representing adrenarche, thelarche, thelarche variant and precocious puberty was sent electronically to consultant paediatricians carrying out specialist endocrine clinics across Scotland and to all consultant paediatricians in the South East of Scotland.
A guideline incorporating responses from the questionnaire was developed and discussed at a SPEG meeting.
Results
The questionnaire was sent to 87 consultant paediatricians, with a response rate of 54%. 20 respondents answered all scenarios, 14 (70%) were endocrinologists or those with a special interest in endocrinology.
A wide variety of approaches to investigation and management of adrenarche were reported. The median number of investigations proposed by endocrinologists was three (range 0–8) compared to a median of six investigations (range 4–9) in the non-specialist group. The guideline, which will be presented, was designed to guide referral from general practice and general paediatric clinics and standardise specialist investigations.
Conclusions
This guideline for assessment of features of adrenarche will be used locally and has been submitted for approval by the SPEG Guideline Group.

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P14

Bone mineral density and vertebral compression fractures in patients with recessive dystrophic epidermolysis bullosa

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Introduction
Severe generalised recessive dystrophic epidermolysis bullosa (RDEB) is a rare disorder resulting from loss of function mutations in the type VII collagen gene

(*COL7A1*). Although RDEB is characterised by severe trauma induced skin blistering and erosions, it is a multisystem disorder with low bone mass as one of the many complications.

Objectives

We sought to describe the prevalence of low bone mass, vertebral fractures and scoliosis in children with RDEB between the ages of 7–8 years and compare this to children of the ages 15–18 years.

Method

This was a retrospective, observational study of 22 patients aged 7–8 years and 15 patients aged 15–18 years. Primary outcome measures were BMD *Z* scores, areal BMD (aBMD), presence of vertebral fractures and scoliosis.

Results

The mean lumbar spine aBMD $\pm$ S.D. of children aged 7.7 $\pm$ 0.5 years *Z* score was -1.8 ± 1.2 and aBMD 0.550.1 g/cm^2. Twenty-seven percent of the children had vertebral compression fractures and 5% had scoliosis.

This compared with mean lumbar spine aBMD of children aged 16.5 $\pm$ 1.2 years *Z* score of -4.4 ± 1.2 and aBMD of 0.68 $\pm$ 0.2 g/cm^2. Thirty-eight percent of these children had vertebral compression fractures and 33% had scoliosis.

Whilst there was a significant increase in the aBMD ($P < 0.006$) in the older cohort, there was a highly significant decrease in BMD *Z* score ($P < 0.0001$) with over a third of children aged 15–18 years having vertebral compression fractures and scoliosis.

Conclusions

Children with RDEB have low BMD *Z* scores in childhood which declines with age. Despite early preventative interventions such as optimising nutrition, vitamin D supplementation and physiotherapy, there is still an increase in complications including vertebral compressions and scoliosis. The cause of low bone mass is multifactorial in nature but we are beginning to understand the major role of chronic inflammation in fuelling this process.

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P15

Hyperostosis-hyperphosphataemia syndrome: shortening a diagnostic odyssey

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Introduction

Hyperostosis-hyperphosphataemia syndrome (HHS) is a rare autosomal recessive condition caused by inactivating mutations in the *GALNT3* gene, characterised by elevated serum phosphate and 1,25$(OH)_2$ vitamin D, increased urinary tubular reabsorption of phosphate and hyperostosis of long bones.

Case report

A 15-year-old boy (weight + 1.05 S.D.; height -0.1 S.D.) with consanguineous parents of Palestinian descent, presented with a 6 year history of recurrent episodes of flitting pain located in the forearms and lower legs. Episodes typically lasted 1–4 weeks were associated with erythema of the overlying skin, swelling of the underlying tissue and had no obvious triggers. Previous investigations had included a biopsy of the ulna which revealed only non-specific findings (ossified material surrounding calcified cartilaginous tissue). Diagnoses of osteopetrosis and chronic recurrent multifocal osteomyelitis (CRMO) had been made in the past. Treatment with intermittent glucocorticoids and NSAIDS had produced symptomatic benefit. General examination was unremarkable apart from thickening and widening of the right ulnar border and anterior border of the right tibia. Biochemical investigations showed a persistent high fasting serum phosphate (2.29 mmol/l) with an inappropriately elevated TmP/GFR (3.11 mmol/l). Serum 25(OH) vitamin D concentration was low (13 nmol/l), 1,25$(OH)_2$ vitamin D was elevated (195 pmol/l) and PTH was previously normal (6 pmol/l).

Radiographs showed mild periosteal reaction, cortical irregularity and poor cortico-medullary distinction throughout the shafts of the radius, ulna, tibia and fibula. MRI revealed high signal lesions within the medullary cavity of the diaphyses of the left fibula and right tibia on T2-weighted and STIR, corresponding to low signal on T1 sequences.

Mutation analysis of the *GALNT3* gene revealed a homozygous *GALNT3* frame shift mutation (c.803dupC), confirming the clinical diagnosis of HHS.

Conclusion

This case illustrates the value of both thorough clinical assessment and targeted genetic screening in the prompt diagnosis of rare disorders.

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P16

Leptin is associated with bone microstructural changes in obese children

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Background

Bone mass is low and fracture risk is higher in obese children. We wished to ascertain the relationships of obesity-related changes in hormones with skeletal microstructure.

Method

Children aged 8–15 years matched by gender and pubertal stage were recruited into lean and obese groups (18 pairs). We used high resolution peripheral quantitative computed tomography (HRpQCT – resolution-82 μm) to assess three-dimensional cortical and trabecular microstructure at load-bearing and non-load bearing sites. Lean and fat mass percentage (%) were measured by DXA. Leptin, adiponectin, testosterone and oestrogen were measured by immunoassay.

Results

Lean and obese children were 12.9 $\pm$ 2.0 years and 12.6 $\pm$ 1.9 years ($P = 0.23$) respectively. There was no difference in height SDS between groups. Radial cortical porosity (mean difference -0.01 (95% CI: -0.02, -0.004), $P = 0.004$) and cortical pore diameter (mean difference -0.005 mm (95% CI: -0.009, -0.001), $P = 0.009$) were lower in obese children. Tibial trabecular thickness was lower (mean difference -0.009 mm (95% CI: -0.015, -0.004), $P = 0.002$) and trabecular number was higher (mean difference 0.23/mm (95% CI: 0.08, 0.38), $P = 0.006$) in obese children. At the radius, fat mass % negatively correlated cortical porosity ($r = 0.57$, $P < 0.001$) and cortical pore diameter ($r = 0.38$, $P = 0.02$) and negatively correlated with tibial trabecular thickness ($r = -0.62$, $P < 0.001$).

Leptin was higher in obese children (805.3 $\pm$ 440.6 vs 98.1 $\pm$ 75.4, $P < 0.001$) and was inversely related to radial cortical porosity ($r = 0.60$, 95% CI: (-0.80, -0.30), $P < 0.001$), mean radial cortical pore diameter ($r = 0.51$, 95% CI (-0.75, -0.16), $P = 0.002$), and tibial trabecular thickness ($r = 0.55$, 95%CI: (-0.78, -0.21), $P = 0.001$). In multivariate analyses that included all measured hormones, leptin remained inversely correlated to radial cortical porosity ($r^2 = 0.48$, $P = 0.002$), mean radial cortical pore diameter ($r^2 = 0.26$, $P = 0.01$) and tibial trabecular thickness ($r^2 = 0.22$, $P = 0.02$).

Conclusion

Childhood obesity improves radial cortical porosity but negatively impacts on tibial trabecular microstructure. Leptin appears to be a key hormone mediating these changes. Maladaption of tibial trabecular microstructure may result in an increased risk of tibial fracture in obese children.

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P17

Neonatal seizure: a rare presentation of maternal hyperparathyroidism

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Introduction
Hypocalcaemia is a recognised cause of neonatal seizures most often related to vitamin D deficiency in the mothers of exclusively breast fed infants. There have also been case reports of an underlying diagnosis of hyperparathyroidism in a reportedly well mother becoming apparent after the infant presents with hypocalcaemic seizures. Maternal hypercalcaemia suppresses parathyroid activity in the foetus, which causes transient neonatal hypocalcaemia.
Case description
A 7-day-old male baby born at term following an uneventful pregnancy presented with focal seizures. Admission blood tests revealed hypocalcaemia Ca 1.45 mmol/l (2–3 mmol/l) alongside low magnesium 0.65 mmol/l (0.7–1.0 mmol/l) and vitamin D levels 37 nmol/l (24–76 nmol/l) with an inappropriately low PTH of <3 ng/l (14–72 ng/l). The baby required i.v. boluses of calcium followed by a calcium infusion. MRI head, renal ultrasound, metabolic screen and chest X-ray were all normal. Maternal bloods revealed hyperparathyroidism with a PTH of 105 ng/l (14–72 ng/l) and hypercalcaemia 2.95 mmol/l (2.2–2.6 mmol/l). The patient became seizure free 4 days after admission. The patient was discharged on calcium, cholecalciferol and alfacalcidol. Calcium and vitamin D normalised and were stopped after 5 weeks of treatment. The patient is currently undergoing weekly blood tests with gradual weaning of the alfacalcidol. Maternal parathyroid scan showed a left sided upper pole adenoma measuring 17.5 mm $\times$ 10.3 mm. Mother has been referred for a parathyroidectomy and further investigations.
Conclusion
Maternal hyperparathyroidism is a rare cause of neonatal hypocalcaemia which can be both severe and prolonged with treatment required for up to 5 months. Although rare, this and other case reports highlight the importance of checking the parathyroid hormone and the calcium levels of mothers when their infant presents with hypocalcaemic seizures even if the mother is asymptomatic.

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P18

Suppression of bone turnover and its determinants in children receiving bisphosphonate therapy

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Introduction
Bisphosphonate therapy (BPT) reduces osteoclast activity and may be associated with adynamic bone turnover. The extent of suppression of bone turnover and its determinants are unclear.
Methods
Markers of bone metabolism were evaluated in 15 children (9M/6F) receiving cyclical BPT intravenously for osteoporosis. The median age at first biochemical assessment was 10.8 years (0.16, 16.3). Serum type I collagen cross-linked C-telopeptide (CTX), alkaline phosphatase (ALP), calcium (CA), phosphate (P), parathyroid hormone (PTH) and 25 hydroxy vitamin D (VitD) were measured on day 1 of each BPT cycle. The CTX was expressed as a centile of the reference range in healthy children. The results are presented in Table 1.

Table 1

		Time since start BPT (years)					
	Reference range	0.5	1	1.5	2	3	>3
n		7	10	8	8	5	5
CTX centile		2.8 (0.7,4.1)	2.8 (0.6,4.9)	2.7 (0.5,3.8)	2.8 (0.5,5.5)	2.1 (1.4,7.1)	2.1 (1.0,4.9)
ALP (U/l)	60–424	351 (62,500)	261 (49,421)	192 (36,455)	141 (39,396)	215 (136,346)	145 (105,274)
PTH (pmol/l)	1.6–7.5	2.9 (1.4,4.5)	2.35 (1.0,6.9)	3.35 (2.8,6.0)	3.4 (2.1, 7.8)	2.95 (2.5,5.1)	4.3 (2.8,5.6)
VitD (nmol/l)	>50	47 (26,78)	36 (19,108)	15 (14,44)	23 (14,36)	31 (23,38)	57 (34,98)

Values:median (range)

Results
The median interval between the first BPT cycle and first biochemical assessment was 0.67 years (0.15, 8.12). The median duration of observation was 1.1 years (0.58, 3.3) and the median number of samples per patient was 5 (2, 8).
The median CTX centile was 2.4 (0.5, 7.1), thus below 10th centile, throughout the duration of observation ($P<0.0001$). ALP was negatively correlated with the duration of treatment ($r-0.35$, $P<0.05$) and positively correlated with CTX ($r=0.72$, $P<0.0001$). Median CTX in patients with (n, 4) and without (n, 11) consistently low VitD was 2.61 (1.3, 5.1) and 1.96 (0.34, 3.6) ($P<0.05$). Median ALP in the same two groups was 302 U/l (180, 455) and 141 U/l (36, 500) ($P<0.0001$). PTH was positively correlated with CTX ($r=0.51$, $P<0.05$).
Conclusion
Bone resorption is markedly suppressed compared to bone formation. Vitamin D and PTH status influence the extent of suppression of bone turnover. An assessment of bone turnover markers may allow improved titration of BPT.

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P19

Young adults with Klinefelter syndrome and congenital anorchia treated with testosterone from adolescence have normal bone and muscle mass but increased central adiposity

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Background
Decreased bone mineral density using dual energy absorptiometry (DXA) is reported in mixed cohorts of testosterone treated and testosterone naïve men with Klinefelter syndrome (KS). Bone mass and body composition in men with congenital anorchia (CA) have not been reported.
Hypothesis
Men with KS and CA treated with testosterone from adolescence have normal bone mass and body composition.
Methods
DXA and pQCT were performed in 20 hypogonadal men (12 KS and eight CA), all and compared with 20 aged matched healthy controls. Results expressed as median (range).
Results
Age, height, BMI were not different between groups. No differences were seen between patients and controls for the following parameters-DXA total body BMD Z score -0.7 (-2.4, $+3.0$) vs -0.6 (-2.3, $+1.2$) ($P=0.93$); pQCT total density Z score at 4% radius: -1.1 (-3.2,$+2.6$) vs -1.4 (-3.5,$+1.4$) ($P=0.13$), cortical density: 469.5 mg/cm^3(301,753.1) vs 466.1 mg/cm^3(271.4, 723.2) ($P=0.28$) and trabecular density: 223.7 mg/cm^3(151.9, 334) vs 198.6 mg/cm^3(147, 263.9) ($P=0.06$). DXA lean mass, lean mass for height and lean mass for fat mass were similar in both groups. Muscle density and muscle area on pQCT at 66% tibia were not different between patients and controls: 77.4 mg/cm^3(56.7, 80.4) vs 77.4 mg/cm^3(73.7, 80.7) ($P=0.86$) and 8079 cm^2 (6486.4, 1922.6) vs 8122.2 cm^2(5429.1, 10 258.60 ($P=0.92$).%fat was similar in both groups but trunk: leg fat ratio1.53 (0.88, 3.0) vs 1.17 (0.78, 2, 42) ($P=0.01$), visceral adiposity mass: 464.9 g (156.5, 981.5) vs 289.3 (137.2, 582.2) ($P=0.006$) and volume: 502.6 cm^2(169.2, 1061.1) vs 312.8 cm^2(148.3, 629.4) ($P=0.006$)were higher for patients.
Conclusion
This first report of bone assessment using pQCT in adults with KS and CA treated with testosterone from adolescence demonstrates BMD within the normal population range, without deficits in cortical or trabecular bone. However, despite androgen replacement, increased central adiposity was seen and this requires further exploration.

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P20

Denosumab therapy for refractory hypercalcaemia secondary to squamous cell carcinoma of skin

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Introduction
Hypercalcaemia secondary to malignancy is rare in children. PTH-rP secreted by malignant cells increases bone resorption and renal calcium retention causing hypercalcaemia. We report a case of hypercalcaemia refractory to bisphosphonate and corticosteroid therapy, but responsive to treatment with Denosumab.
Case report
A 17-year-old boy with epidermolysis bullosa presented with advanced squamous cell carcinoma of the left leg and symptomatic hypercalcaemia (serum adjusted calcium, 4.2 mmol/l). PTH was suppressed at 0.7 pmol/l. Serum 25 hydroxy vitamin D level was 31 nmol/l (normal range >50 nmol/l) and serum phosphate 1.51 mmol/l (normal range, 0.74–1.55). The hypercalcaemia was initially managed with hyper hydration and prednisolone, followed by administration of i.v. pamidronate. Following two infusions of pamidronate (1 mg/kg per dose), serum calcium fell to 2.87 mmol/l with improvement in symptoms. However the hypercalcaemia relapsed within a week (serum calcium, 3.61 mmol/l) and despite aggressive management with intravenous fluids, prednisolone, oral phosphate and two further doses of pamidronate, there was only temporary normocalcaemia (serum calcium 2.58). 72 h later the patient was once again symptomatic with serum calcium 3.39 mmol/l. As the hypercalcaemia was refractory to bisphosphonate treatment, he was given a trial dose of SUBCUTANEOUS Denosumab (60 mg), following which the calcium fell to 2.86 mmol/l within 24 h and normocalcemia was sustained a week later. No adverse effects were noted.
Conclusion
We report a case of refractory hypercalcaemia secondary to malignant squamous cell carcinoma, which responded well to Denosumab therapy. To our knowledge, this is the first case of humoral hypercalcaemia of malignancy managed with Denosumab in the paediatric population. Denosumab could be considered as a treatment option in patients with bisphosphonate resistant hypercalcaemia.

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P21

Hypercalcaemia, hypercalciuria and nephrocalcinosis secondary to a CYP24A1 mutation

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Background
The 24-hydroxylase enzyme is responsible for the degradation of 1,25-dihydroxyvitamin D_3. Loss of function mutations of the gene encoding 24-hydroxylase, CYP24A1, may cause hypercalcaemia, nephrolithiasis and nephrocalcinosis, and are responsible for some cases of idiopathic hypercalcaemia of infancy.
Case
The index case presented with faltering growth at 4 months old. She was hypercalcaemic with serum calcium 2.79 mmol/l (normal range 2.15–2.60 mmol/l), ionised calcium 1.61 mmol/l (normal range 1.1–1.35 mmol/l), intact parathyroid hormone 1.1 pmol/l (normal range 0.5–6.4 pmol/l) and phosphate 1.58 mmol/l (normal range 0.78–1.53 mmol/l). Her initial 25-hydroxyvitamin D was 155 nmol/l (normal range 72–374 nmol/l). There was hypercalciuria, bilateral medullary nephrocalcinosis and unexplained aminoaciduria, without a history of dietary supplementation. Subsequently, her growth was normal and her secondary dentition had poor enamel and increased sensitivity. Bendroflumethiazide was instituted for persistent hypercalciuria. Screening of her younger, asymptomatic sister at 8 weeks of life confirmed hypercalcaemia, hypercalciuria and nephrocalcinosis. The siblings were treated with low-calcium and low-vitamin D diets and the calcium returned to normal. Calcium was gradually re-introduced and normal feeds were re-commenced from between 12 and 18 months of age. Hypercalciuria persisted, however the hypercalcaemia resolved, the nephrocalcinosis did not progress and neither sibling had fractures. The siblings were found to have loss of function mutations of CYP24A1 at R396W and L409S. Their father has short stature and mild hypercalciuria but no nephrocalcinosis and has not yet had mutation testing.
Conclusions
We highlight that CYP24A1 mutations are a cause of transient hypercalcaemia in infancy. As hypercalcaemia resolves spontaneously, CYP24A1 mutation screening should be considered in older children without hypercalcaemia but with nephrocalcinosis and hypercalciuria, particularly if other family members are affected.

