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40th Meeting of the British Society for Paediatric Endocrinology and Diabetes 2012

7–9 November 2012, Leeds, UK

Abstract Book

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CONTENTS

40th Meeting of the British Society for Paediatric Endocrinology and Diabetes 2012

SPEAKER ABSTRACTS

CME TRAINING DAY

CME Session	S1–S6
-----------------------	-------

MAIN MEETING

Symposium 1 Gender Identity Development – Care and Controversies	S7–S8
Symposium 2 Controversies in Paediatric Endocrinology	S9–S10
Symposium 3 The Olympiad!	S11–S12
Symposium 4 Hot topics In Diabetes	S13–S14
Symposium 5	S15–S16
Symposium 6 Diabetes and Sport	S17–S18
Keynote Lecture	S19

ENDOCRINE NURSES DAY

Ipsen Award Winners	S20–S21
Endocrine Nurse Session 1	S22
Case Presentation Endocrinology in Sport	S23
Endocrine Nurse Session 2	S24

ORAL COMMUNICATIONS

Oral Communications 1	OC1.1–OC1.8
Oral Communications 2	OC2.1–OC2.10
Oral Communications 3	OC3.1–OC3.5
Oral Communications 4	OC4.1–OC4.5
Oral Communications 5	OC5.1–OC5.4

POSTER PRESENTATIONS	P1–P66
---------------------------------------	--------

INDEX OF AUTHORS

Speaker Abstracts

CME Session**S1****Physiology and developmental disorders of the pituitary**

Mehul Dattani

University College London, London, UK.

The pituitary gland is a central regulator of growth, homeostasis and reproduction. It is in turn regulated by the hypothalamus, which generates a number of releasing factors (GHRH, TRH, GnRH, CRH) and the inhibitory hormone somatostatin. The pituitary gland consists of the anterior and posterior lobes, both of which have separate developmental origins. The anterior lobe derives from the oral ectoderm, whilst the posterior lobe derives from the neuroectoderm. The anterior pituitary contains five different cell types secreting six different hormones, namely GH, prolactin, TSH, ACTH, LH and FSH. The posterior pituitary secretes vasopressin and oxytocin.

Normal hypothalamo-pituitary development is closely related to that of the forebrain, and is dependent upon a complex genetic cascade of transcription factors and signalling molecules that may be either intrinsic or extrinsic to the developing Rathke's pouch. These factors dictate organ commitment, cell differentiation, and cell proliferation within the anterior pituitary. Abnormalities in these processes due to mutations in genes encoding both signalling molecules and transcription factors are associated with congenital hypopituitarism, a spectrum of disorders that includes septo-optic dysplasia (SOD), combined pituitary hormone deficiencies (CPHD), and isolated hormone deficiencies, of which the commonest is GH deficiency (IGHD). These include *HESX1*, *LHX3*, *LHX4*, *PROPI*, *POU1F1* and, more recently, *GLI2*, *OTX2*, *SOX3* and *SOX2*. Phenotypes associated with mutations in genes encoding these factors may be highly variable, as may the inheritance. Genes that are implicated in early pituitary development are more likely to be associated with complex phenotypes, whilst those expressed later have more defined phenotypes.

To conclude, normal pituitary ontogeny in mouse and human is the result of a carefully orchestrated genetic cascade. To date, genetic mutations account for a small proportion of cases of hypopituitarism in humans. However, these mutations have led to a greater understanding of the genetic interactions that lead to pituitary development. It is also likely that mutations will be identified in other genes that are implicated in normal pituitary development.

S2**Causes, diagnosis and management of pituitary dysfunction**

Mohamad Maghnie

University of Genova, Genova, Italy.

Only small advances were made in the field of pituitary imaging until the advent of magnetic resonance imaging (MRI), which led to an enormous increase in our detailed knowledge of pituitary morphology, thus improving the differential diagnosis of hypopituitarism. Indeed, MRI represents the examination method of choice for evaluating hypothalamic-pituitary-related endocrine diseases thanks to its ability to provide strongly-contrasted high-resolution multi-planar and spatial images. Specifically, MRI allow a detailed and precise anatomical study of the pituitary gland by differentiating between the anterior and posterior pituitary lobes. The MRI identification of pituitary hyperintensity in the posterior part of the *sella*, now considered a marker of neurohypophyseal functional integrity, has been the most striking finding contributing to the diagnosis and understanding of some forms of 'idiopathic' and permanent GH deficiency (GHD).

Published data show a varying correlation between pituitary abnormalities as observed on the MRI scan and a patient's endocrine profile. Indeed several trends have emerged and have been confirmed: i) normal MRI scan or anterior pituitary hypoplasia mainly indicates isolated GHD that is generally transient and not confirmed after adult height achievement; ii) patients with MPPH seldom have a normal pituitary gland and iii) the classic triad of ectopic posterior pituitary gland, pituitary stalk hypoplasia/agenesis and anterior pituitary gland hypoplasia is more frequently reported in MPPH patients and its generally associated with permanent GHD. Pituitary abnormalities have been reported in patients with GHD carrying mutations in several genes encoding transcription factors such as *POU1F1*, *PROPI*, *HESX1*, *LHX3*, *LHX4*, *GLI2*, *PITX1*, *PITX2*, *SOX3*, *SOX2* and *OTX2*. Establishing endocrine and MRI phenotypes is extremely helpful in the selection and management of patients with hypopituitarism, both in terms of possible genetic counseling and of early diagnosis of evolving anterior pituitary hormone deficiencies.

S3**The surgical management of pituitary tumours**

Saurabh Sinha

Sheffield Children's NHS Foundation Trust, Sheffield, UK.

In the UK, ~ 1000 new patients are diagnosed with a pituitary tumour every year and 4.2% of all paediatric tumours are craniopharyngiomas. Although these tumours are predominantly benign, untreated they can lead to visual compromise, raised intracranial pressure and the endocrine effects of hypersecretion or hypopituitarism, resulting in significant morbidity and mortality. This talk provides an overview of the presentation and management of pituitary tumours and craniopharyngiomas.

S4**Genetic disorders of thyroid physiology and development**

Nadia Schoenmakers

University of Cambridge, Cambridge, UK.

Congenital Hypothyroidism (CH) is the commonest inborn endocrine disorder (prevalence 1 in 3000), and occurs either due to failure of normal gland development (thyroid dysgenesis), or due to defective thyroid hormone synthesis in a structurally normal gland (dysmorphogenesis). Mutations in known thyroid transcription factors, and in genes encoding components of the thyroid hormone biosynthetic machinery, have been implicated in CH, attesting to the role of these genes in human thyroid physiology and development. Dysmorphogenetic CH accounts for 15% of primary CH and usually demonstrates autosomal recessive inheritance; genetically ascertained cases harbour mutations in *TPO*, *TG*, *SLC5A5* (*NIS*), *SLC26A4* (*Pendrin*), *DUOX2*, *DUOX2*, or *IYD*. Thyroid dysgenesis is more common, comprising 85% of CH, but its genetic basis remains largely unknown, with mutations in the transcription factors *PAX8*, *Nkx2.1*, *Nkx2.5* and *FOXE1*, or biallelic *TSHR* mutations, underlying less than 5% of cases.

Thyroid hormone action is mediated by receptors encoded by the *THRA* and *THRB* genes generating receptor subtypes (*TRa1*, *TRb1*, *TRb2*) with differing, tissue-specific expression. Dominant negative *THRB* defects are well-recognized causes of resistance to thyroid hormone in *TRb*-expressing tissues, (e.g. hypothalamus and pituitary), manifesting as impaired negative feedback in the HPT axis (elevated *ft4* and *ft3*, unsuppressed TSH), and variable hyperthyroidism in *TRa*-expressing tissues, (e.g. myocardium) which retain thyroid hormone sensitivity. Conversely, the first reported cases of human *TRa*-mediated thyroid hormone resistance due to dominant negative *THRA* mutations exhibit only borderline abnormal thyroid hormone levels (low-normal *ft4*, high-normal *ft3*, low *rT3*) associated with tissue-specific hypothyroidism (skeletal dysplasia, constipation, bradycardia), reflecting preserved hormone responsiveness in *TRb*-expressing tissues (hypothalamus, and pituitary) but resistance in *TRa*-expressing tissues (skeleton, gastrointestinal tract and myocardium). Clinical features of these two syndromes will be reviewed.

S5**Hypothyroidism**

Malcolm Donaldson

Royal Hospital for Sick Children, Glasgow, UK.

Hypothyroidism exists when function of the hypothalamic-pituitary-thyroid axis is impaired, either with normal or subnormal thyroid hormone levels – compensated and decompensated hypothyroidism. Hypothyroidism is called primary when the abnormality is at the level of the thyroid gland itself and central when the defect is in the hypothalamo-pituitary axis.

Central hypothyroidism, whether congenital or acquired, almost always occurs in the context of panhypopituitarism. It is rarer than primary hypothyroidism and lower thyroxine doses are required compared with primary disease.

Primary congenital hypothyroidism (CH) is the commonest endocrine disorder with a prevalence in Scotland between 1994–2003 of 1/3655. TSH elevation in the newborn period is usually due to CH but may be transient in nature, or of uncertain cause. Of 95 infants undergoing dual ultrasound and isotope scanning in Glasgow 2004–2011 the causes were transient (8), uncertain (7), thyroid dysgenesis (due to ectopia (39), athyreosis (21), hypoplasia (4)) and dysmorphogenesis (20). With newborn TSH screening on days 4–6, notification on days 10–12 and immediate treatment by days 13–15 (unless TSH elevation is

mild, e.g. $<40 \mu\text{l}$), the outlook for CH is good. Further improvements might be expected by instituting screening on day 3 so that severely affect infants can begin treatment within 10 days of life; setting the TSH referral cut-off at 8–10 mU/l; adopting a disciplined national diagnostic algorithm to evaluate referred cases, with measurement of venous free T_4 , TSH and thyroglobulin combined with dual ultrasound and radioisotope imaging; initial treatment with a thyroxine dose of 50 μg daily in infants weighing $\geq 2.5 \text{ kg}$ and 15 $\mu\text{g}/\text{kg}$ per day in infants weighing $<2.5 \text{ kg}$ followed by weekly review until thyroid function is normalised; and maintenance of free T_4 levels between 15–26 pmol/l and TSH between 0.5–5 mU/l thereafter to avoid both under- and overtreatment.

Primary acquired hypothyroidism is usually due to autoimmune thyroiditis, also called Hashimoto's thyroiditis (HT). HT is commoner in girls ($\sim 4:1$) and often has a family history (40%). Its frequency in type 1 diabetes, Turner's syndrome and Down's syndrome is sufficiently high for annual screening to be justified. We have found school-based capillary TSH screening to be helpful in Scottish children with Down syndrome, in whom minimum prevalence of TSH elevation is $\sim 6\%$. Presentation of HT in the general population is with goitre which may be tender $+/-$ symptoms of hypothyroidism such as pallor, fatigue and weight gain, and occasionally slipped capital femoral epiphysis. The complete replacement dose of thyroxine is 100 $\mu\text{g}/\text{m}^2$ per day. However, in severe cases initial doses must be low to try and preempt symptoms of the transition from hypo- to euthyroidism. These include tearfulness, fatigue, poor concentration and poor school performance. HT may fluctuate in severity and even remit, so the family should to report early with symptoms suggestive of either under- or overtreatment with thyroxine.

S6

Hyperthyroidism and its management

Tim Cheetham

Newcastle University, Newcastle, UK.

Thyrotoxicosis is uncommon in young people with a UK incidence around 1/100 000 (<15 years). Most cases of persistent thyroid hormone excess are due to Graves' disease although transient episodes are seen in Hashimoto's thyroiditis. Thyroid peroxidase antibodies can frequently be identified in both forms of autoimmune thyroid disease with antibodies to the TSH receptor more typical of Graves'. Patients with Graves' are usually managed initially with the anti-thyroid drug (ATD) carbimazole using a dose titration (DT) regimen or a block and replace (BR) approach. Propylthiouracil should generally be avoided in the young because of the risk of hepatic dysfunction. There is an association between ATD exposure and likelihood of remission in paediatric practice although to what extent this is an effect of the medication on the autoimmune process, the impact of establishing a euthyroid state or the natural history of the disease is unclear. Unfortunately Graves' disease tends to be more severe in the young with low remission rates following ATD therapy. Side-effects of ATD are also more common in this age group and the recent American Thyroid Association guidelines suggest that the BR regimen in children should 'in general be avoided'. However this recommendation was not based on studies conducted in young people and the potential for greater biochemical stability with the BR approach means that this strategy may be the preferred option in some patients. Recent data has shown that radioiodine therapy as a 'definitive' treatment for Graves' is being used more frequently in the UK although a lengthy period of ATD administration is still used in some parts of Europe. Surgery (total thyroidectomy) remains an important therapeutic option. Although management options need to be tailored to the individual many patients will ultimately be rendered hypothyroid and require long term thyroxine replacement.

Symposium 1 Gender Identity Development – Care and Controversies

S7

Abstract unavailable.

S8

Gender reassignment surgery in GID

James Bellringer

Charing Cross Hospital, London, UK.

In this presentation, the main techniques for genital gender reassignment surgery, both male to female and female to male will be described. A brief outline of other surgery in both groups will also be presented.

Symposium 2 Controversies in Paediatric Endocrinology

S9

GH in transition

Mohamad Maghnie

University of Genova, Genova, Italy.

The diagnosis of GHD in young adults is not straightforward and represents a major clinical challenge. The key predictors of persistent GHD are the severity of the original GH deficiency, the presence of additional pituitary hormone deficits, severely low IGF1 concentrations, and structural hypothalamic-pituitary (HP) abnormalities. We have demonstrated that patients with GHD and congenital HP may not require re-evaluation of GH secretion, whereas patients with isolated GHD and normal or small pituitary gland should be retested well before the attainment of adult height. MRI findings of the HP area in patients with GHD may be the most important criterion upon which the decision to re-evaluate a patient can be based, as opposed to response to pharmacological stimulation.

Two recent consensus statements on the management of young adults with childhood onset GHD during transition phase state that there are various groups of patients have a high likelihood of permanent GHD after adult height attainment; these include those with severe GHD in childhood with or without two or three additional hormone deficits possibly due to a defined genetic cause, those with severe GHD due to structural HP abnormalities and with CNS tumors, and patients having received high-dose cranial irradiation.

A subgroup of subjects with idiopathic GHD of childhood onset presenting with congenital structural HP abnormalities confirms that GHD patients – defined 'a priori' as those with GH response $<5 \mu\text{g}/\text{l}$ and with anterior pituitary hypoplasia, pituitary stalk agenesis and posterior pituitary ectopia at the level of the median eminence – are likely candidates for permanent GHD in adult life, while those with less severe MRI features have an uncertain diagnosis or a likelihood of normal GH response after stimulation tests. These findings have important clinical implications in the diagnosis and prognosis of GHD after adult height achievement.

The comparison between a cohort of subjects with a high likelihood of permanent GHD and a control group showed that the lowest values observed in normal subjects of peak GH after insulin tolerance test (ITT) of 6.1 $\mu\text{g}/\text{l}$ and IGF1 of -1.7 SDS could identify GHD subjects with a sensitivity of 96 and 77% respectively and a specificity of 100% for both groups. Another recent study that compared two groups of subjects with high and low likelihood of permanent GHD confirmed that a peak GH response after insulin tolerance test of less than 5.62 $\mu\text{g}/\text{l}$ can distinguish between the two groups, correctly classifying 87.34% of subjects (with sensitivity of 77.42% and specificity of 93.75%). Indeed, IGF1 measurement is a useful marker of the degree of GHD, ensuring an accurate classification of patients with severe GHD for cut-off levels of ≤ -2.8 SDS (40). Pituitary function should be periodically assessed in subjects with pituitary stalk agenesis and IGHD or CPHD, as they may develop additional pituitary hormone deficiencies and deterioration of metabolic parameters. In our recent study, ACTH deficiency characterized a subset of patients with idiopathic GHD and pituitary stalk abnormalities, revealing that several of them had undiagnosed subclinical ACTH deficiency.

S10

MEN syndromes – genetics and ethics of screening

Carol Chu

UK.

The multiple endocrine neoplasia syndromes comprise a group of heredity conditions which predispose individuals to various tumours of the endocrine glands. The conditions are inherited in an autosomal dominant fashion.

Children can be affected by the conditions and it is important to recognise who is at risk because of the options of preventative strategies (MEN2) and screening to reduce morbidity (MEN1). However, genetic testing of children is problematic particularly as very young children may not understand the information and may not recognise the possible long term effects of a positive test results. The presentation will cover the genetics of the MEN syndromes and will discuss some ethical issues regarding screening children for these conditions.

Symposium 3 The Olympiad!

S11

Beyond reasonable doubt: catching the GH cheats

Richard Holt

University of Southampton, Southampton, UK.

There is widespread anecdotal evidence that GH has been misused by athletes, including adolescents, for its anabolic and lipolytic properties since the early 1980s, at least a decade before GH was used therapeutically by adult endocrinologists. Since then a number of high profile athletes have admitted using GH. Despite its widespread abuse, there is debate about whether GH is ergogenic. Until recently most scientific studies have not shown a performance enhancing effect but most have employed an inappropriate design to show a benefit.

Although GH is on the World Anti-doping Agency (WADA) list of banned substances, the detection of abuse with GH is challenging. Two approaches have been developed; the first is based on the measurement of pituitary GH isoforms and was introduced at the Athens Olympic Games in 2004. The first analytical adverse finding using this test was made in February 2010 following an out-of-competition blood sample. The second approach is based on the measurement of IGF1 and N-terminal pro-peptide of type III collagen, both of which are markers of GH action. Both markers rise in a dose dependent manner and are largely unaffected by other regulators of GH secretion. When combined with gender specific discriminant function analysis, they achieve a greater sensitivity and longer window of detection than the isoform test. The development of this test is nearing completion. Because these markers are age-dependent, there are additional challenges in detecting GH in adolescent athletes.

S12

Physical Activity and Athletic Training in Children and Adolescents

Alan Rogol

University of Virginia, Charlottesville, USA.

Physical activity is any body movement produced by the skeletal muscle and that results in a substantial increase over the resting energy expenditure (REE). Training is physical activity and systematic, specialized practice for a specific sport discipline. This activity may have an effect on growth and biological maturation of young athletes. For males the more successful age group athletes are on-time or advanced in biological maturation, but the opposite is true (on-time or behind) for girls, especially in the aesthetic sports such as rhythmic gymnastics. The gymnasts are often at a large daily energy deficit.

Bone mineral accrual is an important component of biological maturation and is most plastic before and during early puberty than at virtually any other time in life. The reproductive system is particularly vulnerable to energy deficits and to a greater extent in gynecologically younger adolescents. I shall close with an example in the male to show the metabolic consequences of a high energy output at lower energy intake in the weight-class related sport of wrestling.

Symposium 4 Hot Topics in Diabetes

S13

Abstract unavailable.

S14

Continuous age appropriate structured education for children and young people with diabetes

Karin Lange

Hannover Medical School, Hanover, Germany.

Diabetes education for children, adolescents and their parents is recommended by several guidelines and widely accepted as an integral part of type 1 diabetes therapy. Structured comprehensive courses at disease onset are regularly followed by education updates until transition to adult diabetes care. Especially in paediatric diabetes care age-appropriate, demand-oriented and individualized practical information and skills-training are mandatory for achieving good metabolic control and psychosocial well-being. A paediatric multidisciplinary diabetes team experienced in an intensified insulin therapy with a differential substitution of prandial and basal insulin needs (MDI or CSII) and in child psychology is required to initiate and maintain lifelong diabetes self-management. In Germany an education program for children aged 6–12 years, another program for adolescents and young adults and one for their parents have been evaluated in multicenter studies. Programs were considered with respect to applicability, acceptance by target groups and efficacy (knowledge, competence, quality of life, social integration and glycaemic control). Contents, modular structures, developmental psychological background and didactic concepts of all programs will be presented. Apart from teaching principles of insulin therapy special emphasis is laid on translating this knowledge into everyday self-management behaviour and positive parent–child communication. In addition, emotional coping with the chronic disease and its psychosocial consequences is supported. In the context of the Disease-Management-Program for Type 1 Diabetes in Germany these programs for young people were certified and reimbursed nationwide by health insurances. Currently published data of the nationwide prospective dpv-program reported of slightly decreasing HbA1c and normal quality of life of young people with diabetes. Compared to this a survey run by the European SWEET project on established diabetes education concepts in several countries pointed to a significant lack of evaluated concepts that are integrated into holistic care of young people with type 1 diabetes in the majority of European countries. Furthermore, there is a lack of quality assured education of the multidisciplinary paediatric team members on introducing such programs and tools to patients and caregivers. New concepts of sourcing of quality assured paediatric diabetes education in Europe should therefore become one goal of the SWEET initiative towards improving the equality and access to modern diabetes care across the continent.

Symposium 5

S15

Structured Knowledge and Information Programme-the SKIP course

Noeleen Lovell

University Hospitals Bristol NHS Foundation Trust, Bristol, UK.

The SKIP Course – A STRUCTURED KNOWLEDGE and INFORMATION PROGRAMME – An education programme specifically designed to meet the educational needs of the young person with Type 1 Diabetes and their family. The structured curriculum of the ‘SKIP’ course enables those attending develop their knowledge and skills and improve day to day self-care of their diabetes, in an interactive process with the diabetes team and other families, to achieve good glycaemic control and help to improve long-term outcomes and thereby reducing the risk of adverse effects and complications.

NICE requires an HbA1c of less than 7.5% (IFCC 58 mmol/mol) to indicate good control of diabetes. In our centre patients and families have previously received education in managing self-care of diabetes on an individual basis. The need for a new approach to patient education was identified in an earlier research study undertaken by the PDSN team where parents expressed a desire for additional education projects and diabetes updates, including opportunities to meet with other families with similar experiences.

Recommendations from the National Service Framework (NSF Standard 3 2001/2002) and NICE guidelines advise the use of Structured Education Programme Models to empower patients and teach them how to manage self-care of their diabetes. Key criteria of such a programme demands an evidence-based, structured curriculum which is flexible, quality assured, dynamic and auditable (DoH NICE 2005). Furthermore, Standard 6 of the Children’s NSF states ‘all children, young people and their families should have an opportunity to become ‘expert patients’ developing effective self-management skills’.

The programme has been designed to provide knowledge and information to build on the one-to-one Care Plan and education all parents and children receive from the Diabetes Team on diagnosis prior to discharge from hospital.

The PDSN and Dietitian deliver the programme in a group setting to the young people and adult participants.

Each session is structured to ensure consistency in subject matter, level of information, timing and presentation. The programme is interactive with an emphasis on the use of visual aids; anatomical models, food maps, and written information including quizzes and games to illustrate clinical scenarios and role play are all used to reinforce the diabetes education.

S16

How paediatric diabetes nurse specialists support schools

Marie Marshall

Central Manchester University Hospitals, Manchester, UK.

Intensive insulin regimes are widely accepted as the best way to control diabetes in children as well as adults, and most centres in the UK offer support for intensive regimes. The emphasis on intensification of diabetes management in children and young people has implications for schools because children need injections, or to use an insulin pump, during the school day, which may not have been required in bi-daily injection regimes.

Diabetes teams need to liaise regularly with school staff involved in supervising children and young people with diabetes to provide education and practical information about diabetes management. Diabetes nurse specialists have a key role to play in training and supporting school staff and are the major NHS investment in the support of children with diabetes at school.

There has been little research about how to optimise the quality of children's diabetes care while in school. This presentation reports a qualitative study to examine the role of nurses in supporting the care of children with diabetes in schools and early years' settings.

Symposium 6 Diabetes and Sport

S17

Physiology of exercise and endurance sport in type 1 diabetes

Rob Andrews

University of Bristol, Bristol, UK.

Exercise induces an increase in cardiac output, respiration and fuel mobilisation. Whilst the cardio-respiratory response to exercise is similar in type 1 diabetes to that seen in non-diabetic individuals, the response to mobilisation of fuel source to support exercise is impaired.

Normally when exercising changes in insulin and counterregulatory hormones secretion are made which are dependent on the type of exercise being performed. These changes facilitate an increase in liver glucose production which matches skeletal muscle glucose uptake during exercise and (see table below). A change in the secretion of these hormones is also seen post exercise to facilitate recovery and adaption to exercise. As a result of these changes, blood glucose levels remain stable before, during and after exercise.

Table 1 Normal hormone response to exercise

	Endurance exercise	Anaerobic exercise
Insulin during exercise	Decrease	No change or slight increase
Insulin after exercise	Slow increase	Rapid increase
Glucose during exercise	No change	No change or slight increase
Catecholamine levels	Two-fold to four-fold rise	14-fold to 18-fold rise
Glucagon level	No change	No change

In type 1 diabetes, the pancreas does not regulate insulin levels in response to exercise and there may be impaired secretion of counterregulatory hormones, making normal fuel regulation difficult. Post exercise the lower levels of insulin and counterregulatory hormones can hamper recovery and adaption to exercise. This means that hypoglycaemia both during and following exercise becomes a significant risk. Furthermore, hyperglycaemia prior to and following some types of exercises can also be problematic. If changes in insulin dosage and nutritional intake are made in line with the normal expected physiological responses to the particular exercise being performed, then these deficiencies can be overcome and enable ideal glucose control to be maintained before, during and after exercise.

S18

Optimising sports performance in type 1 diabetes

Gill Regan

Royal Gwent Hospital, Wales, UK.

Athletes with type 1 diabetes need to be advised on the most appropriate diet to maximise their performance.

I will review the recommendations stated in the 2010 Position Statement on Physical Activity and Exercise in Diabetes and to look at sports supplementation. Sports supplements can assist athletes to achieve improved performance. However, poor regulation of the supplements industry allows athletes to be bombarded with products that may or may not give them the 'performance edge'.

I aim to look at the classifications of sports supplements, according to their effectiveness and safety and to look at the most commonly used supplements by athletes.

Putting the theory into practise or not ... a challenging case study of a body builder with type 1 diabetes.

Keynote Lecture

S19

Insulin pumps and continuous glucose monitoring: the evidence

John Pickup

King's College London School of Medicine, Guy's Hospital, London, UK.

The benefits of continuous subcutaneous insulin infusion (CSII, insulin pump therapy) in type 1 diabetes, compared to multiple dose insulin injections (MDI), include a reduction in HbA1c, the frequency of all grades of hypoglycaemia, insulin dosage and glycaemic variability, and improved patient satisfaction with therapy and improved quality of life. The evidence base for this is now well established from meta-analyses of randomised controlled trials (RCTs) and from clinical observation over more than 30 years. Improvements occur in both adults and children. The greatest improvements are in those worst controlled on injection therapy. The best and most cost effective use of CSII in adults is therefore probably in those who have failed to achieve acceptable glycaemic control with MDI and structured diabetes education. CSII is approved by NICE for use in children < 12 years of age without them having first 'failed' on CSII, though the evidence for pumps as the best first-line therapy in children is still emerging.

An important contributor to HbA1c and glycaemic variability in diabetes is the postprandial rise in blood glucose and research with insulin pumps in recent years has seen attempts to reduce this by several strategies, including integrated bolus calculators, administration of the meal-time insulin bolus about 15 min before rather than at the time or after eating, improved attention to carbohydrate counting (and possibly also fat and protein counting), identification of missed meal boluses from computer downloads, and the use of square- or dual-wave boluses for fatty or high-protein meals. Much of the evidence for these new strategies comes from research in children with diabetes.

Modern insulin pumps have the potential for continuous glucose monitoring (CGM) connectivity (and CGM can be used with MDI), and there is strong evidence from RCTs that HbA1c and exposure to mild-to-moderate hypoglycaemia is reduced in the worst controlled patients and in those who use sensors frequently. Children benefit as much as adults, providing they use the sensor often. The effects of CGM on severe hypoglycaemia and quality of life are uncertain, as well designed RCTs have not been reported yet. Low-glucose suspend (LGS) insulin pumps are now available, where the basal rate of the pump is suspended for a period when the sensor-monitored glucose falls below a preset threshold, thereby allowing glucose to return into the target range. LGS pumps reduce the duration of hypoglycaemia in adults and children with type 1 diabetes, though RCT evidence for effects on severe hypoglycaemia frequency is still awaited.