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P22

An unusual presentation of eating disorder in type 1 diabetes

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Background
We present a teenager with type 1 diabetes who sustained a substantial weight loss of 20 kg over 15 months. He had minimal insulin requirements with an extraordinarily low HbA1c.
Presentation
During his presentation with excessive weight loss, he had blood tests which revealed pre-renal failure, following which he was admitted for rehydration and assessment. Apparently he was consuming fluid in excess of 2 l/day. Ultrasound of kidneys was normal. A discussion regarding healthy weight and exercise ensued with the dietitian. A referral to Child and Adolescent Mental Health Service (CAMHS) was made to consider a possibility of anorexia. The teenager had a pre-morbid history of obsessive compulsive behaviour. However, the diagnosis was disregarded and he was discharged by CAMHS.
Early morning paired serum and urine tests were done to rule out diabetes insipidus as a cause for polydipsia.
He continued to lose weight and was supported by the dietitian. His HbA1c was as low as 34 mmol/mol and he denied manipulating insulin. He was having disabling hypoglycemia on insulin requirements of <10 units/day. Autoantibodies were positive and he had minimal urine C-peptide at 3 years into diagnosis to suggest type 1 diabetes.
In due course, he broke down and confessed to throwing food away and having a low carbohydrate diet to explain low insulin requirements. Subsequently, with support from CAMHS and the diabetes team, his weight has improved and insulin requirements have standardised.
Discussion
Eating disorders are very common in type 1 diabetes due to a constant focus on food and carbohydrates to match the insulin.
Control would usually deteriorate with eating disorders and these children are at an increased risk of developing microvascular complications.
This case was unusual due to the very low insulin requirements and possible co-existing honeymoon period to explain the low HbA1c.

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P23

Audit of insulin doses in children with newly diagnosed type 1 diabetes

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Introduction
The initial insulin doses for children with newly diagnosed type 1 diabetes mellitus (T1DM) are dependent on the degree of ketosis at presentation, reflecting the presence of insulin resistance. The concept of metabolic memory has heightened the importance of improving glycaemic control following diagnosis.
Aim
To determine whether current local prescribing guidelines accurately predict insulin requirement at initiation of treatment following a new diagnosis of T1DM.
Methods
The paper and electronic medical records of all children with newly diagnosed T1DM presenting to a tertiary paediatric hospital over a 6-month period were reviewed to obtain data on insulin dosing at presentation, at hospital discharge and 6 weeks after diagnosis.
Results
23 patients (11 male, 11 in diabetic ketoacidosis (DKA)) presented over a 6-month period. Results were analysed in three cohorts: patients in DKA ($n=11$); those not in DKA with ketones $\geq$ 1.5 mmol/l ($n=5$); patients not in DKA with ketones $<$1.5 mmol/l ($n=7$). SUBCUTANEOUS insulin doses tended to be higher in the DKA and elevated ketones group prior to discharge (Table 1).
Conclusion
Children with significant ketosis (including DKA) at presentation appear to require more SUBCUTANEOUS insulin at initiation of treatment than is currently given. We have revised our care pathways to provide between 0.5 and 1 unit/kg per day depending on degree of ketosis and acidosis.

Table 1 Insulin dose; (median (range), units/kg/day) in each cohort

Patient cohort	IV insulin during last 24 hours of treatment	Initiation of SC treatment	Hospital discharge	6 week clinic follow-up
DKA	0.98 (0.48–2.07)	0.70 (0.61–0.80)	0.97 (0.62–1.45)	0.60 (0.4–1.1)
Non-DKA Ketones $\geq$ 1.5	N/A	0.70 (–)	0.87 (0.7–1.4)	0.50 (0.31–0.97)
Non-DKA Ketones $<$ 1.5	N/A	0.50 (0.45–0.83)	0.56 (0.46–1.1)	0.57 (0.18–0.85)

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P24

Be wary of hyperglycaemia in newborn: a case of monogenic permanent neonatal diabetes

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A small for gestational age baby boy (weighing 2.3 kg) was delivered at term by emergency section for foetal bradycardia, to a 35-year-old mother with type 1 diabetes.
He was admitted with suspected sepsis because of maternal colonization with group B streptococcus. He had hyperglycaemia (6–12 mmol/l), initially attributed to sepsis and was treated as such. Hyperglycaemia persisted, despite treatment and being clinically well.
Further enquiry revealed that mother presented at 1 month of age, in coma in Malawi, when she was diagnosed to have 'type 1 diabetes'. This left her with paraplegic cerebral palsy, now wheel chair bound.
Currently, mother's diabetes is fairly well controlled on multiple daily dose insulin. Both parents are non-consanguineous of African origin.
Genetic testing for neonatal diabetes for baby and mother confirmed previously reported insulin gene (INS) missense mutation, p.L30P. This is predicted to be pathogenic and confirmed a diagnosis of permanent neonatal diabetes (PND).
Baby was started initially on long acting insulin and later continuous insulin pump, on a basal profile, and subsequently with insulin boluses for milk feeds.
Discussion
PND is a rare condition with estimated incidence of 100 000–500 000 live births. PND has been previously described in clinical arena of developmental delay, epilepsy (DEND syndrome). This will thus warrant a close monitoring of baby's developmental milestones.
Conclusion
Persistent hyperglycaemia in the first 6 months of life should not be labelled as type 1 diabetes as the latter usually presents later than the first 6 months of life. Genetic testing for monogenic diabetes is important in this group to identify the optimal treatment. No alteration in his mother's insulin treatment is needed.

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P25

Bone markers in children with type 1 DM

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Background
Care of patients with diabetes should include an assessment of bone health. It is now clear that patients with type I DM have lower bone mineral density which may be manifested as osteopenia in growing skeleton and higher risk of fractures.
Objective
To assess bone modelling through the measurement of bone formation and resorption indexes in diabetic children and their correlations with metabolic parameters.
Methods
We study 120 patients with type 1 DM (F=68, M=52) follow up diabetic clinic paediatric clinic at Benghazi children hospital, and we divided them to two groups according to duration of disease; group I (diabetic children with $<$1 year duration of disease) and group II (diabetic children $>$1 year duration). The following informations were collected gender, age, duration of disease, weight, height measurements were taken, Ca, Po4, ALK, PTH, osteocalcin, B-crosslaps, fasting blood glucose were taken during these visits in all groups and compared them with 99 healthy children (F=44, M=55) as control (group III).
Results
Fasting blood glucose significantly higher in both diabetic groups and s.Ca, s.Po4, PTH, were normal in diabetic groups, ALP levels were high in diabetic groups s.Osteocalcin and s.B-crosslaps values decreased in both diabetic groups. The changes in serum OC levels significantly correlate with changes in B-crosslaps, negative weak correlation between changes in OC levels, B-Crosslaps levels with FBG, NO correlation were found between changes in metabolic bone markers and duration of disease.
Conclusion
Poorly controlled type 1 diabetes mellitus groups are accompanied with low bone formation rate, and metabolic bone markers correlated positively with age but not with the duration of disease, and insulin has anabolic effect on bone, and it is tempting to hypothesize that abnormal insulin levels contribute to abnormalities of bone metabolism.

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P26

Can proportion of children achieving HbA1c below 58 mmol/mol within the first year of diagnosis be used as a standard of quality of care provided for children with type 1 diabetes?

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Background
Children with HbA1cs in target within the first year of diagnosis of diabetes show tracking of future results[1] and experience fewer long term complications.[2] This phenomenon is called 'metabolic memory.[3] HbA1C depends on a combination of patient factors and quality of care offered by the team (intensive insulin, communication, and support). We hypothesized that well managed, supported, patients should achieve target HbA1cs at least once during the first year (when they are often in partial remission). Currently the National Diabetes Audit excludes HbA1c data during this time.
Aims
i) To compare number of children achieving $\geq$1 HbA1C $<$58 mmol/mol in the first year of diagnosis across Eastern England and ii) attempt to set an audit standard, to improve long-term health.

Methods
Data was collected for HBA1C values (at diagnosis and 3 monthly for 1 year), hypoglycaemia requiring hospital attendance, and basic demographic details for patients diagnosed with T1DM between 1/9/2011 and 31/8/2012
Results
6/17 units in the region participated in this survey (n = 98). 6/98 patients were excluded because they moved. Overall 69% of patients achieved ≥1 HBA1C <58 mmol/mol. Results for individual hospitals were 30, 56, 69, 78, 80, and 81%. Less than 2% of patients had hypoglycaemic episodes.
Discussion
It is possible to achieve at least 1 HbA1c <58 mmol/mol in the first year of diagnosis without causing severe hypoglycemia in the majority of patients. The hospital with worse outcomes was experiencing staffing difficulties. We propose that units should aim to achieve HBA1C <58 mmol/mol at least once in the first year of diagnosis in greater than or equal to two out of three of patients to provide a good start to long term control. This could be used as a standard of assessing quality of care provided. Underperforming units can learn from practices of better performing units.
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P27

Children with type 1 diabetes and coeliac disease at Nottingham Children's Hospital: a service review and evaluation

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Introduction
The prevalence of coeliac disease (CD) in type 1 diabetes (T1DM) is 4.4–11.1 vs 0.5% in the general population. The compliance to gluten free diet (GFD) in symptomatic patients vs those diagnosed on screening is significantly higher as expected. The impact of untreated CD on patients with T1DM ranges from malabsorption and frequent unexplained hypoglycaemia to no symptoms.
Aims
i) To describe the demographics of our children with CD.
ii) To review compliance with GFD and to compare glycemic control and growth 1 year before and after diagnosis of CD.
Methods
Demographic details at diagnosis of CD and 1 year pre and post were retrospectively extracted from the diabetes database. A comparison was made between HbA1c, height SDS and BMI SDS at diagnosis and at 1 year pre and post to identify if the compliance with GFD was a predictor for this.
Results
20 children (14 females) with CD (prevalence of 5.13%). Average age at CD diagnosis 7.8 years (range 3–14.8). 18/19 patients had a biopsy undertaken for diagnosis. Ten patients symptomatic at diagnosis of CD (low ferritin and abdominal pain), six diagnosed on annual review and three at T1DM diagnosis. Compliance with GFD as assessed by TTG reverting to normal was 63% at 1 year. Only 58% of patients had had their CD discussed within the MDT clinic in the last 12 months.
The height and BMI SDS was not significantly different in those compliant to a GFD, although anecdotal reports of 'feeling well' were documented. The HbA1c was however significantly higher and could be related to increasing duration of diabetes and the lower incidence of hypoglycaemic episodes.
Conclusion

	1 year before CD diagnosis	1 year after CD diagnosis	*P* value (pre and post)
Height SDS	−0.325	−0.303	0.959 (NS)
BMI SDS	0.24925	0.436	0.604 (NS)
HbA1c (mmol/mol)	62.1	63.75	0.024 (S)

CD prevalence and compliance with GFD in our group of patients with T1DM is similar to the literature. It is important to look at how best we can address the needs of this group of YP with two chronic life-changing conditions.

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P28

Diabetes A&E attendances and ward admissions pre and post implementation of an out of hours telephone service

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Introduction
Daytime support from the diabetes-team reduces pressure on acute services however out-of-hours less support exists and diabetes related attendances to A&E are a potentially avoidable burden on resources. With the introduction of paediatric diabetes best-practice-tariff, recommendations included 24 h access to trained diabetes professionals for patients with known diabetes. In 2013 our three institutions created a consultant led out-of-hours paediatric diabetes support telephone service (OOHS). Its impact on A&E attendances and admissions is shown.
Methods
Diabetes related attendances to A&E out-of-hours and ward-admissions were retrospectively analyzed in the year before and after the implementation of the OOHS. Unavoidable attendances i.e.: first presentation of diabetes, were excluded along with patients not registered with our diabetes service. Dates covered: Evelina: pre-OOHS Feb 2012–Feb 2013, post-OOHS March 2013–March 2014; Lewisham: pre-OOHS Oct 2011–Sept 2012, post-OOHS Feb 2013–March 2014; Kings: pre-OOHS Jan 2012–Dec 2012, post-OOHS; Jan 2013–Dec 2013.
Results
A&E attendances: Evelina: 23 pre-OOHS, 16 post-OOHS (−30%); Lewisham: 28 pre-OOHS, 25 post-OOHS (−11%); King's: 70 pre-OOHS, 54 post-OOHS (−33%).
Admissions to ward: Evelina: 12 pre-OOHS, 13 post-OOHS (+8%); Lewisham: 3 pre-OHHS, 11 post-OOHS (+266%); King's: 30 pre-OHHS, 22 post-OOHS (−27%).
Conclusions
Out-of-hours A&E attendances of patients with known diabetes has declined however the effect on admissions is inconsistent. A possible explanation for this is poor patient engagement with the OOHS. Review of Evelina's cohort who had multiple A&E attendances were found to have poor diabetes control reflected by a high HbA1c and poor compliance with their treatment regimen reflected in clinic letters. One family did not speak English. Thus advocating the use of OOHS more aggressively to these families and providing leaflets advertising it in different languages, may help reduce the numbers of re-attenders presenting in DKA, and thus reducing admissions.

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P29

Does continuous subcutaneous insulin infusion therapy improve diabetic control in a district general hospital population?

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Background
Type 1 diabetes mellitus is an autoimmune condition resulting in insulin deficiency, causing both long and short term complications. The Diabetes Control and Complications Trial (DCCT) demonstrated that tight glycaemic control and consequent lower HbA1c values reduced the risk of long-term complications. This can be achieved using multiple daily injections (MDI) or newer continuous subcutaneous insulin infusion (CSII) therapy. This is recommended by NICE for those over 12 years with T1DM who are unable to reach their target HbA1c level with MDI without experiencing disabling hypoglycaemic episodes. In children under, 12 if MDI is inappropriate or not practical, CSII is also recommended.
Objective and hypotheses
The objective of this study was to discover whether CSII had a significant impact on the HbA1c of the children at St Peter's Hospital (SPH) and to determine what other parameters should be measured in these children.

Method
HbA1c levels and number of hypoglycaemic episodes before and after starting CSII were analysed from the children's annual review data of 56 patients at SPH. The HbA1c averages before and after implementation of CSII were taken.
Results
Of the 56 children on CSII at SPH, 47 had data that could be analysed. HbA1c decreased from an average of 8.86 (73.3 mmol/mol) before starting CSII to 7.97 (63.6 mmol/mol) afterwards ($P=0.0001$). The percentage of children reaching their target HbA1c increased from 2.13 to 27.66%. Disabling hypoglycaemic episodes were not reliably recorded at the annual reviews.
Conclusion
There was a statistically significant improvement in HbA1c when children were switched to CSII, supporting its use in this population. It was not determined whether the number of disabling hypoglycaemic episodes reduced, or whether quality of life improved. We recommend that these should be monitored as part of the annual review.

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P30

Epidemiology and risk factors for diabetic retinopathy in CYP with type 1 diabetes mellitus in a DGH

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Introduction
Nearly all patients with type 1 diabetes mellitus develop diabetic retinopathy (DR) within 20 years of diagnosis. It is the second largest cause of blindness in those of working age in the UK. Several risk factors have been accepted by the Royal College of Ophthalmologists, including gender, duration of diabetes, glycaemic control, blood lipid profile, blood pressure, and renal impairment.
Aim
To study the epidemiology of DR and its associated risk factors in Children and Young People (CYP) with type 1 diabetes mellitus under care of East Cheshire NHS Trust (ECNT).
Method
Retrospective comparison of risk factors with the development of DR in all CYP aged 12–18 years between March 2013 and April 2014 was carried out. The variables analysed were gender, HbA1c, and duration of diabetes.
Results
7/44 (16%) had a positive retinopathy screen. All of them had background retinopathy (R1). 57% were females and the rest were male. All seven of them were on Multiple Daily Injections (MDI regime). Age at diagnosis was under five in majority (57%) of them, with only one of them diagnosed after the age of 10. The average HbA1c for the group that developed retinopathy was 90 mmol/mol compared to 76 mmol/mol for the rest of the group.
Conclusion
Results show a positive correlation between duration of diabetes, poor glycaemic control and DR, supporting previous acceptance of these variables as risk factors. However, in contrast to the suggested increased risk of DR in males, females within the population are more likely to have diabetic retinopathy.

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P31

Eruptive xanthomas as a presenting feature of diabetes mellitus

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Introduction
Dyslipidaemia and diabetes mellitus have a complex relationship. Uncontrolled diabetes can result in hypertriglyceridaemia through decreased adipose tissue and muscle lipoprotein lipase activity. Conversely, insulin resistance and diabetes can occur in association with primary familial hyperlipidaemia. Eruptive xanthomas can be a presenting feature of the severe hypertriglyceridaemia found in familial hyperlipidaemia.
Although there are reports of adults presenting with hypertriglyceridaemia and new-onset diabetes there are none that we have found in paediatric cases.
Case report
A 14-year-old girl presented to accident and emergency with a 2-week history of a widespread itchy and painful rash. On further questioning she also complained of polydypsia and polyuria. The rash was diagnosed as eruptive xanthomas and investigations revealed a severe hypertriglyceridaemia (triglycerides: 189 mmol/l – normal <1.7 mmol/l, cholesterol 34.2 mmol/l – desired <5 mmol/l), hyperglycaemia and high ketones.
Ophthalmological examination demonstrated lipaemia retinalis, and ultrasound scan revealed xanthogranulomatous infiltration of her kidneys. Autoantibody and diabetic antibody screens were negative and C-peptide was low. Lipid electrophoresis confirmed type 5 hyperlipidaemia phenotype. This girl's diabetes was controlled with s.c. insulin injections, and the hyperlipidaemia with a combination of a very low fat diet (fat content <20 g/day) and a fibrate. Six weeks later her lipid profile was within normal limits and her blood sugar control is now excellent. DNA analysis provided no evidence of familial hyperlipidaemia and maternal lipid profile was also normal.
Conclusions
Secondary type 5 hyperlipidaemia can be caused by the decreased adipose tissue and muscle lipoprotein lipase activity found in uncontrolled diabetes. Eruptive xanthomas can be a presenting feature of this severe hypertriglyceridaemia.
This case highlights the relationship which can occur between diabetes mellitus and hyperlipidaemia, and how hyperlipidaemia can be part of the initial presentation of diabetes. We have found no other cases of children or young people presenting in this fashion.

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P32

How effective was the national '4T's' diabetes awareness campaign for a local paediatric population and did specific interventions reduce admissions for DKA?

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Up to 25% of children and young people present in diabetic ketoacidosis (DKA) at diagnosis with type 1 diabetes (T1D). The '4 T's' campaign, a national Education awareness programme, was led by Diabetes UK in 2013. Our aim was to assess the effectiveness of this campaign locally, after our team also raised local awareness by promotion to primary care.
This was a retrospective audit of referrals of children newly presenting with T1D from primary care between 2012 and 2013. The diabetes team promoted awareness of the campaign locally at the start of 2013, by contacting all primary care units via letter, posters and flyers. Data collection included: patient demographics, presenting symptoms, rapidity of GP referral and length of stay both before and after the local intervention.
In 2012, 95% (21/22) received a same day referral from primary to specialist care. 27% (6/22) patients presented in DKA. Patients in DKA had a longer length of stay (4 vs 2) days. In 2013, 90% (18/20) received a same day referral from primary to specialist care. 20% (4/22) patients presented in DKA. Patients in DKA had a longer length of stay (5 vs 3) days.
There is local awareness of the signs and symptoms for T1D amongst primary care colleagues and the need for same day referral but this is achieved in 90–95% of cases. Patients presenting in DKA reduced after the campaign had been promoted locally by the diabetes team in primary care.
A possible limiting factor for diagnosis in T1D is symptom recognition in the community setting. We intend to re-promote awareness by writing to all future referring primary care practitioners to highlight the '4 T's' campaign, with the results of this audit, as well as specific information regarding their patient.

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P33

Improving the clinical pathway for diabetic retinal screening in paediatric diabetes

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Background
Diabetic retinopathy is a frequent cause of vision loss in young adults. NICE guidelines require services to offer annual retinal screening to all diabetic children aged ≥ 12 years. A local 2009–2010 audit identified 57% underwent screening but only 16% had results documented with the paediatric diabetes service, both

areas requiring improvement. In 2011, the paediatric diabetes service formulated a standard operating procedure with the eye-screening programme to improve referrals, screening, and data collection.
Methods
Retrospective analysis of paediatric diabetes patients aged $\geq$12years, attending a large paediatric diabetes service April 2012–April 2013. Data (obtained from diabetes database, eye screening database, and GP) included: evidence of referral, screening attendance, screening results, results reaching paediatric diabetes database, age diagnosed, duration of diabetes, and HbA1c. Statistical analysis used Fisher's exact test and independent two-tailed *t*-test.
Results
From 479 patients, 282 were aged $\geq$12years. 14 transitioned prior to their annual eye review date. Out of eligible 268, evidence of referral was available for 259 and nine had no data. 241 (90%) had results recorded for submission to National Paediatric Diabetes Audit (NPDA). Remaining 18 received screening but paediatric services had no data recorded. 256 attended screening and three patients did not attend, i.e. screening rate 96% (256/268). Of 251 with gradable images, 18 patients (7.2%) had retinopathy. Those with retinopathy had higher HbA1c (85 mmol/mol) than those without (73 mmol/mol) $P=0.011$. No correlation was found with age of diagnosis or duration of diabetes.
Conclusion
Increased prevalence of retinopathy in those with worse glycaemic control was confirmed. Screening programmes to improve overall outcomes need to include effective communication. The structured clinical pathway improved screening rates from 57 to 96% and recording rates from 16 to 90%, compared to national recorded 37% screening rate (NPDA 2011–2012), clearly demonstrating effective collaboration between eye screening and paediatric diabetes services.

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P34

In-patient care for children with type 1 diabetes across hospitals in the Yorkshire and Humber region in the north of England

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Introduction
An important part of diabetes management is maintaining high standards of in-patient care. A previous audit in the south of England demonstrated difficulties consistently achieving standards identified as good practice. This audit aimed to identify current standards of in-patient care provided to children with type 1 diabetes across the Yorkshire and Humber region.
Methods
The audit was conducted against in-patient care standards identified by the Children and Young Person's Diabetes Implementation Support Group (CYPDISG). Questionnaires were sent to clinical leads of all paediatric diabetes units in the region, which serves 2599 children and young people with diabetes.
Results
Sixty-three per cent of units, consisting of two tertiary and eight secondary care units, responded. Nine out of ten units had paediatric nurses in areas where children were cared for, but only tertiary centres always had trained paediatric nurses in the emergency department (ED). Paediatric wards and EDs in all units had protocols for management of new diagnosis of diabetes, diabetic ketoacidosis (DKA), hypoglycaemia, and surgery. All units had regular education sessions for ward staff, although only 50% had education sessions for ED staff. A 24 h on-call service was only provided by 40% of the units. The diabetes team was usually contacted within 2 h of an admission in tertiary centres and within 24 h in secondary care units. All units actively involved paediatric diabetes specialist nurses in in-patient management. Only two units had insulin prescription charts and only tertiary centres routinely audited insulin prescription and administration errors.
Conclusions
This audit demonstrates on-going difficulties achieving current standards of in-patient care for children and young people with diabetes. There needs to be standardisation across the region and feasibility of implementation needs to be explored.

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P35

Kaempferol, a dietary flavonoid improves glucose homeostasis in streptozotocin diabetic tissues by altering glycolytic and gluconeogenic enzymes

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Diabetes mellitus is life threatening endocrine disorder with high morbidity and mortality, which is featured by persistent high blood glucose levels due to defect in the insulin secretion, insulin action or both. Extreme high blood glucose levels associated with diabetes leads to various organ dysfunction particularly nervous system, eye, cardiovascular system, and kidney. Kaempferol is a dietary bioflavonoid that is common in plant-derived foods and used in traditional medicine. In this study, we proposed to study the effects of kaempferol on carbohydrate metabolic enzymes in streptozotocin diabetic rats. Diabetes was stimulated in male Albino rats (wistar strains) of 180–200 g via i.p. streptozotocin injection (40 mg/kg). Plasma glucose, insulin, hemoglobin (Hb) and HbA1c, glycogen, and carbohydrate metabolic enzymes such as glucokinase, glucose 6-phosphatase, fructose 1,6-bisphosphatase and glucose-6-phosphate dehydrogenase and hepatic marker enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gammaglutamyl transferase (γ-GGT) in normal and streptozotocin-diabetic rats were altered in diabetic rats. Administration of three different doses of kaempferol (50, 100, and 200 mg/body weight (BW)) or glibenclamide disolved in dimethyl sulfoxide (DMSO), to different groups of diabetic rats were done for 45 days. Kaempferol prevented the above changes and improved towards normalcy. No significant effect was observed in normal rats treated with kaempferol (200 mg/kg per BW). Thus, our results show that kaempferol at 100 mg/kg of BW possesses a potential antihyperglycemic effect that is comparable with glibenclamide.

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P36

Lessons learnt from starting an insulin pump service in Forth Valley, Scotland: challenges, solutions, and outcomes

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Aims
We aimed to assess the effectiveness of an insulin pump service for children, describe the demographics of the pump population and to review the change in glycaemic control following initiation of pump therapy. We also assessed patient and staff perceptions of the service.
Method
Patients commenced on CSII from July 2013 to July 2014.
Data collected included demographics, deprivation scores, HbA1c before and during pump therapy. Comparison was made with the patients on conventional insulin therapy.
Results
32 pump patients were included. They were compared to 151 non-pump patients. There was a difference in deprivation scores between the pump and non-pump populations, but the difference was not statistically significant.
HbA1c significantly reduced after pump therapy, from a mean of 70 mmol/mol to a mean of 64 mmol/mol in 12 months.
BMI improved after pump start, from a mean of 18.14 kg/m^2 to a mean of 18.97 kg/m^2 in 12 months.
19 of 32 questionnaires sent to families were returned, and revealed that families felt well supported by the diabetes team. Their main reasons for choosing insulin pump therapy were a wish for better control and quality of life, and more freedom around food. The main problems experienced included kinking of cannulas, technical pump failure, and setting rates.
Conclusions
The study showed high levels of satisfaction for pump patients and families. Suggested improvements included: regular formal education sessions to cover topics such as uploads and advanced pump features.
There was significant improvement in glycaemic control in the pump population. There were demographic differences in deprivation scores between pump and non pump patients. Owing to patient numbers it is difficult to make firm conclusions. This needs to be further explored to ensure there is equity of choice across the population.

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P37

Management of paediatric diabetic ketoacidosis: are we doing it right?

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Introduction
Diabetic ketoacidosis (DKA) is a medical emergency, requiring careful fluid management and insulin administration. The guidelines published by the British Society for Paediatric Endocrinology and Diabetes (BSPED) in 2009 aim to standardise the approach to the management of paediatric DKA across NHS hospitals. Our aim was to report our experience in managing DKA in children in a district general hospital setting.
Method
Retrospective case review of 19 cases of paediatric DKA (patients aged <19 years) presenting to a district general hospital between January 2012 and December 2012.
Results
The median age of presentation was 15 years (interquartile range 11.5–16.5 years). The history and general examination findings were adequately documented for all patients assessed. Blood glucose, ketones and pH were measured in all children. The weight was only documented in 12 patients (63%). The hydration status was documented in seven children (36%) only. The timing of insulin was appropriate in 16 patients (84%). Two children (10%) received fluid boluses inappropriately.
Once treatment was initiated, blood tests were monitored as per the BPSED protocol in 13 patients (68%). The average length of stay in hospital was 3.5 days. All patients and their families received a discharge planning meeting and further education.
Prior to the introduction of the integrated care pathway for paediatric DKA (DKA ICP) in our trust, doctors were trained to apply it into their practice. Despite this, the DKA ICP was only used in three patients in our study group (16%).
Conclusion
The management of DKA is still suboptimal despite robust guidelines which are in place. Children with diabetes commonly present to their local hospitals in emergencies such as DKA. Hence we believe that paediatric trainees nationwide should receive further interactive education on the management of DKA. The use of the DKA ICP, devised to reduce errors in fluid calculations, should be encouraged across all NHS trusts.

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P38

An evaluation of a hospital-based diabetes education program provided for schools and nurseries

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Introduction
The diabetes education program for schools and nurseries at an inner city hospital was introduced in 2010. The team offers 3 h sessions $\sim$5–6$\times$/year with the diabetes CNS and specialist diabetes dietician.
Aims
To assess the uptake of the sessions; to look at how sessions were offered and delivered; to analyse the evaluation forms filled out by the participants with particular focus on good points and suggestions for improvement; and to improve the existing feedback forms.
Methods
The study period was between April 2010 and October 2013. The number of people booked to attend each session was analysed and compared with the attendance sheets signed on the day. The feedback forms completed were analysed.
Results
A total of 16 sessions took place in the study period with 29 schools/nurseries represented. Up to 24 people attended each session mostly comprising nursery/school staff. 137 feedback forms were received (217 attendees in total). All 137 (100%) found the course useful and 133/137 (97%) felt more confident working with children with diabetes. Participants commonly listed the following positive aspects: glucose testing and insulin injections, 103/137 (75%); carbohydrate counting session, 83/137 (60.5%); and explanation of diabetes and pathogenesis, 46/137 (33.5%). Suggestions for improvement included: providing a printout of slides; teaching how to recognise undiagnosed cases; practicing carbohydrate counting on individual school menus; longer and increased number of sessions; and dealing with behavioural aspects and parents.
Conclusion
Group sessions are an effective and innovative way to deliver paediatric diabetes education for schools. We suggest this should be adopted nationally and become part of the paediatric diabetes best practice tariff.

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P39

Meeting the training needs of paediatric trainees in managing children with diabetes

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Introduction
Following the introduction of best practice tariffs for paediatric diabetes, there are now clear guidelines that paediatric units should be able to provide 24 h medical cover and advice for diabetes children. This is a challenge most paediatric diabetes units are struggling to meet with mainly due to limited availability of consultant and diabetic nurse cover. Currently in most hospitals this responsibility lies with the on call registrars. Previous studies in the UK have shown that trainees lacked confidence in diagnosing, treating and managing complications of diabetes (George *et al.* 2008).
Method and results
I conducted a survey of paediatric trainees in the Severn deanery to identify their training needs in practical aspects of managing diabetes in children. Questions related mainly to the level of confidence in dealing with children presenting acutely, explaining the condition to parents, knowledge of various diabetes regimes including pumps and advising parents over telephone. 72% of the trainees felt their confidence level was average or below average when it came to knowledge about various insulin regimes and this was even less when it came to knowledge about insulin pumps. 97% of them agreed that there was a need for training in dealing with practical aspects of diabetes management. As part of my post graduate medical education degree (TLHP, module 008- course designing) at University of Bristol, I have designed a half day training program in managing practical aspects of diabetes for senior paediatric trainees integrating principles of constructive alignment and using advanced methods of teaching and assessment.
Conclusion
Enhancing the competence and confidence of paediatric trainees in managing diabetes would not only be desirable but will become necessary as part of our attempt to offer best possible care for children with diabetes in the UK.

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P40

Neonatal diabetes: the great masquerader experiences from one hospital

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Background
Neonatal diabetes can present from birth to 6 months of age. This can often be confused with sepsis as there is considerable overlap of symptoms in this age group as illustrated below. We recommend an initial check of blood glucose concentrations in all sick infants who present to accident and emergency.
Case report
A 7-week-old, born to nonconsanguineous parents presented with a temperature of 38.6 °C and a 1 day history of poor feeding. Clinical examination was unremarkable. The working diagnosis was possible sepsis. A blood gas that was done for monitoring of electrolytes showed a glucose concentration of 39 mmol/l with a normal pH. The baby was started on an insulin infusion and then managed on an insulin pump. Genetic analysis showed a KCNJ11 mutation. Insulin was stopped and baby is on glibenclamide.
A second baby, born to consanguineous parents (birth weight of 2.7 kg) presented at 24 days of age with a 1 day history of vomiting and poor feeding. The baby was mildly tachypnoeic. A diagnosis of sepsis was made. Again an incidental blood gas showed the baby to be in ketoacidosis with a blood glucose of 43 mmol/l.

Insulin infusion was commenced and the baby was subsequently managed on a pump. Genetic analysis revealed a recessive non coding *INS* mutation. The baby went into remission in 2 weeks and is currently off insulin.
Conclusions
The cases described above illustrate the importance of blood glucose monitoring in sick infants presenting to emergency care settings. Both infants were clinically well and the diagnosis could have been missed. Finally, the phenotype of the diabetes in both infants correlated with the respective mutations.

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P41

Prevalence, clinical profile, and glycemic variability of celiac disease in patients with type 1 diabetes mellitus in western, Uttar Pradesh, India

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Background
Celiac disease is frequently associated with type 1 diabetes mellitus, but is usually ill-defined and not usually suspected until the disease become advance.
Aim
To study the prevalence, clinical profile and glycemic variability and the effect of gluten free diet on growth and diabetic control in celiac type 1 diabetes patients in a tertiary care referral centre in north India.
Materials and method
Total of 256 patients were screened (149 males and 107 females) during the study period of 2 years, patients were evaluated for the clinical signs, biochemical investigations and family history of celiac disease in tertiary care health center in western U.P.
Results
Twenty-four (9.37%) patients were diagnosed to have celiac disease; the mean age at diagnosis of diabetes was 9.34 ± 7.3 years. Only 1/24 patients with celiac disease had been diagnosed before detection of diabetes mellitus. The common manifestations were normocytic normochromic anemia (66.6%) followed by diarrhoea (62.5%), abdominal pain/bloating sensation (58.3%), and short stature (58.3%). Weight SDS increased from -0.12 ± 1.3 at the start of gluten free diet to 0.8 ± 0.9 after 12 months later ($P < 0.05$). Height SDS increased from -2.46 ± 1.1 at the start of gluten free diet to -2.14 ± 0.9 after 12 months later ($P = 0.087$). Bone age SDS increased from 9.2 ± 6.3 at the start of gluten free diet to 10.3 ± 6.7 after 12 months later. Height velocity increased from 4.7 ± 0.7 cm/year in the year before treatment to 5.1 ± 1.2 during treatment ($P = 0.05$). The increased in hemoglobin, serum calcium, and serum iron is statistically significant ($P < 0.05$).
Conculsion
Celiac disease was found to be significantly associated with type 1 diabetes, timely identification of these disorder are of paramount important for better glycemic control and to reduced the morbidity and mortality associated with the conditions.

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P42

Prognostic factors in patients hospitalised with diabetic ketoacidosis

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Background
Diabetic ketoacidosis is characterized by biochemical tired of hyperglycemia, acidosis, and ketonemia. It remains a life threatening condition despite improvement in diabetic care, timely identification and intervention remains the backbone of treatment.
Aim and objectives
i) To evaluate the clinical and biochemical prognostic markers in diabetic ketoacidosis. ii) To correlate the various prognostic markers with mortality in diabetic ketoacidosis.
Settings and design
A prospective multicenteric observational study done at tertiary care center.
Methods and materials
87 patients of type 1 diabetes hospitalized with diabetic ketoacidosis over a period of 1 year were evaluated clinically and by laboratory tests. Serial assays of serum electrolytes, glucose and blood pH, and clinical outcome of either discharge home or death were evaluated.
Statistical analysis used
Data were analyzed by SPSS version 17 and were presented in the values of mean, median, and percentages. The P value of < 0.05 was considered significant.
Result
The significant predicators of final outcome obtained were further regressed together and subjected with multivariate logistic regression (MLR) analysis. The MLR analysis further revealed that the male sex had 7.93-fold higher favorable outcome as compared to female sex (OR = 7.93, 95% CI = 3.99–13.51) while decrease in mean APACHE II score (14.83) and S. PO_3^- (4.38) at presentation may lead 2.86 (OR = 2.86, 95% CI = 1.72 − 7.03) and 2.71 (OR = 2.71, 95% CI = 1.51 − 6.99) fold better favourable outcome respectively as compared to higher levels (APACHE II score: 25.00; S. PO_3^-: 6.04).
Conclusions
Sex, baseline biochemical parameters like APACHE II score, and phosphate level, were important predicator of mortality from DKA.