Ipsen Award Winners

S20

Congenital hyperinsulinism the American experience

Lindsey Rigby

Central Manchester University Hospitals, Manchester, UK.

This presentation will focus on congenital hyperinsulinism (CHI) management within the Children's Hospital of Philadelphia (CHOP), USA. This is following the inaugural endocrine nurses' award presentation in 2010. The award was presented to allow travel to Philadelphia. Reports following a two day medical conference on CHI and a two day parent's conference on CHI, as well as reports on two days working alongside the CHOP medical, nursing and research team will all be presented.

S21

Abstract unavailable.

Endocrine Nurse Session 1

S22

The Bare Bones

Paul Arundel

Sheffield Children's NHS Foundation Trust, Sheffield, UK

A clinically oriented, whistlestop tour through bone biology for the specialist nurse working in paediatric endocrinology, including bone growth, control of serum calcium, vitamin D metabolism and bisphosphonate therapy.

Case Presentation Endocrinology in Sport

S23

Abstract unavailable.

Endocrine Nurse Session 2

S24

Egg and Ovarian tissue preservation. What can we offer to preserve fertility options for the future?

Susie Nicholas

Leeds Teaching Hospitals NHS Trust, Leeds, UK.

The world of reproductive medicine is unrecognisable from the early days of Mr Patrick Steptoe and Professor Robert Edwards, who pioneered the technique of In Vitro Fertilisation (IVF) which after the first birth in 1978, has led to over 5 million children being born worldwide. Throughout this time ethical dilemmas have been debated a plenty, but none the less the technology has widened the opportunities for many who would otherwise have been left infertile from illness, genetic disposition or age. These technologies also provide the possibility for preserving the fertility for those who may be rendered sterile because of treatments for cancer.

Women need to go through a cycle of IVF treatment with stimulation of their ovaries, collection of the eggs which may be frozen directly or fertilised with sperm and frozen as embryos. Embryo cryopreservation is the most successful option if sperm can be supplied. Oocyte cryopreservation and ovarian tissue preservation are potential options that can offer some hope for future fertility.

Particular reference will be made to those with mosaic Turner's syndrome and other conditions that predispose to premature ovarian failure and young people facing potentially sterilizing surgery, chemotherapy or radiotherapy for oncology treatments. There is also an ethical debate about elective cryopreservation of oocytes from young women before embarking upon a career, in order to defer parenthood until an older age when natural fertility will have declined.

Oral Communications

Oral Communications 1**OC1.1****Iodine status in UK pregnant women and implications for fetal brain development**Sarah Bath¹, Colin Steer², Jean Golding², Pauline Emmett² & Margaret Rayman¹¹University of Surrey, Guildford, Surrey, UK; ²University of Bristol, Bristol, UK.

Iodine deficiency was common in the UK until the 1960s and was eradicated mainly through the adventitious increase in milk-iodine concentration. Iodine sufficiency was subsequently assumed in the UK, until a recent national study revealed mild iodine deficiency in adolescent girls, giving cause for concern. Iodine, as a component of the thyroid hormones, is crucial for brain development, and particularly during gestation. This study aimed to evaluate the relationship between iodine status in UK pregnant women and offspring cognition. As urinary iodine is a biomarker of iodine status, iodine concentration (and creatinine for adjustment of urine volume) was measured in urine samples collected during pregnancy from 1000 women of the Avon Longitudinal Study of Parents and Children (ALSPAC). Women were grouped as iodine-deficient or sufficient according to WHO criteria. The relationships between maternal iodine status and child IQ (age 8), reading ability (age 9), and key stage 2 (age 11) were analysed using logistic regression and up to 21 confounders were included in the analyses. Suboptimal outcome was defined as the bottom quartile of scores. The group was mildly-to-moderately iodine deficient based on a median iodine concentration of 91.8 µg/l (123 µg/g creatinine). The children of women deficient in iodine were more likely to have scores in the bottom quartile for total IQ (OR 1.58, 95% CI 1.09–2.29), reading accuracy (OR 1.83, 95% CI 1.22–2.74) and key stage 2 mathematics score (OR 1.60, 95% CI 1.07–2.41). When the iodine deficient category was subdivided into 'severe' and 'mild-to-moderate' there was evidence of a trend of increasing cognitive scores with improved maternal iodine status. Although these results cannot prove causality, they are suggestive of the importance of achieving adequate iodine status during pregnancy and suggest that iodine deficiency can pose a risk to the developing infant, even in regions of mild iodine deficiency.

OC1.2**Disease- and treatment-related factors implicated in late neuroendocrine morbidity after paediatric optic pathway gliomas: a preliminary multivariate analysis of 96 patients treated over 30 years**

Hoong Wei Gan & Helen Alexandra Spoudeas

Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.

Introduction

Low-grade gliomas (LGGs) are the commonest benign childhood brain tumour and typically affect the optic tracts, chiasm and suprasellar diencephalon, thus potentially causing serious neuroendocrine deficits from tumour mass or treatment effects. In the absence of any major studies, we sought to comprehensively evaluate patient-, disease- and treatment-related risk factors for neuroendocrine morbidity in a large single-centre survivor cohort treated by varied, primarily non-surgical strategies over 30 years.

Methods

Retrospective case note analysis of the first 96 randomly audited patients with optic pathway and diencephalic LGGs diagnosed between 1980–2010 at Great Ormond Street Hospital by multivariate Cox and linear regression.

Results

Patients were of median age 5.15 (range 0.18–15.07) years at diagnosis and followed up for a median of 6.57 (0.25–26.12) years. 81.2% had midline suprasellar tumours of which 37.5% were hypothalamic. Five year overall survival, progression-free survival (PFS) and endocrine event-free survival (EEFS) were 96.9, 68.8 and 50.0% respectively. However, EEFS continued to fall up to 15 years from diagnosis, being independently reduced by hypothalamic involvement ($P=0.002$) and grade II histology ($P=0.003$) more than radiotherapy ($P=0.028$). The number of deficits (endocrine morbidity score) however was increased by radiotherapy ($P=0.000$) rather than hypothalamo-chiasmatic tumour position ($P=0.042$). GH deficiency was most frequent (36.5%), followed by central precocious puberty (20.8%), TSH deficiency (13.5%), ACTH deficiency (12.5%), LH/FSH deficiency (10.4%), and hyperprolactinaemia (7.3%). Five patients, all with hypothalamic involvement, suffered with salt-water balance disorders (one cerebral salt-wasting, two SIADH and two DI); 4/5 of these were postoperative (three biopsied only and one debulked).

Conclusion

This very long term multivariate analysis of detailed endocrine morbidity in a rare LGG survivor cohort provides new evidence to suggest hypothalamic tumour position is more important than irradiation in the incidence of endocrinopathies, and challenges the perception that surgery is less neurotoxic, especially in the diencephalic area where even minor surgical intervention such as biopsies may result in significant posterior pituitary dysfunction.

OC1.3**Potential novel insights into the control of the fetoplacental unit by kisspeptin**Harshini Katugampola¹, Leo Dunkel¹, Peter J King¹, John A Achermann², Andrew J Duncan², Ulla Sankilampi³ & Helen L Storr¹

¹Centre for Endocrinology, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; ²Developmental Endocrinology Research Group, Clinical and Molecular Genetics Unit, University College London (UCL) Institute of Child Health, London, UK; ³Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland.

Introduction

Kisspeptin is the endogenous ligand for the G-protein coupled receptor-54 (GPR54 or KiSS1R). During human pregnancy, maternal levels of placental kisspeptin dramatically increase 7000-fold. The physiological significance of this is unknown. A potential target could be the fetal adrenal cortex (FAC), which undergoes rapid growth from 10 weeks gestation, predominantly of the inner fetal zone (FZ). The FZ expresses the steroidogenic enzymes needed for conversion of DHEA to its sulphate. Placental estrogen synthesis is dependent on the aromatization of C19 steroid precursors, primarily DHEAS supplied from the FZ. Fetal adrenal steroidogenesis is therefore essential for the function of the fetoplacental unit, postulated to play an integral role in the maintenance of pregnancy.

Methods

Immunofluorescence studies were used to characterise the spatio-temporal expression of Kiss1R protein in the human FAC at a range of gestational ages. qRT-PCR was used to investigate *Kiss1R* mRNA expression in H295R adrenocortical cells as a model of the human FAC. Enzyme immunoassay was used to examine the functional effects of kisspeptin stimulation on steroidogenesis in H295R cells.

Results

Confocal studies demonstrated Kiss1R protein is highly expressed throughout the human FAC, predominantly within the inner FZ, from as early as 10 weeks gestation. RT-PCR studies revealed *Kiss1R* mRNA is expressed in H295R cells and is significantly decreased following treatment with kisspeptin for 24 h ($P<0.001$). Enzyme immunoassay demonstrated that kisspeptin stimulation increases DHEAS production by threefold compared to untreated H295R cells ($P<0.01$).

Conclusions

High levels of kisspeptin may stimulate DHEAS production by the FAC. As pregnancy progresses, down-regulation of *Kiss1R* may occur to fine-tune steroidogenesis from the FAC. Kisspeptin may be a novel factor with critical regulatory roles in human FAC development and function, and in the maintenance of pregnancy. This reveals a novel insight into the endocrine regulation of the fetoplacental unit.

OC1.4**Skeletal effects of hypothyroidism are mediated by thyroid hormone receptor α** Moiria Cheung¹, Alan Boyde², Holly Evans³, Duncan Bassett¹ & Graham Williams¹

¹Imperial College, London, UK; ²Biophysics OGD, Barts and the London, London, UK; ³Mellanby Centre, University of Sheffield, Sheffield, UK.

Childhood hypothyroidism results in delayed skeletal maturation and impaired growth. Thyroid hormones act via thyroid hormone receptors α (TR α) and TR β which are tempo-spatially regulated. In the skeleton, TR α is the predominant receptor, thus we hypothesise that the skeletal effects of hypothyroidism are mediated by TR α . To investigate this we assessed the response of wild type (wt), TR α knockout (TR $\alpha^{0/0}$) and TR β knockout (TR $\beta^{-/-}$) mice to hypothyroidism. Adult mice from each genotype were rendered/remained hypothyroid (hypo) or euthyroid (eu) for six weeks before skeletal phenotyping. Hypo wt mice had increased bone mineral content (BMC) by faxitron analysis compared to eu controls. ($P<0.001$, $n=6$). Trabecular bone volume (BV/TV) by micro CT was

elevated in hypo wt mice compared to controls (15.6 ± 1.3 vs $10.9 \pm 1.1\%$, mean \pm s.e.m., $n=5-6$, $P < 0.05$ *t*-test). Bone formation rate (BFR) in hypo wt mice was reduced compared to controls (0.04 ± 0.03 vs $0.45 \pm 0.04 \mu\text{m}^3/\mu\text{m}^2$ per day, mean \pm s.e.m., $P < 0.001$ students *t*-test, $n=4$). Hypo $\text{TR}\beta^{-/-}$ mice also had increased BMC ($P < 0.001$, $n=6$) and BV/TV ($13.4 \pm 0.8\%$ vs $7.7 \pm 0.8\%$, $P < 0.001$, $n=5-6$) and BFR was similarly reduced compared to controls (0.03 ± 0.01 vs $0.33 \pm 0.06 \mu\text{m}^3/\mu\text{m}^2$ per day, $P < 0.01$, $n=4$). In contrast to wt and $\text{TR}\beta^{-/-}$ mice, hypo $\text{TR}\alpha^{0/0}$ mice had similar BMC ($P = \text{NS}$, $n=6$) and BV/TV ($12.1 \pm 0.5\%$ vs $13.1 \pm 0.4\%$, $P = \text{NS}$, $n=5-6$) compared to controls. BFR was reduced in hypo $\text{TR}\alpha^{0/0}$ mice compared to controls (0.18 ± 0.07 vs $0.53 \pm 0.04 \mu\text{m}^3/\mu\text{m}^2$ per day, $P < 0.001$, $n=4$). In summary, wt and $\text{TR}\beta^{-/-}$ mice had similar responses to hypothyroidism resulting in increased BMC and BV/TV and reduced BFR. In contrast, $\text{TR}\alpha^{0/0}$ mice showed no change in BMC or BV/TV. BFR in hypo $\text{TR}\alpha^{0/0}$ mice, although reduced compared to controls, was fourfold higher than hypo wt or $\text{TR}\beta^{-/-}$ mice. In conclusion these studies indicate that $\text{TR}\alpha$ has a key role in the skeletal response to hypothyroidism.

OC1.5

Ethnic differences in vascular growth factor levels in early life in relation to arterial stiffness in the Manchester heart and growth study
Sophia Khan¹, Simon Anderson¹, Andrew Whatmore¹, Phillip Pemberton¹, Avni Vyas¹, Kennedy Cruikshank² & Peter Clayton¹
¹University of Manchester, Manchester, UK; ²King's College and Health Partners, London, UK.

Cardiovascular risk factors are more prevalent in south Asian (SA) adults compared to White Europeans (WE), although the reasons for this are not fully known. Vascular growth factors (VGFs) are increasingly recognised to have various roles in arterial development, function and remodelling. We hypothesised that ethnic differences in VGFs in early life contribute to the later differences in CV risk. We further hypothesised that arterial stiffness, as a measure of large artery structure and function, could correlate to VGF levels

Methods

Serum samples were obtained from children (WE 95, SA 45, and other 12) at various ages between 3 and 48 months, with repeated sampling in some children. Samples ($n=80-151$) were assayed for platelet derived GF, osteoprotegerin, fibroblast GF, vascular endothelial GF, epidermal GF, hepatocyte GF, and placental GF. Aortic pulse wave velocity (aPWV) was measured in 63 children.

Results

Across ethnic groups, significant differences were seen in VEGF (Kruskal-Wallis, P value = 0.04), HGF ($P = 0.016$), and PIGF ($P = 0.011$). Even with these small numbers, SA samples showed significantly higher levels of EGF (median (range); SA 15.7 pg/ml (0.9-119) vs WE 8.6 (1.6-50), $P = 0.036$), HGF (0.79 ng/ml (0.1-2.8) vs 0.47 (0.01-3.1), $P = 0.039$), and PIGF (58.5 pg/ml (7.8-193) vs 30.8 (3.4-160), $P = 0.014$) compared to WE samples. Across all ethnic groups, only EGF was significantly correlated to aPWV ($r_s = +0.31$, $P = 0.034$). When this correlation was analyzed by ethnicity, the slope of the regression line for SA children was markedly steeper than that for WE children (SA: $\text{EGF} = (7.2 \times \text{PWV}) - 31$ vs WE: $\text{EGF} = (1.4 \times \text{PWV}) + 4.4$), suggesting possible ethnic differences in the effect of EGF on aPWV.

Conclusions

VGF levels in early life differ between ethnic groups and EGF is related to aPWV, as a marker of arterial status. These relationships need to be reassessed through childhood and adolescence and may be relevant to the genesis of later life CV risk.

OC1.6

A novel syndrome characterized by hypothalamic hormonal insufficiency, neonatal seizures, congenital abnormalities of the kidneys and urinary tract and obesity due to mutation in a gene regulating hypothalamic development

Emma Webb¹, Dan Kelberman¹, Angham Al Mutairi², Cynthia Andoniadou¹, Chiara Bacchelli¹, Estelle Chanudet¹, Robert Kleta¹, F Lescai¹, E Stupka¹, P Beales¹, Jane Sowden¹, JP Martinez¹ & Mehul Dattani¹
¹UCL Institute of Child Health, London, UK; ²KAMC, Riyadh, Saudi Arabia.

Introduction

Mutations affecting hypothalamic development in humans have been identified in genes that affect isolated domains of hypothalamic function leading to restricted

phenotypes, such as obesity or hypogonadotropic hypogonadism. We describe the first human cases of diabetes insipidus and combined pituitary hormone deficiency due to a mutation in a gene regulating hypothalamic development.

Results

Six affected individuals from a highly consanguineous pedigree presented with cortisol deficiency and central diabetes insipidus. Four also presented with or developed central hypothyroidism and three showed an abnormal growth curve, with maintenance of linear growth in conjunction with obesity. Despite initial cerebral sparing, progressive microcephaly was present in all patients in association with global developmental delay and seizures (onset 5 days-2.5 years) as well as hydronephrosis, vesicoureteric reflux and a neurogenic bladder. Using a combination of whole genome homozygosity mapping coupled with exome sequencing we have identified a single novel homozygous variant, c.1373_1374insTC, segregating between affected family members. This mutation resides in a transcription factor essential for normal hypothalamic development and is predicted to result in a frameshift and consequent loss of function. Moreover, levels of the mutant transcript were significantly reduced in patient fibroblasts compared to controls. We demonstrate high levels of expression in the hypothalamus, telencephalon and renal tract in the developing human embryo identical to that previously observed in the mouse.

Conclusion

We describe a mutation in a transcription factor known to regulate development of the paraventricular, supraoptic and anterior periventricular nuclei in mice. The affected patients display several features of hypothalamic insufficiency, including obesity, diabetes insipidus, ACTH and TSH deficiency. Oxytocin and somatostatin are also likely to be deficient. The growth pattern of three of these children, the first human cases of somatostatin deficiency, is significantly abnormal with increased weight appearing to be the main driver of linear growth.

OC1.7

Novel therapies herald novel diseases: The first paediatric case series of Graves' immune reconstitution disease

Akash Sinha, Mario Abinun & Tim Cheetham
Newcastle University, Newcastle upon tyne, UK.

Introduction

The use of haematopoietic stem cell transplantation (HSCT) as a curative therapy for life threatening immunodeficiency signalled a paradigm shift in clinical outcomes. However, a subset of patients may experience Thyroid Immune Reconstitution Inflammatory Syndrome (IRIS) following immune reconstitution. This is recognised in the adult population but has received little attention in the paediatric literature. We present, what we believe to be, the first case series describing the clinical, biochemical and cytological course of Graves' IRIS following HSCT in the paediatric population.

Case Series

Four children (median age 3.5 yrs, range 11 months-12 years) developed Graves IRIS (out of 395 HSCT conducted over a 25 year period). The median time interval between HSCT and Graves' disease (GD) was 20.5 months (range 9-25 months). The diagnosis of GD was made on the basis of clinical and biochemical parameters: suppressed TSH, raised FT4 and TSH receptor antibodies. 3 patients were hypothyroid initially (suggestive of a Th1 profile) prior to GD (suggestive of a Th2 profile). In some instances, the clinical picture changed rapidly with hypothyroidism quickly followed by profound thyroid hormone excess. Importantly, the onset of Graves IRIS coincided with a rapid expansion in naïve CD4 T cells.

Discussion

There are several potential pathogenic mechanisms that may contribute to IRIS although all of our patients had a rapid expansion in naïve and total CD4 cell counts coinciding with the onset of GD. This suggests that a combination of immunological dysregulation and an inability to delete cells with the capability to produce TSH reactive autoantibodies (loss of tolerance) was responsible for Graves IRIS in our patients. Clinicians need to be aware that HSCT-engendered immune recovery may result in a particularly aggressive form of autoimmune thyroid disease with a rapid change in thyroid status. Careful surveillance of thyroid function post HSCT is essential.

OC1.8**Loss-of-function mutations in IGSF1 cause a novel, X-linked syndrome of central hypothyroidism and testicular enlargement**

Nadia Schoenmakers¹, Beata Bak², Yu Sun³, Paul van Trotsenburg⁴, Wilma Oostdijk⁵, Peter Voshol¹, Luca Persani⁶, Timothy Davis⁷, Paul le Tissier⁸, Neda Gharavy⁹, Natasha Appelman-Dijkstra¹⁰, Alberto Pereira¹⁰, Johan den Dunnen³, Martijn Breuning³, Raoul Hennekam⁴, V Krishna Chatterjee¹, Mehul Dattani¹¹, Daniel Bernard² & Jan-Maarten Wit³
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Introduction

Congenital central hypothyroidism occurs either as isolated TSH deficiency or in conjunction with other pituitary hormone deficits. Undetected central hypothyroidism is associated with developmental delay in children and adverse cardiometabolic sequelae in adults. Hitherto, mutations in the TRH receptor (TRHR) or TSH β subunit (TSHB) genes are the only known causes of isolated TSH deficiency.

Methods

Using whole exome and candidate gene sequencing, we have studied ten unrelated families with males exhibiting isolated TSH deficiency, testicular enlargement and variably low serum prolactin levels.

Results

We have identified nine distinct mutations in the X-linked immunoglobulin superfamily member 1 (IGSF1) gene in affected males. IGSF1 encodes a pituitary-enriched plasma membrane glycoprotein; disease-associated mutations block trafficking of IGSF1 from the endoplasmic reticulum to the membrane, consistent with loss-of-protein function. We have also characterised IGSF1-deficient mice. Adult male IGSF1 null mice show decreased pituitary TSH content and circulating T₄ levels, together with increased body weight and fat mass, recapitulating features of the human disorder. Decreased TRHR mRNA levels in pituitaries from null mice, together with reduced TSH bioactivity in patients with IGSF1 mutations, suggest that impaired TRH signalling may be the basis for hypothyroidism.

Conclusions

Collectively, our observations delineate a novel X-linked syndrome in which loss-of-function mutations in IGSF1 cause central hypothyroidism, testicular enlargement and variable prolactin deficiency, and identify a previously unsuspected role for IGSF1 in hypothalamic-pituitary control of thyroid and testicular function.

Oral Communications 2**OC2.1****Assessment of adrenal function in female to male adolescents with gender identity dysphoria**

Michal Ajzensztejn, Mahalakshmi Gopalakrishnamoorthy, Anne Dawnay, Russell Viner, Caroline Brain & Gary Butler
 University College London Hospital NHS Trust, London, UK.

Introduction

Most adolescents with GID have no overt functional or phenotypic abnormalities to explain their presentation. Currently all female to male (FtM) persons undergo detailed evaluation of adrenal function. This study aimed to determine whether subtle abnormalities of adrenal were present and what the appropriate investigation schedule should be.

Methods

Over the past 4 years, 55 biological females aged mean age 16.54 years (13.46–18.37) were referred to the UK National GID service and underwent a standard short synacthen test (250 μ g), with baseline A4, DHEAS and testosterone

measurements. One additional patient with previously known non-classic 21-OH deficiency CAH was excluded. Results were compared with 15 age-matched controls, mean age 16.19 years (15.04–19.87).

Results

Baseline, 30 and 60 min mean 17OH progesterone concentrations were 1.77, 4.24 and 4.31 nmol/l respectively, ranges 1–8.4, 1–12.4, 1.2–10.7, not different from the control group means 2.1, 4.75, and 5.02 at 0, 30, 60 min (ranges 1–4.9, 2.5–7.4, and 1.8–10.9 nmol/l). Parallel cortisol concentrations were 358 (101–975), 738 (206–1228), and 880 (537–1298) nmol/l at 0, 30, 60 min compared with 273 (79–681), 694 (419–1166), and 840 (506–1426) nmol/l in the controls. The one GID adolescent with a baseline 17OHP of 8.4 nmol/l, greater than the normal laboratory range (<6) did not have an exaggerated rise on stimulation and other adrenal androgens were normal.

Conclusion

In this national cohort of FtM GID adolescents, we have not been able to demonstrate any variations, subtle or otherwise in adrenal steroid secretion to differentiate them from the control group or from predicted normal ranges. Baseline adrenal steroid profile may be evaluated but unless the androgens and precursor concentrations are elevated, synacthen testing does not appear to be indicated.

OC2.2**Deficiency of the triple A syndrome gene product, ALADIN, renders human adrenal cells susceptible to oxidative stress with subsequent impact on steroidogenesis**

Rathi Prasad, Adrian Clark & Helen Storr
 William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, QMUL, London, UK.

Background

Triple A syndrome is a rare, autosomal recessive cause of adrenal insufficiency. Additional features include alacrima, achalasia of the oesophageal cardia, and neurodegenerative disease in 60%. The AAAS gene product is the nuclear pore complex protein ALADIN of unknown function. AAAS patient dermal fibroblasts have been described as hypersensitive to oxidative stress^{1,2,3}.

Objective

To establish a better disease model by knockdown of AAAS-gene expression in H295R human adrenocortical tumour cells.

Methods

AAAS-knockdown was achieved using synthetic shRNA lentiviral transduction. H₂O₂ was used as an inducer of oxidative stress.

Results

Cell viability, measured by MTS assay, was significantly reduced in AAAS-knockdown cells compared with controls at baseline ($n=4$, $P<0.01$) and following H₂O₂ treatment ($n=3$, $P<0.05$). Application of the anti-oxidant *N*-acetylcysteine resulted in a significant increase in cell viability compared with controls ($n=4$, $P<0.01$).

A baseline increase in oxidative stress was suggested by a significant decrease in the ratio of reduced to oxidised glutathione in AAAS-knockdown cells compared with controls ($n=3$, $P<0.05$). Cell cycle arrest is observed in ALADIN deficient cells ($n=4$, $P<0.05$). Following H₂O₂ treatment there is an increase in apoptosis, assessed by cleavage of poly-ADP ribose polymerase, of AAAS-knockdown cells compared with controls ($n=3$, $P<0.05$).

We observe a significant reduction in the protein expression of the steroidogenic acute regulatory protein (StAR) in AAAS-knockdown cells compared with controls at baseline ($n=4$, $P<0.01$) and following H₂O₂ treatment ($n=4$, $P<0.001$). An impact on function is seen with a significant decrease in cortisol production in ALADIN-deficient cells compared with controls ($n=6$, $P<0.0001$).

Conclusion

Steroidogenic activity in the adrenals induces a highly oxidative environment. A model for H₂O₂ mediated control of steroidogenesis has recently been proposed⁴. Our data suggests that an imbalance of redox homeostasis in ALADIN-deficient adrenal cells results in a reduction in StAR protein expression with subsequent impact on steroidogenesis.

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OC2.3**Does vitamin D modulate mitochondrial oxidative phosphorylation?**Akash Sinha, Steve Ball, Kieren Hollingsworth & Tim Cheetham
Newcastle University, Newcastle Upon Tyne, UK.**Introduction**

Mitochondria are critical organelles which generate most of the energy (ATP) in the eukaryotic cell by oxidative phosphorylation. Impaired mitochondrial function will, therefore, restrict myocellular function. Vitamin D deficiency is widely prevalent with fatigue amongst its commonest manifestation. ³¹P-MRS is a non-invasive technique used to measure skeletal muscle bioenergetics *in vivo*. We have examined the relationship between vitamin D and mitochondrial oxidative capacity.

Methods

We evaluated skeletal muscle bioenergetics using ³¹P-MRS in 64 volunteers. Resting metabolites and parameters of oxidative phosphorylation and peripheral vascular supply – $\tau_{1/2}$ PCr and proton efflux – were calculated using a validated exercise protocol. Regression analysis was undertaken to determine the predictors of oxidative phosphorylation (Minitab v16). Serum 25OHD was used as a surrogate of vitamin D status. Body fat assessment was undertaken using bioimpedance.

Results

Only serum 25OHD was a significant predictor of $\tau_{1/2}$ PCr ($P=0.012$) in multiple regression analysis. In order to describe the relationship between serum 25OHD and $\tau_{1/2}$ PCr, a fitted line model was created. A negative correlation between serum 25OHD and $\tau_{1/2}$ PCr ($r=-0.42$, $P=0.009$) suggests that mitochondrial oxidative phosphorylation potential decreases with diminishing serum 25OHD levels. Vitamin D was negatively correlated with body fat% ($r=-0.36$, $P=0.019$) but no relationship existed between $\tau_{1/2}$ PCr and body fat%. There was no relationship between serum 25OHD and proton efflux.

Conclusion

Serum 25OHD may facilitate mitochondrial oxidative phosphorylation. The coupling efficiency of oxidative phosphorylation is correlated with many factors including hormone-responsive elements on the mitochondrial genome and our data suggest that vitamin D may modulate mitochondrial energy transduction. This may represent the bioenergetic basis for the fatigue experienced by vitamin D deficient adolescents and adults, although further studies are required to establish causality.