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P43

The effect of the introduction of best practice tariff for paediatric diabetes care on service provision and staffing in the West Midlands

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Objectives
The Department of Health introduced a Best Practice Tariff (BPT) to finance Paediatric Diabetes Services in England, in response to variation in service provision and outcome. The tariff became mandatory in April 2013 and depends on achievement of 13 quality standards (QS). The West Midlands (WM) Region covers an area of 5020 square miles, where 2700 Children with Diabetes receive care from 15 Hospital Trusts who are members of the Regional Paediatric Diabetes Network (WMPDN). The WMPDN, works to ensure services are supported to achieve QS and undertook a regional peer review of diabetes care across the WM.
Aim
To determine the impact of BPT on compliance with the 13 QS and staffing of services.
Methods
A questionnaire survey was conducted of lead clinicians at each Trust pre and 6 months post BPT introduction to assess compliance with QS and determine staff ratios of Consultants, Diabetes Nurses (PDSNs), Dieticians and Psychologists.
Results
A 100% response rate was achieved. Less than 80% compliance with six of the QS was observed pre BPT; including an inability to:
i) offer four HbA1c measurements per year,
ii) discuss a newly diagnosed child with a senior diabetes team member within 24 h of diagnosis.
iii) offer at least eight additional contacts for every patient per year,
iv) offer an annual additional dietetic appointment,
v) provide 24 h advice to parents and health care professionals.
vi) offer annual screening.
6 months following BPT Trusts reporting compliance increased to over 80% for ten out of 13 QS. 8/15 Trusts comply with over 90% of QS, compared to 2/15 trusts pre BPT. There were significant improvements in staffing ratios of PDSNs, dieticians, and psychology provision.
Conclusions
Introduction of the Best Practice Tariff has facilitated investment in paediatric diabetes services in the WM improving staffing levels and compliance with QS.

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P44

Transition and beyond in childhood onset type 1 diabetes

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Introduction
Achieving optimum glycaemic control in young adults is challenging. Furthermore, transfer of care to adult services has been associated with deterioration in glycaemic control. We aimed to establish glycaemic control and rate of microvascular complications in young adults with childhood onset type 1 diabetes (T1D) and looked specifically at a subset of patients before and after transfer to adult care.
Methods
A retrospective study of patients with T1D currently attending the transition clinic and those transferred to adult services between August 2009 and August 2012 at a single tertiary centre.
Results
A total of 104 (55 males) patients with a median age of 19.2 years (range: 17–23) and mean duration of diabetes of 9.4 ± 3.9 years were identified. Mean HbA1c was 77 ± 18 mmol/mol. Majorities were on multiple daily injections (66.3%) and others on pump (27.9%) and twice daily injection regimen (5.8%). Microalbuminuria was noted in 5.6% and retinopathy in 43.2% with the majority (41.3%) having only background changes. 14% had raised blood pressure but ambulatory BP was normal.
54 patients were in transition clinic and 50 post transfer to adult care. In the latter group, mean age of transfer was 18.5 ± 1.2 years. Mean HbA1c 1 year pre and post transfer was similar (78 ± 20 and 78 ± 22 mmol/mol, respectively; $P = 0.22$). Mean HbA1c 2 and 3 years pre and post transfer were also similar. Clinics attended per calendar year before and after transfer were 3.2 vs 2.4. A small subset of patients ($n = 7$) who opted for e-mail support demonstrated improved mean HbA1c over 1 year from 68 ± 8 to 63 ± 10 mmol/mol, $P = 0.051$.
Conclusions
Glycaemic control is stable following transfer of care of young diabetes patients with only 12.5% achieving national targets of HbA1c (< 58 mmol/mol). Large percentages of patients have retinopathy, although majorities have background changes only. Email support may represent one strategy to improve glycaemic control in this population and warrants further investigation.

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P45

Using an electronic tablet to survey patient satisfaction in an adolescent transitional diabetes clinic at York, United Kingdom

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Objectives
To assess patient satisfaction with the transitional diabetes clinic service. Our transitional diabetes clinics (for 14–19 year olds) are run monthly by a multi disciplinary team comprising of a consultant, nurse and dietician each, from both adult and paediatric diabetes teams.
Methods
An electronic tablet with the pre-programmed survey was handed out to 42 young people while they were waiting to be seen in clinic.
Results:
39 young people completed the survey, giving a response rate of 92.8%. 51% were males and 69% were aged 16–17 years. 73 and 27% were on insulin injections via pen and pump respectively. 82% were transferred from paediatric services. Overall, young people rated their experience of moving into the transitional clinic very highly. Clinic venue and timing (4–6 pm) were considered suitable by 90 and 94% respectively. 52% reported to have waited for at least 15–30 min to be seen by one of the team. Around 80% received information regularly on achieving better glycaemic control, treating complications and managing diabetes around sports, exercise, alcohol and school/university. However, 43% were unaware of the availability of psychology support in the service. Around 40% met with the doctor or the nurse at each clinic visit. However, 74% could only meet the dietician at their request. Nearly all (97%) found the diabetes team to be open and honest, accessible, supportive and knowledgeable in diabetes care. Around 90% felt that the service prepared them well in moving to the adult services.
Conclusions
Using an electronic tablet for feedback can prove really successful in improving participation among young people who have greater technology awareness. Although we received a very positive feedback on the transitional diabetes service, it could be improved further by reducing waiting time as well as providing better access to dietetics and psychology services.

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P46

Visual disturbance in diabetes mellitus: don't be blind to alternatives to retinopathy

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Introduction
We present the contrasting cases of two siblings diagnosed with Wolfram's syndrome aged 2 and 10 years old. We discuss several family factors which have made management of this rare condition even more complex, emphasising the importance of holistic medicine.
Case
The older sibling was diagnosed with diabetes mellitus age 4. Parents struggled to cope with the diagnosis, however, and emotional and psychological support was offered. She developed visual difficulties at age 8, necessitating several Ophthalmology reviews. She was found to have impaired colour vision and significant bilateral optic disc pallor. Neurological examination and cranial MRI were normal. Blood tests found no mitochondrial DNA deletion to suggest Leber's optic atrophy. Genetic analysis has subsequently revealed she is homozygous for the *WFS1* gene mutation (type 1 Wolfram syndrome). Parents, first cousins, are heterozygous for WFS1.
Soon after, she reported polyuria and polydipsia, however pituitary function tests were normal and urinary investigations suggested symptoms were due to poor glycaemic control. A basal-bolus insulin regime provided better control, and she now has an insulin pump. Now age 13, she has developed diabetes insipidus.
At present hearing is ok, but parents have been counselled about the natural history of Wolfram's syndrome, including eventual deafness. Her latest renal ultrasound is normal, though it is known that up to 90% have a urinary tract problem.[1]
The diagnosis of Wolfram syndrome caused further upset for parents, who struggled to tell the child the diagnosis. Communications are frequently difficult due to English language difficulties. A child psychologist is helping to address fluctuations in glycaemic control related to multiple family stresses. They have two younger children. One was diagnosed with type 1 diabetes mellitus aged $2\frac{1}{2}$, and subsequent genetic analysis has shown he has Wolframs syndrome too. He does not currently have any evidence of optic atrophy, and hearing is normal.
Conclusion
Ophthalmic pathologies are well-recognised complications of diabetes mellitus, with retinopathy screening indicated at all ages.[2] However, alternative ophthalmic/non-ophthalmic aetiologies must be considered. Additional diagnoses cause cumulative stresses on the child and family, which can hinder disease management.
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P47

An ovulating testis

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Introduction
Ovotesticular disorders of sexual development (DSD) are a rare form of DSD with co-existence of both ovarian and testicular tissue in one or both gonads.
Case report
A term infant (weight + 1.38 SDS) presented at birth with severe penoscrotal hypospadias, a small phallus and a right hemiscrotum with descended gonad (external masculinization score 1.5). Pelvic ultrasound revealed no mullerian

structures, a small right gonad with probable epididymis, and no gonad on the left. Karyotype showed 46 XX with no mosaicism. A 3-day HCG test demonstrated functioning testicular tissue with a testosterone rise (7.9–13.4 nmol/l). Laparoscopy showed a vestigial uterus and a left gonad associated with fallopian tube which was removed. Histology confirmed ovotestes on both sides. Gonadal karyotype was 46XX. A diagnosis of 46XX ovotesticular DSD was made and a male gender was assigned with parental concurrence. He underwent hypospadias repair with good results. Family were keen to preserve gonad hence right ovotestis was left in the scrotum with a view to monitoring carefully at puberty.
From age 13 there was evidence of virilisation. His testosterone was 4.4 nmol/l, oestradiol 88 nmol/l, LH 10.3 nmol/l and FSH 23 nmol/l, indicating a failing gonad producing predominantly testosterone. Subsequently he developed progressive gynaecomastia. Repeat blood tests showed a fall in testosterone (0.8 nmol/l) but detectable oestradiol (34 nmol/l) levels. Hence a 3-day HCG test was undertaken (testosterone 1 → 14 nmol/l; Oestradiol 168 → 83 nmol/l); shortly afterwards he presented with acute right scrotal pain. Intra operatively he was found to be bleeding from the ovarian tissue within the testicular capsule. In view of progressive gynaecomastia and future malignant risk, his right ovo-testis was removed after extensive discussions with the family. Sperm counts prior to surgery had shown azoospermia and sperm harvesting was also unsuccessful. He had bilateral prosthesis sited and testosterone replacement commenced.
Conclusion
This case emphasises the complexity involved in the management of such rare conditions and the importance of systematic patient and family centred approach.

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P48

Initial care of babies born with ambiguous genitalia: a service evaluation

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Introduction
Disorders of sex development (DSD) may present in the newborn as ambiguous genitalia. Gender determination and diagnosis must occur as quickly as possible to minimise parental distress. Aim: to evaluate the initial care of babies born with DSD, and identify areas for improvement.
Methods
Detailed assessment of 14 neonatal presentations at a tertiary centre between 2012 and 2014 was undertaken. Based on local trust guidelines, several parameters identified as important during initial management were assessed.
Results
Final diagnoses – three virilised females with congenital adrenal hyperplasia, one male with a micropenis, eight males with bilateral impalpable testes (±hypospadias. Two patients were excluded due to multiple congenital abnormalities. The median (range) times for different parameters were as follows: 1 day (<1–3 days) to refer to the DSD team, 1 day (<1–4 days) to transfer to tertiary centre (for 8/12 regional patients), and 1 day (<1–4 days) to assessment by the DSD team. The time to send a sample for karyotype was 1 day (<1–6 days), with results returning in 3 days (1–8 days). Hormone investigations were taken at 3–4 days, but time to return was variable and poorly recorded. The times of sending the sample for karyotype were also poorly documented. The time taken to determine gender was 5 days (2–12 days). In three cases, gender was assumed before review by the DSD team. Communication with parents was always documented by the DSD team.
Conclusion
Strengths of current care include usually rapid referral, transfer and assessment by the DSD team. Areas to improve involve reducing time to send samples for karyotyping, documentation of sending and receiving blood tests and ensuring gender is not discussed before assessment and definitive testing. These aspects should be considered in the creation of national standards to improve overall patient care.

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P49

Pubertal gynaecomastia: when is reverse rhythm testosterone treatment in adolescent boys with delayed puberty effective?

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Introduction
Gynaecomastia (GM) is a major contributor to psychological morbidity in adolescent boys, yet there is a lack of evidence for effective treatment. It is known to develop due to the relatively higher diurnal oestradiol–testosterone ratio in early to mid puberty.
Aims
We retrospectively looked to identify possible criteria for the selection of patients to predict optimal management of GM. We also examined the effect on the persistence of GM of testosterone given for delayed onset/completion of puberty, but in reverse diurnal rhythm.
Methods
16 patients had adolescent GM. We recorded age; BMI; Tanner G and B stages; testis volume; breast disc size; testosterone, oestradiol, FSH and LH blood levels; follow-up time; and if so any treatment received at each visit. When puberty was delayed, oral testosterone undecanoate (TU; Restandol) 40 mg was commenced, but in the morning increasing 6 monthly in order to counterbalance the rapid decline of testosterone levels in the afternoon/evening in the physiological diurnal rhythm of normal puberty and thus reduce the time of unopposed oestrogen exposure to the breast.
Results
We identified three groups with differing outcomes. Younger patients with lower BMI and smaller disc size required no intervention, as the GM resolved spontaneously. Patients with a higher BMI, larger disc size and smaller testis volume for their age benefited from intervention, and it was more effective on the group that also had low levels of testosterone at the start. Older, heavier patients, more advanced in puberty had less of a reduction of breast disc size despite the testosterone treatment.
Conclusions
We were able to outline criteria to predict the likelihood of success with reverse rhythm testosterone treatment. Younger patients with lower BMI and smaller disc size required no intervention. Patients presenting slightly older; with a larger disc size; with signs of delayed puberty and low testosterone levels may benefit from reverse rhythm TU to hasten resolution of GM. Patients with a particularly high BMI; large disc size; or presenting at a later stage in puberty are best referred directly for surgery.

Group (*n*)	Mean BMI	Start disc (size/cm)	Start (TV/ml)	Start (T nmol/l)	Start (age/y)	Mean disc (reduction/ cm)	Follow-up (m)
(5) no T	20.58	1.65	12.2	–	13	1.58	12.2
(4) T effective	23.4	3.33	8.5	2.10	14	1.92	16.3
(7) T ineffective	26.0	4.30	11.9	7.98	15	0.68	9.7

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P50

Sex chromosome mosaicism in males: our experience

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Introduction
45XO/46XY karyotype has varied phenotypic spectrum ranging from short stature, ambiguous genitalia (60%), clinical signs of Turner's syndrome in both males and females and normal male phenotype. We report six phenotypically male cases with a varied clinical presentation.
Case 1 and 2: Short stature
Two pre-pubertal, phenotypical males, were referred with concerns regarding short stature (height <0.4th centile, height velocity – 2.6 cm/year). Chromosomes showed 45XO/46XY karyotype in both the boys. Both were commenced on GH with height SDS change of +1 SDS. Renal scan, echo was normal.

Case 3 and 4: Antenatal diagnosis
The first child's antenatal CVS showed 45XO/46XY/46X ring Y chromosome which was confirmed on postnatal testing (indication was previous sibling with Trisomy 21). The second child with 45XO/46XY karyotype had an antenatally diagnosed nasal glioma. Both were phenotypical male. Both continue to grow within target centile range with normal echo and renal scans.
Case 5 and 6: Ambiguous genitalia
The first child was born preterm at 30 weeks following an IVF pregnancy and was referred with concerns of ambiguous genitalia. The child was phenotypically male with palpable gonad in the right scrotum and left gonad in the inguinal region, severe hypospadias and penoscrotal web. He continues to grow well.
The other child was referred to urologist at 3 months of age, with chordee and hypospadias with B/L descended testes. He was started on GH at 4 years of age with an excellent response and height SDS change of +1 SDS. Both had 45XO/46XY karyotype.
Conclusion
In summary, karyotype analysis should be performed more regularly when investigating short stature in males outside of target centile range particularly those with urogenital anomalies, as is recommended in short stature for girls. These young people should be followed up regularly as they tend to respond well to GH treatment but also to monitor for late onset problems such as gonadal tumours and infertility.

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P51

What is the optimum cardiovascular screening in Turner syndrome during childhood and adolescence? Is it achievable?

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Introduction
Women with Turner syndrome (TS) have a 13-year reduction in life expectancy compared to the general population. Cardiovascular disease (CVD), whether congenital or acquired, is the cause of death in around half of these women. Therefore, early identification of congenital heart defects, aortic abnormalities and risk factors for CVD is extremely important, and may have a significant impact on long-term outcomes of CVD in TS.
Aim and methods
To determine whether patients attending our paediatric Turner clinic are being appropriately screened for CVD. The audit standard was set with current available guidelines. Twenty-five patients are under regular review at the dedicated paediatric Turner clinic at the Royal Hospital for Sick Children, Edinburgh. A retrospective review of the patients' records was performed. Cardiovascular data were recorded from three consecutive clinic visits prior to December 2012.
Results
At diagnosis, 84% of patients had an assessment by a cardiologist and 95% had echocardiography (echo). Thirty-three percent of patients had an abnormality on echo. In one patient a biscupid aortic valve could not be excluded but no further imaging was organised. Seventy-seven percent of all clinic visits had at least one BP recorded. However, 71% of these readings were in the prehypertensive or hypertensive range, requiring repeated BP measurement and confirmation by the auscultatory method (which was not performed). No patient had an assessment of aortic dimensions.
Conclusions
To improve screening for CVD at our paediatric Turner clinic we have produced an algorithm for cardiovascular imaging and a proforma for BP measurement. All patients should have an assessment of aortic valve morphology at diagnosis, regular assessment of aortic dimensions, and undergo routine BP measurement from 3 years of age. We have found that the role of the specialist nurse at clinic is vital, in helping us to adhere to these standards.