OC2.4**Prenatal dexamethasone for treatment of congenital adrenal hyperplasia: a possible association with late gestational fetal demise in two cases**Amanda Peacock¹, Ianthe Abbey¹, Sabah Alvi¹, Chris Bennett², James Dwyer³, Tracey Glanville⁴ & Talat Mushtaq¹
¹Children's Hospital, Leeds, UK; ²Chapel Allerton Hospital, Leeds, UK; ³York Hospitals NHS Foundation Trust, York, UK; ⁴Leeds General Infirmary, Leeds, UK.**Introduction**

The prenatal treatment of Congenital Adrenal Hyperplasia (CAH) with Dexamethasone (Dex) is effective at minimising virilisation in affected females. Treatment is initiated with Dex at 20 mcg/kg per day (max 1.5 mg/day) as soon as pregnancy is confirmed and continued to term in affected females only. There are concerns regarding neurocognitive difficulties in children exposed to prenatal Dex, but no reports of late intra-uterine deaths (IUD) attributed to prenatal Dex. Case studies

We report 2 cases over a 6 year period, where women with previous CAH affected children received prenatal Dex from 6 weeks gestation for the duration of the pregnancy. **Case 1:** A 38 year old woman received Dex 1.5 mg/day. Normal fetal growth on ultrasound (USS) was documented at 36 weeks. At 39+6 weeks she had a spontaneous rupture of membranes, but no fetal heart beat and thus an IUD was confirmed. The birth weight was 2570 gms (−1.9 SDS). Placental histopathology revealed chronic villitis and it is possible that Dex could have had an influence on any underlying pathology. **Case 2:** A 34 year old woman received Dex 1.0 mg/day. A normal USS at 34 weeks was documented. At 40+11 weeks; the day prior to planned delivery there were reduced fetal movements and an IUD was confirmed. The birth weight was 2150 gms (−2.95 SDS), with asymmetrical IUGR. Placental histopathology was unremarkable. In both cases no maternal side effects of DEX were noted, a congenital infection screen was negative and the deceased offspring had normal female genitalia.

Conclusions

Although the rate of late gestation IUD is low, these two cases raise concern that the use of Dex during pregnancy for CAH may be associated with an increased

rate. This should be carefully considered when counselling families regarding prenatal treatment with additional vigilance maintained during pregnancy, and serious consideration given to offering delivery at 38 weeks.

OC2.5**Abnormal neurological and developmental outcomes in children with persistent and spontaneously resolving congenital hyperinsulinism**Bindu Avatapalle¹, Sajni Shah¹, Megan Pryce¹, Jacqueline Nicholson¹, Lindsey Rigby¹, Louise Caine¹, Mohammed Didi³, Sarah Ehtisham¹, Leena Patel², Mars Skae², Raja Padidela¹, Indraneel Banerjee² & Peter Clayton²

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Introduction

Neuroglycopenia is recognised with abnormal neurology and development (Ab Dev) in 26–44% of children with persistent congenital hyperinsulinism (P-CHI). The prevalence of Ab Dev in spontaneously resolving CHI (R-CHI) is not known. We aimed to investigate Ab Dev in R-CHI and P-CHI children in a contemporary cohort.

Methods

All children ($n=67$) were assessed for Ab Dev in the domains of speech, language, motor and vision, and categorised as mild or severe. All children (>2.5 years at assessment) were classified into 3 groups. i) P-CHI, who had undergone surgery or remained on medical therapy, ii) R-CHI, who were off all treatment and, iii) CHI patients with no clinical concern about development.

Results

The median (range) age at diagnosis of CHI was 1.0 (1; 630) days, while age at follow up was 3.6 (1.8; 13.0) years. Ab Dev was present in 26 (39%) children, of whom 18 (69%) were severe. While spontaneous resolution was achieved in 33 (49%), the prevalence of Ab Dev was similar between R-CHI and P-CHI (30 v 47%, $P=0.16$). Severe speech, motor and vision abnormalities were present in 61, 50, and 27% respectively with limb weakness being present in 8 (31%) of Ab Dev children. Seizures occurred in 12 (46%) children, including infantile spasms in four children. When variables at diagnosis including prematurity, gender and presence of mutations were tested for correlation with Ab Dev in stepwise backward logistic regression, diazoxide dose (odds ratio (95% confidence intervals) 1.3 (1.1; 1.6), $P=0.03$) indicating CHI severity, and presentation within one week (5.9 (1.3; 27.9), $P=0.02$), indicating early diagnosis, were most significant.

Conclusions

Ab Dev was present in a third of children with both R-CHI and P-CHI. The association of Ab Dev with an early presentation and severe disease indicates that early aggressive treatment of hypoglycaemia is important to improve long-term prognosis.

OC2.6**Childhood body composition is associated with maternal plasma polyunsaturated fatty acids status in late pregnancy**Rebecca J Moon¹, Nicholas C Harvey¹, Georgia Ntani¹, Justin H Davies², Hazel M Inskip¹, Keith Godfrey¹, Elaine M Dennison¹, Philip Calder³ & Cyrus Cooper¹

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Introduction

Maternal diet during pregnancy has been linked to offspring body composition, but the specific nutrients and mechanisms involved are not well understood. Higher *n-3* polyunsaturated fatty acid (PUFA) status is associated with lower risk of adiposity in adults, whereas *n-6* PUFA are adipogenic. The effect of maternal PUFA in determining offspring body composition is unknown.

Method

We evaluated the relationships between maternal plasma PUFA (*n-3* and *n-6*) status at 34 weeks gestation and offspring body composition assessed by whole body DXA at 4 and 6 years in a UK population-based prospective mother-offspring cohort study. Linear regression was used to explore these associations, yielding standardised regression coefficients.

Results

Complete data was available in 287 mother-child pairs. Maternal *n-3* and *n-6* PUFA concentrations had differing associations with offspring body composition: maternal total *n-3* PUFA concentration positively predicted offspring lean mass (LM; $r=0.12$, $P=0.05$), but not offspring fat mass (FM; $r=0.05$, $P=0.42$) at 4 years, whereas maternal total *n-6* PUFA concentration was positively associated with offspring FM ($r=0.18$, $P=0.002$), but not LM ($r=0.09$, $P=0.14$). Similar associations were seen at 6 years. Maternal total *n-3* PUFA as a percentage of the total fatty acid pool negatively correlated with percentage FM at 4 years ($r=-0.18$, $P=0.003$), but no associations were identified between percentage *n-6* PUFA and proportionate body composition.

Conclusion

This observational study suggests that maternal PUFA status in late pregnancy might influence offspring body composition in childhood. These findings may help inform nutritional advice in pregnancy aimed at optimising offspring health and reducing obesity.

OC2.7

Growth, GH-IGF1 status and response to r-hGH therapy in 3-M syndrome, related to mutation status

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Background

3-M syndrome is associated with severe proportionate pre- and postnatal growth restriction, and is caused by mutations in *CUL7*, *OBSL1*, or *CCDC8* genes.

Aims and methods

To define baseline growth and GH-IGF1 axis status as well as response to r-hGH in relation to mutation status in 3-M children, using retrospective analysis of data from clinical notes.

Results

50 individuals (19 *CUL7*, 19 *OBSL1*, and 12 *CCDC8* mutations) were identified. The mean (range) birth weight SDS was -2.6 (-0.8 to -4) at a mean gestational age of 38 weeks. The mean (range) height SDS at presentation was -4.9 (-2.7 to -7.3), at a mean age of 4 years; those with *CCDC8* mutations were taller than those with *CUL7* ($P=0.07$) or *OBSL1* ($P=0.045$) mutations (*CCDC8*, -3.8 SDS; *OBSL1*, -5 SDS; and *CUL7*, -5.4 SDS).

The mean peak GH to arginine stimulation was 13.3 $\mu\text{g/l}$ (range 3.7 to 38.3, $n=12$) and mean IGF1 SDS was -1.6 (range $+0.2$ to -5 , $n=14$). Results were consistent with GH resistance (peak GH ≥ 7 $\mu\text{g/l}$ and IGF1 SDS ≤ -2) in five.

Twenty had been treated with r-hGH therapy (with doses escalating over time from 24–74 $\mu\text{g/kg}$ per day); mean height gains of $+0.2$ and $+1.1$ SDS were observed over one and 5 years of treatment respectively, but marked inter-individual variation was noted. IGF1 SDS increased to a mean of $+2.2$ in the 1st year despite a modest growth response, suggesting IGF1 resistance. A better response over 5 years was noted in those with a *CCDC8* mutation (mean $+1.7$ SDS) compared to those with an *OBSL1* mutation (mean $+0.8$ SDS).

Discussion

3-M children respond less well to r-hGH than SGA children in general. Those with *CCDC8* mutations have a milder growth phenotype and respond better to r-hGH. 3-M mutations appear to be associated with partial GH and IGF1 resistance.

OC2.8

Genetic screening in a large cohort of patients with congenital hypopituitarism; current knowledge and future directions

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Background and aims

Congenital hypopituitarism (CH) encompasses a spectrum of phenotypes. Known genetic factors account for variable percentage of cases depending on the cohort

screened. We analysed the results of genetic screening in a large cohort of patients with CH with the following aims: i) to clarify the genetic aetiology of CH ii) identify any phenotype genotype correlations and iii) propose a screening strategy.

Patients and methods

Over 15 years we screened 2032 patients with CH and 334 unaffected family members referred from national and international centres. Our cohort included 540 patients with combined pituitary hormone deficiencies (CPHD), 522 with variable hypopituitarism, 540 with septo-optic dysplasia (SOD) and its variants (26%), 368 with isolated GH deficiency (IGHD) (18%) and 62 with midline clefts including holoprosencephaly (3%). In 17.4% ($n=362$) there was a positive family history. According to phenotype, patients were screened for mutations in known genetic factors including *HESX1*, *SOX2*, *SOX3*, *OTX2*, *LHX3/LHX4*, *SIX3*, *SHH*, *GLI2*, *CHD7*, *FGF8/FGFR1*, *KAL-1*, *PROK2/PROKR2*, *PROPI*, *POU1F1*, *GHI*, *GHRHR*.

Results

In patients with SOD *HESX1* mutations were identified in 1.3% (7/540), whilst changes in *SOX3* dosage were rare ($n=6$). Mutations in *SOX2* ($n=13$) and *OTX2* ($n=4$) were also rare in patients with SOD, but accounted for 28% and 4.5% respectively of patients with severe eye phenotypes (13/45 and 4/45). *PROKR2* variations were the commonest (2%), whilst variations in *FGF8* and *KAL-1* were rare (<1%). In patients with CPHD 3.3% ($n=18$) had mutations in *PROPI* whilst *POU1F1* mutations were identified in 2.2% ($n=12$). Genetic changes (*GHI*, *GHRHR*) were identified in 34 patients (9%) with IGHD. Six patients with complex phenotypes had variations in genes including *SHH*, *GLI2*, *LHX3* or *CHD7*.

Conclusion

With the current screening methods, known genetic factors account for 7% of cases of CH ($n=115$); this percentage is higher in familial cases or if specific phenotypes are taken into account. Next generation sequencing in combination with careful phenotyping will be critical in the identification of other factors implicated in its aetiology.

OC2.9

GH neuro-secretory dysfunction following traumatic brain injury in childhood

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GH deficiency is recognised as a complication of adult traumatic brain injury (TBI) but there are conflicting data in children possibly due to the influences such as age at TBI, trauma mechanism but also by timing, method and criteria of hormonal evaluation.

Objectives

To assess the long-term impact of TBI on the GH-IGF1 axis following TBI in childhood.

Patients

Longitudinal study of 28 participants with a history of moderate/severe TBI. Age (median (range)) at TBI 10.8 (1–17) years; 9 were prepubertal, 12 peripubertal, 8 postpubertal. Age at study 19 (11–26) years, time post TBI 8.7 (7–10.8) years, 2 were prepubertal. All subjects had clinical review, auxology and pubertal assessment. 24/28 participants had a GH stimulation test (ITT) and a 12-h overnight growth hormone profile (15 min sampling). For comparison a non-TBI control group with normal GH status ($n=7$, aged 18 (14–20) years) also had an overnight GH profile. There were no differences in age, BMI, gender and fat composition between TBI and control group.

Results

Deconvolution analysis of the overnight profiles showed that the number of secretion events, mean secretory pulse mass and mean secretory pulse interval were significantly different between the TBI and control group ($P<0.05$). In 6/24 of the TBI group the ITT GH response was abnormal (<3 $\mu\text{g/l}$ in four postpubertal and <5 $\mu\text{g/l}$ in two peripubertal participants). One had a suboptimal cortisol response. All other endocrine baseline blood samples (thyroid function, sex steroids) were normal and there was no clinical evidence of diabetes insipidus. The mechanism of injury was high speed RTA in 12 participants and falls and other type of low speed injury in the remaining.

Conclusions

GH deficiency and neurosecretory dysfunction occurs following moderate/severe TBI in childhood.

OC2.10**When is it justifiable to await venous thyroid function tests before starting thyroxine treatment in infants referred with capillary TSH elevation?**Tzveta Pokrovska, Jeremy Jones, Guftar Shaikh & Malcolm Donaldson
Royal Hospital for Sick Children, Glasgow, UK.**Background**

In Scotland median age at notification with elevated capillary (c) TSH (>25 initially or >8 μl on repeat testing) is 10 (range 3–35) days. If cTSH elevation is >100 μl decompensated hypothyroidism (moderate: free (f) T4 5 – <10, severe: <5 pmol/l) is likely and thyroxine treatment should start without delay. If TSH elevation is mild the clinician may prefer to wait for venous (v) fT4 result and observe the infant's progress rather than commit the child and family to 2–3 years of thyroxine.

Aim

To determine the cTSH value below which the probability of vT4 <5 pmol/l is <5%.

Method

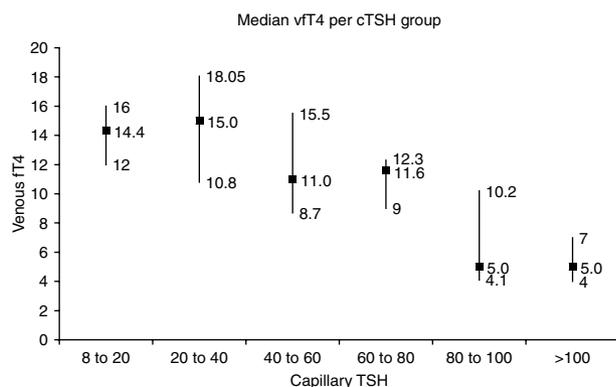
We examined capillary TSH vs venous fT4 values in all newborn infants referred in Scotland since 2002 (when the assay and cut-off TSH values were last changed).

Results

Of 275 infants referred, 254 were suitable for study, comprising definite/probable hypothyroidism (169), transient TSH elevation (42) and status uncertain (41). The correlation between cTSH and vT4 was 0.6. Of 94 infants with cTSH <40 μl , fT4 was 5.0 – <10 in 11 and <5 in 4.

Conclusion

Our data suggest that when cTSH is <40 μl the risk of severely decompensated hypothyroidism is sufficiently low to justify waiting for vT4 before starting treatment provided that the infant is not displaying hypothyroid symptoms.

**Oral Communications 3****OC3.1****HbA1c league tables: does selection policy encourage foul play to support promotion to the 'premier league'?**Merna Wassef¹, Charlotte Elder¹ & Neil Wright²¹University of Sheffield, Sheffield, UK; ²Sheffield Children's NHS Foundation Trust, Sheffield, UK.**Introduction**

The National Paediatric Diabetes Audit (NPDA) provides a benchmark of performance for paediatric diabetic services across the UK. Whether intentional or not, a league table is created comparing units based on their mean HbA1c. Although the coordinators suggest submitting the patients' most recent HbA1c, this may not necessarily be a universally adopted phenomenon. We examined the effect of selecting patient's best, yearly average, and latest HbA1c on our unit's overall mean HbA1c and its impact on our position in the 'league'.

Design

All patient HbA1c values were collected for two NPDA periods, January 2010–March 2011 and January 2011–March 2012. From the four HbA1c results collected during that period, the patients best, average for the year and last HbA1c were compared. The impact of omitting 'occasional' higher results was also

examined. Our clinic average HbA1c was calculated and compared to Yorkshire regional and National data to assess the impact on our ranking.

Results

For the period 2010–2011, our clinic mean HbA1c varied significantly from 8.0% using best HbA1c to 8.5% with average HbA1c, moving us from 2nd to 13th in the league table (historical data). There was a significant difference of 8.0 vs 8.4% taking best rather than most recent HbA1c values. Similarly, for 2011–2012, there were significant variations from 7.8 to 8.2 and 8.3% using the best, last and mean HbA1c variables.

Conclusion

Dependent on the variable submitted a clinically relevant difference of 0.5% was noted in the overall mean HbA1c. Such a difference could see you as champions or candidates for relegation in the league table! The system is potentially open to foul play and tighter regulation of selection policy is required as HbA1c is increasingly used as a performance indicator and in some cases the basis for quality payments.

OC3.2**An audit of the management of diabetic ketoacidosis in children in a large teaching hospital**

Ambika Shetty & Justin Warner

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Introduction

Diabetic Ketoacidosis (DKA) is a life threatening complication of type 1 diabetes mellitus (T1DM) in children. An integrated care pathway (ICP) for management of DKA based on guidelines published by the British Society for Paediatric Endocrinology and Diabetes has been established in Wales with the 2nd edition published in May 2010.

Aims

To audit the management of DKA in a teaching hospital following the introduction of the second edition of the ICP and identify the precipitants of DKA.

Methodology

Retrospective case note review of all children admitted with DKA between June 2010 and September 2011.

Results

24 episodes of DKA were recorded in 17 patients (12 male). The median age was 12.9 years (range 4–16.6 years). Seven of the DKA events were in newly diagnosed T1DM and omission of insulin was the most common precipitant in the other cases.

In all cases the diagnosis of DKA was made appropriately using blood sugar >11 mmol/l and pH <7.3.

The initiation of intravenous fluids was delayed and calculated wrongly in a quarter of the patients.

Hypoglycaemia was documented in 17 of the 24 episodes whilst on the pathway despite having dextrose in their fluids.

Conclusion

The ICP was used in all cases and in general followed well. The increased incidence of hypoglycaemia despite following the pathway needs further evaluation and comparison with other centres using the ICP. In a significant proportion of episodes, treatment was delayed and fluids calculated inappropriately. However, no adverse outcomes were identified.

OC3.3**Quality of life and HbA1c outcomes in children and young people commencing insulin pump therapy**Jenny Cropper¹, Latha Kanchi², Martha Ford-Adams², Tony Hulse¹,Charles Buchanan² & Estelle Barker¹¹Guy's and St Thomas' NHS Foundation Trust, London, UK; ²King's College Hospital NHS Foundation Trust, London, UK.**Objective**

To determine the impact on quality of life and metabolic control of insulin pump therapy in a cohort of young people in south London.

Methods

Seventeen children and young people with type 1 diabetes aged 5–17 undergoing assessment for pump therapy were routinely seen by a clinical psychologist as part of their assessment. The majority were aged 13–17. Measures quantifying quality of life (PEDS-QL generic and diabetes specific modules) were administered to both parent and child, prior to and six months following commencement of pump therapy. The two London boroughs in which the

hospitals are situated have high levels of socio-economic deprivation, both are in the top 5% areas of deprivation in England (Lesser 2010).

Results

Parents and children reported an increase in quality of life post pump in both the diabetes specific and generic measures (mean score on the diabetes module for parents: 364–392; for young people: 381–400). Correlational analyses showed a statistically significant increase in quality of life for parents on the diabetes specific measure ($r=0.647$, $P=0.005$). HbA1c results showed a statistically significant improvement pre to post pump from a mean of 9.12–8.33 ($t=3.63$, $P=0.002$), with a pre pump range of 13.2–7.0 reducing to 10.3–6.5 post pump.

Conclusions

Initial findings here suggest that insulin pump therapy improves both young person and parent rated quality of life. This is important and highly valued by families and young people themselves. In addition, overall blood glucose control significantly improved. These findings are particularly pertinent in the context of the high levels of socio-economic deprivation in this area. This cohort of young people has been shown to be particularly hard to reach and often have high HbA1c. It is very encouraging that insulin pump therapy has been seen to be successful here.

OC3.4

Continuous glucose monitoring: are there more barriers than benefits?

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Introduction

Currently despite NICE (2004) recommending continuous glucose monitoring (CGM) in the presence of hypoglycaemic unawareness or glucose excursions successful funding applications remain low with only children under 5 years of age being consistently successful within our service. Variability has also been noted as to whether children young people (CYP) and their families use sensors continuously or intermittently. This audit aimed to highlight effectiveness of continuous and intermittent use and any variation across the age ranges, barriers to use and critical feedback for service provision.

Methodology

A one page questionnaire was developed to audit existing users and elicit information regarding frequency, usability, patient experience and effectiveness.

Results

Despite a large cohort of our caseload using Insulin pump therapy (IPT) and CGM (provided by the specialist team) just nineteen children are funded by their PCT for both technologies. Twelve out of 19 CYP were under five years of age at CGM initiation. Fourteen commenced CGM at IPT initiation. This audit identified eight out of nineteen were funded to use sensors continuously and of this group all but one of the patients consistently achieved a HbA1c $<7.5\%$.

Of those that do not wear CGM continuously ($n=11$) the most frequently cited reasons included:- constant reminder of diabetes, additional demands (psychologically and physically), skin irritation, not accurate enough, nuisance alarms, too large for small kids and discomfort. The benefits included significantly reduced blood glucose testing, feeling more in control, being able to prevent highs and lows, having the confidence not to test and for parents sleeping more soundly.

Conclusion

CGM can incrementally improve diabetes management but improvements in the accuracy and practicalities remain. A CGM workshop with opportunities for interactive learning using increasingly complex scenarios, to facilitate consistent and comprehensive analysis both within clinic consultations and the home setting were also suggested.

OC3.5

Childhood type I diabetes education at time of diagnosis: what patients want to know

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Introduction

National and International Guidelines on the education of children and families when diagnosed with type I diabetes are largely based on clinicians' opinion but not patients' or parents' views on this important issue. We conducted a literature search using EMBASE, MEDLINE and CINAHL databases from 1980 to present which found no articles relating to patient opinion.

Methods

We developed a questionnaire from a list of 34 education topics related to diabetes based on existing national and international guidelines (ISPAD, NICE, ADA, SIGN) and sent it to 160 patients (or parents) with type I DM. For each topic patients were asked to give their opinion on A. the importance of the topic at the time when a child is diagnosed and B. the urgency of timing from diagnosis that education on this topic should be provided.

Results

79 respondents with a mean age from diagnosis of 4.7 years (range 3 months–15 years) and mean age at time of completing questionnaire of 11.7 years (range 1.5–17.8 years). Results of interest included mean scores for timing (67 and 55% respectively) indicating that patients want to meet the Paediatric Diabetes Specialist Nurse and lead consultant within 24 hours of diagnosis. Mean scores for information on pumps, carbohydrate counting and different types of insulin regimens (28, 28 and 45%) indicated patients prefer to wait for within 2, 2 and 1 week respectively for this information. Education on long term complications scored 25% (i.e. within 2 weeks of diagnosis).

Conclusions

In the current climate of best practice tariffs formal education of patients is increasingly important. This study provides information on patients' opinions on the importance and timing of topics for this education. This study can therefore lend weight to support guidelines on diabetes education.

Oral Communications 4

OC4.1

Metformin in obese children and adolescents: the MOCA trial
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¹Manchester Children's Hospital, Manchester, UK; ²Birmingham Children's Hospital, Birmingham, UK; ³Sheffield Children's Hospital, Sheffield, UK; ⁴The James Cook University Hospital, Middlesbrough, UK; ⁵Hull Royal Infirmary, Hull, UK; ⁶University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK; ⁷Salford Royal NHS Foundation Trust, Manchester, UK; ⁸Manchester Academic Health Sciences Centre, Manchester, UK; ⁹The University of Sheffield, Sheffield, UK.

Background

Childhood obesity is increasingly associated with type 2 diabetes (T2D). Metformin reduces the risk for T2D in adult obese non-diabetic patients, but the evidence in obese children and young people (CYP) is inconclusive.

Design

The metformin in obese children and adolescents (MOCA) trial was a prospective, multi-centre, randomized, double-blind, placebo-controlled trial of 1.5 g metformin daily in CYP with raised fasting or post-prandial insulin or glucose.

Aim

The primary objective was to assess the effects of metformin on body composition (primary outcome BMI-SDS at 6 months), metabolic risk factors and adipokines.

Methods

Auxology, arterial blood pressure measurement and fasting blood tests (insulin, glucose, fasting lipids, liver function, hs-CRP, lactate, resistin, adiponectin and leptin) were performed at baseline, 3 and 6 months with a prolonged oral glucose tolerance test at baseline and 6 months.

Participants

One hundred and fifty-one obese CYP participated in the trial (metformin: 74, placebo: 77). 67.5% were female, 65.6% post-pubertal, 23.8% British Asian or Afro-Caribbean. Age range 8–18 years, mean age 13.7 (s.d. 2.3) years and mean BMI-SDS 3.4 (0.5).

Results

Metformin was associated with a significant reduction in BMI-SDS compared to placebo at 6 months (mean difference: 0.1 s.d. (95% confidence interval 0.02–0.19), $P=0.01$). Fasting glucose (0.16 mmol/l (0–0.33), $P=0.05$, and adiponectin/leptin ratio (ALR) (0.27 (–0.52 to –0.02), $P=0.03$) significantly improved at 3 months in the metformin group, but the changes were lost at 6 months. No significant changes were found in the other secondary outcomes.

Conclusion

Metformin therapy has a beneficial treatment effect over placebo for BMI-SDS, fasting glucose and ALR ratio at 3 months, with changes in body composition sustained at 6 months. MOCA is the largest study of its kind to date, and indicates that metformin is clinically useful, safe and well tolerated in obese CYP.

OC4.2**Patterns of presentation and initial management of type 1 diabetes mellitus in the UK: the early care survey**

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Background

Unrecognised type 1 diabetes (T1DM) can have serious consequences which may be avoidable with early diagnosis. Many children have delayed diagnosis, however contributing factors are unclear.

Aims

To evaluate the patient pathway before diagnosis and initial hospital management of children with T1DM.

Methods

Over a 3-month period, parents of children newly diagnosed with T1DM across the UK completed a questionnaire. Additional medical information was collected regarding initial hospital management.

Results

Data was available for 261 children (54% male), median age 10.1 years (range 0.2–16.6 years). 26% presented with diabetic ketoacidosis (DKA); those without classical symptoms of diabetes were more likely to present with DKA ($P=0.016$).

Median duration of parental concern was 14 days (range 0–548 days). There were positive correlations between HbA1c and both age and symptom duration (both $P<0.001$). No relationship was identified between duration of parental concern/reported symptoms and age, deprivation index, caregiver education level or family structure.

65% of parents had considered a diagnosis of T1DM, which was more likely if their child had polyuria and/or polydipsia ($P<0.001$). 86% discussed their concerns regarding a possible diagnosis of T1DM with a healthcare professional (HCP). 76% of children were admitted on the day of first HCP contact: of the remaining patients, median time to admission was 5 days (range 1–152 days). Children with multiple HCP contacts had lower pH on admission and were more likely to require intravenous insulin, whereas if the family had considered the diagnosis the converse was true (all $P<0.05$).

Median time following admission to diabetes team referral was 1.5 h. First subcutaneous insulin administration occurred at median 2.0 h after admission in children not requiring intravenous insulin.

Conclusions

Parental and HCP consideration of T1DM reduced severity of presentation. Increased awareness of T1DM symptoms in HCP and the general public could reduce time to presentation and the frequency of DKA.

OC4.3**White UK children are older, more obese and more insulin resistant than non-White UK children at diagnosis of type 2 diabetes: baseline results of the UK national type 2 diabetes cohort**

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Objectives

Type 2 diabetes (T2DM) has increased in UK children since the first reports in 2000; however it is poorly characterised and management practice varies across the UK. We aimed to describe the characteristics of the first 125 children recruited to the UK national study.

Methods

We recruited children with: paediatrician diagnosis of T2DM; body mass index (BMI) above 85th centile for age and sex; other diagnoses such as monogenic diabetes excluded. Clinical data was collected into a national database. Blood was taken for DNA and diabetes auto-antibody status.

Results

We were notified of 256 presumed affected children and have recruited 145 so far. Exclusions: auto-antibody positive (13); secondary diabetes (7). After exclusions M:F ratio was 1:2.6; white UK origin (49%); South Asian (SA) origin (29%); African-Caribbean (A-C) (12%); other (10%). Mean age at diagnosis was 13.2 yrs and mean duration of diabetes 3.0 years. White children were older at diagnosis

(mean 13.4 years vs SA (13.2 years), A-C (12yrs; white vs A-C $P<0.04$)); fatter at diagnosis (BMI-SDS white (3.2), SA (2.8), A-C (2.7); white vs S-A $P<0.01$). White children trended towards lower HbA1c (white 9.2%, SA 8.7%, A-C 10.5%); and higher fasting C-peptide (white 1594 pmol/l; SA 1229 pmol/l; A-C 935 pmol/l). 19% of A-C children had resting heart rate more than 2 SD's above the mean, vs 8% in SA and 7% in white children. There were no significant differences in resting blood pressure between groups.

Conclusion

White UK children are older at diagnosis than non-White children, more obese, and probably more insulin resistant. African-Caribbean children have poorer metabolic control and signs of cardiovascular dysfunction compared to white and SA children. A significant proportion of children still have raised C-peptide levels soon after diagnosis of diabetes, raising the possibility of therapeutic intervention to preserve pancreatic beta cell function early in the disease process.

OC4.4**Vacuolar-type H⁺-ATPase V1A subunit is a molecular partner of Wolfram syndrome 1 protein, which regulates its stability and expression**

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Wolfram syndrome is an autosomal recessive disorder characterised by neurodegeneration and diabetes mellitus. The gene responsible for the syndrome (WFS1) encodes an endoplasmic reticulum (ER) resident transmembrane protein, that also localises to secretory granules in pancreatic β cells. Although its precise functions are unknown, WFS1 protein deficiency affects the unfolded protein response, intracellular ion homeostasis, cell cycle progression, and granular acidification. In this study, immunofluorescent and electron-microscopy analyses confirmed that WFS1 also localizes to secretory granules in human neuroblastoma cells. We demonstrated a novel interaction between WFS1 and the V1A subunit of the vacuolar-type H⁺-ATPase (proton pump) by co-immunoprecipitation in HEK293 cells, and with endogenous protein in human neuroblastoma cells. We mapped the interaction to the WFS1-N terminal, but not the C-terminal domain. V1A subunit expression was reduced in WFS1 stably and transiently depleted human neuroblastoma cells and depleted NT2 cells. This reduced expression was not restored by adenoviral over-expression of BiP to correct the ER stress. Protein stability assays demonstrated that the V1A subunit was degraded more rapidly in WFS1 depleted neuroblastoma cells compared with wild type. We conclude that WFS1 has a specific interaction with the V1A subunit of H⁺-ATPase; this interaction may be important both for pump assembly in the ER; and for granular acidification.

OC4.5**The effect of insulin intensification on glycaemic control and lipid levels in children and young persons with type 1 diabetes differs in relation to ethnic group**

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Background

Previous studies identify non-White ethnicity as predictive of poor diabetes related outcomes. However, many of these reports originate from the United States and may, in part, reflect complex interactions between ethnicity, healthcare inequality and social deprivation.

Objective and hypotheses

We aimed to prospectively determine the effect of insulin intensification on glycaemic control and lipid levels in relation to ethnicity in a UK cohort of children and young persons (CYP) with type 1 diabetes (T1D).

Methods

Data were collected prospectively between 2008 and 2011 in CYP from a single paediatric diabetes centre ($n=222$; 40% White, 28% South Asian, 32% Black). By 2009 nearly all CYP were treated with multiple daily injections or insulin pump therapy. Deprivation scores were derived from the UK 2010 Index of Multiple Deprivation.

Deprivation. We used linear mixed level modelling to identify longitudinal differences between ethnic groups.

Results

At study end; Black CYP had higher HbA1c levels (9.4 (standard deviation 2.4) v South Asian 8.4 (1.9) v White 8.6 (1.7)%, P value for ANCOVA=0.007) but South Asians had lower HDL-cholesterol (1.4 (0.4) v White 2.0 (1.2) v Black 1.6 (0.4) mmol/l, P value=0.03) and higher triglyceride levels (1.8 (1.1) v 0.9 (0.4) v 1.0 (0.5) mmol/l, P value=0.001). In linear mixed models, after adjustment for socio-economic deprivation and other predictors; i) Black ethnicity associated with poorer glycaemic control ($P<0.001$) and ii) South Asian ethnicity associated with higher triglyceride levels ($P<0.001$), independent of HbA1c.

Conclusions

The effect of insulin intensification on glycaemic control and markers of future cardiovascular disease risk in CYP with T1D differs in relation to ethnic group. Ethnic specific thresholds for intervention should be considered during childhood.

Oral Communications 5

OC5.1

Adolescent transition clinic: a review of the young person's self-confidence and future concerns

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Introduction

There has been a joint transition clinic in our tertiary centre for over 10 years. We have recently undertaken a questionnaire based review of this service.

Methodology

The questionnaire comprised two components: what the young adults understood about their condition and the medications they were currently taking using both a written response and a score of 0–10 for how confident they felt in this. They were also asked to complete a concerns checklist of issues such as body image, fertility issues and emotional wellbeing.

Results

Thirty-nine questionnaires were completed (males 13, females 26) by patients with a variety of endocrine disorders. The mean age was 16.8 years (Range 13.0–20.4). There was a wide range in both the level of understanding and confidence in managing their condition. Thirteen (33%) felt they fully understood their condition, 18 (46%) were completely confident about managing their medication. Of the 13 (33%) that understood their condition 12 (30%) were completely confident about managing their medication. The confidence in managing their condition did not depend on the endocrine condition or correlate with the written response on the questionnaire. The most common causes for anxiety were fertility issues (25%), growth and development (17%), medications (20%), hormonal issues (17%), medical condition (13%), sexual issues (13%) and educational/employment issues (13%).

Conclusion

Use of a questionnaire has enabled us to identify gaps in the knowledge and understanding of our young adults and focus their consultation on issues most important to them. Adolescents have a range of capabilities regarding the management of their condition and a number of concerns regarding their future health and wellbeing which should be addressed at the appropriate time.

OC5.2

Comparison of patient experiences of the glucagon and insulin pituitary provocation tests: time for a reappraisal

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Introduction

The debate surrounding the most suitable pituitary provocation test in children is controversial. There is a perception that the gold standard insulin tolerance test (ITT) is 'dangerous' and that the glucagon stimulation test (GST) is 'safer' and a more tolerable alternative, particularly in younger children. There have been no reports in the literature comparing patient experiences of these tests.

Aim

To examine the tolerability of the GST compared to the ITT in children aged 8 or more years.

Methods

A prospective, qualitative cohort study was carried out over 3 months. The occurrence of adverse symptoms and children's level of distress following

glucagon or insulin was ascertained using semi-structured interviews and structured questionnaires.

Results

16 children aged 8–17 years were studied (ITT $n=8$; GST $n=8$). 100% of children undergoing an ITT reported a fall in their distress score post-test, however 63% undergoing a GST reported a rise. With age and pre-test scores taken into account this difference was significant by linear regression. The duration of nonspecific (abdominal pain ($P=0.007$), hunger ($P=0.001$)) and neuroglycopenic (headache ($P=0.007$)) symptoms was significantly greater after GST, whereas autonomic and non-specific symptoms were more common, and of greater severity, after ITT but of shorter duration. Glucagon caused a delayed hypoglycaemia in 37% of cases, which occurred 90–120 min post injection.

Conclusion

The ITT, as performed at our centre (following a strict protocol including breakfast with oral glucose 20–30 min post injection), is surprisingly well tolerated in children over 8 years of age. By contrast the GST is poorly tolerated and does not necessarily avoid a delayed, unpredictable, and hence potentially more risky, hypoglycaemia. These novel findings in a small cohort highlight the need for reappraisal of the comparative risk-benefit and predictive values of these tests in a larger randomised biochemical and qualitative crossover study.

OC5.3

A comparison of patient's preferences for attributes of GH delivery devices: children starting versus children established on GH treatment

Stephanie How Yaw, Talat Mushtaq, N S Alvi, Jenny Walker & Amanda Whitehead

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Background

Several devices are available for the administration of recombinant GH. A prospective study was undertaken to look at those attributes of GH delivery device most important to patients when making their choice.

Objectives

i) To understand which features of a GH device are considered most important to patients when choosing a device. ii) Comparison of patient's device preferences at start of GH treatment and after 2 years of treatment. iii) Correlation of these factors to the actual GH device chosen after demonstration of devices.

Methods

Children attending a large tertiary paediatric endocrine centre were enrolled in the study. Ethical approval was obtained. The parent/child's preference for various device characteristics was evaluated through two questionnaires. The eight delivery devices currently available were then demonstrated. Children were divided into two groups: i) Treatment-naive (Group I) and ii) Treatment-established (Group II).

Results

There were 40 children (aged 1.7–16.0 years) in Group I and 40 children (aged 3.8–17.8 years) in Group II. The option of prefilled GH cartridges was ranked as the top most desirable device characteristic in both groups (73% Group I, 55% of Group II, $P=0.09$). The Easypod™ device was the most commonly chosen device in both groups (50% Group I, 33% Group II, $P=0.13$). 30% of Group I and 65% of Group II chose a device with at least 2 of the desirable device characteristic ($P=0.002$). 38% of Group I and 88% of Group II picked the device identified as their top preference ($P<0.05$).

Conclusions

Both children starting and already on GH treatment preferred devices with electronic features and prefilled GH cartridges. The patient's top device preference was similar at the start of treatment and after 2 years of treatment. These questionnaires can be used to streamline the number of devices demonstrated to patients.

OC5.4

The role of the paediatric endocrine nurse in supporting the information needs of girls with Turner syndrome and their parents

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Aim

To explore the role of paediatric endocrine nurse specialists in supporting information needs of girls with TS and their parents.

Methods

A purposive sample of 15 families with daughters aged 9–16 years were recruited from a tertiary paediatric growth clinic to participate in an exploratory qualitative

study. 27 semi-structured interviews were recorded. Data were analysed using the framework approach and constant comparative method. Analysis revealed how girls and their parents interpreted and used information within the context of their everyday experiences of living with TS.

Findings

Commencement of GH treatment was the point at which girls and their parents stated they met the nurse specialist. Parents of children with other lifelong conditions are reported in the literature as being introduced to clinical nurse specialists at the initial diagnosis. However the majority of the girls interviewed did not fit a clinical picture of daily threats of physical crises. Their orientation to physical wellness meant that some parents and girls did not easily perceive themselves as a patient or recognise the need for a nurse. With the exception of

infertility, there was limited reference by parents or girls to long-term health implications of TS. Parents and girls valued the input from paediatric endocrine nurse specialists commenting favourably on their personal qualities. However, they described their relationship with them as specific and transient. The lifelong nature of TS requires an educational approach that incorporates ongoing assessment of understanding of TS including future health implications.

Conclusion

The role of the paediatric endocrine nurse specialist did not reflect patterns of engagement with these girls and their parents that are reported in other clinical nurse specialist roles. Further research to determine how paediatric endocrine nurse specialists work in different tertiary centres is worthy of further detailed exploration.

Poster Presentations

P1**A homozygous glutathione peroxidase 1 mutation, p. Arg130-Leu133del, in a patient with familial glucocorticoid deficiency**

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Familial glucocorticoid deficiency is an autosomal recessive disorder characterised by resistance to ACTH of the adrenal cortex, leading to isolated glucocorticoid deficiency and life-threatening hypoglycaemia. Half of all cases are caused by mutations in *MC2R*, *MRAP*, *MCM4* or *STAR*. Recent work in our group has identified defects in nicotinamide nucleotide transhydrogenase (*NNT*) to be causal in a further 10% of cases. *NNT* generates the high concentrations of NADPH necessary for detoxification of reactive oxygen species (ROS) by enzymes such as the glutathione peroxidases. Previous studies have demonstrated high ROS levels inhibit steroidogenesis by suppressing *StAR* protein expression in human Leydig cells.

In one patient with FGD of unknown aetiology, we identified a homozygous mutation, c.del388-399; p.Arg130-Leu133del in glutathione peroxidase 1 (GPX1). The mutation was heterozygous in his parents and one unaffected sibling. Using qRT-PCR, we examined GPX1 mRNA expression in multiple human tissues and showed that GPX1 expression was highest in adrenal with significant levels also seen in spleen and adipose tissue. Knockdown of GPX1 by shRNA in the human adrenocortical H295R (KD-GPX1) cell line led to a 90% decrease in GPX1 protein expression and 50% decrease in total GPX activity. KD-GPX1 cells were less viable and had increased levels of apoptosis than their scrambled counterparts. Interestingly *StAR* protein levels were significantly decreased in KD-GPX1 cells.

A non-functional GPX1 may cause FGD by increasing levels of ROS in the adrenal cortex, leading to reduced *StAR* protein levels and decreased mobilisation of cholesterol to the inner mitochondrial membrane for steroidogenesis. Taken together our data suggest that GPX1 may have a role in ROS detoxification in human adrenal glands.

P2**Outcome of endoscopic transsphenoidal pituitary surgery in four paediatric Cushing's disease patients: a new therapeutic approach**Helen L Storr¹, William M Drake², Scott A Akker², John P Monson², Martin O Savage¹, Ghassan Alusi³ & H Ian Sabin⁴

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Selective transsphenoidal adenomectomy remains the accepted first line treatment for Cushing's disease (CD), until recently by microscopic (sublabial) transsphenoidal pituitary surgery. Endonasal transsphenoidal endoscopic surgery is emerging as a novel, less invasive treatment for pituitary adenomas with lower postoperative complications and morbidity. The safety of endoscopic surgery has been extensively reviewed in adult patients and is now considered best practice for the treatment of pituitary tumours. There are no published series of the treatment of paediatric CD by endoscopic pituitary surgery and we report our centre's preliminary results.

Methods

Four paediatric patients (median age 14.4 years; range 11.7–16.8 years) fulfilled standard diagnostic criteria for CD. Preoperatively no abnormality was identified on pituitary MR scanning in three (75%) patients. Bilateral petrosal sinus sampling demonstrated central ACTH secretion (IPS/P ACTH ratio > 2.0, pre- or post-CRH) in three (75%) patients with lateralisation of ACTH secretion (IPSG post-CRH ≥ 1.4) in two patients. The same neurosurgeon and endoscopic nasal surgeon undertook all the operations. 'Cure' was defined as a 0900 h cortisol level of <50 nmol/l postoperatively on two separate occasions associated with regression of the clinical features of CD.

Results

Clinical recovery and biochemical 'cure' was achieved in 3 (75%) patients and a corticotroph adenoma was confirmed histologically in all cured cases. One case developed postoperative CSF leak requiring lumbar drain insertion and patching. At a mean interval of 5.9 years (0.49–8 years) postoperatively, cured patients have shown no recurrence. One patient, who had a large diffuse adenoma requiring more extensive surgery has panhypopituitarism, another patient has GH and gonadotrophin deficiencies.

Conclusions

Our experience shows that endonasal transsphenoidal endoscopic surgery for removing corticotroph adenomas in children, in most cases not visualized on MRI imaging, is minimally invasive and gave excellent postoperative recovery/results. In skilled hands this technique provides an alternative to conventional transsphenoidal microscopic surgery in managing paediatric CD.

P3**The accuracy of diagnosing adrenal insufficiency in children undergoing glucagon stimulation test (GST)**Anbezhil Subbarayan, Helen Spoudeas, Catherine Peters, Mehul Dattani, Peter Hindmarsh, Caroline Brain & Rakesh Amin
Great Ormond Street Hospital, London, UK.**Background**

Glucagon (GST) is used as an alternative to insulin (ITT) to diagnose GH deficiency (GHD) and adrenal insufficiency (ACTHD). However the peak cortisol response to diagnose adrenal insufficiency varies (550, and 500 nmol/l), has been extrapolated from adults undergoing intraoperative stress and not fully validated. Aim

To determine the peak cortisol 'cut off' level which most accurately predicts clinically significant adrenal insufficiency requiring therapy in children undergoing GST for suspected hypopituitarism or short stature.

Method

140 records of all patients undergoing GST at our tertiary centre between January 2011 and December 2011 were retrospectively assessed. Patients on steroid therapy ($n=1$) or with incomplete test results ($n=2$) were excluded. All 6 cortisol components of the 3 h test results were collected. The sensitivity and specificity of different cut-off peak cortisol levels in accurately diagnosing adrenal insufficiency were calculated.

Results

Of 137 patients, aged (median) 8.7 (range 0.94–19.17) years, 112 (82%) achieved the peak cortisol response between 150 and 180 min but in 14 (10%) this was achieved at baseline. 29 (21%) and 25 (18%) had peak cortisol responses of <550 and <500 nmol/l respectively. Of these only 7 (24%) clinically warranted further investigation and 4 (14%) were then confirmed adrenally insufficient and received treatment. The rest 25 (86%) remained well without hydrocortisone replacement 6 months later.

Conclusion

Lower cut-off peak cortisol of <450 nmol/l increases the specificity without altering the sensitivity in diagnosing childhood adrenal insufficiency using a GST and may be more reflective of adrenal capacity than higher levels (550, and 500 nmol/l).

Table 1 Sensitivity and specificity at different peak cortisol levels:

Peak cortisol	<550 nmol/l (n=29)	<500 nmol/l (n=25)	<450 nmol/l (n=15)	<400 nmol/l (n=7)
Sensitivity (95%CI)	100% (39–100)	100% (39–100)	100% (39–100)	75% (23–98)
Specificity (95%CI)	81% (73–87)	84% (76–90)	92% (85–95)	97% (91–99)
Positive predictive value (95%CI)	13% (4–32)	16% (5–37)	27% (8–55)	43% (12–80)
Negative predictive value (95%CI)	100% (95–100)	100% (5–100)	100% (96–100)	99% (95–99)

P4**The management of 21-hydroxylase deficiency: a retrospective audit in south east and west of Scotland**

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Introduction

The management of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase (21-OH) deficiency is challenging and clinical practice is known to vary. Clinical guidelines were published in the Consensus Statement in 2002 encompassing evidence for best practice.

Aims

To compare the management of paediatric patients with severe 21-OH deficiency in South East and West of Scotland (SE and WoS) with consensus guidelines. To determine the nature and timing of initial clinical presentation.

Methods

A retrospective audit of case notes. Inclusion criteria were patients with 21-OH deficiency, presenting in the first year of life from 1993 to 2012 in SE and WoS. Cases were identified through contact with local clinicians. Data extracted included details of initial presentation, surgical and current medical management. Results

28 patients were identified (15 girls), with a median age of 11.2 years (range 1.1–19.9 years). All girls were identified at birth. Boys presented at a median age of 14 days (range 0–51 days). Glucocorticoid doses ranged from 4–25 mg/m² per day (median 13.4 mg/m² per day), with 15 of 28 (54%) patients receiving the recommended dose of 10–15 mg/m² per day. Mineralocorticoid doses ranged from 0.1–0.3 mg/day (median 0.15 mg/day), with 26 of 28 (93%) patients receiving 0.05–0.2 mg/day. In conflict with guidelines none of the 14 girls who have had surgery had initial procedures performed between 2 and 6 months of age. 13 girls had surgery aged between 12 months of age and adolescence.

Conclusion

The medical and surgical management of 21-OH deficiency frequently diverges from clinical guidelines. This may arise from variation in the needs of individual patients but may also reflect variation in the approach of different clinicians. Specific national guidelines would aid clinical practice ensuring more uniform management and optimising patient care.

P5**A rare case of virilizing adrenocortical carcinoma in a child presented with peripheral precocious puberty**

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Introduction

Adrenocortical carcinoma, is an aggressive cancer originating in the cortex of the adrenal gland. Adrenocortical carcinoma is a rare tumor, in United State <25 new cases of adrenocortical tumours (benign and malignant) are diagnosed annually (0.1–0.4 cases/million per year) and malignant adrenal tumours comprise ~1% of all carcinomas diagnosed prior to 20 years of age. Adrenocortical carcinoma has a bimodal distribution by age, with cases clustering in children under five, and in adults 30–40 years old. Adrenocortical carcinoma is remarkable for the many hormonal syndromes which can occur in patients with steroid hormone-producing ('functional') tumors, including Cushing's syndrome, Conn syndrome, virilization, and feminization. Because of the relative rarity of these tumors, little is known about their cause and the influence of genetic factors, adrenocortical carcinomas are associated with numerous constitutional syndromes, including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, Carney complex, multiple endocrine neoplasia 1, and hemihypertrophy syndrome. The incidence is associated with a mutation in the *P53* gene.

Case report

A 8.5-year-old boy evaluated in our clinic for excessive pubic hair (pubarche), his condition dated back to 1 year ago. On examination: he looks well, normal blood pressure, the height 121 cm (above 50th percentile for the family target), weight 30 kg (75th percentile). Tanner stages for pubic hair, penile size and testes were Iv, Iv, II respectively (Fig. 1A and B). No palpable abdominal mass, the rest of his physical examination unremarkable. Laboratory findings: FSH 0.10 IU/l normal for stage Iv (1.4–15.4), LH 0.15 IU/l normal (1.2–7.8), testosterone 8 nmol/l normal (0.10–1.04), 17 hydroxyprogesterone 2.1 ng/ml normal (0.2–3.5), cortisol level 346 nmol/l normal (168–728). Thyroid function tests, renal function tests and serum electrolytes tests were all normal. Medical imaging data: bone age 11 years, abdominal ultrasonography revealed well defined mass at right suprarenal region heterogeneous texture with some calcification measures (49×48) mm, abdominal magnetic resonance revealed well defined mass at right suprarenal region measures about (5×5) cm (Fig. 2A and B) Interpretation was adrenal carcinoma or adenoma. Dynamic computed tomography of adrenal glands revealed: right adrenal mass (5×4.4) cm well defined, heterogeneous, associated with perilesional vessels, no invasion to surrounding structures or lymph nodes without distant metastasis in the visualized area. Interpretation: most probably adrenocortical carcinoma. Brain magnetic resonance imaging was normal. Scrotal ultrasonography revealed both testes slightly enlarged in size with normal echogenicity. Chest X-ray normal. Based on these clinical, imaging data and laboratory tests, our diagnosis after consulting the radiologist, paediatric surgeon and paediatric oncologist was adrenal androgen-secreting tumour either adenoma or carcinoma, surgical management was decided and the patient underwent right open adrenalectomy at 14 April 2012. Pathology report revealed grossly single piece measuring 5×5×4 cm, soft yellow cut section with hemorrhagic foci. Microscopically section shows malignant tumour composed of atypical cells with

dense compact eosinophilic cytoplasm, some cells have intranuclear inclusion, capsular invasion, sinusoidal invasion, focal clear cell component and fibrous bands (Fig. 3A and B). The histological picture is consistent with adrenocortical carcinoma, confirmed by immunohistochemistry (epithelial membrane antigen and cytokeratin both positive). Tumour staging: stage I; can removed completely. Post-operatively: serum cortisol 0.500 nmol/l for morning and evening (N: 171–536), so he put on hydrocortisone replacement therapy, and he was scheduled for follow-up examination monthly for the first 2 years, scanning every 3 months for the first 2 years, 4 months for the next 2 years and every 6 months during the 5th year.

Conclusion

To our knowledge, this is the first case report of virilizing adrenocortical carcinoma with unique pathologic findings presented with peripheral precocious puberty in our country in this age group. Three years ago, we submitted a project to establish a center of excellence for the speciality of the paediatric endocrinology and diabetes in Iraq to Minister of Health, as a project for change management after our clinical attachment course in UK for two months, and we gained the agreement for that. Now it is a center for teaching, training of postgraduate medical students, referral center for management and consultation of paediatric endocrine diseases, diabetes and sex disorders. Our case is one example for that, this considered a success especially in a developing country suffered and still suffers from wars, terrorism and violence.

P6**The use of GH and anastrozole can help optimise linear growth in congenital adrenal hyperplasia due to CYP11B1 mutations**

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Introduction

11 β -Hydroxylase deficiency is the second most common form of congenital adrenal hyperplasia (CAH) occurring in 1 in 100 000 births. The mainstay of management is with glucocorticoids to prevent virilisation and optimise growth. In this case, a novel approach was applied to improve linear growth in a patient who presented late with an advanced bone age.

Case report

The patient was born in Turkey to consanguineous parents. Aged 3 years, he was found to have pubic hair and a bone age of 8 years. Hormonal profiles confirmed a diagnosis of 11 β -hydroxylase deficient CAH and he was treated with hydrocortisone.

On arrival in the UK aged 6 years, his pubertal staging was G3, P3 with 2 ml testes and he was hypertensive (146/98). His bone age was 14 years with a height of 131 cm. The predicted final height was 140 cm (mid-parental height 166 cm). His height velocity was poor (2.2 cm/year). Genetic analysis revealed a mutation in exon 5 of the CYP11B1 gene.

His dose of hydrocortisone was increased from 9 to 20 mg/m² per day and his dose of enalapril was increased. In an attempt to optimise his final height, at age 7 years, he was given GH (0.9 mg/m² per day) and the aromatase inhibitor anastrozole (1 mg o.d.) to prevent further bone age progression.

With this novel treatment, his height velocity increased to 10.5 cm/year. Currently, at age 12 years, his pubertal staging is G4, P4 with 8 ml testes. His height is 159 cm and he is still growing at a height velocity of 6 cm/year.

Conclusion

The predicted final height in a patient with CAH and an advanced bone age was significantly exceeded following treatment with GH and anastrozole. This treatment has not been previously reported to be effective in short children with CAH. Further research into the effectiveness and long-term safety of this treatment would be beneficial.

P7**Growth and pubertal delay in autoimmune Addison's disease**

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Introduction

There is a known association between delayed puberty in autoimmune Addison's disease in presence of polyglandular involvement, but constitutional delay still needs to be considered in these cases.

Case

We report a 14-year-old boy who presented with a 4 month history of dizziness, fainting episodes and weight loss at the age of 12 years. He was stabilised on a reasonable dose of hydrocortisone and fludrocortisone after a diagnosis of Addison's was made.

He then presented with growth failure and pubertal delay after being stable on steroid replacement for the next seventeen months. Examination revealed a reduced testicular size for age and prepubertal tanner staging and reduced height velocity and static weight for the last 5 months with a bone age delay of ten months. Investigations at this stage, suggested that he was well controlled with no evidence of over or under replacement and with no acute hospital attendances or periods of being unwell.

A provisional diagnosis of constitutional delay of growth and puberty was made and he was started on a trial of 4weekly testosterone for next 7 months during which marked improvement of his height velocity and pubertal development was noted.

Conclusions

i) Growth and pubertal delay in well controlled Addison's could present as a diagnostic dilemma. ii) Appropriate investigations for growth and pubertal delay with optimising replacement before starting hormonal treatment is probably best practice in this condition, as this case demonstrates.

iii) Although linear growth is normal in adequately treated Addisons disease, further studies will be needed to see whether these patients achieve their final predictive height based on their appropriate mid parental centiles.

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P8

The effect of homozygosity versus heterozygosity for IGFALS gene mutations on growth, bone strength and insulin resistance

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Background

Acid-labile subunit (ALS) deficiency inhibits ternary complex formation leading to primary IGF1 deficiency and short stature. Potential metabolic consequences such as diabetes and low bone mass are not well studied.

Objective

This study measured insulin sensitivity, lipid profile, bone density and structure in members of 4 affected families and explore possible gene-dose effects.

Methods

Four patients (7–21 years) with homozygous *IGFALS* gene mutations and 12 heterozygous carriers had i.v. glucose tolerance tests performed. Dual-energy X-ray absorptiometry of spine, hip and total body, peripheral quantitative computer tomography of the radius and metacarpal (MC) radiogrammetry were performed.