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P52

Improving health-related outcomes for childhood craniopharyngiomas with a modern individualised conservative surgical strategy and adjuvant focussed radiation; experience at a single centre (great ormond street hospital – GOSH) 2009–2013

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Introduction
Craniopharyngiomas are rare, pituitary tumours which, though benign with good survival, carry high neuroendocrine morbidity. Optimum management remains controversial despite a UK consensus strategy (2005).
Aim
To study disease- and treatment-related neuroendocrine, visual and cognitive outcomes in our most recent cohort, managed with individualised multi-disciplinary decision making to limit hypothalamic morbidity.
Patients and methods: Retrospective longitudinal case review of 19 new patients to GOSH (12M and 7F) between 01/01/2009 and 31/12/2013, median age 7.43 (1.91–15.46) years. Patients' endocrine, visual and cognitive outcomes were categorized by initial treatment strategy at diagnosis and last follow-up.
Results
At a median follow-up of 2.3 (0.7–4.7) years, there was an evolving endocrinopathy from diagnosis which was hierarchical (GHd 100% >TSHd 73.7% >ACTH 63.2% >DI 47.7% >high BMI-SDS (>+2) 10.5%) and aggravated by any surgical debulking rather than cyst aspiration, with little additional impact of radiation to residual disease. Our prevalence rates of ACTHd, DI and obesity are significantly lower than our own and other historic series (70–100%) at a shorter follow-up, without an increase in disease relapse rates (36.8%). All children maintained or improved their vision; only 6.2% were visually impaired. 78.9% received adjuvant radiation (nine protons, six IMRT), up front (12) or at recurrence (3), which effectively stabilised disease in 83.3%. Despite this in all seven patients with longitudinal cognitive assessments, performed at a median interval of 21.5 months, IQ remained unchanged.
Conclusion
Endocrine morbidity is caused by disease and surgery more often than radiation, which is highly effective in stabilising disease. Despite concerns of radiation neurotoxicity, especially in the youngest children, cognitive outcomes are currently stable and the rates of life-threatening DI, ACTHd and morbid obesity are significantly improved. Although there is a possibility that these may increase over time, rates are still lower than similar follow-up time from centres opting for a predominant surgical strategy (avoiding early radiation).

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P53

Bone age study in children (BASIC): a study of the quality of bone age X-rays and an intervention to improve quality and reduce re-X-ray rates

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Background
Bone age studies require X-ray of the left hand and wrist to assess skeletal maturity. The Tanner-Whitehouse 3 (TW3) scoring method provides an objective framework for calculating bone age and specifies exact placement of the hand. In our service we have noted a number of poor quality films, caused by difficulty with hand placement, e.g. scrunching of the fingers. This compromises the ability to score accurately and in a proportion necessitates re-X-ray, with time, financial and radiation exposure consequences.
Aim
To assess X-ray quality and need for re-X-ray in patients having TW3 bone ages.

Method
We performed a prospective study of all bone age X-rays conducted at Sheffield Children's Hospital from May 2013 to February 2014. The quality of bone age X-rays was rated by a single specialist Auxology Nurse. The position of the thumb, fingers and the overall clarity of the X-ray were scored on a simple 1–3 scale (poor, adequate, good), generating a score out of 9. The need for re-X-ray was noted.
Results
Of the 259 bone ages studied, from patients aged 1.92 to 18.48 years, 123 were females. There were 12 X-rays scoring 1 (4.63%) (poor quality) for both the finger and thumb positions and nine for X-ray clarity (3.47%). The number of studies scoring <3 for position of fingers, thumb and overall clarity was 38 (14.67%), 26 (10.04%) and 77 (29.73%) respectively. The number of re-X-rays required was 28 (10.81%).
Discussion
We have shown that achieving good quality films on which to assess bone age may be more difficult than presumed. We believe the re-X-ray rate to be unnecessarily high and have devised a simple hand outline template, placed on the X-ray plate, to encourage the correct positioning of the hand. We are currently evaluating its efficacy using the same scoring system.

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P54

Transient hyperphosphatemia and hyperparathyroidism in a preterm neonate

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Introduction
I report the case of a premature neonate who developed a transient hyperphosphatemia at 1 month of age with associated hyperuremia, hypercreatininemia and hyperparathyroidism.
Case report
This baby girl was born by emergency caesarean section for maternal APH at $27+6$ weeks. She had an uneventful neonatal period with minimal ventilation. She was treated with ibuprofen, amilorone and frusemide for a PDA with associated heart failure. Her enteral feeds had been increased and fortified due to poor weight gain and she was taking caffeine citrate, erythromycin, ranitidine, sodium chloride supplements and vitamins. At 1 month of age she developed a hyperphosphatemia (phosphate 3.93 mmol/l) with associated hyperuremia (urea 14.3 mmol/l) and hypercreatininemia (creatinine 58 μmol/l). Potassium remained on the higher end of normal (5.1 mmol/l) and sodium was stable on supplements (134 mmol/l). Urine output was good and weight gain was a little below target. Wrist and knee X-rays, ultrasound kidneys and gas were all normal. Frusemide was changed to chlorthiazide, fortifier was stopped and calcium supplements were started (despite normal calcium 2.53 mmol/l and adjusted calcium 2.63 mmol/l). Following this the phosphate levels returned to normal.
Conclusion
Despite thorough investigations we were not able to identify a cause for this hyperphosphataemia. Parathyroid hormone resistance was considered which may have been driven by relative hypocalcaemia even though the serum calcium levels were normal. One possible explanation was the frusemide causing a hypocalcaemia which in term caused the hyperparathyroidism but resistance to the parathyroid hormone occurs to avoid calcium depleting the bones which explains the normal calcium.

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P55

Journey through setup of adolescent gender identity dysphoria service for Notheren Ireland

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We describe the development of a new adolescent gender identity dysphoria (GID) service in Northern Ireland (population 1.8 million). Historically patients with GID <18 years were referred to The London joint Tavistock UCH adolescent GID service on a case by case basis. Following the commissioning of a GID service in Northern Ireland, a team of clinical psychologists, paediatric endocrinology nurse specialists, psychiatrist and paediatric endocrinologists, the first GID clinic was held in January 2013 at the Royal Belfast Hospital for Sick Children (RBHSC) with four patients. The number of new referrals has increased and to date there are 12 patients.
Patient's aged 15–18 years are referred from GPs or Local CAMHS services to the clinical psychologist within the GID service becoming the patient's key worker. After ensuring the diagnosis of persistent GID through at least six sessions over 6 months, new cases are discussed with the Tavistock Team in a biannual meeting held in Northern Ireland. Patients diagnosed with GID are referred to the Paediatric Endocrinology service at the RBHSC and are seen within 1–3 months, in a clinic with the key worker, paediatric endocrinology nurse specialist and endocrinologist. Each new patient undergoes physical examination and investigations to ensure no underlying health conditions. Subsequently, patients are seen 3 monthly and commenced on GnRH analogues. After a year on treatment patients are considered for cross-sex hormones and referred to the local adult services once >18 years.
Several challenges were faced during the development of the service such as staff recruitment, finding appropriate space for clinics, training of the GID team, setting up the referral pathway, awareness of service users, smooth transition to Adult GID services, developing local information leaflets and consent forms for cross-sex hormones. Clinical audit and patient feedback will help shape the future of this new exciting service.

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P56

Low birth weight is not a feature of polycystic ovarian syndrome in a British cohort of adolescents, but obesity and metabolic syndrome are common associations

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Background
Adolescent polycystic ovarian syndrome (PCOS) is being diagnosed more frequently as the prevalence of childhood obesity increases. Adolescent PCOS has been associated with low birth weight (LBW), exaggerated adrenarche (EA) and metabolic syndrome in Mediterranean populations. This study describes the clinical phenotype of a cohort of northern European girls.
Methods
A retrospective study of adolescents with PCOS, diagnosed according to the Rotterdam criteria, seen in a single centre between 2005 and 2013.
Results
Data are presented as median (range).
Of 42 girls age 14.7 (11.8–17.9) years, 22/42 (52%) had hyperandrogenic anovulation (hyperandrogenism and oligo-anovulation), 15/42 (36%) classic PCOS (hyperandrogenism, oligo-anovulation and ultrasound changes), 4/42 (10%) non-hyperandrogenic PCOS (oligo-anovulation and US changes) and 1/42 (2%) girl had ovulatory PCOS (hyperandrogenism and ultrasound changes). 33/42 (79%) of girls presented with hirsuitism and 41/42 (98%) had menstrual irregularity. 5/42 (12%) girls had a history of EA.
Birth weight SDS was 0.19 (-3.28 to 2.76). BMI SDS at presentation was 2.67 (-0.55 to 4.22) and 31/42 (76%) of girls were overweight/obese (BMI SDS >1.75).
Androgen levels were elevated in 28/42 (67%) of girls, SHBG was low (<25 nmol/l) in 26/42 (62%) and LH: FSH ratio was >2 in 12/42 (29%).
28 (67%) girls underwent an oral glucose tolerance test of whom 4 (14%) had impaired glucose tolerance (glucose >7.8 mmol/l at 2 h). Fasting glucose and insulin was measured in 26/42 (62%) girls of whom 17 (65%) had insulin resistance (HOMA-IR >3). Fasting lipid profile was measured in 32 (76%) girls of whom 27 (84%) had an unfavourable profile in one or more parameters (cholesterol, triglycerides, HDL cholesterol and LDL cholesterol).
Conclusions
In our population PCOS is not associated with LBW however, obesity, insulin resistance and dyslipidaemia are common. Effective interventions need to be developed to mitigate the long-term burden of metabolic disease and infertility.

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P57

Effect of vitamin D treatment on glucose and insulin metabolism, and bone turnover in children with symptomatic vitamin D deficiency

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Background
There are limited data in paediatric population on the association between vitamin D deficiency/treatment and glucose/insulin metabolism.
Objective and hypotheses
This study aimed to investigate the effect of vitamin D therapy on glucose homeostasis, insulin resistance and bone turnover, in children with vitamin D deficiency.
Method
22 children aged 3 months to 10 years (nine males) who were diagnosed with vitamin D deficiency were recruited from August 2011 to October 2013. Treatment consisted of 6 weeks of 5000 IU units cholecalciferol orally once a day. At baseline and completion of treatment serum 25 hydroxyvitamin D (25OHD), parathyroid hormone (PTH), alkaline phosphatase (ALP), serum collagen type 1 cross-linked C-telopeptide (CTX), HbA1c, sex hormone binding globulin (SHBG), fasting insulin, fasting blood glucose, and homeostasis model assessment index-estimated insulin resistance (HOMA-IR) were measured.
Results
After treatment, 25OHD had increased to a median of 126 from 28 nmol/l ($P=0.00$). PTH decreased from a median of 5.5 to 4.1 pmol/l ($P=0.001$). ALP also decreased significantly, median 236 to 195 u/l ($P=0.03$). There was a non-significant reduction in CTX from a median of 1.98 to 1.76 ng/ml ($P=0.4$) and SHBG from a median of 121 to 116 nmol/l ($P=0.3$). There was no change in fasting glucose (median 4.3 and 4.4 mmol/l, $P=0.8$) or HbA1c (median 33.5 and 34 mmol/l, $P=0.5$), There was a trend towards a reduction in both insulin levels and insulin resistance, with the median insulin falling from 11.1 to 8.1 μIU/ml and HOMA-IR falling from 1.84 to1.59, however this was not statistically significant ($P=0.7$ and 0.9 respectively). There was a weak negative correlation between vitamin D deficiency and elevated PTH at the base line (r_s, -0.19) and insulin level after treatment (r_s, -0.22).
Conclusion
There is no clear evidence of an abnormality of insulin sensitivity with no significant change on vitamin D replacement.

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P58

An audit of paediatric obesity in secondary care

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Introduction
One third of children in the UK are overweight or obese. The Obesity Services for Children and Adolescents (OSCA) group have agreed upon a guideline for paediatricians on the assessment and management of obese children.
Audit aim
To evaluate and improve the care of obese and overweight children.
Method
Obese patients seen in secondary care were retrospectively audited from 2008 to 2014.
Results
82 patients were included with a median age of 10.9 years. 52.4% ($n=43$) were male. Median BMI at presentation was 29.20 kg/m^2. 53.7% patients ($n=44$) were morbidly obese (BMI >3.33 s.d. above mean). 76.8% patients ($n=63$) had ≥ 1 blood investigation within the first year. 53.7% ($n=44$) had thyroid function tests, 9.1% ($n=4$) showed raised TSH. 39.0% ($n=32$) had fasting glucose performed, 6.3% ($n=2$) showed raised fasting glucose. 19.5% ($n=16$) had a fasting insulin level, 43.8% ($n=7$) showed hyperinsulinaemia. 35.4% ($n=29$) had lipids investigated, 31.0% ($n=9$) showed dyslipidaemia. 50.0% ($n=41$) had an ALT level, 4.8% ($n=2$) showed ALT >70 U/l. 20.7% patients ($n=17$) had an OGTT. 94.1% of OGTT ($n=16$) were normal. 5.9% ($n=1$) was diagnostic of T2DM. 86.6% patients ($n=71$) were offered follow-up with a median interval of 4 months. 70.7% patients ($n=58$) were referred to dieticians, 55.2% of these ($n=32$) attended. Lifestyle changes were reported by 76.9% patients ($n=52$) at follow-up. 8.5% patients ($n=7$) were started on metformin. 3.7% patients ($n=3$) were trialled on orlistat.
Conclusions
The management of obese children was variable. Data suggests 20–25% obese children in the UK population could have ≥ 2 cardiovascular risk factors. Co-morbidities may have been missed in this cohort. Local guidelines are to be implemented in order to standardise care with re-audit in 2 years.

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P59

Is there a role for medical management in childhood obesity? A review of the Manchester Metabolic Obesity Service

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Background
Childhood obesity is a growing problem worldwide, with serious effects on child health. Obese children are at a higher risk of developing metabolic co-morbidities earlier in life (WHO, 2013). Manchester has worse than national average levels of obesity, with an estimated 14 000 obese children (PHE, 2014).
Aims and methods
A retrospective case note analysis of 117 obese paediatric patients, seen in our service between March 2012 and 2014, was conducted, aimed at reviewing monitoring standards, frequency of metabolic co-morbidities and treatment outcomes.
Results
In our cohort, 38.5% were male (national average 55.2% in year 6). 90.6% of patients had a BMI centile $\geq$ 99.6th (BMI SDS ≥ 2.7) with median age 9.87 (range 0.58–16.88) years. 7.7% had a genetic diagnosis of obesity (excluding Prader–Willi syndrome). 70.1% had ≥ 2 metabolic co-morbidities, with insulin resistance (IR), dyslipidaemia and hypertension being the most prevalent ($n=75$, 65 and 38 respectively). 38 patients with IR were treated with metformin. In those rescreened within 24 months of treatment, 72% (13/18) demonstrated improved IR. For BMI SDS change analysis, 28 patients were excluded (nine genetic diagnosis, four hypothyroidism, 15 incomplete data). 80.9% of patients demonstrated BMI SDS loss or maintenance. In these patients, mean maximum BMI SDS loss achieved on lifestyle interventions (LI) ($n=36$) and LI and medication ($n=36$), were 0.38 (0.04–1.47) and 0.28 (0.00–1.16) SDS respectively.
Conclusions
Obese male children are likely to be under referred to paediatric services hence attention should be given to this cohort in the community. The high prevalence of co-morbidities within our cohort suggests that metabolic screening is indicated in children with severe obesity. Metformin treatment for up to 24 months in those with IR may improve longer term metabolic outcomes.

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P60

Melanocortin 2 receptor accessory protein 2 (Mrap2) regulates hypothalamic melanocortin-4-receptor trafficking *in vivo*

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Recently, rare loss-of-function mutations of melanocortin-2-receptor accessory protein 2 (*MRAP2)* have been associated with severe, early-onset obesity in humans. In addition, whole body deletion and targeted brain specific deletion of the *Mrap2* gene resulted in severe obesity in mice. *In vitro* data have shown

Mrap2 interaction with the melanocortin-4-receptor (MC4R) affecting receptor signalling as a consequence. However, the mechanism by which Mrap2 regulates body weight *in vivo* is less well understood with differences between Mrap2 and Mc4r knockout (KO) mice phenotypes. In this study we show that Mrap2 complete KO mice, derived from an independent line and on two separate genetic backgrounds, have severe early obesity without detectable changes to food intake or energy expenditure. Hence, replicating recently published data. To further investigate the *in vivo* role of Mrap2 as a Mc4r accessory protein we used a plasma membrane enrichment technique to demonstrate a reduction of hypothalamic Mc4r protein surface expression in Mrap2 KO mice compared with WT littermates. Taken together, this work corroborates the role of Mrap2 in obesity and confirms that, at least in part, this is due to defective central melanocortin trafficking.

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P61

Challenges of managing a 9-month old child with congenital hyperinsulinism within a secondary care setting

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Introduction
Congenital hyperinsulinism (CHI) typically presents in the neonate, however a minority of cases (~ 35%) present later in infancy and childhood. We report the challenging case of an older infant presenting with hypoglycaemia, diagnosed with CHI and managed entirely within a secondary care setting.
Case report
A 9-month-old macrosomic (99th centile) infant presented to the Children's Emergency Department with hypoglycaemia and a 1 week history of seizure-like episodes. Parents reported a voracious appetite, and distress with delayed feeds, but no significant medical background. Hypoglycaemia was confirmed and initially two incomplete hypoglycaemia screens were performed. Prompt central venous access enabled controlled induction of hypoglycaemia (2.6 mmol/l) allowing a full panel of investigations, with the safety of prompt treatment with secure intravenous access. Although intravenous glucose requirements were 6–7 mg/kg per min, which is borderline for CHI, the results (glucose 2.6 mmol/l, insulin 51 pmol/l and β-hydroxybutyrate 0.1 mmol/l) confirmed CHI. Other endocrine and metabolic investigations were normal. Genetics for ABCC8/KCNJ11 were negative. Results are awaited for other genes responsible for CHI and Beckwith–Wiedemann. The patient responded to diazoxide at a dose of 5 mg/kg per day. He was discharged with regular follow-up, including long-term neuro-developmental assessment due to the week-long delay in presentation.
Conclusion
Following this case, a local non-diabetic hypoglycaemia guideline (including a 'hypo screen' pack containing the relevant blood bottles) was developed, advising clinicians of the differentials, essential investigations and initial management, and indications for urgent central access. This case highlights the diagnostic challenges of an uncommon presentation of CHI in later infancy to secondary care. The safe diagnosis (controlled induction of hypoglycaemia), and management exclusively in secondary care, was permitted by the expertise of a paediatrician with a special interest in hypoglycaemia, and local facilities to place secure central venous access, avoiding untreatable hypoglycaemia with long term neuro-developmental sequelae.

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P62

Lanreotide therapy for congenital hyperinsulinism

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Introduction
Congenital hyperinsulinism (CHI) is the commonest cause of recurrent and persistent hypoglycaemia during the newborn period. The management of CHI in patients who are unresponsive or do not tolerate diazoxide includes the use of octreotide therapy which is given as a SUBCUTANEOUS injection, three to four times daily. We report a case of persistent CHI successfully treated with once monthly Lanreotide (a long acting somatostatin analogue).
Case
A 15-year-old girl with a diagnosis of CHI from infancy was managed with diazoxide therapy. Genetic analysis revealed a *denovo* ABCC8 mutation. 18-Fluro dopa positron emission tomography (PET) CT scan revealed diffuse disease. Although the glycaemic control was stable on diazoxide, she experienced troublesome hypertrichosis not amenable to therapies including waxing and laser. This had a huge impact on the quality of life with episodes of deliberate self-harm needing psychological assistance. A trial off diazoxide resulted in hyperinsulinaemic hypoglycaemia. Hence SUBCUTANEOUS octreotide was commenced (four daily injections) and a good glycaemic response was noted. The baseline ultrasound scan of the liver and gallbladder prior to starting octreotide was within normal limits. However, she disliked the daily SUBCUTANEOUS therapy. Hence a long acting somatostatin analogue (Lanreotide, 30 mg) was given subcutaneously following which the daily octreotide was gradually weaned and stopped. The continuous blood glucose monitoring system following the administration of Lanreotide revealed good glycaemic control with no episodes of hypoglycaemia. Currently she is on monthly Lanreotide therapy and off octreotide and diazoxide with good glycaemic control. This has led to a significant improvement in her quality of life.
Conclusion
Lanreotide is a safe and effective therapeutic option for patients who experience significant side effects of diazoxide. The long acting effect of once monthly injection confers an improved quality of life in these patients.

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P63

Hyperinsulinaemic hypoglycaemia and cochlear hypoplasia in a rare case of Pallister–Hall syndrome

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Introduction
Pallister–Hall syndrome (PHS) is characterized by a spectrum of anomalies which includes polydactyly, hypothalamic hamartoma, laryngotracheal cleft, bifid epiglottis, imperforate anus, and renal abnormalities. Hypoplastic cochlea is an infrequently reported association of PHS. The association of PHS with hyperinsulinaemic hypoglycaemia (HH) has not been previously reported in the literature.
Case report
A baby girl was born by elective caesarean section at 31 weeks of gestation with a birth weight of 1.2 kg (−1.2 SDS) to non-consanguineous Caucasian parents. She required ventilator support. The endotracheal intubation was extremely difficult due to a very narrow trachea. She was noted to be dysmorphic with two umbilical vessels, abnormal hands and feet and imperforate anus. MRI scan of the brain revealed the presence of a large hypothalamic hamartoma. The cochlea was noted to be truncated bilaterally with reduced number of turns. She was noted to have recurrent hypoglycaemic episodes in the first few days of life and required high concentration of glucose infusion to maintain normoglycemia (glucose infusion rate, 15 mg/kg per min). The investigations revealed a plasma insulin level of 65 pmol/l and C-peptide of 775 pmol/l during hypoglycaemia (blood glucose 1.4 mmol/l) confirming HH. The free fatty acids and β-hydroxy butyrate were suppressed. She was commenced on diazoxide and a good glycaemic response was noted. This enabled weaning down intravenous fluids and she was established on enteral feeds. The cytogenetic analysis revealed GLI3 mutation consistent with diagnosis of PHS.
Conclusion
This is the first reported case of HH in association with PHS. The genetic mechanism(s) in this syndrome that leads to dysregulated insulin secretion is unclear. Our patient also had hypoplastic cochlea which has been described only once before in the literature in association with PHS.

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P64

Cellular proliferation is increased in both the lesion and non-lesion pancreas in focal congenital hyperinsulinism

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Introduction
Focal congenital hyperinsulinism (F-CHI) is caused by dual-hit pathology, comprising a paternally-inherited *ABCC8/KCNJ11* mutation and somatic loss of the maternal allele at chromosome 11p15. This leads to dysregulation of insulin secretion and β-cell overgrowth with a focal domain.
Objectives
To compare the proliferative index (PI) of the F-CHI lesion and non-lesion pancreatic tissues to age-matched control pancreata and insulinoma tissues.
Methods
Ki67 immunostaining was used to quantify the PI of paraffin-embedded F-CHI tissue ($n=8$; age 2–10 months at pancreatic surgery; positive for *ABCC8* mutations), age-matched control pancreata ($n=12$) and insulinomas ($n=3$, age 5–16 years). The PI was derived from the total number of Ki67-positive cells expressed as a percentage of the total cell count using digitized images of histological sections of tissue, ~35 000 cells per tissue ($n=30$ tissue sections in total).
Results
Control tissue showed age-related decline in PI from >8% of total cells at 2 days to <0.5% at 10 months. In comparison, F-CHI tissue retained a high PI inside and outside the lesion. Within the lesion, PI was increased by an average (±SEM) 1.4-fold (4.7%±0.5) ($n=5$) vs controls in children <4 months of age at surgery, which became statistically significant at age >4 month, ninefold (4.2%±0.8) ($n=3$) $P=0.025$. Interestingly, the PI of non-islet and islet tissue outside the focal lesion was also increased; at >4 months this was increased to 7.3-fold (3.4%±0.4) in non-islet tissue ($P=0.02$, $n=3$) and 2.3-fold (1.2%±0.4) in islets ($P=0.01$). These trends were not seen in insulinoma tissue as PI values were ≤ 0.5% in both the lesion and non-lesion tissue.
Summary/conclusion
Enhanced proliferation is retained both inside and outside the F-CHI lesion with more gradual age related decline. The increased proliferation rate in F-CHI cannot be solely attributed to maternal 11p15 deletion as this is confined to the lesion.

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P65

A heterozygous STAT5B variant in a family with short stature and transient hyperprolactinaemia: a possible dominant negative effect

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The index case, born to non-consanguineous British parents, was born with a normal birth weight. He grew along the −2.9 S.D. centile from the age of 2 years. Eczema was diagnosed at the age of 2 weeks. Investigations at 3–4 years of age showed: IGF1 <25 ng/ml, IGFBP3 1.29 (*N* 0.8–3.9), prolactin 265–653 mU/l (*N* 59–271), GH peak (glucagon test) 17.3 ug/l, normal GH peaks on overnight sampling, and an IGF1 <25 ng/ml on a standard IGF1generation test. His younger brother had short stature (−2.9 S.D.) with poor height velocity, eczema and mild speech delay, undetectable IGF1, and a GH peak of 13.9 ug/l.
Heights of his mother, maternal aunt and maternal grandmother are ~155 cm (−1.2 S.D.). Mother and maternal aunt were previously investigated for transient hyperprolactinaemia. The mother had low normal IGF1 (113 ng/ml (69–268)) and a detectable random GH (0.3 ug/l).
An extended three step IGF1-generation test (2 weeks GH S.C. at 0.7, 1.4 and 2.4 mg/m^2 per day, with wash-out periods) showed little response; index case: step1 IGF1 56 ng/ml, IGFBP3 2.62 mg/l, step 2 IGF1 61 ng/ml, igfbp3 2.87 ng/ml, step 3 IGF1 83 ng/ml (*N* 57–316), IGFBP3 3.33 (*N* 1.4–6.1) and brother: step1 and step 2: IGF1 <25 ng/ml, step3, IGF1 32 ng/ml, IGFBP3 2.37 mg/l.
Exons and intron–exon boundaries of *STAT5B* were sequenced. A heterozygous variant c.1433C>T (p.A478V) was found in the index case. The brother and mother but not the father, had the same variant, suggestive of a dominant negative effect or haplo-insufficiency. *STAT5B* sequencing in maternal aunt and grandmother is underway. The variant occurred in a highly conserved residue and is predicted to alter helix 6, at the end of the DNA-binding domain, and would potentially disrupt function. We hypothesise that this variant has a dominant negative effect on STAT5B function, given the requirement for dimerization of the protein, resulting in moderate short stature with a poor growth rate.

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P66

Growth characteristics in children with Temple syndrome: an under-diagnosed imprinting disorder

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Background
Temple syndrome (TS) is a disorder caused by dysregulation of imprinted genes at chromosome 14q32. It is important to distinguish the growth pattern from other imprinting disorders such as Russell–Silver and Prader–Willi syndromes.
Aims
To describe the growth pattern in TS.
Methods
51 cases were identified from 11 countries. Height, weight, birth weight and head circumference were converted to SDS using country-specific growth reference data. Where multiple growth measurements for an individual were available, the mean value over 12 months was used.
Results
Intra-uterine growth retardation (IUGR) was documented in 75% (27/36) of cases. The median SDS for birth weight and birth length were −1.88 and −1.64 respectively with a mean birth occipito-frontal circumference (OFC) SDS of −0.8. Preterm births occurred frequently (12/40, 30%) however these had similar SDS values.
Between birth and 16 years, 87% (39/45) of children had a height SDS of ≤ −1.0. Relative macrocephaly, where the difference between OFC and height SDS was ≥1.0, was present in 55.9%. Median adult height and weight SDS were −2.04 and −1.07 respectively. Obesity was recorded in 49%. The median BMI of patients >16 years was 26.6 kg/m^2 ($n=8$).
Early puberty was reported in 86% (19/22) with a mean age at menarche of 10 years 2 months. Type 2 diabetes mellitus was reported in three of 19 patients aged above 12 years. Oral treatment was required. In contrast, two patients were reported with recurrent hypoglycaemia between 3 and 5 years: one was GH deficient and required replacement therapy.
Conclusions
The growth pattern in TS is characterised by IUGR, short stature, and a relatively higher weight for height in later life. Final height is similar to untreated Russell–Silver syndrome. We highlight that early puberty, obesity and diabetes are complications of TS that may be amenable to early intervention.

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P67

A rare thyrotropinoma complicated by cerebral salt wasting: a case report

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Introduction
Thyrotroph adenomas are extremely rare accounting for only 0.5–2.8% of paediatric pituitary adenomas. Almost 90% of thyrotropinomas are macro-adenomas.
Case report
A 9-year-old boy presented with acute onset of a right divergent squint on a background of 6 months of visual disturbance. Opthalmological assessment confirmed reduced visual acuity and visual field defects.
MRI revealed a large macroadenoma invading the cavernous and sphenoid sinuses. Pre-operative pituitary function assessment showed low cortisol (74 nmol/l), normal gonadotrophins and testosterone, mildly raised prolactin and borderline low free T_4 (10.7 pmol/l) with normal TSH (6.39 mU/l) and marginally raised T_3 (7.7 pmol/l).
On extended biopsy histology showed an atypical pituitary adenoma which, based on its hormone expression profile, was classified as a thyrotroph pituitary adenoma.

The patient was critically unwell postoperatively with polyuria up to 10 l/day (13 ml/kg per h), hyponatraemia (lowest value 121 mmol/l) with high urinary sodium losses (290 mmol/l). Serum osmolality was initially low and then normalised (lowest value 256 mosm/l). He was diagnosed with severe cerebral salt wasting (CSW) requiring high-volume fluid replacement with hypertonic saline and high dose fludrocortisone. His condition was exacerbated by diabetes insipidus (DI) requiring an infusion of vasopressin. Both of these resolved 2–3 weeks postoperatively. On discharge he had partial hypopitutitarism with secondary hypothyroidism and ACTH deficiency. He is currently under follow-up with plans for resective surgery.

Conclusions

Thyrotropinomas classically present with clinical hyperthyroidism and / or neuro-opthalmological signs due to mass effect. Surgery is usually considered first line therapy but results in cure for only a third of patients as they are often difficult to resect due to their marked fibrosis and proximity to vital structures, as illustrated in our case. This case highlights the post-operative complication of CSW which can co-exist with DI, making diagnosis and management very challenging.

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P68

Assessing the diagnostic value of testosterone, basal LH and LHRH test in predicting pubertal progression in boys

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Introduction

Central precocious puberty (CPP) is rarer in boys than girls, therefore evidence is limited for interpreting LHRH testing in boys. Current recommendations also suggest use of basal LH.

Objectives

i) Test efficacy of using basal LH and testosterone for predicting CPP in boys. ii) Establish diagnostic cut-offs for LHRH testing in boys.

Method

Retrospective data collection of LHRH test results in 67 boys aged 2–10 years old, from a regional paediatric centre between 2005 and 2013.

Measure of progression into puberty based on clinician's judgment following LHRH testing: ten boys in progression group and 57 boys in non-progression group.

Results

Statistically significant difference between the basal LH, LHRH-stimulated LH levels and stimulated LH/FSH ratio between the groups.

Using basal LH $\geq$0.3 IU/ as cut-off yielded 60% sensitivity, 80.7% specificity and NPV 92.0%. In addition, using basal testosterone $\geq$3.3 nmol/l produced 83.3% PPV and 91.4% NPV, 98.2% sensitivity. There was, however, no correlation between testicular volumes and testosterone level.

Different diagnostic cut-offs were found which have not been previously reported: $>$5.3 IU/l for stimulated LH level at 30 min and $>$3.5 IU/l at 60 min; stimulated LH/FSH ratio $>$1.26 at 30 min and $>$1.0 at 60 min respectively.

Stimulated LH/FSH at 60 min was found to be have the most diagnostic value with 100% sensitivity (95% CI: 71.3–100%), 94.6% specificity (85.1–98.8%) and 100% NPV (93.2–100%).

Conclusion

Using basal LH and testosterone together can be a useful screening test to rule out CPP in boys. If a LHRH test is required; we report new diagnostic cutoffs, and have shown that the stimulated LH/FSH ratio provides the greatest diagnostic value.

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P69

Bone mass and body composition in adolescents with childhood onset GH deficiency

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Background

Childhood-onset GH deficiency (CO-GHD) is perceived to be a cause of low bone density and osteoporosis in adulthood. Data on bone mass and body composition of GH-treated adolescents with CO-GHD at final height are inconsistent.

Aims

To compare size/height corrected parameters of bone mass and body composition in adolescents with CO-GHD at final height.

Method

Review of CO-GHD treated patients at final height between 2005 and 2012 in a single tertiary paediatric centre. BMD-*Z*-scores of patients were compared to height-matched local healthy controls. Percent predicted bone area for age (ppBAforAge), percent predicted bone mineral content for bone area (ppBMCforBA), and bone mineral apparent density (BMAD) was calculated to reflect body size and degree of mineralisation respectively.

Results

Lumbar spine (LS) and total body (TB) DXA scan results of CO-GHD at final height (n=23, seven with isolated GHD) median age 17.8 years (15.5–20.5, 12 males) were compared to controls (n=23) median age 16.8 years (14.7–19, 12 males). Median uncorrected BMD-Z-scores in GHD were lower at TB ($-$1.4 ($-$3.2–1.2) and LS ($-$2.1 ($-$4.2–1.1)) compared to TB (0.2 ($-$0.9–2.3)) and LS ($-$0.1 ($-$1.6–2.8)) in the controls ($P<0.001$). Size corrected analysis showed male adolescents with GHD, unlike females, have lower TB (ppBA for Age) (81%(68–97)) and (ppBMC for BA) (95%(91–108)), and lower LS (ppBMC for BA) (91.5% (80–120)) and BMAD (g/cm^3) (0.15 (0.13–0.20)) compared to controls males TB (ppBA for Age) (106%(87–118)), TB (ppBMC for BA) (109%(97–117)) and LS (pp BMC for BA) (106%(100–124)) and BMAD (0.17 (0.16, 0.20)), $P<0.05$. Males with GHD also have increased fat-mass (FM)(kg) (16.2 (4.5–70.7) in GHD: 7.7 (5.6–32.5) in controls, P=0.03) and decreased lean mass (LM)(kg) (47.1 (26.8–62.3) in GHD: 57.9 (49.1–61.2) in controls, $P<0.001$), whereas females with GHD have a higher FM compared to matched females (22.4 (11–44.9) vs 19.1 (8.8–48.10), (P=0.04)) with no difference in LM (12.7 (9.4–15.6) vs 13.8 (4.9–17.3), P=0.8) respectively.

Conclusion

Male adolescents with CO-GHD appear to have reduced mineralisation, together with narrower bones, and alteration in body composition when compared to controls.

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P70

Evaluating the diagnostic value of basal LH and LHRH test in predicting progression into precocious puberty in girls

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Introduction

Current recommendations for diagnosing central precocious puberty (CPP) in girls suggest using basal LH levels $>$0.3 IU/l to predict progression into CPP and using stimulated LH values $>$5 IU/l in the LHRH test to diagnose CPP. Our objectives were to test the efficacy of using basal LH values as well as to establish diagnostic cut-offs for LHRH tests.

Method

Retrospective data collection of LHRH test results of 173 girls between 2 and 10 years old, from a regional paediatric centre between 2005 and 2013. Measure of progression into CPP was based on clinician's judgment following LHRH testing: 56 girls were in progression group and 117 girls in non-progression group.

Results

There was a statistically significant difference in basal LH, basal FSH, LHRH-stimulated LH levels and stimulated LH/FSH ratios between the two groups. A basal LH level $\geq$3.4 IU/l yielded a negative predictive value (NPV) of 89.2%. When basal LH $\geq$3.4 IU/l or basal FSH $\geq$3.4 IU/l were used; there was 80.4% sensitivity and 79.3% specificity. If both conditions were present, sensitivity rose to 92.2%. There were different diagnostic cut-offs between 30 and 60 min, which have not been previously reported. The optimal diagnostic cut-off for stimulated LH levels at 30 and 60 min was $\geq$5.4 and $>$4.1 IU/l respectively. Optimal cut-offs for stimulated LH/FSH ratio at 30 and at 60 min were $>$0.63 and $>$0.88 respectively. A stimulated LH/FSH ratio at 30 min $>$0.63 produced 89.3% sensitivity, 85.5% specificity, PPV 74.6% and NPV 96.2%.

Conclusion

Using basal LH and FSH levels together is a useful screening test to rule out CPP in the majority of girls. If an LHRH test is required, we have reported novel cut-offs for LH levels at 30 and 60 min, and have shown how the LH/FSH ratio has overall greatest diagnostic value.