Results

Height z-scores in patients (median -3.75 (range -4.25 to -0.62)) were lower compared to carriers (-1.77 (-2.21 to +0.26), $P < 0.001$), a reflection of their significantly lower IGF1, ALS and IGFBP3 levels ($P < 0.005$). Glucose disappearance rate (k), HOMA-IR, fasting insulin, glucose and lipid levels were similar between the two groups. Three carriers (age 29, 53 and 55 years) had k rates below 1%, and elevated fasting glucose levels, indicating diabetes mellitus.

Lumbar spine BMD was lower in patients (z-score -2.0 (-2.6 to -1.1)) compared to carriers (-0.7 (-2.5 to 0.9), $P = 0.04$), likely influenced by their short stature since size-corrected spine BMAD as well as radial total and trabecular BMD were not different between groups. Structurally, MC bone width (-2.67 (-3.5 to -2.56) vs -1.28 (-1.92 to -0.54), $P = 0.004$) and length (-1.72 (-2.83 to -0.11) vs 0.33 (-0.6 to 2.65), $P = 0.015$) were lower in patients compared to carriers but the MC bone health index was similar.

Conclusions

3/12 *IGFALS* gene carriers had type 2 diabetes and there was some evidence of insulin resistance in this cohort. ALS deficiency affects bone lengthening and widening (growth). There is sufficient evidence for a gene-dose effect on bone size but insufficient evidence for a true reduction in bone density and strength.

P9

Vitamin D trending: trends in vitamin D status, measurement and prescribing in Northern England, 2002–2011

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Introduction

The vitamin D (25OHD) status of a population will reflect genetic and environmental factors. We evaluated all 25OHD assays undertaken at a regional centre in an area at high risk of vitamin D deficiency, over a 10 year period on the basis that this would provide insight into annual, seasonal and age based trends in 25OHD status. We planned to correlate vitamin D measurement with trends in vitamin D prescribing.

Methods

Data (66 694 samples) from a 10 year period (2002–2011) were collected from the regional biochemistry department. Age, gender, month of sampling and 25OHD status were obtained and the average sunshine hours/month for Northern England obtained via the Meteorological Office. Local prescribing data were obtained from the pharmacy department. Regression and time series analyses were performed.

Results

There was a near ten-fold increase in 25OHD assay requests from 2170 (2002) to 19 954 (2011) and a concomitant rise in prescriptions. This pattern also applied to the paediatric population ($P < 0.01$). 25OHD levels fell year by year despite the change in vitamin D prescriptions. Seasonal analysis showed peak vitamin D levels from Jul to Aug and nadir levels from Jan to Mar. There was a significant relationship between mean 25OHD levels and mean sunshine hours ($r = 0.51$, $P < 0.01$). In the 0–20 year group there was a decrease in 25OHD levels with age with a nadir at 13–17 years (ANOVA, $P < 0.01$).

Conclusions

The number of vitamin D analyses and prescriptions has increased steadily over the last decade. Vitamin D levels in the population follow a seasonal trend which is strongly dependent on sunlight exposure. There has been a downward trend in 25OHD levels which could reflect several factors including increased testing in a rising ethnic minority population. Vitamin D levels fall from birth with a nadir during puberty, possibly due to the increased conversion of 25OHD to 1,25OHD to meet increased skeletal demands.

P10

A case of Noonan syndrome with a *SHOC2* mutation associated with cortical and trabecular osteopenia and early onset fragility fractures

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Introduction

Noonan syndrome (NS) (OMIM 163950) is an autosomal dominant clinically heterogeneous disorder characterised by multisystem involvement. Mutations in genes in the RAS/MAP signaling pathways are known to be responsible for ~70% of cases of NS. We report an infant with NS with early onset fragility fractures.

Case report

A 15-month-old male infant with a history of atopic eczema, sparse hair on the scalp, slow motor development, feeding difficulties, faltering growth, congenital cardiac problems (atrial septal defect, pulmonary valve stenosis and branch pulmonary artery stenosis) and macrocephaly, presented with a painful and swollen left leg. Radiographs revealed an undisplaced spiral fracture of the mid shaft of the left femur. The skeletal survey showed generalised osteopenia and anterior wedging of T12 vertebral body. MRI of the spine showed compression fractures of multiple mid and lower thoracic vertebral bodies. His serum concentrations of calcium, phosphate, alkaline phosphatase, parathyroid hormone and 25-hydroxyvitamin D were within normal limits. With history of significant unexplained fractures child safeguarding procedures were initiated. The infant

was thought to have clinical features of NS; genetic testing revealed a heterozygous mutation in SHOC2 c.4A>G (p.ser2Gly), confirming the diagnosis of Noonan syndrome with loose anagen hair. An unlabelled trans-iliac bone biopsy revealed marked cortical and trabecular osteopenia with relatively normal osteoblastic and osteoclastic activity. The patient has been commenced on cyclical intravenous Pamidronate therapy in order to reduce his risk of fracture.

Discussion
Generalised osteopenia is a recognised feature in RASopathies, such as neurofibromatosis type 1 and Costello syndrome. Stevenson *et al.* (*Clinical Genetics* 2011 **80**(6) 566–73) have shown that NF subjects have increased bone resorption as measured by urinary excretion of pyridinium crosslinks. However, to the best of our knowledge, osteopenia with early onset fragility fractures of axial and appendicular skeleton have not been previously described in NS.

P11

Dietary calcium restriction in idiopathic infantile hypercalcaemia does not adversely affect spinal and distal radial bone mineral density: report on nine patients

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Idiopathic infantile hypercalcaemia (IIH) (OMIM 143880) is characterised by severe hypercalcaemia, failure to thrive, vomiting, dehydration and nephrocalcinosis. Laboratory evaluation of infants affected with this condition reveals hypercalcaemia, suppressed parathyroid hormone and hypercalciuria. Recently loss of function mutations in *CYP24A1* gene have been found to cause IIH (*New England Journal of Medicine* 2011 **365** 410–21). Short-term treatment for this condition includes intravenous rehydration, furosemide, glucocorticoids, and pamidronate. Low-calcium diet is the mainstay for managing IIH until there is resolution of hypercalcaemia with age.

The aim of this study was to determine if dietary calcium restriction during infancy and early childhood adversely affected bone mineral density (BMD) in patients with IIH, when they were between 5- and 15-year-old. Nine patients with IIH who were treated with dietary calcium restriction for a period ranging from 1.7 to 4 years were studied. BMD of L1–L4 was measured using the dual energy absorptiometry and data was expressed as bone mineral apparent density (BMAD; g/cm³). The lumbar spine (LS) BMAD values transformed to Z-scores using the normative data (*ADC* 2007 **92**(1) 53–59). A peripheral quantitative computed tomography was used to measure the total and trabecular volumetric bone density (vBMD (mg/mm³)) of the distal radial metaphysis, at 4% of the non-dominant forearm length. Distal radial (DR) total and trabecular vBMD values were transformed to Z-scores using the normative data (*Osteoporosis International* 2009 **20**(8) 1337–1346). A one sample *t*-test was used to determine if measured bone parameters were significantly different to zero.

The mean (s.d.) Z-score of BMAD (0.09 (0.97)), DR total vBMD (0.32 (0.87)) and DR trabecular vBMD (−0.04 (0.76)) were not significantly different from zero.

From these results, we conclude that dietary calcium restriction for management of IIH during infancy and early childhood does not appear to adversely affect the distal radial and spinal BMD, when the patients were between 5- and 15-year-old.

P12

An unusual case of hypercalciuria with hypophosphataemia and hyperphosphaturia

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Hypophosphataemic rickets with hypercalciuria (HHRH) is a rare autosomal-recessive condition, typically reported in consanguineous families. Milder forms, with less significant hypophosphataemia, present with hypercalciuria and nephrolithiasis, without bone disease and may be underdiagnosed. The underlying pathophysiology is due to mutations in the *SLC34A3* gene, which encodes a sodium-phosphate transporter in the proximal renal tubules. Our patient, a 13-year-old Caucasian girl from a non-consanguineous family, presented with a history of intermittent loin pain, haematuria and passage of a kidney stone. Ultrasound showed a right-sided renal calculus with bilateral nephrocalcinosis. She did not have clinical features of osteomalacia. Urine biochemistry showed hypercalciuria (0.2 mmol/kg per day (normal <0.1)) and hyperphosphaturia (TmP/GFR 0.59 mmol/l (0.93–1.71)), with hypophosphataemia 0.78 mmol/l (0.95–1.5), suppressed serum parathyroid hormone (9 pg/ml (15–65)) and

elevated serum 1,25-dihydroxyvitamin D 109 pg/ml (20–50). Genetic studies found a heterozygous missense mutation c.413C>T (an extremely rare but known SNP) and a homozygous inframe deletion c.1576_1578delCTC. Parental DNA analysis found mother is heterozygous for both the missense mutation c.413C>T and the inframe deletion c.1576_1578delCTC, but no evidence of any mutation in her father. Treatment of the patient with oral phosphate supplements (introduced in incremental doses to prevent side-effects) has reduced urinary calcium excretion to 0.096 mmol/kg per day, with no further episodes of renal calculi. HHRH has only been described in a large Bedouin kindred and a few other sporadic cases worldwide. It is underdiagnosed and requires treatment with oral phosphate supplementation alone, without Vitamin D supplementation, which will worsen the condition. Treatment prevents renal calculi and allows normal bone development and growth.

P13

Managing hypercalcaemia in subcutaneous fat necrosis of the newborn

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Subcutaneous fat necrosis (ScFN) of the newborn is an uncommon self-limiting panniculitis, often associated with a complicated delivery. Hypercalcaemia can be a major complication, usually occurring within the first 6 months of birth and this may result in irritability, constipation, nephrocalcinosis, seizures and sometimes even death. Treatment options are variable with a number of different regimens including intravenous fluids, loop diuretics, prednisolone and bisphosphonates having been described in the literature. We report a series of five neonates who presented recently with ScFN and related hypercalcaemia.

All five patients were born after a difficult delivery and each manifested varying degrees of hypercalcaemia. One neonate had mildly elevated calcium levels (2.72 mmol/l) and was monitored with no further intervention required. Two were managed effectively with the use of low calcium milk feeds and the remaining two received intravenous hydration and multiple pamidronate infusions (peak calcium levels were 3.09, 3.13 mmol/l respectively). One patient in this series was diagnosed with ScFN and discharged home with no investigations or follow up and was subsequently readmitted with hypercalcaemia that required active treatment.

Our unit's experience reiterates the importance of monitoring calcium levels in all neonates with ScFN and highlights a management strategy, which successfully minimises significant co-morbidities.

P14

A neonate with hypocalcaemia caused by co-existing vitamin D deficiency and congenital hypoparathyroidism

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Introduction

Vitamin D deficiency is increasingly recognised as an important cause of neonatal hypocalcaemia. In this case report, we discuss the impact of co-existing vitamin D deficiency on the diagnostic process in a preterm infant who had refractory hypocalcaemia due to hypoparathyroidism resulting from a homozygous *GCM2* mutation.

Case report

A 33-week gestation male infant of Pakistani extraction was found to be profoundly hypocalcaemic with seizures and cataract formation. The hypocalcaemia was initially ascribed to vitamin D deficiency, as the neonate and his mother were both found to have low levels of vitamin D. However, the refractory nature of the hypocalcaemia and high doses of calcium supplementation required even when the vitamin D levels had normalised prompted a search for co-existing pathology. A persistently low parathyroid hormone level was identified in the baby, with normal PTH level in both parents, and he was subsequently found to have a homozygous *GCM2* mutation recognised to result in hypoparathyroidism.

Conclusions

Although it is well-recognised that 'common things are common', it is important to reassess a clinical situation when the clinical response is not as expected to standard treatment. Both rare and common pathologies can co-exist within the same presentation.

P15**Generalised arterial calcification of infancy**Pratik Shah¹, Philip Murray¹, Senthil Senniappan¹, Caroline Brain¹ & Jeremy Allgrove²¹Ormond Street Hospital, London, UK; ²Barts and The London NHS Trust, London, UK.**Introduction**

Generalised arterial calcification of infancy (GACI) is a rare autosomal-recessive disorder, associated with high mortality rate, due to inactivating mutations in ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) gene that results in arterial stenosis secondary to unregulated hydroxyapatite deposition.

Case report

A female baby was born at 34+5 weeks to consanguineous parents with a birth weight of 3.97 kg. Baby was born in poor condition at birth and subsequently developed Persistent Pulmonary Hypertension. She required high frequency ventilation and nitric oxide. On day three of life, echocardiogram showed severe pulmonary regurgitation with echogenic aorta and main pulmonary artery. CT chest and abdomen on day five of life showed heavy calcification throughout almost all of pulmonary arteries and aorta and subclavian, internal mammary, cephalic, and axillary arteries. She developed renal failure due to left renal artery stenosis and hepatic failure with left liver lobe infarction due to calcification in portal and hepatic veins. Serum calcium, phosphate, PTH and alkaline phosphatase levels were normal. Sequencing of *ENPP1* identified a novel homozygous frameshift mutation in exon 25 (c.2662_2662del, p.R888FsX), predicted to result in production of a truncated protein. Despite treatment with IV pamidromate at 0.1 mg/kg per week, there was a progressive decline in neurological function from day twenty of life and intensive care was subsequently withdrawn.

Conclusion

We report a novel nonsense mutation causing a severe phenotype of GACI affecting the heart, lungs, kidney, liver and brain. Although treatment with bisphosphonates improves outcomes in small proportion of cases, in our case there was no discernable response to therapy and the infant died due to multi organ failure secondary to GACI.

No formalised treatment approach exists for individuals affected by GACI although bisphosphonates are reported to reduce arterial calcification and improve in mortality rate. The optimum duration of bisphosphonate therapy for patients with GACI remains unclear.

P16**A case of Camurati-Engelmann disease with endocrine complications due to a missense mutation of the TGFB1 gene**Harshini Katugampola¹, Jemma Say¹, Meropi Toumba², Vassos Neocleous³, Christos Shammias³, Elisavet Efstathiou⁴, Violetta Anastasiadou⁴, Leonidas A Phylactou³, Nicos Skordis⁵ & Jeremy Allgrove¹

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Introduction

Camurati-Engelmann disease (CED) is a rare progressive bone dysplasia with ~200 cases documented worldwide. The hallmark is gross thickening of the diaphysis of long bones, usually presenting in childhood, with bilateral, symmetrical pain in the extremities. Endocrine complications include vitamin D deficiency, osteoporosis, delayed puberty, tall stature, hypogonadotropic hypogonadism and gonadal dysfunction. The disease has been ascribed to activating mutations in the TGFB1 gene encoding transforming growth factor TGFβ1.

Case

A 14-year-old Cypriot girl was referred with oligomenorrhoea and hyperprolactinaemia. She reported a 5-year history of bilateral leg and arm pain, with associated fatigue. Her father described a history of leg pains from childhood. Her X-rays showed symmetrical increased thickening of the cortical bones of the femurs and humeri with mild cystic changes. An initial diagnosis of polyostotic fibrous dysplasia was made, however symptoms worsened with pamidronate treatment. Examination revealed proximal muscle wasting and weakness. Her

bone scan showed symmetrical uptake of tracer in the femurs and humeri leading to a diagnosis of CED. This was confirmed by sequence analysis of the TGFB1 gene, which showed a known heterozygous missense mutation pR218C (an arginine-cysteine amino acid change at codon 218 in the latency-associated peptide domain of TGFβ1) in exon 4. The same mutation was identified in her father. She was commenced on prednisolone. At follow-up her limb pain and weakness had resolved, she had regular menses and her prolactin level had normalised.

Conclusion

This case report illustrates a rare, autosomal dominant, symmetrical bone dysplasia, associated with an activating mutation in the TGFB1 gene. Glucocorticoid therapy can potentially ameliorate symptoms, as well as correcting radiological findings. Endocrine complications, although of unknown mechanism, are important to identify and treat accordingly. Early recognition, genetic diagnosis and counseling, together with psychological support, play a crucial role in the management of these patients.

P17**Acute mesenteric ischaemia: a thrombotic complication of diabetic ketoacidosis?**Hannah Bailey^{1,2} & Rachael Barber^{1,2}¹Newcastle University Medical School, Newcastle-upon-Tyne, UK; ²Royal Manchester Children's Hospital, Manchester, UK.**Introduction**

Increasing evidence is emerging that demonstrates the increased prothrombotic risk associated with DKA.¹ We present the case of a child who developed multiple complications which we believe can be explained by his hypercoagulable state.

Case history

A 14-month-old male was admitted in DKA at first diabetic presentation, complicated by cardiovascular shock. Initial blood tests showed blood glucose 80 mmol/l, blood ketones 5.9 mmol/l and venous pH 7.2. He initially responded well to fluid replacement and insulin therapy according to BSPED guidelines, but subsequently developed abdominal distension and fulminant hyperkalaemia (K⁺ 10.3 mmol/l). Following stabilisation, laparotomy was performed with excision of 106 cm of necrotic jejunum and formation of a duodenal-ileal anastomosis. Post-operative course was complicated by multi-organ failure, development of arterial and venous femoral vasculature thrombosis, high stoma losses and difficult diabetes control. Despite this the patient survived and was eventually able to be discharged home following reversal of his ileostomy.

Conclusions

Acute mesenteric ischaemia (AMI) is a rare complication of DKA. While there are a number of cases described in the adolescent and adult population with long term IDDM^{2,3}, only two cases have previously been described in the literature of children developing AMI at first diabetic presentation^{4,5}. These authors differ in their conclusion as to whether non-occlusive ischaemia or thrombotic causes are responsible for AMI in DKA. We believe our report puts a strong case for a thrombotic aetiology, given the level of hyperosmolarity present in our patient and, more significantly, the concurrent development of arterial and venous thromboses. This also provides a platform for discussion of the recommendation in the latest BSPED guideline to give prophylactic anticoagulation in DKA. Furthermore we highlight the diagnosis and management of a rare aspect of DKA which nevertheless has important lessons for the clinician due to its associated morbidity and mortality.

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P18

The Euro-WABB Registry: differences in prevalence of diabetes between Wolfram, Alström, and Bardet-Biedl syndromes

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Objectives

We aimed to develop a registry for the rare genetic diseases Wolfram (WS), Alstrom (AS), Bardet Biedl (BBS) and other diabetes syndromes, containing clinical, genetic diagnostic and outcome data. The purpose is to establish the natural history of these diseases; to assess clinical management; to characterize cohorts for future clinical trials; and to establish genotype phenotype relations. This abstract describes the first 50 patients recruited.

Methods

Patients with a confirmed diagnosis (clinical or genetic) were recruited from both within and beyond Europe by their physicians. Information was collected for 42 'core' data fields, reached by consensus to differentiate between syndromes. We analysed prevalence of core clinical symptoms including obesity and diabetes.

Results

The age range was 2–44 years (interquartile range 6–20 years). There were 15 patients with WS (median age 18 years (range 9–44 years)), 16 with AS (14 years (2–30 years)), 17 with BBS (8 years (4–16)), 1 with Wolcott-Rollison and 1 with vision and hearing impairment of unknown cause. The prevalences of diabetes and median ages of onset were: WS (14/15; 6 years); AS (5/16; 13 years); BBS (2/17; 10 years); $P < 0.01$ for ages of onset WS vs AS and BBS combined). The prevalences of obesity and median ages of onset were: WS (2/15; 8 years); AS (12/16; infancy); BBS (16/17; 2 years); $P < 0.001$ for obesity prevalence WS vs AS and BBS combined).

Conclusions

The core dataset captured sufficient data to differentiate between diabetes syndromes. Diabetes mellitus presented before puberty in WS, was not associated with obesity, and is known to be insulin dependent; whereas it presented during puberty in AS and BBS, was associated with obesity, and is insulin resistant. The prevalence of diabetes is low in AS and BBS during childhood. Further patient recruitment and longitudinal data collection will use a consensus extended dataset of 400 fields to accurately characterize the phenotypes.

- Longer duration of appointments, open access to service with immediate appointments, named DSN to stay in telephonic contact
 - Telephone reminder service 3 days prior to the clinic, to improve attendance rates at appointments
 - Seen 1–4 times/year for up to 3 years based on clinical needs, then transfer to adult diabetes clinic
 - Transition empowerment evenings: organized by both teams on an annual basis for patients/families going through the transition
 - YAC also caters to young patients with new onset of diabetes (17–30 years)
- The last HbA1c from paediatric clinic, JTC and YAC were taken for statistics.

Results**JTC:**

31 clinics; 90 patients

266 patient appointments; 1–8/patient; 72.2% attendance rates

YAC:

35 clinics; 143 patients so far (65 from JTC, rest new referrals to the service)

254 patient appointments; 1–5/patient; 75.2% attendance rates

Transition care:

65 patients have been through joint transitional care

n=65	Clinic parameters	
	Joint transition clinic (JTC)	Young adult clinic (YAC)
Mean age at entry	17.1 years (15.6–19.0)	18.5 years (16.7–20.5)
Number of appointments/patient	2.9 (1–8)	2.7 (1–7)
Attendance rates	72%	67%
No. of patients with failure to attend at least 1 appointment	52% (20 – once, 10 – twice, 2 – thrice, 2 – four)	49% (17 – once, 7 – twice, 7 – thrice, 1 – four)
Failure to attend any appointment	12% (1–4 appointments)	6% (2–3 appointments)
Mean change in HbA1c	–0.1% (–4.7 to +9.9%)	+0.2% (–4.4 to +4.3%)
Proportion of patients with HbA1c worsening by >1%	25%	19%
Mean duration of follow up	453 days (49–1323)	326 days (0–763) (n=25)
Mean HbA1c at entry	9.8% (5–17.5%)	9.7% (5.3–15.5%)
Mean HbA1c at exit/ last appointment	9.7% (5.3–15.5%)	9.8% (6.7–15.6%)
Proportion of patients with overall improved HbA1c	49.2%	50.8%

39 on-going care in YAC; 25 transferred to other services (1 for insulin pump; 2 to pregnancy clinic; 15 to adult care; 7 to primary care (4 for repeated non-attendance)); 1 died (non-diabetic complication).

Conclusion

The attendance rates in the transitional care pathway clinics are high (72% in comparison to previous adolescent diabetes clinic attendance rates of 45% prior to the introduction of this pathway), with majority getting sustained improvement in glycaemic control. Our care pathway provides an effective, patient-centred, coordinated, multi-professional team based staged approach to deliver transitional care to this at-risk vulnerable group of patients.

P19

Adolescent diabetes and emerging adulthood: effectiveness of a robust and staged joint-care transition pathway

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Background

An effective care pathway is required for the smooth 'transition' (rather than swift 'transfer' of care) from the paediatric to adult diabetes clinic. Engaging the patient in the service, with a clear, smooth and robust pathway, is required to bridge this very challenging period. The aim of our study was to assess the effectiveness of a staged transition process based on a shared-care protocol that has been existent over the last 3 years at our centre.

Materials and methods

The transition care happens in a two staged process

Joint transition clinic (JTC)

- Paediatric team identify patients ready for transition
- Patients seen in JTC over 3–4 appointments over a year
- Adult diabetologist and diabetes specialist nurse (DSN) sit in
- Paediatric team lead first two clinics; adult team lead subsequent clinics and transfer to the young adult clinic

Young adult clinic (YAC)

- Same adult team conduct this clinic at the same site

P20

Uptake of 2009 BSPED guidelines in Northern East England and North Cumbria

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Background

Diabetic ketoacidosis (DKA) remains the leading cause of morbidity and mortality in children with type 1 diabetes. In the past few years, both the International Society for Paediatric and Adolescent Diabetes (ISPAD) and the British Society for Paediatric Endocrinology and Diabetes (BSPED) have recommended key changes in the management of DKA. These changes incorporate new evidence to reduce the incidence of cerebral oedema and the increased use of insulin pumps.

Aim

To assess the uptake of the 2009 BSPED guidelines for paediatric DKA management in Northern England.

Method

Telephone/email questionnaire survey of General Paediatric and Accident and Emergency Consultants and Registrars and review of the written guidelines in use at the 15 acute centres in Northern England who manage children < 16 years with DKA. The analysis centred on compliance with the key changes recommended in 2009.

Results

The response rate was 100% (15/15).

Conclusion

The changes suggested in the BSPED guidelines have been adopted by 8/15 of the centres. Worryingly, recommendations commensurate with reducing the risk of cerebral oedema were not uniformly followed: 7/15 of centres have not altered their local fluid protocol and 2/15 of the units still do not explicitly recommend delay in insulin administration during fluid replacement in DKA. We recommend that all centres review and address barriers to implement these national guidelines and that a national mechanism be put in place to evaluate whether changes in guidelines have the desired effect.

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Table 1

Recommended changes	Compliance rates
Reduction in estimated degree of dehydration	8/15 (53.3%)
Reduction in maintenance fluids rates	8/15 (53.3%)
Delay in insulin administration for the 1st hour	13/15 (86.7%)
0.9% Saline for first 12 h	8/15 (53.3%)
Preference of 3% saline over mannitol	8/15 (53.3%)
Option to continue Glargine during treatment	8/15 (53.3%)
Reminder to stop insulin pump therapy during treatment	10/15 (66.7%)
Capillary blood ketone measurement	13/15 (86.7%)

P21

Pigmentary hypertrichosis and non-autoimmune insulin dependent diabetes mellitus syndrome is associated with severe chronic inflammation and cardiomyopathy, and represents a new monogenic autoinflammatory syndrome

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Introduction

Mutations in SLC29A3 lead to PHID and H syndromes, familial Rosai Dorfman Disease and Histiocytosis-lymphadenopathy plus syndrome. PHID syndrome is associated with short stature, pubertal delay, endocrine and exocrine pancreatic insufficiency. We report a new association of PHID syndrome with severe systemic inflammation, scleroderma-like changes and cardiomyopathy.

Case report

A 12-year-old girl with PHID syndrome presented with shortness of breath, hepatosplenomegaly, lymphadenopathy, short stature, anaemia and ascites. ESR (110 mm/h), CRP (76 mg/l) and serum amyloid (SAA) levels were elevated. Prednisolone therapy provided some symptomatic relief however treatment with Anakinra (IL1 receptor antagonist) and Adalimumab (TNF α inhibitor) was ineffective. An echocardiogram showed biventricular myocardial hypertrophy and pericardial effusion. A cardiac MRI showed circumferential, epicardial, late gadolinium enhancement of the LV and RV myocardium, with sparing of the endocardial layer. This pattern is distinct from that usually caused by cardiac amyloidosis. No systemic amyloid deposits were observed on a whole body serum amyloid P scintigraphy (SAP) scan at the age of 10 years and normal urinary protein excretion further mitigated against renal amyloidosis. Abdominal ultrasound revealed large amounts of intra-abdominal fat surrounding the solid organs suggesting a possibility of evolving lipodystrophy with visceral adiposity.

Conclusion

PHID syndrome is a novel monogenic autoinflammatory syndrome (AIS) associated with severe elevation of SAA. Lipodystrophy, cutaneous scleroderma-like changes and cardiomyopathy were also present in this case. In contrast to other AIS, blockade of IL1 and TNF α was ineffective. The mechanism of severe autoinflammation is unknown, although nucleoside accumulation in macrophages could contribute to immune activation. It is important to further understand the mechanism of auto inflammation in PHID and related syndromes, since effective therapy so far has remained elusive.

P22

Newly diagnosed type 1 diabetes: similarities and differences in initial management guidelines

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Introduction

The number of children with type 1 diabetes continues to rise by 3% per year. As part of an audit of in-patient care of children up to 16 years with diabetes, the guidelines for management of the newly diagnosed children from participating hospitals were reviewed and compared to national and international recommendations.

Methodology

Across the Oxford, Wessex and South West Paediatric Diabetes Networks 21 out of the 27 requested services submitted their current protocol for children presenting with newly diagnosed diabetes. Themes around referral, home vs hospital management, initial screening investigations, starting insulin regimen and education were examined.

Results

Referral and location: 62% highlighted the need for same day referral. 24% described admitting children for several days and 38% advocated home management. Investigation: Thyroid and Coeliac screening were advised by 95%, Islet cell antibodies 90%, anti GAD 76%, HbA1c 76% and C-peptide by 38% services. Initial Insulin Regimen: All services start some children on 0.5 units/kg per day. However, 38% vary the dose with age/puberty status, and 14% give higher doses with ketonuria. 86% advocate basal bolus regimen for all or a subgroup of patients. The percentage of total daily dose given as basal insulin varied from 20 to 60%. Almost half of the services would start primary school children on twice or trice daily regimens. Education: Diabetes team were to be informed in all protocols; and education was mentioned in all but one. The described content varied and provision of written information was mentioned in 76%.