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P71

A novel *de novo* heterozygous mutation in *FGFR1* is associated with Hartsfield syndrome

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Introduction
Hartsfield syndrome (#OMIM 615465) describes the rare co-occurrence of holoprosencephaly with ectrodactyly, associated with a spectrum of developmental defects including specific pituitary dysfunction.
Case report
Our patient, a male infant, had several congenital abnormalities: bilateral cleft lip and palate, right sided microtia, bilateral ectrodactyly of the hands and feet and semilobar holoprosencephaly. Aged 5 weeks he was noted to be hypernatraemic and paired serum/urine osmolalities (301 mOsmol/kg, 75 mOsmol/kg respectively) were indicative of cranial diabetes insipidus, with good response to DDAVP. He had microphallus and inguinoscrotal testes, with a poor response to LHRH stimulation (peak LH 0.7 IU/l, FSH 0.9 IU/l). His pituitary function was otherwise normal. His clinical features are consistent with Hartsfield syndrome. Novel homozygous/heterozygous mutations in *FGFR1* have recently been associated with the condition in eight patients. Interestingly *FGFR1* mutations have also been associated with Kallman's syndrome, in which gonadotrophin deficiency is also a feature. *FGFR1* encodes fibroblast growth factor (FGF) receptor 1. FGFs play a crucial role during embryonic development with downstream effects on cell motility, cell survival and cell mitosis. Fgfr1 deficiency in mice is reported to lead to olfactory bulb absence, failure of midline axonal migration, and a variety of limb defects. Direct Sanger sequencing of *FGFR1* in our patient reveals a novel, *de novo* heterozygous missense mutation, c.1883A>G; p.Asn628Ser. Another heterozygous missense mutation at this site has previously been reported in association with the syndrome. The p.Asn628Ser mutation affects an amino acid residue located in the ATP binding pocket of the intracellular tyrosine kinase domain, with potential effect on FGFR1 kinase activity.
Conclusions
Identification of this novel mutation in *FGFR1* in our patient provides further compelling evidence of the association of *FGFR1* mutations with Hartsfield syndrome. This has informed genetic counselling and allowed for targeted surveillance of pituitary function in our patient.

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P72

'Can I gain a greater height?': a case of metaphyseal chondrodysplasia, Schmid-type

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Objectives
1) When and how to investigate rarer causes of short stature.
2) Evidence for interventions to improve growth in metaphyseal chondrodysplasia, Schmid-type (MCDS).

Background
The incidence of skeletal dysplasia is one in 5000, however individually these conditions are rare and prognosis unclear. There is genotypic and phenotypic heterogeneity and no current consensus on classification, which may include clinical, radiographic, molecular or histological criteria.
Presentation may range from mild arthropathy to incompatibility with life. Here we present a case of MCDS, presenting with short stature and initial diagnostic uncertainty.
MCDS, autosomal dominant inheritance, results from mutation in COL10A1; coding collagen type X. X-ray demonstrates metaphyseal widening, coxa vara, without associated cervical spine abnormalities or extra-skeletal manifestations. Growth hormone is only recommended in SHOX deficiency as a cause of skeletal dysplasia; otherwise it risks disproportionate limb lengthening and worsening of spinal deformities.
Case
A 15-month-old boy presented with faltering growth, bowed limbs, waddling gait, bilateral wrist swelling and height 68 cm (−3.9 S.D.). The wrist X-ray was consistent with rickets.
Normal 25-hydroxy vitamin D, calcium, phosphate, parathyroid hormone and alkaline phosphatase made vitamin D deficient and dependent rickets unlikely. A sitting height of −2 S.D. and sub-ischial leg length −4 S.D. was suspicious of skeletal dysplasia, supported by a skeletal survey demonstrating metaphysal widening, coxa varum and genu varum.
A novel heterozygous transversion 2001T>A in exon 3 of COL10A1 confirmed the diagnosis.
Learning points
1) Consider rarer causes of rickets with clinical suspicion and normal vitamin D level.
2) Detailed auxology can guide the differential diagnosis.
3) GH is not recommended in most skeletal dysplasia.

Otherwise classified as idiopathic short stature, evidence suggests skeletal dysplasia or an underlying genetic cause may be more common than previously supposed.

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P73

GH deficiency contributes to short stature in children with chromosome 18 rearrangements

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Introduction
Chromosome 18 rearrangements are postulated to be associated with short stature, of uncertain pathophysiology.
Methods
Retrospective case review (short stature with chromosome 18 rearrangement), investigation for GH deficiency (peak GH <7 μg/l on glucagon or ITT, unless otherwise indicated) and determining response to GH treatment.
Results
In 13 year six such cases were referred from the geneticists, mean referral age, 3.3 years (1.2–10.5 years) with mean parental adjusted (PA) height SDS of −3.8 (−8.6 to −0.6). Cases 1 and 2 were associated with 18 p deletions alone, presenting with PA height SDS of −3.5 and −2.6 and normal peak GH on stimulation (16 and 9.2 μg/l) respectively. GH treatment was not indicated and PA height SDS demonstrates ongoing short stature (case 1: −2.8, case 2: −3.4). Four patients met criteria for GH treatment for GH deficiency. Case 3 had an 18 q deletion, PA height SDS −0.6 with poor height velocity (2.5 cm/year) and suboptimal GH response to stimulation (6.2 μg/l). Case 4–6 were associated with ring chromosome 18 with18 p/q deletions. In all cases suboptimal GH responses were identified on stimulation (cases 4 and 5: 4.9 μg/l, 5 μg/l respectively; case 6: 11 mu/l (peak <20 mu/l on arginine testing). In cases 5 and 6, a small pituitary was identified on imaging. With GH treatment a significant increase in PA height SDS (from presentation to most recent review) is observed in all cases, $P=0.04$ (paired *t*-test, one-tailed), all showing >50% height velocity increase in 1 year.
Conclusion
In our case series, 18 p deletions alone were not associated with GH deficiency-related short stature. 18 q deletions and ring chromosome 18 abnormalities with 18 p/q deletions were associated with GH deficiency, all showing good response to treatment. We propose that GH deficiency is investigated in all individuals with chromosome 18 rearrangements and short stature, particularly 18q deletions and ring chromosome18 abnormalities.

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P74

Impaired insulin and IGF2 signalling in the primordial growth disorder 3-M syndrome

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Introduction
3-M syndrome is associated with mutations in *CUL7*, *OBSL1* and *CCDC8* with the three proteins interacting within a novel growth pathway. The impact of this pathway on cellular growth has not been fully defined. We have shown that i) GH and IGF1 signalling are altered; ii) *IGF2* expression is reduced and iii) expression of insulin receptor isoforms are altered in 3-M fibroblasts.

Aim
To characterise the activation of AKT by IGF2 and insulin in 3-M fibroblasts.
Methods
Fibroblast cells from 3-M patients with each of the three 3-M mutations and from normal controls were stimulated with 500 ng/ml IGF2 or 100 ng/ml insulin over 0, 5, 15 and 60 min. Relative phosphorylation of AKT was assessed by western blotting and image analysis. Statistical comparisons were made both within and between cell lines.
Results
Relative pAKT was reduced in 3-M fibroblasts compared to normal cells when stimulated with either IGF2 ($P=0.033$) or insulin ($P=0.048$) over the time course. In both cases, $CUL7^{-/-}$ cells and $OBSL1^{-/-}$ cells had a greater reduction in pAKT than $CCDC8^{-/-}$ cells. $CUL7^{-/-}$ cells had an earlier activation in response to insulin ($P=0.016$). Previous data after IGF1 stimulation showed $CUL7^{-/-}$ cells had 10% of normal AKT activation while both $OBSL1^{-/-}$ and $CCDC8^{-/-}$ were ~50% of normal. However AKT activation was less impaired after IGF2 or insulin: for IGF2, pAKT at 60 min was reduced to 70–80% of normal in all 3-M cells: for insulin, pAKT at 60 min was reduced to 65–70% of normal for $CUL7^{-/-}$ and $OBSL1^{-/-}$ and to 90% for $CCDC8^{-/-}$.
Conclusions
Reduced AKT activation in response to IGF2 and insulin stimulation mirrors that previously seen although the reduction is less than IGF1. Impaired growth factor signalling is one mechanism that could account for the growth failure in 3-M and may contribute to insulin resistance in SGA children.

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P75

Relationship between IGF1 concentration and growth velocity in infants and toddlers

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Background
IGF1 is the biochemical marker of growth as it is supposed to reflect the activity of the GH axis. The usefulness of IGF1 measurements in children under 3 years has not been verified to date.
Aim
We analysed the relationship between serum IGF1 concentration and growth velocity (GV) in children under the age of 3 years.
Methods
We compared 300 IGF1 concentrations taken in children younger than 3 years with their GV at time of collection. We included patients with different diagnoses; patients on GH therapy were excluded.
Three groups of patients were identified according to GV: group A GV-SDS >-0.8, group B GV-SDS <-2, group C $-0.8>$GV-SDS>-2.
Results
Group A ($n=185$): despite the normal GV, IGF1 was less than the lower limit of the normal range in 50.3% of patients, this being more frequent (65.5%) in the first year of life than in the second (41.2%) or the third (40%).
Group B ($n=58$): IGF1 was appropriately low in 74.1% of patients but within the normal range in 25.9% of these patients with poor GV.
Group C ($n=57$): in 71.9% of patients, the IGF1 was low. In the remaining patients, the concentration was within the first quartile of the range in 87.5% of cases.
A total of 120 patients with low IGF1 were formally tested for GH deficiency (GHD) (glucagon stimulation) and 93 of them were GHD (IGF1 specificity 77.5%).
BMI-SDS was equally distributed between the three groups and the quartiles of IGF1, therefore excluding an impact of nutrition on IGF1 concentrations.
Conclusions
These preliminary data suggest that the relationship between IGF1 concentration and GV before 3 years of age is poor. This is even more evident in patients with normal GV, and especially in the youngest ones (<1 year). In this cohort of patients specificity of IGF1, as a preliminary diagnostic test GHD, is 77.5%.

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Septo-optic dysplasia, multiple pituitary hormone deficiency and optic nerve hypoplasia: clinical and neuroradiological characteristics

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Introduction
Multiple pituitary hormone deficiency (MPHD) and septo-optic dysplasia (SOD) are well known causes of hypopituitarism, but children with optic nerve hypoplasia (ONH) may also be at risk of hormone and neurocognitive disturbances. Clinical and neuroradiological findings of these three related conditions are characterised in this study, aiming to understand their pathophysiology.
Design
Data from 140 patients with hypopituitarism (MPHD, SOD) and ONH collected at a tertiary endocrinology centre between 2000 and 2013 were retrospectively analysed.
Results
-*Clinical characteristics*: Male/female ratios for SOD ($n=102$), MPHD ($n=28$) and ONH ($n=10$) were 1.37, 1.33 and 0.66 respectively. Birth characteristics were not significantly different between the three groups.
The mean age at the last appointment in all groups was 8.32–8.42 years and the majority of patients remained prepubertal and pre-adrenarcheal, whilst spontaneous puberty, in those who were of an appropriate age, had started in 86.6% SOD (26/30), 62.5% MPHD (5/8) and in all ONH (4/4). At birth, 27.5% of SOD (16/59), 37.5% of MPHD (6/16) and none of ONH (0/4) presented with abnormal male genitalia. At last appointment, obesity was found in 25.5% SOD (26/102), 32.1% MPHD (9/28) and 30% ONH (3/10). Oral glucose tolerance tests showed insulin insensitivity in 5/7 SOD patients with metformin administered to four of them. SOD patients had associated problems including hearing abnormalities (12.8%), hyposmia (2.9%), cardiovascular accidents (2%), hip dislocation (7.8%), autistic spectrum disorder (24.5%) and sleep disturbances (35.3%). Neurodevelopmental delay was found in 59% SOD (60/102), 14% MPHD (4/28) and 90% ONH (9/10).
-*Neuroradiology*: Table 1 summarises the main pituitary and corpus callosum findings in the three groups.

Table 1 Neuroradiology findings.

		SOD n:102 N (%)	MPHD n:28 N (%)	ONH n:10 N (%)
Septum pellucidum	Absent	29 (28.4)	0 (0)	0 (0)
	Partial/hypoplastic	8 (7.8)	0 (0)	0 (0)
	Normal	57 (55.9)	26 (92.9)	9 (90.0)
	Carvum septum pellucidum	1 (1.0)	0 (0)	0 (0)
Corpus callosum	Absent	7 (6.9)	0 (0)	0 (0)
	Partial/hypoplastic	38 (37.3)	0 (0)	0 (0)
	Normal	49 (48.0)	26 (92.9)	9 (90.0)
Anterior pituitary	Partial/hypoplastic	78 (76.5)	25 (89.3)	0 (0)
	Normal	16 (15.7)	1 (3.6)	9 (90.0)
	Enlarged	1 (1.0)	0 (0)	0 (0)
Posterior Pituitary	Absent	20 (19.6)	2 (7.1)	0 (0)
	Partial/hypoplastic	7 (6.9)	0 (0)	0 (0)
	Normal	39 (38.2)	5 (17.9)	9 (90.0)
	Enlarged	1 (1.0)	0 (0)	0 (0)
	Ectopic	28 (27.5)	19 (67.9)	0 (0)
Stalk	Absent	20 (19.6)	6 (21.4)	0 (0)
	Partial agenesis/thin	25 (24.5)	4 (14.3)	0 (0)
	Normal	47 (46.1)	14 (50.0)	9 (90.0)
	Interrupted	1 (1.0)	1 (3.6)	0 (0)
	Thick	1 (1.0)	0 (0)	0 (0)

Conclusion
Despite the phenotype variability within each condition, common clinical and neuroradiological features between SOD, MPHD and ONH denote a spectrum of disorders affecting midline brain development.

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P77

Thickened pituitary stalk (TPS) and/or idiopathic central diabetes insipidus (ICDI): a single centre experience of occult causative pathology evolving in 54 children over 30 years

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Introduction
Thickened pituitary stalk (TPS) and/or idiopathic central diabetes insipidus (ICDI) are rare in childhood, presenting to different (endocrine, oncology, ophthalmology) specialties. In the absence of other diagnostic features, agreed radiological definitions, biopsy (often too dangerous) or consensus management guidance, subsequent surveillance and treatment are uncertain. Cases may remain undiagnosed or evolve over decades.
Aims
i) To longitudinally characterize a large childhood cohort presenting with TPS and/or ICDI, ii) to identify any underlying occult pathology over a long follow-up, iii) to assess clinical, visual and endocrine correlates over time.
Methods
We searched the terms 'thickened pituitary stalk' or 'idiopathic diabetes insipidus' in electronic radiology and clinical document libraries at our split-site centre (UCLH/GOSH) over the last 30 years. 63 retrospective longitudinal data sets in patients with TPS, ICDI or both, were collected and MRI scans reviewed. Nine patients with a clear diagnosis at presentation (two: infection, seven: histiocytosis) were excluded from subsequent analysis.
Results
Patients with TPS were older (TPS: 9.8 ± 4.9 years) at presentation than those with ICDI (5.5 ± 4.4 years) and TPS + ICDI (6.2 ± 3.4 years) ($P < 0.04$). TPS + ICDI patients were more likely (38.5%) than ICDI (5.6%) and TPS (none) to have histiocytosis. Tumours were identified in 26.9% TPS + ICDI and 27.9% ICDI, 1.0 ± 1.4 and 1.9 ± 2.4 years later respectively, but not in TPS. 80% TPS cases remained unexplained (vs 61.1% ICDI and 34.6% TPS + ICDI) though at a shorter follow-up (2.5 vs 5.2 and 5.8 years). Multiple anterior pituitary deficits evolved with time across groups (GHd, 45–58%, TSHd 19–30%, ACTHd 13–21%, GnRHd 7–17%) but visual deficits, present in 8–23% at presentation, increased only in TPS + ICDI (7.6 to 34.6%).
Conclusions
ICDI is a negative prognostic factor for malignant disease, whilst the combination with TPS may be a progressive phenomenon and is more often associated with histiocytosis. TPS alone is unlikely to lead to malignancy but should be prioritized for endocrine follow-up.

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P78

Three year experience of a national interdisciplinary initiative to improve outcomes for children with hypothalamic pituitary axis tumours (HPATs) using multi-site videoconferencing for decision making on Behalf of the UK HPAT Interest Group

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Background
Childhood tumours of the hypothalamic pituitary axis (HPATs) are very rare and hence any single centre experience is limited. Without evidence-based guidance, treatment is individualised on a case basis. Survival rates are high, but at the expense of significant morbidity. Centralised care or wider multi-professional consultation may improve neuroendocrine and visual outcomes.
Objective and hypotheses
1. To facilitate multi-professional dialogue across centres nationally (including adult pituitary specialists) in a videoconference format.
2. To enhance diagnostic and treatment decision making through education and sharing audits, knowledge and experience.

Method
From April to October 2011, a live, monthly videoconference was piloted across three sites. Pituitary physicians and surgeons, paediatric neurooncologists, neuroradiologists, neurosurgeons, neuropathologists and clinical oncologists all contributed. Having overcome initial technical limitations, monthly meetings continued over the next 2 years.
Results
In 27 meetings spanning 2.5 years, the clinical cases (including quality imaging) of 67 HPAT patients were discussed in relation to formulating management plans. Of these, 16 were discussed on multiple occasions. Of the 67 cases, craniopharyngiomas (17) were the most common tumour type. In addition, three guest lectures and five new audits of centre experience in craniopharyngiomas (3), prolactinomas (1) and suprasellar gliomas (1) were presented. To date, there are seven participating centres, increased attendees and 3–4 case discussions per month, even attracting international participation from centres in Ireland and Australia.
Conclusion
A national, regular, multidisciplinary consultation for discussing rare HPATs is feasible and welcomed, facilitating dialogue amongst a wide specialist professional grouping and influencing management. With appropriate funding, such collaborative experience with outcome monitoring, regular on-going audits and an educational programme should enhance the management of this rare group of patients, resulting in better outcomes and shaping the national standard of care.

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P79

UK GH stimulation test survey

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Background
Previous studies show poor consensus on the use of GH stimulation tests. Sex steroid priming and re-testing in the transition period are areas not previously surveyed. In light of more recent guidance and expert opinion, this survey aims to analyse the diagnostic processes employed in the diagnosis of GH deficiency (GHD) in the UK.
Methods
Data were collected from tertiary paediatric endocrinologists, paediatricians with a specialist interest in endocrinology, and biochemists across the UK. Surveys were distributed with support from the British Society of Paediatric Endocrinology and Diabetes and the Association for Clinical Biochemistry and Laboratory Medicine.
Results
Diagnostic tests: 48 paediatric departments and 57 biochemistry departments responded. 33% of departments used at least three different tests. Glucagon and insulin doses varied most. The frequency of sampling varied most following insulin administration.
All laboratories use a recommended chemiluminescence immunoassay with an acceptable CV. The GH peak for diagnosing GH deficiency varied (6 – 8 μg/l) across departments, most commonly 7 μg/l (35%).
Retesting: Most reported stopping GH at least one month before re-testing, most commonly with glucagon (56%), however re-testing was undertaken in a wide range of clinical scenarios suggesting non-standardised current practice.
Priming: 75% of departments use sex steroid priming, but by a range of criteria, including bone age (61%), age (50%), pubertal stage (50%) and variation in type/dose of steroid.
Conclusion
Although recognised as a contentious diagnostic test due to poor reliability, sensitivity and specificity, GH stimulation tests remain the gold standard for diagnosing GHD. Variation was found amongst all aspects of indication, protocol, assay and interpretation of GH stimulation tests between departments. Hopefully these data, together with the latest research, reviews and guidance, will encourage review of practice in the investigation, diagnosis and follow-up of these children to, over time, eventually find consensus.

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P80

Variable presentation of xanthogranulomatous hypophysitis: a case series

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Introduction
Xanthogranulomatous hypophysitis (XGH) is a very rare form of pituitary hypophysitis that may present both clinically and radiologically as a tumour. Our case series compares paediatric and adult presentations of XGH.
Case series
Patient 1: A 15-year-old female presented with refractory headache, lethargy, short stature, delayed growth (weight (−3.36) SDS, height (−1.73) SDS, BMI 14 kg/m^2), and pubertal arrest over 18 months. Formal visual fields demonstrated bitemporal quadrantanopia.
Patient 2: A 21-year-old female presented with lethargy, frontal headaches and secondary amenorrhoea, 3 years after delivery. *Postpartum* she had normal lactation and menstrual irregularity followed by secondary amenorrhoea. Visual examination was normal.
Patient 3: A 67-year-old man was diagnosed with hypopituitarism following an episode of collapse and intermittent temporal headaches. He had a long standing history of rheumatoid arthritis and rheumatoid nodules within the prostate. Eye examination was normal.
Endocrine investigations demonstrated panhypopituitarism in all three patients. Patient 2 had hyperprolactinaemia requiring Cabergoline.
Pituitary MRI revealed a suprasellar mass compressing the optic chiasm suggestive of craniopharyngioma or rathke's cleft cyst in patient 1; suspected non-functioning pituitary macroadenoma in patients 2 and 3. MRI demonstrated mixed signal intensities on T1- and T2-weighted sequences.
Following endoscopic trans-sphenoidal surgery, histology revealed areas with cholesterol cleft formation associated with multinucleate giant cells and numerous macrophages in patients 1, 2 and necrobiotic granulomatous chronic inflammatory infiltrate with neutrophils in patient 3. Immunohistochemical staining for IgG4 performed in patient 3 showed IgG4 positive plasma cells (>5%) raising possibility of a systemic IgG4 related process more commonly associated with ocular necrobiotic xanthogranuloma.
Conclusion
This case series describes the spectrum of XGH disease which is yet to be defined. Mixed signal intensities on T1- and T2-weighted MRI sequences may indicate XGH and diagnosis is confirmed by histology. Histological variation may indicate an underlying systemic process.

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P81

A case report of TRβ mutation leading to raised T_4 levels presenting with abnormal body habitus

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Introduction
We present a 5-year-old girl with thyroid hormone resistance, subsequently discovered to be heterozygous for TRβ mutation. This case highlights the necessity to investigate, in detail, all children with persistently high thyroxin with normal TSH levels in order to aid future management and the necessity to follow them up.
Case report
SD was born at term by normal delivery weighing 3.34 kg (50th centile). She was referred at 6 months of age for poor weight gain (2nd centile). Blood tests showed an elevated free T_4 (43.4) with normal TSH (3.10). Systemic examination was normal and remained so over the following months. Repeat thyroid function tests showed persistently elevated T_4 with normal TSH. At 2 ½ years old, genetic analysis revealed she is heterozygous for TRβ mutation (thyroid hormone receptive gene). Mum has no mutation detected and SDs father cannot be tested for unavoidable reason. Since then, she has had slow growth, idiopathic thrombocytopenic purpura, vitamin D deficiency, and coeliac disease. Broader antibody testing has not revealed an underlying autoimmune aetiology to date. Recently, SD has been investigated for recurrent falls and abnormal gait. She has right sided hemi hypotrophy with drooped shoulder and pelvis, along with winged scapulae, flared ribs and prominent abdomen. Her gross motor skills are generally delayed.
Conclusion
Mutation of the beta thyroid hormone receptor is usually either autosomal dominantly inherited or is a de novo mutation, resulting in defective patterns of gene expression. This is a rare disorder, usually presenting with goitre. TRβ mutation should be considered in children with persistently elevated T_4 levels in conjunction with a normal TSH. The other immune conditions like ITP and changes in body habitus are new associations, cause of which is yet not identified.

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P82

An audit to assess the impact of increasing the borderline blood spot TSH cut-off on the detection of cases of congenital hypothyroidism (CHT) identified via newborn screening

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Background
The UK Newborn Screening Programme Centre Clinical Referral Standards and Guidelines for CHT (2013) define TSH cut-offs for screen positive (>20 mU/l) and borderline (>10 and <20 mU/l) results. In Manchester levels >8 and <20 mU/l are classified as borderline. This audit aims to assess whether adopting the national cut-off would result in babies with significant and permanent hypothyroid disease being missed.
Patient population
All babies screened by the Manchester laboratory from October 2007 to April 2014,
Audit methodology
A search of the laboratory screening information system identified all babies with an initial TSH result of >8 and <10 mU/l and a repeat TSH of >8 mU/l. Diagnostic test results and details of thyroxine therapy were obtained on this cohort and in confirmed cases now >2 years of age we attempted to ascertain whether thyroxine therapy was continuing and if thyroid status had been reassessed after 4–6 weeks off therapy as guidelines recommend.
Results
399 babies had an initial TSH of >8 mU/l and <10 mU/l and 19 of those had a valid repeat TSH >8 mU/l. A diagnosis was confirmed in 17/19 and all were commenced on Thyroxine. There was no evidence on thyroid imaging of an absent or ectopic thyroid in any of the cases. 11/19 babies are now >2 years and follow-up data has so far been obtained in 4/11. In 2/4 permanent CHT is confirmed, 1/4 was transient and has ceased thyroxine and 1/4 remains on thyroxine but has not been re-tested.
Conclusion
In Manchester adoption of the national borderline TSH cut-off would re-classify an average of three confirmed cases CHT/year as normal. Work is on-going to establish the proportion of these babies in whom hypothyroidism is permanent.

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P83

Congenital central hypothyroidism due to a *TSHB* mutation with uniparental inheritance

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Introduction
Biallelic mutations in the *TSHB* gene are a recognized cause of isolated congenital central hypothyroidism (CH), with autosomal recessive inheritance. In countries where neonatal CH screening relies on detection of an elevated TSH, such cases

are missed, with the potential for delayed diagnosis and subsequent developmental impairment.
Case
A female infant presented aged 8 weeks with prolonged jaundice, poor weight gain, constipation, sleepiness and poor feeding. She exhibited coarse facial features and a prominent tongue, in addition to hypotonia, cool peripheries and an umbilical hernia. Biochemistry revealed profound central hypothyroidism (TSH 3.06 mU/l, free T_4 <3.89 pmol/l), with a flat response to TRH testing, but otherwise preserved pituitary function. Thyroxine treatment was initiated; however, aged 7 years, she has residual mild motor delay.
Genetic analyses in the Proband revealed a homozygous, previously reported *TSHB* mutation (c.373delT, p. Cys125Valfs*10), however, despite paternal heterozygosity for 373delT, the mother exhibited only WT *TSHB* sequence. Haplotype analysis delineated a 251kb region with loss of heterozygosity at 1p13.2, including the *TSHB, TSPAN2* and *SYCP1* genes, and an informative SNP 4.4 kb proximal to *TSHB* (rs1321108), confirmed uniparental (paternal) inheritance (A/A), since no maternal allele (G/G) was inherited. This suggested either maternal deletion of one *TSHB* allele, or paternal, uniparental isodisomy as the likely genetic basis.
Conclusions
Published literature is devoid of UK or Irish cases with *TSHB* defects. Our patient, from Dublin, exhibits a novel genetic mechanism (paternal *TSHB* mutation and absent maternal allele), and characteristic clinical features. Her motor delay probably reflects delayed treatment, since central hypothyroidism is missed on CH screening in the UK and Ireland. This observation supports inclusion of T4 measurement in the CH screening programme.

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P84

Delayed recognition of neonatal thyrotoxicosis in a baby born to a mother previously treated for Grave's disease

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Introduction
Neonatal Grave's disease is rare, affecting one in 25 000 neonates, and results from transplacental passage of TSH receptor antibodies (TSHR-Ab). Whilst hyperthyroidism occurs in <5% of babies born to mothers with active Grave's disease; those born to mothers who were previously treated may still be affected. Neonatal Grave's disease is usually self-limiting, however, complications include craniosynostosis, growth retardation, hyperactivity, developmental and behavioural problems.
Case report
A female infant was born at term to a mother previously treated with radioiodine for Grave's disease. Mother received routine antenatal care and remained euthyroid throughout pregnancy. However, TSHR-Ab were not assessed until 34 weeks gestation, delaying the routine alert system until after delivery. Raised maternal antibody levels were identified during routine postnatal care. The infant developed a tachycardia and an increased frequency of bowel motions. She was admitted to NNU where thyroid function tests (TFTs) at 48 h of age were highly suggestive of neonatal thyrotoxicosis; T_3 22.7 (2.6–5.7 pmol/l), T_4 64.3 (9–22 pmol/l), TSH <0.01 (0.35–5.00 mU/l), transplacental TSHR-Ab 25 (<0.4 U/l). Carbimazole and propranolol were started. Symptoms resolved by day 6 of life and the baby was discharged. At 6 weeks of age TFTs had normalised and propranolol was stopped. At 16 weeks of age TSHR-Ab were 0.2 U/l and carbimazole was stopped.
Conclusions
This case highlights the importance of actively exploring the risk of neonatal thyrotoxicosis in all gravid women presenting with a history of hyperthyroidism, including measuring TSHR-Ab levels at booking. We emphasise the importance of effective information sharing between adult and paediatric specialists, midwives and patients to identify high risk women early. Locally we have implemented an education programme to increase awareness of the impact of maternal factors on neonatal health. This has focused on early recognition and communication, including the use of neonatal alert cards.

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P85

Goitre: a presenting feature of acute myeloid leukaemia

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Introduction
The commonest pathological cause of goitre in adolescence in the UK is autoimmune thyroid disease. Other thyroid pathologies may occasionally co-exist either linked to the autoimmune process or occurring together by chance.
Case report
A previously fit and healthy 15-year-old male presented as an emergency with a 10-day history of painless neck swelling. He had no breathing difficulty, dysphagia or voice change and was also clinically euthyroid. There was a family history of autoimmune thyroid disease and type 1 diabetes mellitus. On examination he had a diffuse smooth swelling in the neck of 10 cm by 6 cm in size, moved on swallowing and was consistent with goitre. There was no cervical lymphadenopathy. The rest of the examination was normal. Investigations revealed a TSH of 76.5 mIU/l, free T_4 of 2.2 pmol/l and a raised thyroid peroxidase antibody titres suggestive of autoimmune thyroid disease. Neck ultrasonography confirmed a diffusely enlarged thyroid. He was commenced on thyroxine and was discharged with follow-up. He represented 4 days later with left calf swelling. Examination showed a swollen, red, tender calf and investigations revealed an abnormal white cell count (>200×109/l) with blast cells. He was transferred to the oncology team and a bone marrow biopsy confirmed acute myeloid leukaemia. He was treated with chemotherapy and bone marrow transplantation. His thyroid function normalised together with resolution of the goitre within 4 weeks of starting thyroxine and chemotherapy. The patient is making good progress and remains on thyroxine replacement.
Conclusions
Autoimmune thyroid disease involves T-cell mediated targeting of thyroid antigen and the presence of thyroid gland enlargement in our patient suggests that myeloid leukaemic cells also have the capacity to migrate to the sites of autoimmune damage in the thyroid gland. Nodular and diffuse thyroid enlargement may reflect an underlying malignant process.

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P86

Management of congenital hypothyroidism: audit of our experience over a decade vs the new national standards

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Background
About one in 3000 babies born in the UK have congenital hypothyroidism (CHT), which is usually due to an agenesis of the thyroid gland, but some are due to dyshormogenesis, which can be transient or permanent.
Method
Retrospective analysis of medical notes of infants referred as 'suspect' congenital hypothyroidism from the newborn blood spot screening centre to the paediatric endocrinology service at our hospital from January 2002 to January 2013. Data collection and analysis was performed on Microsoft Excel.
Results
Sixty-seven infants were referred to our service, of which 33 infants had 'confirmed' CHT. Thyroxine was started at 12 days (median) at a dose of 8.5 μg/kg per day (median) with a dose range from 6.1 to 11.7 μg/kg per day. Serum free T_4 reached the upper end of reference range at 2.1 weeks (median) and serum TSH normalised at 3.4 weeks (median) after start of treatment. Three infants developed significant elevation of free T_4 levels at follow-up, requiring reduction of thyroxine dose. Assessment of permanence of CHT was done at 3 years of life in two infants, who came off thyroxine and five infants were eligible for trial off thyroxine treatment.
Conclusion
Although we are using less than the recommended dose of thyroxine (recommended dose is 10–15 μg/kg per day), we are able to normalise the thyroid function tests in line with the national standards. Thus we have chosen to continue with our current starting doses. The audit has highlighted the importance of assessing permanence of congenital hypothyroidism at 2–3 years of age by a trial off thyroxine and checking thyroid function tests in 6 weeks.

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P87

Prevalence of short stature in juvenile hypothyroidism and the impact of treatment in a tertiary care center

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Background
Juvenile hypothyroidism is very common problem in developing parts of world, and produces various skeletal manifestations. One of them is short stature and it is the most common reason for referral to endocrinologist.
Aim and objectives
To study the prevalence of short stature in juvenile hypothyroidism, to study the various radiological manifestations of juvenile hypothyroidism and to study the impact of treatment on growth velocity and various skeletal manifestations.
Material and methods
Out of total 900 hypothyroid patients, 87 patients found to be of juvenile hypothyroidism were enrolled in the study that were 6–18 years of age with newly diagnosed or on follow in the endocrine clinic over a period of 1.5 years were evaluated clinically and by laboratory tests. Serial assays of TSH, T_4, and skeletal X rays and anthropometry were done at regular interval and clinical and radiological outcome of patients were analyzed.
Statistical analysis
Data were analyzed by SPSS version 17, the p value of <0.05 was considered significant.
Result
The mean age of diagnosis of juvenile hypothyroidism was 11.2 years, and the females had twice the incidence than that of males, the mean TSH value were 118 ± 24.3 μIU/ml. Prevalence of short stature was found to be 45% while delayed bone age was found to be 72% in juvenile hypothyroid populations. Height SDS increased from -2.9 ± 0.9 at the start of thyroxine therapy to -1.8 ± 0.8 after 12 months later ($P<0.001$). Bone age SDS increased from 8.9 ± 2.5 at the start of thyroxine therapy to 10.8 ± 2.7 after 12 months later. Height velocity increased from 4.9 ± 0.8 cm/year in the year before treatment to 8.7 ± 1.3 during treatment ($P<0.001$).
Conclusion
The presentations of juvenile hypothyroidism may be varied; prompt recognition of the findings can lead to early and effective treatment, and improving the skeletal defects.

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P88

Severe hypothyroidism developing in an infant with hepatoblastoma and Beckwith–Wiedemann syndrome: could there be a link?

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Hypothyroidism presents diagnostic challenges when occurring in an extremely unwell infant with hepatoblastoma. This case indicates a possible link between Beckwith–Wiedemann syndrome (BWS) and severe hypothyroidism.
Antenatally, the baby had polyhydramnios and an abdominal mass. After normal vaginal delivery at $38+4$ weeks, examination showed macrosomia (4007 g) small nose, low set ears and inverted V-shaped mouth. Transient hypoglycaemia on day 1 required two glucose boluses, and thereafter resolved. The mass caused abdominal expansion, significant IVC compression and artificial ventilation requirement and Pretext IV hepatoblastoma was diagnosed. Chemotherapy (cisplatin/doxorubicin) was commenced aged 2 weeks but he ultimately required a liver transplant.
At 1 month he developed seizures, paucity of limb movements, abnormal tone and did not fix and follow. EEG showed right sided abnormalities. MRI showed oedema and bilaterally small hippocampi. Array CGH identified a maternally inherited 16p11.2 microduplication (187 kb) most likely of no clinical significance.
Severe hypothyroidism (TSH >100 mU/l, $fT_4<2.6$ pmol/l) was noted at 3 months and thyroxine commenced. Normal Guthrie test was verified and the deterioration in function remains unexplained. Ultrasound showed normal thyroid location and size. No significant iodine exposure had occurred, neither chemotherapeutic agent was known to cause hypothyroidism and he was too young to invoke autoimmunity. Small hippocampi are reported in hypothyroidism, but do not infer aetiology. Hepatoblastoma cannot directly explain onset of hypothyroidism.
The baby died aged 4 months, his course complicated by sepsis, increased ventilation and worsening neurology. Molecular analysis showed significant loss of methylation at ICR2/KvDMR1, confirming a diagnosis of BWS and explaining the hepatoblastoma and hypoglycaemia but not clearly the hypothyroidism.
A tenuous link between BWS and congenital hypothyroidism appears in a small number of reports. Our case is the first reported with non-congenital onset. Additionally, the phenotypic features and severity are atypical for BWS indicating a possible additional genetic mechanism.

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