Discussion

Local guidelines predominantly follow NICE and ISPAD recommendations. There were however a variety of initial insulin regimens and dosages across just these three regions of England. It would be preferable to have nationally agreed starting insulin regimens and achieve a validated education program.

P23

Results from 23 years of continuous diabetes audit

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Audit data were prospectively collected on establishing a multidisciplinary children's diabetes service in a small district general hospital serving a mixed urban and rural community in 1989. Only two team members DSN and paediatrician were unchanged until 2009.

The number of children diagnosed with diabetes more than doubled, with overall incidence rates of ~27/100 000. From 1998 until 2008 all newly diagnosed children were managed as outpatients unless presenting with significant ketoacidosis. Most children used twice daily pre-mixed insulins until 2002 when multiple daily injection therapy (MDI) was promoted. The first insulin pumps were introduced from 2003. By 2007 over 50% of children were using insulin pumps, while more than 30% used MDI. Metabolic control as measured by HbA1c showed steady improvement, allowing for changes in assays, from 9.79% in 1989 to 7.97% in 2006. Subsequent significant organisational changes led to a marked deterioration in HbA1c results. Further analysis has shown the best outcomes in this service were seen in pre-school children starting on insulin pumps at diagnosis, with worst control for children starting on MDI. Whilst a formal transition process to the adult service began in 1991 their control generally deteriorated for the next four years following transition.

This audit has been a driver for change and improvement as well as demonstrating evolution in the epidemiology and management of a children's diabetes service over two decades.

P24

Severe hypercalcaemia secondary to severe, prolonged metabolic acidosis in a patient with DKATafadzwa Makaya, Paul Arundel, Clifford Bevan & Neil Wright
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Background

Children presenting with diabetic keto-acidosis (DKA) as an initial presentation of diabetes mellitus are often unwell, with associated increases in mortality and morbidity. While electrolyte imbalances such as hypokalaemia and hypophosphataemia are well recognised, the incidence of hypercalcaemia is less well documented.

Case

A previously healthy 12-year-old boy presented to hospital with a history suggestive of new onset diabetes. Initial bloods indicated DKA: pH 6.84, BE -28.9 and plasma glucose 30.4 mmol/l. Clinically he was severely dehydrated (estimated 8%). Despite standard management according to national guidelines he developed a reduced GCS, presumed secondary to cerebral oedema, requiring intubation and ventilation.

He remained severely acidotic, which was initially secondary to keto- and lactic-acidosis but was then propagated by hyperchloraemia. Over the next few hours he gradually developed acute severe hypercalcaemia, with maximum corrected calcium of 3.75 mmol/l. Possible causes for hypercalcaemia including hyperparathyroidism, malignancy, and thyrotoxicosis were ruled out. He developed mild-moderate renal failure (maximum creatinine 269 mmol/l). He was treated cautiously with rehydration as part of a neuro-protective strategy and latterly treated with frusemide infusion and hydrocortisone. Calcium levels and renal function normalised within a week.

Discussion

Potassium and phosphate disturbances are common in DKA, however significant abnormalities in calcium haemostasis are less common. Severe hypercalcaemia in DKA is likely due to diminished bone formation mediated in part by metabolic acidosis, paired with increased bone resorption due to severe insulin deficiency and metabolic acidosis. We suggest that calcium concentrations are checked routinely in all DKA patients.

Table 1

	Cor- rected calcium (mmol/l)	PO4+ (mmol/l)	Mg2+ (mmol/l)	PTH (ng/l)	Total vitamin D (nmol/l)	Urine cal- creat ratio	Na2+	Cl- mmol/l	pH	BE
D0	2.57								6.84	-28.9
D2	3.75	0.36	1.01	8.3	22	0.17	161	137	7.08	-21.2
D4	3.72	0.62	0.92				167	149	7.32	-14.4
D6	2.76	0.91					148	121	7.38	-4.7
D8	2.56	1.23					142	108		
D10	2.46	1.56		45.4				100		

P25

Review of guidelines for the management of children and adolescent with diabetes requiring surgery in three regions of EnglandAzriyanti Anuar^{1,3}, Rajput Shailendra¹, Trevelyan Nicola² & Julie Edge¹¹Paediatric Diabetes Service, Oxford Children's Hospital, Oxford, UK;²Paediatric Department, University Hospital Southampton NHS Trust,Southampton, UK; ³Paediatric Department, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia.

Introduction

The management of diabetes during surgery in children is not evidence-based although the ISPAD has produced consensus guidelines.

Aims

To explore the variability of guidelines in three regional diabetes networks in South West and South Central England and to compare them to the current ISPAD 2009 Guidelines.

Methods

Within an audit of in-patient care, a copy of the surgical guidelines was requested from 27 paediatric diabetes centres. Care plans including timing of surgery, blood glucose (BG) target, insulin and fluid regimens were analysed.

Results

Twenty-two guidelines were submitted. 19/22 (86%) clearly split their guidelines into major, minor and emergency surgery. For major surgery, 77% gave clear information to admit a day before surgery but 68% did not advise about time of

admission for minor surgery. All guidelines documented the importance of placing first on the surgical list. Only 5/22 (22%) used ISPAD BG target range (5–10 mmol/l), 4/22 did not mention a glucose target. 15/22 (68%) services instructed the usual dose of insulin the evening before. Almost all (21/22) gave advice for patients on multiple daily injections, 18/22 (82%) mentioned twice-daily insulin and only 4/22 (18%) mentioned three times daily insulin. 10/22 (45%) gave advice for patients on insulin pumps but only 2 followed ISPAD guidelines. 19/22 (86%) provided infusion rates for insulin; these range from 0.3 to 0.5 units/kg per h (ISPAD recommends 0.025 units/kg per h). Only 10/22 (45%) used 0.45% sodium chloride with 5% dextrose and potassium as the main fluid regime. 59% gave advice for Emergency surgery but only one service gave additional advice for children with T2DM.

Conclusion

In spite of availability of international guidelines, a large degree of variation still exists in many aspects of management. In particular, variation in insulin and fluid regimens is confusing. National guidelines should be standardised to improve care quality.

P26

Co-morbidities in children and young people with type 1 diabetes: who is responsible for management?Suruchi Agarwal, Verghese Matthew, Trudy Tapson & Sanjay Gupta
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Introduction

Children and young people with type 1 diabetes are usually managed by multidisciplinary teams (MDT) based in secondary care. Many of them have co-morbidities, which may or may not be associated with diabetes. Presence of co-morbidity increases health care needs and costs. Such co-morbidities in adult patients with diabetes are primarily managed by the general practitioners (GP) (Struijs, Baan *et al.*; 2006). Our aim was to analyse the prevalence of co-morbidities in paediatric patients with type 1 diabetes in our local population and to identify the responsible professional for management of these co-morbidities.

Method

In this cross sectional, retrospective audit we identified all current patients with type 1 diabetes registered in the Twinkle database. The co-morbidities in these patients were identified by case note analysis, information from the database and recall from MDT members. Patients with psychological, behavioural, eating disorders and type 2 diabetes were excluded.

Results

We identified 245 active paediatric patients with type 1 diabetes (ages 0–18 years) on the Twinkle database. Fifty patients (20%) had a total of 68 co-morbidities with 12/50 (24%) patients having more than one co-morbidity. Of the 68 co-morbidities, 18/68 (26%) were diabetes associated. The majority 43/68 (63%) of the co-morbidities were managed by secondary care, 22/68 (32%) were managed by the diabetes team and 3/68 (5%) were managed by the GP.

Conclusion

Co-morbidities are common in children with type 1 diabetes. Majority of these are managed in secondary care and the diabetes team manages more than one third of these. It is important to identify these during the MDT consultation to address any unmet needs of patients and families.

P27

Cerebral oedema in toddlers; risks and challenges: a case seriesManu Sundaram, Loveline Ayuk & Raffeeq Parakkal
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Prevention, diagnosing, and adequate management of cerebral oedema in diabetic ketoacidosis are of vital importance. This can be very challenging in infants and toddlers as symptoms can be very subtle or difficult to interpret. Young age, new diagnosis of diabetes, and severe acidosis at presentation has been reported as risk factors for the development of cerebral oedema. We report our experience in managing one infant and two toddlers newly diagnosed diabetics who were referred to our paediatric intensive care unit with cerebral oedema in a 6 months period.

Their ages ranged from 8 to 17 months. They all presented to their local hospitals with short histories of vomiting, tachypnoea, and being generally unwell. Their blood sugars readings on admission ranged from 22 to 77 mmol/l, with severe acidosis, high blood ketones, high plasma sodium, high urea and they received 20–40 ml/kg of fluid boluses. They were referred to our unit following diagnosis

and initial management of probable cerebral oedema. They were managed using various guidelines all based on the ISPAD consensus 2009. Mannitol is known to cause a huge diuresis following its administration and hypertonic saline 3% raises plasma sodium by 0.8–1 mmol/l both posing a challenge in the presence of high plasma osmolality, fluid restriction and plasma sodium of more than 160 mmol/l. Managing these un-intubated children in the PICU was challenging, as they were irritable and fit into the major and minor criteria for the bedside evaluation of the neurological state and difficulties in placing monitoring lines without sedation.

P28

Improvement in HbA1c following change from three times daily injections to a basal bolus insulin regimen in the Lothian paediatric diabetes population

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Background

The need for improved glycaemic control in children with type 1 diabetes in Scotland is well recognised; DIABAUD 3 identified that only 9.7% achieved the national HbA1c target.

Aim

To evaluate whether a change from three times daily injection regimen to a basal bolus regimen with carbohydrate counting at diagnosis will result in an improvement in immediate and longer term glycaemic control.

Method

We included children <16 years of age admitted to Royal Hospital for Sick Children, Edinburgh with a new diagnosis of non-decompensated type 1 diabetes Mellitus. A retrospective case note review was performed for children admitted before August 2010 ($n=36$) started on three times daily injections and a prospective case note review for children admitted after August 2010 ($n=36$) started on basal bolus regimen. Data collected consisted of HbA1c and initial blood glucose and blood ketone results, as well as HbA1c values at 6 and 12 months follow up.

Results

Children on the basal bolus regimen showed better control in the last 24 h before discharge, with 37% of readings under 10 mmol/l vs 30.5% on the previous regimen. HbA1c was measured at diagnosis, 6 and 12 months. At 6 months after diagnosis mean HbA1c had decreased further in children commenced on basal bolus regimen, compared with children commenced on the standard regimen (44.7 vs 36.6%, $P<0.05$). This was despite the fact that 25/36 of those originally commenced on the standard regimen subsequently switched to a basal bolus during the follow up period.

Conclusion

In the Lothian population children started on a basal bolus regimen at diagnosis showed better glycaemic control during admission and at 6 months post diagnosis. Data collection is ongoing for HbA1c results at 12 months. The reasons for this improved glycaemic control may be multifactorial and further studies are required.

P29

Should we check vitamin D status at time of diagnosis of type 1 diabetes mellitus?

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Physiology shows vitamin D has a role in the immune system and glucose metabolism. Experimental and epidemiological studies demonstrate associations between type 1 diabetes mellitus (T1DM) and vitamin D levels. Vitamin D deficiency appears undesirable in T1DM, although its significance in aetiology and progression is controversial.

We reviewed the outcome of implementing vitamin D screening at T1DM diagnosis. Methods were review of diabetes register, hospital case notes and pathology systems. Of the 46 T1DM cases diagnosed March 2011–2012, 42 were tested (seven sampling errors: six insufficient, one wrong tube). Within 1 month of diagnosis, three were re-sampled and a further child also tested, giving 39 evaluable vitamin D results (85% cases). Only 26% (10/39) had optimal levels (>75 nmol/l), 46% (18/39) suboptimal (50–75 nmol/l), 18% (7/39) insufficient (25–50 nmol/l) and 10% (4/39) were deficient (<25 nmol/l). Vitamin D levels

showed no correlation with age, HbA1c or pH. There was a seasonal trend in vitamin D levels, with all four vitamin D deficiency cases diagnosed December–March (2/4 were non-Caucasian). 91% of hospital notes reviewed contained documented results. All four cases of deficiency had a treatment plan, although two had unclear documentation of implementation. Local practice guidelines have achieved increased identification and treatment of vitamin D deficiency. Vitamin D deficiency is problematic in the UK. Ideally more children would receive preventative Vitamin D supplements if national recommendations are followed (all children under 5 years old, particularly children with other risk factors for vitamin D deficiency). The prevalence in our newly diagnosed T1DM population may simply reflect that of the wider community. Screening Vitamin D status at T1DM diagnosis provides an opportunity to address Vitamin D deficiency (<25 nmol/l) in this subgroup. Screening and treating Vitamin D at diagnosis can be advocated for the broader non-diabetes health benefits, although the potential effect on ameliorating T1DM progression requires further evaluation.

P30

Audit of diabetic ketoacidosis management in adolescents in paediatric and adult care settings

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Introduction

Guidance on the management of diabetic ketoacidosis (DKA) has recently been updated in an effort to reduce the risk of complications, in particular, cerebral oedema. However, differences in recommendations for children and adults persist making the care of teenagers with DKA confusing and potentially hazardous.

Aims

To compare the management of DKA in teenage patients in paediatric and adult care settings in the context of the latest national guidelines^{1,2}.

Methods

A retrospective review of DKA cases aged 14–19 years, admitted with DKA to a teaching hospital between June 2010 and May 2011.

Key findings

Ten cases were reviewed with a median age 15.9 years (range 14.2–18.6). Four patients were cared for by the adult team (age range 17.8–18.6 years) and six patients by the paediatric team (age range 14.2–16.0).

Fluids: All adult patients received fluid boluses (4/4) compared with only one of the paediatric group (1/6). All paediatric patients received potassium in their maintenance fluid from the outset in contrast to only two adult patients (2/4).
Complications: Neuro-observations were recorded in only one of the adult patients (1/4) and 4 of the paediatric patients (4/6). No patients developed cerebral oedema. One paediatric patient developed hyperkalaemia, this resolved without specific treatment. One drug error occurred in each group.

Outcome: Only one patient, belonging to the adult group, required high dependency care. The mean inpatient stay in the adult group was 49 h (range 20–72 h), and in the paediatric group 26.5 h (range 8–40 h).

Summary

This small project highlights noteworthy differences in fluid therapy in adolescent DKA managed by different teams. Some aspects fell below recommended standards in both paediatric and adult care, in particular careful monitoring of neurological status.

P31

Type 1 diabetes in a child with aplastic anaemia

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Introduction

Abnormalities in glucose tolerance and diabetes have been described in various types of bone marrow failure including Fanconi's and Diamond-Blackfan anaemia. It is also recognised that transmission of type 1 diabetes can occur following bone marrow transplantation (BMT).

Case report

We report a 9-year-old girl who presented with a three week history of lethargy and petechial spots. She was pancytopenic and subsequent investigations diagnosed a severe aplastic anaemia, Fanconi screen negative. Treatment with transfusions, alongside prophylactic antibiotic and antifungal agents, was

commenced. No steroid treatment was instituted. Blood glucose level on this initial presentation was 16 mmol/l, with a clear urine dip. There was no history of polyuria, polydipsia or weight loss and no family history of diabetes. This result was attributed to a stress response and not further investigated. Whilst awaiting BMT she re-presented 3 months later with mouth ulcers. Blood glucose level at this time was 25.3 mmol/l. There was heavy glycosuria, no ketonuria and no acidosis on blood gas analysis. Diabetes screening bloods were taken and insulin was commenced on a multiple daily injection regime. Results showed: HbA1c 9.3% (78 mmol/mol), Insulin 34.9 mIU/l (taken after 24 h on insulin therapy due to initial sample error), C-peptide 1245 pmol/l. Anti-GAD, islet cell and IA2 antibodies negative. Insulin requirements reached 0.7 µ/kg per day. Due to severe sepsis and suspected invasive pulmonary aspergillosis, which also made anorexia a predominant feature, adjustments were needed frequently to the insulin regimen.

Conclusion

We believe this is the first reported case of diabetes in aplastic anaemia prior to BMT. The case highlights the importance of pursuing raised blood glucose levels in any individual regardless of their diagnosis and clinical status and also the challenges of managing such an insulin regime during severe sepsis.

P32

Gonadotropin independent precocious puberty associated with later diagnosis of testicular embryonal carcinoma

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Introduction

Testicular tumours are very rare in children and usually present as painless enlargement of the testis. Germ cell tumours account for the majority of testicular tumours in young people and embryonal carcinomas are a common component of germ cell tumours.

Case report

A 9.8 year old boy presented with the development of pubic and facial hair over a period of 2 years. He had a growth spurt (Height +3 SDS and bone age advanced to 14.8 years) and examination revealed pubertal staging of G4 P4 A2 with asymmetric testes (right testis 6 mls, left testis 2 mls). Investigations revealed suppressed gonadotropins on GnRH test, testosterone concentration of 10.3 nmol/l, and normal 17OHP and adrenal androgens. Tumour markers including AFP and β-hCG were negative. MRI brain was normal and adrenal ultrasound did not reveal any masses. Following treatment with anastrozole and spironolactone, the height velocity slowed down. At the age of 11 years, the right testis was noted to be 10 mls in size whilst the left testis measured 2 mls. The repeat tumour markers were negative and a testicular ultrasound revealed scattered microcalcifications, but no evidence of tumour. At the age of 13.7 years, his treatment was stopped when he reached near adult height of 164.2 cm (+0.7 SDS, within midparental target range). At the age of 14.8 years, he presented with a grossly enlarged right testis which was hard on palpation whilst the left measured 6 mls in size. His β-hCG was >1400 IU/l. He underwent right orchidectomy and histology revealed an embryonal carcinoma with no vascular invasion. The tumour markers normalised post-surgery. Analysis of luteinizing hormone/choriogonadotropin receptor mutation is being undertaken.

Conclusion

We present a case of testicular embryonal carcinoma in a boy who presented with features suggestive of gonadotropin-independent precocious puberty 5 years previously.

P33

Karyotype-phenotype correlations in height and pubertal outcomes of Turners patients

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Introduction

Turner syndrome (TS) is caused by the absence of all or some of the second sex chromosome. Consequences include short stature and ovarian failure. This study aimed to characterise karyotype-phenotype correlation in patients with TS.

Methods

This was a retrospective audit of TS patients from the young person's endocrine clinic (YPC). The karyotype, final height, pubertal progress and treatment were recorded for each patient and outcomes were compared by karyotype category.

Results

We identified 37 TS patients in the YPC aged 17–24 years. 24% had 45XO, 76% had other karyotypes (mosaicism or structural abnormalities of the second X). The mean final height of the cohort was 1.50 m (range 1.38–1.64), i.e. –2.00 s.d. (population reference) or 0.61 s.d. (Turner reference). 32 received GH treatment. There was no significant difference in height between 45XO patients and others. Patients with Y chromosome material were taller, 1.54 m (6 patients). 18 (49%) entered puberty spontaneously (SP) and 8 (22%) achieved spontaneous menarche (SM); none of these were 45XO. Of the eight with an XX cell line, six had SP and five had SM. The average age of spontaneous or induced puberty was 13.0 years, and the average age of menarche was 15.8 years. 25 had pelvic ultrasound (US); 12 had normal ovarian appearance, of whom 8 had SP and 6 reached SM. 26 had FSH measured; mean FSH (IU/l) in those with SM was 4.1, compared to 38.3 in those who only had SP and 86.3 in those with no SP ($P < 0.05$ vs those with SP).

Conclusion

This audit illustrates the karyotype-phenotype correlations in the height and pubertal outcomes of TS patients. If patients have at least one XX cell line, the chances of SP and SM are significantly higher. Prepubertal US and FSH were good predictors of pubertal outcomes.

P34

Abnormal glucose homeostasis in survivors of childhood acute lymphoblastic leukaemia treated with total body irradiation and bone marrow transplantation is associated with increased visceral and intramuscular fat

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Introduction

This study explores the role of different fat depots in the aetiology of abnormal glucose homeostasis in childhood ALL survivors treated with BMT and TBI using detailed body composition assessments with MRI and DEXA scanning.

Method

52 (16–26 year old) childhood ALL survivors treated with (group 1, $n=21$, $M=11$) and without (group 2, $n=31$, $M=13$) BMT and TBI and 20 obese subjects (group 3, $M=10$) were investigated. Each had body composition assessment by single slice abdominal MRI at L4-5, DEXA scans, and standard oral glucose tolerance tests (OGTT). Outcome measures included DEXA total and android (central) fat%, MRI subcutaneous, visceral and intramuscular fat areas corrected for height, and insulin resistance (IR) by insulin area-under-the-curve (AUC) from OGTT. Comparisons between groups were made by ANOVA, with *post hoc* Scheffe test after logarithmic transformation if not normally distributed, and significance at 5%.

Results

Results were reported as mean (s.d.) or geometric means (range). Despite significantly lower total body fat% ($P < 0.001$) and android fat% on DEXA ($P < 0.001$), group 1 compared with group 3 had more cases of impaired glucose tolerance (IGT) or diabetes mellitus (DM) ($n=9$ vs 1, $P=0.001$) and higher IR ($P=0.005$). MRI results showed that group 1 compared with group 3 had more visceral fat ($P < 0.001$) in female, as well as more intramuscular fat ($P=0.003$), less subcutaneous fat ($P < 0.001$) but higher visceral-to-subcutaneous fat ratio ($P < 0.001$) in both genders. Analysis of all participants showed significant correlation between visceral fat ($P < 0.001$) and intramuscular fat ($P=0.002$) with insulin AUC.

Conclusion

Increased intramuscular fat, visceral fat and relative reduction in subcutaneous fat play a role in the aetiology of IGT and DM in childhood ALL survivors treated with BMT and TBI. MRI provides more detailed information in the assessment of body composition in chronic disease patients.

P35

Late endocrine effects of non-craniopharyngioma, non-glioma brain tumours: descriptive analyses of patients referred to late-effects service
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Background

Children with brain tumours are known to be at risk of late neuroendocrinopathies due to anatomical and treatment disturbances to central pituitary function.

Aims

To provide a descriptive analysis of a cohort of children with such tumours, referred to the late-effects neuroendocrine service at UCLH. It aims to describe the types of tumour, treatment and current endocrine morbidity of this cohort.

Methods

Cases were identified from the late-effects referral database maintained at UCLH. Cases were excluded due to incorrect tumour site entry in database, death or incomplete/unavailable endocrine status. Analysis was performed using SPSS version 17. Endocrinopathy was defined by currently receiving treatment or demonstrable insufficiency of hormone on last dynamic function test. Endocrine Morbidity Score was calculated to assess outcomes.

Results

Forty patients were identified from the database. After exclusions, 24 patients were analysed. Mean age at diagnosis was 11.01 (s.d. \pm 3.87); 16/24 (66%) of tumours were Germinomas. 91.3% of patient received radiotherapy, 55% surgery and 50% chemotherapy. ENDOCRINE STATUS: 21/24 patients were growth hormone deficient (84.5%) at latest follow up, with only 7/24 (29.1%) known to have been tested at tumour diagnosis. EMS score was >2 (GHD+Thyroid/DI+ other) in 16/24 (66.6%) patients. Induced puberty was required in 11/24 (45.8%) cases, with precocious puberty occurring in just 1/24 (4.2%).

Conclusions

Neuroendocrine sequelae of non-glioma non-craniopharyngioma type tumours are severe and multiple. Baseline endocrine function of such patients should be investigated prior to treatment to establish origins between tumour and iatrogenic causality, and all patients should be referred to a late neuroendocrine effects service.

P36

Audit of endocrine late effects in survivors of childhood brain tumours
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Brain tumours are the most common solid tumour in children, affecting 400 children in the UK each year. The aggressive treatment required for cure, may have serious consequences, of which endocrine late effects are the most prevalent. This aim of this audit is to ascertain the frequency and nature of endocrine late effects; in a cohort of 30 survivors, diagnosed over a fourteen year period. Data was collected on tumour site, histology, treatments used and endocrine complications.

75% of children underwent surgery, 89% received chemotherapy, 39% received cranial radiotherapy, 26% received craniospinal radiotherapy and 18% children received both cranial & craniospinal radiotherapy.

57% of survivors were referred to the Endocrine clinic, at a mean duration of 1 year following end of treatment.

29% of survivors were diagnosed with GH deficiency (87.5% of these children had received radiotherapy). Impaired spinal growth was seen in all children who received craniospinal radiotherapy. 18% of children were found to have a suboptimal cortisol response; necessitating emergency hydrocortisone treatment. 11% of survivors developed hypothyroidism; all of these children had received radiotherapy. Onset of hypothyroidism ranged from at completion of treatment to 5 years following treatment. 11% of survivors were diagnosed with precocious puberty; which in 1 case had masked a GH deficiency.

In conclusion, this audit confirms the high prevalence of endocrine late effects in survivors of childhood brain tumours. Data support the establishment of a joint oncology and endocrinology late effects clinic; to ensure early identification and treatment of these serious complications.

P37

Long-term morbidity after traumatic brain injury in childhood: fatigue, impact on cognition, health related quality of life and abnormal GH status

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Objectives

To determine long-term functional outcome following traumatic brain injury (TBI) in childhood.

Patients

Longitudinal study of 49 participants with TBI (21 mild, 28 moderate/severe TBI) and 16 healthy controls matched for age, gender and socioeconomic status. Age at TBI (median (range)) 11.8 (1–16) years; 17 were prepubertal, 16 peripubertal, 16 postpubertal. Age at study 19.7 (10–26) years, time post TBI 8.6 (5.8–10.8) years. All subjects had clinical review, auxology and pubertal assessment. Quality of life was assessed with the Paediatric Quality of Life Inventory (PedsQL 4.0) and the Health Utilities Index (HUI), fatigue with the Chalder fatigue questionnaire. 24/28 of the moderate/severe TBI group agreed to GH stimulation testing (ITT) (6 peripubertal, 18 postpubertal).

Results

None of the participants had clinical problems with growth, puberty or thyroid status or were on anti-convulsants. The overall HRQL scores using the HUI3 multi-attribute utility function were significantly lower ($P=0.05$) in participants with moderate/severe TBI (0.82) than in mild TBI (0.91) or in the control group (0.95). Single-attribute utility function analysis showed significant differences ($P=0.006$) in cognition scores between groups (moderate/severe 0.86, mild 0.92 and control 1). PedsQL results did not reach significance but overall and psychosocial health summary scores were lower in the moderate/severe than mild and control group (80 ± 16 vs 81 ± 19 vs 87 ± 7 and 76 ± 18 vs 78 ± 23 vs 87 ± 7 respectively). Physical health summary scores did not differ between groups. Fatigue scores were higher in the TBI vs control group (14/34 vs 0/9 reaching the bimodal score >4 , $P=0.02$). 6/24 had suboptimal GH and one had a suboptimal cortisol response but GH status did not correlate with fatigue or poor HRQL.

Conclusions

Evidence of poor HRQL, cognition difficulties and fatigue are identifiable 8–10 years post TBI. Their aetiology is not explained by GH status in standard provocation tests and requires further investigation.

P38

Cushing's syndrome due to POMC secretion from an abdominal yolk sac tumour in a 2 year old child

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Cushing's syndrome due to ectopic ACTH production is extremely rare in childhood. Ectopic ACTH secretion is most often due to tumours in the chest, but rare cases of carcinoid tumours, neuroblastoma, pheochromocytoma and pancreatic and ovarian carcinoma have been reported. We describe a 2 year old girl with ectopic Cushing's syndrome due to a malignant epithelial abdominal tumour producing POMC. She presented with rapid weight gain, hypertension, body odour, lethargy and moodiness. Urinary cortisol excretion was severely elevated. Cortisol was partly suppressed on low (22%) and high dose dexamethasone (43%) suppression test. CRH test results (12% increase in ACTH) suggested ectopic ACTH secretion. Further imaging led to the identification of an abdominal tumour with marked peritoneal infiltration secreting AFP. Histology revealed a malignant yolk sac tumour, strongly expressing AE1/3 (a pancytokeratin marker) but not CD117, Oct3/4, CD56, desmin, WT1 and S100.

Posttranslational processing of POMC results in the generation of ACTH, the N-terminal POMC fragment, and β -lipotrophin which is cleaved to β -endorphin (bEP). Circulating POMC concentrations (measured by specific ELISA) were increased and then decreased during chemotherapy, whereas ACTH (measured by ELISA which cross-reacts 1% with POMC) concentrations were not elevated. Immunohistochemistry of the tumour utilised antibodies recognising POMC (NIC11) or POMC+ACTH (A1A12) or ACTH and not POMC (A2A3) or, POMC + β -LPH + bEP but not ACTH, (E6B2). This immunohistochemistry also suggested that POMC rather than ACTH was being produced by the tumour. Chemotherapy led to a reduction in tumour mass, AFP concentration and features of Cushing's syndrome.

To conclude, we describe a malignant yolk sac tumour as a new source of ectopic POMC production leading to Cushing's Syndrome in a young girl. Our data suggest that POMC is stimulating cortisol production either directly by binding to the adrenal ACTH receptor or after cleavage within the adrenal to generate ACTH.

P39

The impact of malaria in pregnancy on changes in blood pressure in children over the first year of life

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Introduction

As in most sub-Saharan Africa, hypertension and its complications are increasingly common in Nigeria, where malaria is hyper-endemic. We established a birth cohort in Ibadan to assess the impact of maternal malaria on blood pressure (BP) in Nigerian infants over their first year.

Methods

Healthy pregnant women with singleton pregnancies were followed to delivery. They had regular blood films for malaria parasites through to delivery. Growth and BP were measured on 318 babies, all followed from birth to 3 and 12 months. Analysis used multiple regression techniques for longitudinal data.

Results

Babies exposed to maternal malaria were shorter, smaller and thinner at birth and remained smaller at 1 year, most marked in boys, whose systolic (S)BP adjusted for weight at 3 and 12 months was higher than those not exposed (at 3 months +0.6 mmHg/kg, 95% CI 0–1.2, $P=0.04$). Change in SBP over the first year was greater in boys than girls (20.9 vs 15.7 mmHg $P=0.002$) but greater in girls exposed to maternal malaria (18.7 vs 12.7 mmHg, 95% CI 1–11, $P=0.02$). 11% of boys (> twice expected) had a SBP >95th percentile (hypertensive, US criteria) of whom 68% had maternal malaria exposure. On regression analysis, gender, maternal malaria exposure and weight change all independently increased change in BP to 1 year.

Conclusions

Maternal malaria exposure had a greater adverse effect on growth in boys than girls. Malaria exposed boys had a higher than expected incidence of hypertension at one year, but the girls had a greater increase in BP. Thus intrauterine exposure to malaria has important gender-dependent effects on growth and infant BP and may contribute to the global burden of hypertension.

P40

Diagnostic yield in chondrodysplasias: a single centre study between 2002 and 2012

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Introduction

The chondrodysplasias are a heterogeneous group of genetic conditions affecting growth and form of the skeleton. As genetic knowledge has improved and genetic testing has become increasingly available, we hypothesize that over the past 10 years there has been an increase in the number of children where a genetic diagnosis is reached.

Aims

To ascertain if there had been an increase in the number of chondrodysplasias confirmed by genetic testing over the past 10 years.

Methods

All children seen within the combined complex bone disorder clinic (endocrinology, orthopaedic, occupational therapy and genetic input) at the Royal Hospital for Sick Children, Glasgow between October 2002 and July 2012 with a suspected chondrodysplasia were studied. Case notes for eligible patients were analysed to provide information on the diagnosis and how this was made (clinically/radiologically/on genetic testing).

Results

Of the 318 children identified, 69 with chondrodysplasias were eligible. 44 patients (64%) had short stature and 28 (41%) had disproportion. Disproportion was more correlated with a positive genetic test (61%) than short stature (43%). Of 69 patients, 44 had genetic testing, of which 68% were positive. These

included 16 (36%) who were tested for mutations in FGFR3 (achondroplasia/hypochondroplasia). This test was positive in 5 of 6 cases from 2007 to 2012 and only 6 of 10 from 2002 to 2006. There was no change in the trend of genetic testing over the study period. Of 69 cases, X-ray was diagnostic in 31 (45%) and clinical examination in 19 (28%). There was no change in these modalities over the study period.

Conclusion

Despite advances in genetic testing there has been no clear increase in the use of genetic testing in patients with chondrodysplasias over the last 10 years. Clinical and radiological examination remain the mainstay of diagnosis.

P41

Two hour insulin/C peptide levels in oral glucose test: are they really necessary?

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Introduction

A standard oral glucose tolerance test (OGTT) measures samples at 0, 30, 60, 90, 120 min. Insulin and c-peptide are taken along with blood glucose (BG). Whether samples between baseline and 120 min provide any additional value in detecting children at high risk in clinical practice is not well documented. This audit is looking at the value of doing insulin and c-peptide within 2 h post glucose ingestion in otherwise healthy children seen in Oxford Children's Hospital from 2006–2011.

Methods

All children who have had OGTT were included. Children previously diagnosed with diabetes (either type 1 or type 2 (T2DM)) were excluded. Insulin resistance (IR) was diagnosed by calculating Homeostatic model assessment (HOMA-IR) index >99th centile for age and sex, impaired glucose tolerance (IGT) by 2hr BG >7.1 mmol/l, T2DM when fasting blood glucose (FBG) ≥ 7.0 mmol/l, 2 h BG ≥ 11.1 mmol/l or HbA1c $\geq 6.5\%$. Children with IR, IGT, T2DM were included in disease group (DG) for analysis. The others were grouped as normal group (NG).

Results

Fifty-three children had OGTT. 82% were obese children (BMI SDS >2 s.d.). Mean age 12.4 ± 4.0 years, 57% were female. 18/53 (34%) had normal OGTT, 25/53 (47%) insulin resistance, 3/53 (6%) IGT, 5/53 (9%) IGT + IR and 2/53 (4%) were diagnosed with T2DM. Insulin and C-peptide results were statistical different ($P < 0.001$) when comparing results between DG and NG at all-time points. 10/53 (19%) were diagnosed with IGT and T2DM detected by samples at 0 and 120 min.

Conclusion

This study supports the value of undertaking OGTT. However, there was no additional value from samples at 30, 60 and 90 minutes. There was no additional value in measuring C-peptide to aid in the diagnosis of IR, IGT or T2DM. Reducing the number of samples taken during the test significantly reduces the cost of the investigation.

P42

Feasibility of measuring birth length and parental height for small babies and following-up short children at 2 years

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Background

Small for gestational age (SGA) and short stature at birth can be defined as birth weight (BW) and birth length (BL) ≤ -2 s.d.. Affected neonates can be classified as: i) SGA, ii) Short, iii) SGA + Short. Catch-up growth occurs by age 6 months in 90–95% of Short and SGA + Short infants. A minority remain short after age 2–4 years when the lack of data on BL and parental height (PH) renders assessment difficult.

Aims

To determine the feasibility of: measuring BL and obtaining PH for infants with $BW \leq 9$ th centile; re-measuring Short and SGA + Short children at 2 years.

Method

Hearing Screening Assistants in a single maternity unit were trained to measure BL and PH for infants with BW \leq 9th centile between July 2008 and June 2009. Short and SGA + Short babies were invited for re-measurement at 2 years.

Results

BW was recorded in 3797/3798 liveborn infants. BW was \leq 9th centile in 487 (12.8%) of whom BL was recorded in 347 (71%), mother's height in 115 (24%) and father's height in 104 (21%). Fifty-one infants were Short (1.3% total population) and 61 were SGA + Short (1.6%). At 2-year follow-up, 60/112 (54%) (27 Short, 33 SGA + Short) infants attended: 5 were Short, 3 were Light (not Short), and 1 (with a known underlying medical condition) was Short + Light. Catch-up growth did not occur in 6/60 (10%) infants. Four were identified as requiring further investigation.

Conclusions

The prevalence of short stature at birth (2.9%) was not elevated in our cohort, however 12.8% had BW $<$ 9th centile and 10% of Short infants remained Short at 2 years. Measuring BL in babies $<$ 9th centile is feasible and desirable. Measuring PH at birth and re-assessing Short children at 2 years is useful but requires greater effort.

P43**Prevalence and diagnosis of cholesteatoma in Turner syndrome**

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Background

Cholesteatoma, a serious suppurative middle ear condition, has an increased prevalence in Turner syndrome (TS).

Aims

To estimate its incidence in our TS population; identify risk factors; highlight distinctive operative findings; and suggest strategies for earlier detection.

Methods

Retrospective casenote review for patients attending a TS clinic to identify those with cholesteatoma; each age-matched with three unaffected TS girls for comparison.

Results

179 patients attended the clinic 1989–2012. Middle ear disease, including acute otitis media (OM) and OM with effusion, was found in 7/7 index vs 15/21 comparison girls, with median age at myringotomy and grommet insertion 3.9 vs 1.5 and 5 vs 4 years. Cholesteatoma occurred in 7 (3.9%) girls (45,X [4] or 45,X/46,X,i(Xq)[3]), with 9 affected ears and recurrence in one girl. Median (range) age at first cholesteatoma presentation was 12.5 (7.5–15.2) years. Discharging ear (often purulent and/or foul-smelling) for median (range) 1.3 (1–4) months was the presenting feature in 8/10 ears, with aural polyps in 3/9 ears. Index vs. comparison girls had a higher incidence of myringotomy (5/9 vs 3/42 ears), grommet insertion (6/9 vs 5/42 ears), chronic suppurative OM (5/7 vs 1/21 girls) and tympanic membrane retraction (6/9 vs 2/42 ears). At surgery, 3/9 cholesteatoma ears showed dehiscent facial nerves, one had residual disease not dissectable at initial surgery and another required revision mastoidectomy.

Conclusion

Cholesteatoma has a very high prevalence in TS, affected girls being typically older with a history of chronic ear disease, tympanic membrane retraction and persistent ear discharge. Urgent referral for specialist ENT assessment is recommended for TS girls with otorrhoea $>$ 2 weeks.

P44**Risk factors for short term post-operative complications after pancreatotomy for congenital hyperinsulinism**

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Introduction

Pancreatotomy may be necessary to treat hypoglycaemia due to congenital hyperinsulinism (CHI) following failure of medical management. Post-operative

complications including infection and persistent hypoglycaemia have been reported after pancreatotomy, but factors predictive of these have not been recognised.

Aims

To investigate if early factors or the time to surgery predict risk of CHI surgical complications and hypoglycaemia in the 6 months after surgery.

Methods

A cohort of CHI patients ($n=25$) undergoing focal or subtotal pancreatotomy by laparotomy between 2003 and 2012 was retrospectively examined. CHI was characterised by age at presentation, KATP channel gene mutations (KATP) and focal/diffuse/insulinoma histology. Severity of CHI was assessed by maximum carbohydrate requirement (CHO), maximum dose of Diazoxide (Dz) and maximum glucagon infusion rate (GI). Glycaemic outcome in the medium term was noted at 6 months after surgery.

Results

The median (range) age at presentation was 3 (1; 2920) days with time to surgery being 90 (30; 2765) days. KATP mutations were present in 20 (80%) children. 13 children (52%) had focal lesions, focal CHI ($n=10$) and insulinoma ($n=3$) confirmed by histology. As expected, KATP, CHO, Dz and GI were correlated with an earlier time to surgery ($R^2=0.8$, $P<0.001$). Surgical complications included infection, bleeding, chyle leak, wound dehiscence and pseudocyst in 7 (28%) children. The incidence of surgical complications was greater with delayed compared to earlier subtotal pancreatotomy (180 (69; 330) v 90 (30; 180), $P=0.04$), but not with focal lesionectomy (120 (30; 2765) v 75 (60; 90), $P=0.4$). Persistent hypoglycaemia requiring significant medication at 6 months occurred in 4 (16%) children with diffuse CHI requiring second surgery. KATP, CHO, Dz and GI were not correlated with post-operative hypoglycaemia ($R^2=0.3$, $P=0.06$). One child developed diabetes requiring insulin treatment.

Conclusions

A longer time to surgery, but not mutation status or severity at diagnosis of CHI, may predict risk for post-operative complications in children undergoing pancreatotomy.

P45**Hyperinsulinaemic hypoglycaemia in newborn twins**

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Background

Newborn infants have multiple risk factors for developing hypoglycaemia of which, hyperinsulinism is an important cause of both transient and persistent hyperinsulinaemic hypoglycaemia (HH). It can present in newborns infants at term, preterm and newborns with intrauterine growth retardation (IUGR). There have been no previous reports of HH occurring in twins and triplets.

Aims and objectives

We report the occurrence of HH in 4 sets of twins and one set of triplets where HH was present in only one of the twin and not the other twin.

Methods

Clinical and biochemical data was collected retrospectively from case notes and electronic patient records over a period of 6 years for patients referred to the Centre for Hyperinsulinism at Great Ormond Street Children's Hospital.

Results

Four sets of twins and one set of triplets were identified with HH (two dizygotic and three monozygotic). The mean gestational age of all newborns was 37 weeks, the mean birth weight of the affected twins was 2280 g and the mean birth weight of the unaffected twins was 2450 g (P value 0.537). The age at presentation of hypoglycaemia was day 1. All infants responded to treatment with diazoxide (dose 3–5 mg/kg per day), started at a mean age of 12 days (3–25 range) with mean duration of 5 months.

Conclusion

This is the first study to report the occurrence of HH in twins and triplets. There was no significant difference in the birth weights of the twin with HH and the twin without HH. This suggests that the low birth weight may not be the only reason for the onset of HH. All infants responded well to diazoxide, suggesting that the occurrence of HH in these groups is transient. Further research is required to understand the mechanisms that lead to HH in such groups of patients.

P46**Extraction of high quality RNA from fresh frozen and formalin fixed paraffin embedded human pancreatic tissues samples of patients with congenital hyperinsulinism for gene expression microarray**Senthil Senniappan, Amanda Heslegrave & Khalid Hussain
UCL Institute of Child Health, London, UK.**Introduction**

The molecular research on rare diseases is limited by the availability of tissue samples that yield good quality RNA. Extraction of RNA from human pancreatic tissues are challenging due the high amount of ribonucleases.

Aim

To compare the quality of RNA from fresh frozen (FF) and formalin fixed paraffin embedded (FFPE) human pancreatic samples of patients with congenital hyperinsulinism (CHI).

Methods

Tissue samples were obtained from children CHI who underwent surgery. RNA was extracted from seven FFPE (four focal and three normal) and eight FF samples (six diffuse and two normal) by standard techniques (TRIzol Reagent). RNA Integrity is assessed by Agilent-derived RNA Integrity Number (RIN) and the presence of intact 18s and 28s bands on the Agilent Bioanalyzer trace. The purity is determined by the optical density ratio (OD 260/280).

Results

The RNA yield from FFPE and FF samples were 327 and 1032 ng/µl respectively. FFPE samples yielded a very low RIN (mean 2.3; range 2–2.4) whilst FF samples yielded high RIN values (mean 7.0; range 5.8–8.6). The mean OD 260/280 ratio for the FFPE samples was 2.16 and that of FF samples was 1.9. All the FF samples had intact 18s and 28s bands whilst it was absent in all of the FFPE samples. The microarray Qc from FF samples revealed a mean pos-v-neg auc value of 0.84 which suggests a good quality data.

Conclusion

A RIN factor greater than 7, OD 260/280 ratio between 1.8 and 2.1 and Intact 18s and 28s bands are markers of good quality RNA that could be used for gene expression microarray. Whilst extracting good quality RNA from human pancreatic samples for microarray studies remain a challenge, FF samples yield better quality RNA than FFPE samples.

P47**Beckwith-Wiedemann syndrome with paternally inherited duplication of chromosome 11p and a deletion of the long arm of chromosome 11**Ved Bhushan Arya, Maria Papadopoulou, Senthil Senniappan & Khalid Hussain
UCL Institute of Child Health and Great Ormond Street Hospital, London, UK.**Introduction**

Beckwith-Wiedemann syndrome (BWS) is characterized by hyperinsulinaemic hypoglycaemia (HH), overgrowth, tumour predisposition and congenital malformations. Commonly, BWS is caused by epigenetic or genomic alterations, which disrupt genes in one or both of the two imprinted domains on chromosome 11p15.5. Rarely (~1%), paternally inherited duplications of 11p15 can result in BWS phenotype. We describe the first case of BWS associated with a paternally inherited duplication of almost the whole short arm of chromosome 11 and a deletion of the long arm of chromosome 11.

Methods/Results

This patient was born at 34+4 weeks of gestation with birth weight 2850g (91st–98th percentile) by vaginal delivery to Caucasian non-consanguineous parents. In view of macroglossia, micrognathia, right fixed talipes equinovarus and hypotonia, a karyotype was performed. This showed unbalanced female karyotype with duplication of the short arm of chromosome 11[46,XX,rec(11) dup(11p) inv(11)(p12q24.2)] and a deletion of the long arm of chromosome 11. Analysis of parents karyotype revealed father carrying a balanced pericentric inversion of chromosome 11 [(46,XY,inv(11)(p12q24)]. Postnatally she developed HH (blood glucose 2.3 mmol/l, insulin <2 mU/l, free fatty acids 0.15 mmol/l, β-hydroxybutyrate <0.05 mmol/l) and required high intravenous glucose infusion (18 mg/kg per min) to maintain normoglycaemia. She responded well to 5 mg/kg per day of diazoxide. Following Nissen's fundoplication, her HH was complicated by dumping syndrome. Currently, her blood glucose levels are stable on continuous gastrostomy feeds. She also has problems of developmental delay and obstructive sleep apnea. She is having regular screening with ultrasound of the abdomen and serum tumour markers (AFP, β-hCG).

Conclusion

BWS due to paternally inherited duplications of chromosome 11p15 are rare. Our patient is unique as she has duplication of almost the whole short arm of

chromosome 11 and a deletion of the long arm of 11. As she has a chromosomal imbalance larger than usually found in BWS patients, a more severe phenotype is expected.

P48**Comparing common methods of body composition assessments with magnetic resonant imaging in patients at high risk of sarcopenia and abnormal body proportions**Christina Wei¹, Manigandan Thyagarajan¹, Rachel Cox¹, Ruth Elson¹, Karin Bradley², Michael Stevens³ & Elizabeth Crowne¹
¹Bristol Royal Hospital for Children, Bristol, UK; ²Bristol Royal Infirmary, Bristol, UK; ³University of Bristol, Bristol, UK.**Introduction**

Measures commonly used to assess adiposity are often considered to reflect visceral adiposity and hence used as indicators of cardiovascular risk. This study compares common clinical adiposity measures with abdominal MRI, a direct measure of visceral fat, to assess if this relationship applies in patients with abnormal body composition.

Method

Fifty childhood leukaemia survivors (16–26 years) treated with bone marrow transplantation/total body irradiation (group 1, n=20) or chemotherapy alone (group 2, n=30) were studied: i) auxology: body-mass-index (BMI), waist circumference, waist-to-hip ratio, waist:height ratio, ii) bioimpedance analysis (BIA): total body fat%, trunk fat%, iii) DEXA: trunk fat mass, android:gynoid fat ratio, iv) L4-5 single slice abdominal MRI: subcutaneous and visceral fat area. v) Blood pressure (BP) and cholesterol, triglyceride (TG) and high density lipoprotein were also obtained. Comparisons between outcomes were explored by Pearson's correlations.

Results

MRI visceral fat correlated with cardiovascular risk markers (systolic BP, diastolic BP, TG, cholesterol ($P \leq 0.001$, 0.01, 0.04, 0.03) respectively). In group 2, all auxological outcomes, DEXA trunk mass and BIA trunk % correlated with both MRI subcutaneous and visceral fat. However, in group 1, with significantly lower lean mass ($P=0.009$) and sitting heights ($P < 0.001$), BMI ($P < 0.001$) and DEXA total trunk mass ($P < 0.001$) only correlated with subcutaneous fat although waist:hip ratio ($P=0.003$) and DEXA android:gynoid ratio ($P=0.001$) correlated with visceral fat. Waist circumference and waist:height ratio correlated with both fat types. No correlation was shown between BIA trunk% and MRI results.

Conclusions

Common methods to assess adiposity may not reflect visceral fat if body composition is abnormal. Corrected values e.g. waist-to-hip and DEXA android-to-gynoid ratios are better surrogate markers. This is relevant for other chronic disease subjects with sarcopenia.

P49**Mind over muscle: investigating the biology of fatigue in GH deficiency using ³¹P-MRS**Akash Sinha, Kieren Hollingsworth, Steve Ball & Tim Cheetham
Newcastle University, Newcastle upon tyne, UK.**Introduction**

Even though fatigue is a common complaint in GH deficiency (GHD), its pathophysiology remains poorly understood. Fatigue can reflect central or peripheral disease processes. 31-Phosphorus magnetic resonance spectroscopy (³¹P-MRS) is a non-invasive technique used to measure skeletal muscle bioenergetics *in vivo*. Specifically, mitochondrial oxidative phosphorylation and proton efflux can be measured dynamically and in 'real time'. The aim of this study was to examine the biology of fatigue in GHD using surrogates of central and peripheral fatigue i.e. with a self reported questionnaire and ³¹P-MRS respectively.

Methods

In this cross-sectional study, we compared skeletal muscle bioenergetics using ³¹P-MRS in three groups: untreated GHD, treated GHD and healthy controls (age and sex matched). Resting metabolites and parameters of oxidative phosphorylation- $\tau_{1/2}$ PCr and proton efflux were calculated during a validated exercise protocol. Blood was taken to ensure appropriate hormone replacement. Body composition was assessed using bio-impedance and a validated QoL questionnaire (AGHDA) completed. One-way ANOVA was used for comparisons (Minitab v16).

Results

Patient age and sex were comparable in the three groups (mean age 27.9, 29.8 and 31.0 years; $P=0.53$) but % body fat was greater in the GHD patients compared to controls ($P=0.04$). No significant differences in resting metabolite parameters (Pi, PCr and pH) were detected. Importantly, there was no significant difference in either $\tau_{1/2}$ PCr ($P=0.56$) nor proton efflux ($P=0.44$) despite significant differences in perceptions of fatigue and AGHDA-QoL ($P=0.002$).

Conclusions

Untreated GHD adults do not express an abnormal 'bioenergetic footprint' compared to either treated GHD adults or healthy controls. This suggests that fatigue in GHD does not reflect abnormal mitochondrial oxidative phosphorylation nor delayed proton efflux. The perception of fatigue may, therefore, arise from dysregulation of the neuroendocrine system rather than abnormal muscle function; i.e. 'central fatigue rather than peripheral fatigue'.

P50

Adiponectin levels are inversely related to length in early infancy

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Introduction

The adipokine adiponectin promotes insulin sensitivity and its circulating levels are inversely related to adiposity in adults and older children. In small for gestational age (SGA) infants adiponectin levels decline rapidly with age in early life and have been inversely associated with subsequent weight gain. There are few data in early infancy, especially in non-SGA infants.

We therefore investigated the association between adiponectin levels and growth in early infancy in a general population-based birth cohort.

Method

The Cambridge Baby Growth Study (CBGS) collected detailed infant anthropometry and capillary dried blood spots (DBS) from birth to 2 years. DBS collected at 3 months, and a small pilot subgroup at 12 months, were processed using an adiponectin serum DELFIA immunoassay, adapted for DBS. Results

Mean (s.d.) adiponectin levels at 3 months in 306 infants (142 males) non-SGA infants (13.2 ± 4.8 (4.1–28.2) $\mu\text{g/ml}$) were much higher than at 12 months ($n=63$) 4.4 ± 1.6 (1.5–9.0) $\mu\text{g/ml}$.

Three-month adiponectin levels were inversely related to age ($B = -0.1$, $P < 0.0005$), and were higher in exclusively breast fed vs other infants ($P=0.01$). Adiponectin levels at 3 months were strongly inversely related to birth and 3 month length, weight, and skinfold thicknesses. In multivariate models the strongest correlates with 3 month adiponectin levels were length and infancy age. Additionally, adiponectin was positively associated with 3 month DBS levels of branched chain amino acids.

Conclusions

Circulating adiponectin levels can be quantified in DBS using immunoassay. Three month adiponectin levels were inversely correlated with infancy length, which is a novel finding. Higher levels of branched chain amino acids associated with higher adiponectin levels may indicate decreased insulin secretion. We hypothesise that reduced insulin secretion in infants with short length results in higher adiponectin levels, and consequently increased insulin sensitivity, allowing some (though incomplete) compensation for hypoinsulinaemia.

P51

Growth and glucose homeostasis after 2 years in children with inflammatory bowel disease receiving recombinant GH therapy for growth retardation

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Background

A recent RCT of rhGH in IBD over 6 months showed that improvement in linear growth was associated with a reduction in insulin sensitivity.

Objectives

To investigate the effects of prolonged rhGH on growth and glucose homeostasis in children with IBD.

Patients and methods

Eleven children (10CD/1UC) (9 m) with a median age of 14.7 years (range, 8.9, 16.2) who received rhGH (0.067 mg/kg per day) as part of a 6-month RCT were studied over a longer period of follow up. Of 11 patients, nine received rhGH for 24 months, 1 for 12 months and 1 for 9 months. Anthropometric data were collected at baseline (T0), 6 months (T6), 12 months (T12) and 24 months (T24) following start of rhGH. Fasting glucose, insulin, c-peptide were also measured. Results

At T0, the median HtSDS was -2.5 (-3.3 , -1.4) compared to a MPHSDS of -0.3 (-1.1 , 0.1) ($P=0.0001$). There was significant improvement in median HtSDS following rhGH at T12 (-1.6 (-2.9 , -0.81) $P=0.04$) and T24 (-1.09 (-2.39 , -0.23) $P=0.02$) compared to T0. The median HV at T0 was 3.3 cm/year and improvement was observed during first 6 months (8.3 cm/year (7, 15) $P=0.0004$) and T12 (HV=7.2 cm/year (6, 9.7) $P=0.0006$) in comparison to T0. No significant differences were noticed in BMI and BMI SDS. Similarly no significant alterations were documented in median fasting glucose (mmol/l level) (at T0 4.7 (3.6,5.5), T6 5 (4.3,5.6), T12 4.9 (4.7,6.7) and T24 4.8 (4.3,6.2)) and median insulin (mU/l) (T0 (5.5 (1.9,11)), T6 (9.5 (2.9,13.3), T12 (9 (4.18,15.8) and T24 (7.8 (3.7,24.2)) during treatment period. Although significant increase in median C peptide level (nmol/l) occurred during first year of treatment (T0 0.5 (0.2, 1.15) vs T12 0.8 (0.4, 1) ($P=0.02$), it normalised by 2 years (0.6 (0.3, 1.16)). Conclusion

Our data show that the growth promoting effects of rhGH are maintained over 2 years after therapy without any marked detrimental effect on glucose homeostasis.

P52

Puberty phases: an evaluation of a new system for rating puberty in paediatric practice

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Background and aims

Estimating puberty using Tanner stages is usually done unconfidently by general paediatricians. Self-assessment methods are not reliable. As assessment of growth on the new UK growth charts necessitates establishing pubertal status, we have designed and evaluated a simpler non-invasive approach.

Methods

The new system has three Phases— Pre-Puberty (Tanner stage 1), In-Puberty (stages 2/3) and Completing-Puberty (stages 4/5).

	Pre-puberty All of the following	In puberty Any of the following	Completing puberty All of the following
Girls	No signs of areolar (nipple) or breast development No pubic hair	Any breast enlargement so long as nipples also enlarged Any pubic or axillary (armpit) hair growth	Started periods (menarche) With breast pubic and axillary hair development
Boys	High voice No growth of testes or penis No pubic hair	Slight deepening of the voice Reddening of the scrotum Any testicular or penile enlargement Any pubic or axillary hair growth	Voice fully changed (broken) Early moustache and facial hair growth Adult size of penis and testes with adult pubic and axillary hair growth

The Phase system was tested amongst 28 specialist nurses, 100 general paediatric trainees and 19 consultant general paediatricians after basic training. They evaluated puberty phase and Tanner stage on 10 standard line drawings.

Results

Recognising pubertal development was performed more accurately and fully by each group when using Puberty Phases. Most errors arose due to a failure to recognise the start of puberty.

Mean (range)	Correct %Tanner stage	Correct % phases
General consultants	43 (0–90)	79 (50–100)
General trainees	48 (0–90)	78 (30–100)
Specialist nurses	54 (30–80)	79 (50–100)

Conclusions

The new simpler puberty phase approach was well accepted and allowed a clearer rating of pubertal development, a new requirement for the correct interpretation of the UK growth charts. User education is still required.

P53

High rates of non adherence to daily r-hGH injections revealed by the easypod electronic dose record

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Background and aims

Non-adherence to daily subcutaneous GH (r-HGH) administration may account for discrepancies between dose prescription, growth response and serum IGF1 levels but is difficult to determine. The electronic r-HGH auto-injector Easypod device has the only inbuilt retrievable dosing record, with which we aimed to assess adherence.

Method

Over a 4 month period, we retrospectively retrieved dose history data in 25 clinic patients aged 10–18 (mean 15) years, who freely chose the Easypod r-HGH delivery method (for a variety of treatment indications). We audited rates of successful injection delivery, reasons for missed injections and contact with the patient's SENSE home support nurse.

Results

Average days recorded 117.8 (range 27–184).

% Injections missed	Total (n) patients	Mean age (range)	Mean time on treatment (months)
0	3	17 (16–18)	14
1–10	9	14 (10–17)	29.5
11–40	6	15 (13–18)	29.3
>41	7	16 (13–18)	52.4

Summary

Missed doses were the norm, only a 12% minority being fully adherent even over a short 4 month period. About half missed 10% of doses, but the majority (55%) missed more and a substantial minority (25%) received <60% of their recommended prescription. Adherence deteriorated after the first treatment year and continued to decline to 5 years with no apparent improvement with the SENSE nurse (data not shown).

Conclusion

This small study demonstrates the benefits of inbuilt administration recorders in r-HGH injection devices in assessing growth responses in children. The surprisingly high prevalence of non-adherence, especially after 4 years, is relevant to the cost benefit implications of continued treatment and highlights the importance of addressing patients' (not parents' or physicians') perception of treatment benefit. Switching for a period to the Easypod may allow clinicians to make considered decisions about treatment continuation (and may improve compliance due to the Hawthorn effect).

P54

Management of childhood-onset GH deficiency in young adulthood

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Background

GH therapy in adolescents with childhood onset GH deficiency (CO-GHD) is often necessary to prevent adult GHD syndrome and requires a re-evaluation of the GH axis on attainment of final height. Not all individuals with CO-GHD remain GH deficient and re-evaluation is required to confirm or refute adult GHD.

Aim

Review the care received by young adults diagnosed with CO-GHD.

Design

Retrospective review of young adults with CO-GHD patients between 2005 and 2011 in a single paediatric tertiary centre.

Result

75 former CO-GHD patients, 48 male: 27 female, with median age 19 year (15–26.2) at time of data collection were reviewed. The etiologies of CO-GHD were: craniopharyngioma and other tumours ($n=28$), multiple pituitary hormone deficiencies (MPHD) ($n=8$), isolated GH deficiency (IGHD) ($n=14$), and other causes ($n=25$). Median age at diagnosis was 12.5 year (0.25–16.9) with initial GH peak 2.3 $\mu\text{g/l}$ (0.1–6.5). Of 75 patients, only 66 were treated with GH at a median age 11.5 year (1.2–17.2), and 41 of those who received GH therapy were later referred to the transition clinic at a median age 17.9 year (16–20.7) for re-assessment the GH axis after withdrawal of GH therapy at a median age 16.4 year (10.6–20) with a median duration of treatment 4.5 year (0.3–16.1). Re-evaluation of the GH axis was performed in 41 cases after 0.4 year (0.17–4.3) of GH withdrawal, median repeat GH peak 1.1 $\mu\text{g/l}$ (0.1–7.9) of those 32 who remained GHD only 29 opted to restart GH therapy.

Conclusions

Optimal care of adults with CO-GHD requires a close relationship between paediatric and adult services. A substantial proportion of affected adults continue to have GHD and most opt for GH therapy. There is a need for a study of the current practice of assessment and management of CO-GHD in the UK.

P55

Outcomes of paediatric craniopharyngioma: a single centre experience

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Background

Craniopharyngiomas are rare tumours with an annual incidence of 0.5–2/100 000. Though benign they still represent a management challenge because of morbidity that includes pituitary hormone deficiency, visual impairment, adipsia and morbid obesity. We retrospectively assessed the outcomes of craniopharyngioma patients in our centre over a 10-year period.

Methods

All children ($n=16$) diagnosed with craniopharyngioma and treated in this centre from 1996 to 2011 were identified. Clinical data from presentation to most recent assessment were collected. MRI scans were reviewed with a neuroradiologist. Height, weight and BMI were expressed as standard deviation scores (SDS).

Results

Mean age at diagnosis was 11.2 years (range 3.3–16.1) and they were followed up for a mean of 8.6 years (3.4–16.2). Tumour dimensions ranged from between 12 and 15 mm to between 35 and 41 mm. 56% had radiotherapy after surgery. 75% had biochemical evidence of pituitary dysfunction at presentation. Postoperatively all had 3 or more endocrinopathies. All were GH/ACTH deficient and all but 1 had cranial DI. Transient adipsia was present in 25% postoperatively. Median height SDS was -1.89 (-2.50 to 0.06), increasing on GH replacement to $+0.09$ (-1.78 to 1.54). 80% reached a final height greater than their mid-parental target. Median BMI SDS at presentation was 1.23 (-1.55 to 3.43), increasing to 2.10 (-0.14 to 3.72) at 2 years and 2.24 (-0.06 to 4.75) at last follow up. 2 patients developed type 2 DM. At presentation 44% had visual field defects, increasing to 63% postoperatively.

Conclusion

The outcome in patients with craniopharyngioma in our unit is similar to other larger UK centres. Endocrinopathies are common at presentation and universal postoperatively but no patient had adipsic DI in the long term. Despite short stature at presentation all have a final height within normal limits. BMI is high at presentation and rises postoperatively but may plateau in the long term.

P56

Human GH (somatotropin) for growth failure in children

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GH stimulates the growth of skeletal muscle and connective tissue and increases the rate of protein synthesis. Somatotropin (artificial GH) has been commercially available since 1985 and is most commonly used for the treatment of Isolated GH Deficiency, idiopathic short stature, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, and 'small for gestational age'. GH deficiency has a growing prevalence, affecting 20/million children in the UK. Our aim was to benchmark our performance against NICE guidelines (TA188) and identify areas for improvement. All paediatric patients prescribed GH at our centre since 2011

were included. Available notes were reviewed for evidence of correct initiation, maintenance and discontinuation of GH treatment, as well as the provision of written information and informed consent. Results showed that of 76 patients, GH was mainly started for Isolated GH deficiency (61%), Turner Syndrome (17%) and Prader-Willi syndrome (9%). 93% had documented evidence of GH initiation in line with NICE guidance. In 13 cases there was a documented reason to stop GH and this was done in 62% (8/13) of cases. In 80% there was no documentation of discussion regarding the risks and benefits of GH or provision of written information. Given the significant cost and growing number of patients receiving GH, best practice is an important issue. This audit confirmed that GH was generally initiated in concordance with NICE guidance. The main areas identified for improvement were the documentation of provision of information and discontinuation of treatment. To improve our practice, we suggest the introduction of a pro forma, which will act as an aide-memoire to best practice and assist future auditing. Our earlier work demonstrated pro formas are effective in increasing conformance to best practice. To complete the audit cycle, we plan to re-audit following the introduction of this innovative clinical tool.

P57

Grave problem, unrelated to fracture

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Two weeks after fracturing his humerus a 14-year-old male presented with ongoing epigastric pain and vomiting. He was persistently tachycardic but normotensive. Treatment with intravenous fluids and ranitidine, for a presumed gastritis, was commenced.

Initial blood tests revealed a mildly raised urea and creatinine, normal inflammatory markers and full blood count. Further investigation showed a moderate hypercalcaemia with an albumin adjusted calcium of 3.05 mmol/l. Despite comments on being thin it was a more detailed examination that exposed his exophthalmus, lid lag and goitre.

Thyroid function tests results gave a TSH of <0.05 mIU/l (0.3–5.5 mIU/l), free T4 of >100 pmol/l (12–22 pmol/l) and a free T3 of 28.7 pmol/l (3.1–6.8 pmol/l). Hypercalcaemia is an uncommon consequence of thyrotoxicosis. Thyrotoxicosis can cause sufficient bone resorption to increase serum calcium, decrease serum parathyroid hormone and increase urinary excretion of calcium. Hypercalcaemia should resolve when the patient is euthyroid.

Treating this patient presented some challenges. This case will demonstrate the mechanisms for and management of hypercalcaemia in thyrotoxicosis.

P58

Key efficacy issues in the use of recombinant human GH in children with prader-willi syndrome

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Prader-Willi syndrome (PWS) is a rare genetic condition characterised by hypotonia, early feeding difficulties, hyperphagic obesity, hypogonadism and short stature; with an incidence between 1/15 000 and 1/25 000 live births in the UK. It is caused by failed expression of paternally inherited genes in the imprinting region of chromosome 15q11.2–q13. Recombinant human GH (rhGH) is the main pharmacological treatment used in PWS.

Aims

We aimed to review the use of rhGH in our cohort against current UK National Institute of Health and Clinical Excellence (NICE) recommendations to determine effects on growth outcomes and side effects in patients.

Methods

A retrospective audit of case notes was performed in 30 paediatric PWS patients treated with rhGH at our centre, to analyse monitoring standards, frequency of side effects and auxology outcomes. Results: In our cohort, 37% had biochemical evidence of GH deficiency (GHD) and 93% of our cohort was treated with a lower

median dose of rhGH (mdGH) (24.0 µg/kg per day 16.5–37.0) throughout their treatment period than NICE recommendations for weight (35.0 µg/kg per day). No significant correlation was found between mdGH and change in height SDS or BMI SDS and mean final heights attained in our patients were comparable to the literature (Takeda *et al.*, 2009). 20% of patients developed impaired glucose tolerance prior to or on treatment and fasting glucose and insulin levels were not predictive of glycaemic impairment when compared with oral glucose tolerance testing (OGTT). Scoliosis had a high prevalence in our patients (57%) and 40% worsened on rhGH.

Conclusions

Lower rhGH treatment doses may not significantly impair growth and metabolic composition and demonstrate better cost benefit than current NICE recommendations in PWS patients. We recommend that OGTT be used for effective glycaemic monitoring, whilst regular spinal assessment is essential.

P59

Assessment of endocrinological, ophthalmological and radiological abnormalities in the Irish paediatric cohort of septo-optic dysplasia

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Introduction

De Morsier described an association between optic nerve hypoplasia and an absent septum pellucidum in 1956, termed septo-optic dysplasia. SOD is a common cause of multiple pituitary hormone deficiency in children. Clinical features can evolve. Genetic mutations in regulators of pituitary development have been suggested.

Aims

To determine associated endocrinopathies, ophthalmological and radiological findings in an Irish paediatric cohort of septo-optic dysplasia.

Methods

Index cases were identified through the Endocrinology database system of Our Lady's Children's Hospital Crumlin between 1980 and 2012. Retrospective chart analysis was conducted to determine demographics, endocrinopathies, ophthalmological and radiological findings.

Results

78 patients were identified. Male 41 (53%) female 37 (47%). At referral: 26 (33%) were neonates. The commonest referral indication was visual problems 49 (62%) from ophthalmology (42%). Mean maternal age was 22.7 years. Antenatal risk factors included infection (11%) drug abuse (11%) among others. Mean age of diagnosis of SOD was 1.7 years. 36% had at least one endocrinopathy: GH deficiency (GHD) (28%) being the commonest. 48 (62%) and 26 (33%) had bilateral and unilateral ONH respectively. 16 (33%) children with bilateral ONH and 4 (17%) with unilateral ONH had more than 2 endocrinopathies. 14 children had only ONH clinically and radiologically, of these, 13 (93%) did not have an endocrinopathy. 57 children had neuroimaging: 48 (84%) had abnormal results. 22 (46%) with abnormal MRI had at least 1 endocrinopathy. five deaths were noted: multiple pituitary hormone deficiencies (MPHD) (3), respiratory aetiology (2).

Conclusions

In our cohort, gender distribution was equal. Referrals were mainly ophthalmological in nature. Surprisingly, age at diagnosis was older. GHD was the commonest endocrinopathy. Endocrinopathies were more frequent in bilateral ONH, but were less likely in the absence of MRI findings. MPHD was common in those who died.

P60

Septo-optic dysplasia and X-linked adrenoleukodystrophy: two rare conditions presenting together

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Although pituitary abnormalities are the most commonly reported endocrine feature in septo-optic dysplasia, other endocrine abnormalities have not been described so far. We present a case of septo-optic dysplasia (SOD) and pituitary dysfunction, complicated by X-linked adrenoleukodystrophy (X-ALD) and primary adrenal insufficiency.

A 4-year-old boy was referred with hypoglycaemic episodes and seizures during intercurrent illnesses. He had a history of polyuria and polydipsia. Clinical assessment revealed congenital nystagmus, right-sided hemiparesis and delayed early speech. Endocrine work up revealed a low cortisol concentration of 79 nmol/l (ref. 80–580 nmol/l). A subsequent short synacthen test showed a flat cortisol response (maximum cortisol value at 60 min was 75 nmol/l) suggesting adrenal insufficiency. Paired plasma osmolality (290 mmol/kg) and urine osmolality (87 mosmol/kg) indicated diabetes insipidus (DI). IGF1, TSH and Gonadotrophin levels were however normal. MRI Brain showed characteristic changes of SOD. The diagnosis of hypopituitarism secondary to SOD was made. However, the ACTH level was found unexpectedly to be elevated at 593 ng/l (ref. <46 ng/l). An incidental finding of increased very long chain fatty acids (VLCFA) gave the diagnosis of X-ALD. He was thereafter shown to be hemizygous for the p.(Arg660Trp), c.1978>T mutation in exon nine of the ABCD1 gene, a previously described mutation in X-ALD affected individuals. There was a maternal family history of late onset neurological problems. Thus, the very rare possibility of co-existence of two separate conditions was raised—i) septo-optic dysplasia leading to posterior pituitary dysfunction and hence DI and ii) X-linked ALD leading to primary adrenal insufficiency. The child is now being treated with desmopressin for DI, replacement doses of hydrocortisone for adrenal insufficiency and Lorenzo oil for XALD. MRI scans show no white matter changes of X-ALD and will be repeated 6 monthly. We believe that this is the first reported case of SOD and X-ALD.

P61

A prospective study of pubertal growth in children with inflammatory bowel disease

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Background

Puberty is understood to be commonly affected in adolescents with Crohn's disease (CD) and ulcerative colitis (UC).

Objective

To determine the impact of IBD on pubertal status and pubertal growth.

Methods

Single centre prospective study over 12 months of 45 adolescents (boys, 23) with CD and 18 (boys, 12) with UC with a median age of 13.4 years (10, 16.6). Assessment included details of disease, anthropometry and biochemical markers of growth and puberty at T0 and T12.

Results

Group	T0			HV (cm/year)	Change Ht SDS	T12	
	Ht SDS	IGF1(0) SDS	IGFBP3(0) SDS			IGF1(12) SDS	IGFBP3(12) SDS
CD	-0.14 (-2.6; 2.1)	-0.4 (-5.8; 2.6)	0.45* (-1.5; 2.7)	4.8 (0.2; 8.3)	0.05 (-0.5; 0.6)	-0.93** (-2.3; 0.9)	1.91** (-1.9; 3.6)
UC	0.25 (-1.8; 2.7)	-0.5 (-2; 1.4)	0.3 (-1.9; 1.6)	5.4 (1.4; 8.7)	0.16 (-0.5; 0.4)	0.02 (-1.3; 1.0)	1.3 (-2.0; 2.1)

* $P < 0.001$; ** $P < 0.0001$ as compared to the normal population.

Individually, 10/45 (22%) adolescents with CD had one or more parameter affected: 7 had a HtSDS at diagnosis < -2, 6 had HtSDS < -2 at 0 and 12 months. No subjects remained prepubertal beyond the age at which 97% of population would have expected to enter puberty and only two adolescents with CD showed a delay in progression through puberty. In the whole group, HV showed an inverse association with ESR ($r, -0.286$; $P=0.025$).

At T0 post-pubertal boys with CD had median urinary luteinising hormone:creatinine and follicle stimulating hormone:creatinine ratios that were significantly lower than the healthy population ($P=0.01$ and $P=0.0001$).

Conclusion

As a group, disorders of the pubertal growth spurt are more likely to occur in CD. Achieving disease control may be important in attaining normal growth during puberty.

P62

Audit of children with thyrotoxicosis treated with antithyroid drugs by block and replacement regime: relapse rate and outcomes

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Introduction

Drug-based therapy is usually the initial treatment for thyrotoxicosis in children, but there is some debate about treatment duration. Our objective was to assess the effect of long-term Carbimazole therapy by block and replacement regime on thyrotoxicosis remission in children.

Methods

15 children with thyrotoxicosis seen in endocrine clinic between January 2006 and January 2010 were included in the audit. Data was collected retrospectively from the notes. Minimum of 24 months of treatment by block and replacement regime was considered as one complete course (cycle).

Results

Treatment duration of the first cycle ranged from 2 to 5 year 3 months (average 39 months). 10/15 patients relapsed (66.6%). 7/10 relapsed after treatment was stopped, 5 of these relapsed within a year. 3/10 relapsed while still on treatment. Longer treatment duration did not seem to have any effect on long term remission. 3/15 (20%) did not relapse. 1/15 is still on treatment despite remission as stopping treatment is not appropriate for other medical reasons. 1/15 moved out of area soon after stopping treatment. 4/10 patients who relapsed needed high dose of Carbimazole (60 mg/day). None of these had any noted side effects of Carbimazole. All 10 patients who relapsed were treated with 2nd cycle. 5/10 had total Thyroidectomy and 1/10 had radioactive iodine treatment during this second cycle. 1/10 relapsed after completing the 2nd cycle and then had total thyroidectomy. 3/10 are still under treatment with 2nd cycle.

Conclusion

Relapse rate was high (66.6%) after completion of the first cycle of medical treatment. Longer duration of treatment did not seem to offer any benefit for long term remission. The second course of treatment required higher doses of Carbimazole to induce remission. This was well tolerated and was not associated with side effects.

P63

A regional survey of postnatal management of babies at risk of neonatal thyrotoxicosis

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Neonatal thyrotoxicosis (NT) is a rare condition caused by the transplacental passage of maternal thyroid-stimulating antibodies from mothers with active Graves' disease or a past history of the condition. We suspected that there were wide differences in the way that babies at risk of NT were managed in our locality and undertook a survey to establish the local approach to this clinical problem.

Method

The lead clinician who was considered most likely to be involved in managing infants at risk of NT at each of nine local units was identified and sent an electronic survey that posed questions about how at risk babies should be managed.

Results

A total of eight responses to the survey were received. Most respondents to the survey were general paediatricians with a specialist interest in endocrinology (4/8), with 3/8 being neonatologists and the other respondent being a paediatric endocrinologist from the regional tertiary centre. The majority (87.5%) of respondents used a written policy based on published expert opinion for the management of infants at risk of NT. The variation in notification strategies for at risk infants, follow up pathways and treatment plans was extensive with some units opting for close surveillance of all at-risk infants with at least two clinical assessments and thyroid function tests and others discharging the clinically well baby with no formal follow up. There was no clear management plan in terms of intervention criteria and choice of treatment.

Discussion

This survey identified a wide variation in follow up and treatment approaches to babies thought to be at risk of NT within one region of England. There is a need for further studies and then the development of an evidence based guideline that can provide a framework for clinicians faced with this potentially challenging clinical problem.

P64

Rhabdomyolysis and hypoglycaemia in profound hypothyroidism

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Introduction

Symptoms of hypothyroidism in childhood include tiredness, poor growth, weight gain, dry skin and constipation. Whilst muscular manifestations including myalgia, muscle weakness, aches and cramps, stiffness and delayed tendon jerk relaxation are common, rhabdomyolysis has also rarely been reported.

Case presentation

An 11-year-old female presented to her GP with a history of tiredness and poor growth. Initial blood tests performed by the GP showed: TSH > 100 mU/l, fT4 < 5 pmol/l, ALT 198, creatinine 137, glucose 2.9 mmol/l. On review she described several months of low energy levels, muscle cramps, back pain and feeling cold. On examination, her weight was on the 90th centile and height between the 3rd and 10th centiles with historical heights tracking along the 50th centile. She was pale with dry skin, periorbital puffiness and bilateral non-pitting leg oedema and was bradycardic but normotensive. Further investigation revealed an elevated creatine kinase (CK) of 9830 U/l (0–300 U/l), normal cortisol and blood glucose. She had positive thyroid peroxidase antibodies 1237.1 U/ml (0–50). On starting levothyroxine, her musculoskeletal symptoms resolved and renal function, ALT and CK normalised. Her height velocity improved and weight decreased to 10th centile. There was no recurrence of hypoglycaemia.

Conclusion

Rhabdomyolysis is characterized by muscular symptoms and elevated levels of CK, lactate dehydrogenase and ALT and can cause acute renal failure. The pathogenesis of rhabdomyolysis in hypothyroidism is unclear but may occur as a consequence of abnormal glycogenolysis, impaired mitochondrial oxidative metabolism and triglyceride turnover which impair muscle function. Rhabdomyolysis should be considered in patients with hypothyroidism presenting with muscular symptoms and unexplained deranged renal function. Hypoglycaemia has also been reported as a very rare complication of hypothyroidism and although the cause is unknown, altered glucose-insulin homeostasis and altered hypothalamic-pituitary-adrenal axis activity have been suggested as potential mechanisms.

P65

Thyroid Hormone resistance: a case report

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Thyroid hormone resistance is an inherited disorder with an incidence of about 1 in 50 000 live births. It is characterised by reduced response to the hormone at tissue level. Though many cases have been reported and there is growing awareness of the rare condition, there are reports of many patients being wrongly diagnosed as Graves disease and therefore undergoing various inappropriate treatments. We report the case of a 7-year-old boy who was referred to our service with abnormal thyroid function tests.

He was referred to our service by the community paediatric team where he had presented with a history of behaviour problems, learning difficulties and poor concentration.

He was born preterm at 32 weeks and required a brief stay in the neonatal unit. His weight was initially on the 50th centile but had drifted gradually to the 3rd centile. There was a family history of thyroidectomy for hyperthyroidism. His physical examination was normal with no features of hyper or hypothyroidism. His thyroid function test showed high T4 levels (26, 36 and 39 pmol/l) in the presence of normal TSH (1.2, 0.96 and 1.3 mU/l) respectively. His thyroid peroxidase antibodies and antithyroid antibodies were negative. Genetic testing showed a THR β mutation. Parental screening is currently being undertaken. The community paediatric team and school have been involved to support his behaviour and learning difficulties. He is currently stable on no medication.

Triiodothyroacetic acid, dextro-thyroxine, bromocriptine, corticosteroids, β blockers, and antithyroid drugs are some of the medications that have been used to manage symptomatic patients with varying efficacy, side effects and limitations.

P66

A case of GH deficiency?

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Case report

A 7-year-old girl presented with short stature following removal to the UK from China, where she had been diagnosed with GH deficiency on blood testing, for which GH treatment had been recommended. She had reportedly not grown well over the previous 2 years, and though the oldest in her class, she was the smallest. She had a poor appetite but otherwise was well. She had no constipation, normal activity levels, and was doing well in school. She was born at term weighing 2.9 kg.

On examination her height was 8 cm below the 3rd centile with a height standard deviation score of -3.6. Her weight was on the 3rd centile. She was proportional with no abnormalities of her chest or abdomen excepting some lichen planus on her trunk. She had no goitre and normal reflexes in her legs. Of note, she had marked calf muscle hypertrophy.

Investigations showed severe hypothyroidism with free T4 < 3.9 pmol/l and TSH 1235 mU/l with positive thyroid peroxidase antibodies and bone age of 3.5 years. Thyroxine was initiated at 50 μ g daily. By two weeks, her skin, previously dry, was improving, and by 3 months, her mother noted she was losing less hair and her calf hypertrophy was less noticeable. Her height velocity had improved to 5.6 cm/year.

Discussion

Proximal muscle weakness and hypotonia are well-recognised signs of hypothyroidism. The apparent muscle hypertrophy seen in our case is a rare manifestation of hypothyroidism, known as Kocher-Debre-Semalaigne syndrome.

Conclusion

Muscle pseudohypertrophy is a rare feature of hypothyroidism, which regresses with treatment. Hypothyroidism remains a cause of short stature, and should be excluded prior to a diagnosis of GH deficiency. It should be remembered as a rare differential of myopathy.

Author Index

- Abbey, I OC2.4
 Abinun, M OC1.7
 Acerini, C P50
 Achermann, JA OC1.3
 Adams, J P11
 Agarwal, S P26
 Agbeko, R P20 & P30
 Ahmed, F P61
 Ahmed, J P20 & P30
 Ahmed, SF P40, P51 & P54
 Ahmid, M P54
 Ajzensztejn, M OC2.1
 Akker, SA P2
 Al-Jumaili, A P5
 Alatzoglou, KS OC2.8
 Albazi, M P44
 Allgrove, J OC4.5, P15 & P16
 Alusi, G P2
 Alvi, NS OC5.1 & OC5.3
 Alvi, S OC2.4 & P13
 Amin, R OC4.1, OC4.5, P3, P33 & P58
 Anastasiadou, V P16
 Anderson, M P30
 Anderson, S OC1.5
 Andoniadou, C OC1.6
 Andrews, R S17
 Anuar, A P25 & P41
 Appelman-Dijkstra, N OC1.8
 Arundel, P P24 & S22
 Arya, VB P47
 Astuti, D OC4.4
 Avatapalle, B OC2.5, P10 & P44
 Awad, M P56
 Ayme, S P18
 Ayoola, O P39
 Ayuk, L P27 & P65
- Bacchelli, C OC1.6
 Baggott, L P9
 Bahl, S OC3.5
 Bailey, H P17
 Bailey, S P55
 Bak, B OC1.8
 Balapatabendi, M P31
 Ball, S OC2.3 & P49
 Banerjee, I OC2.5, OC2.7, P33, P44 & P58
 Barber, R P17
 Barker, E OC3.3
 Barnett, A OC4.3
 Barrett, T OC4.1, OC4.3, OC4.4, P18 & P8
- Bassett, D OC1.4
 Basu, S P13
 Bath, L P4
 Bath, LE P28
 Bath, S OC1.1
 Beales, P OC1.6
 Bellringer, J S8
 Bennett, C OC2.4
 Bernard, D OC1.8
 Bevan, C P24
 Bischof-Renner, A P4
 Bishop, J P61
 Boyde, A OC1.4
 Boyle, J P55
 Bradbury, M P12
 Bradley, K P34 & P48
 Brain, C OC2.1, P15 & P3
 Breuning, M OC1.8
 Brogan, P P21
 Brown, F OC4.5
 Bruce, J P44
 Bryan, SM P53
 Buchanan, C OC3.3
 Bulwer, C OC5.2
 Burkitt-Wright, E P10
 Burns, M P14
 Burren, C P22 & P29
 Butler, G OC2.1 & P52
- Caine, L OC2.5
 Calder, P OC2.6
 Chanudet, E OC1.6
 Chatterjee, S P60
 Chatterjee, VK OC1.8
 Cheema, S OC4.5
 Cheetham, T OC1.7, OC2.3, P20, P49, P55, P9 & S6
 Cheney, S P31
 Chetty, T P4
 Cheung, M OC1.4
 Chu, C S10
 Clark, A OC2.2
 Clark, AJL P1
 Clayton, P OC1.5, OC2.5, OC2.7, OC4.1, P33, P39, P44 & P58
 Clayton-Smith, J P10
 Cody, D P59
 Cole, T OC2.7 & P52
 Collin, J OC5.4
 Cooper, C OC2.6
 Costigan, C P59
 Cotter, C OC4.3
 Cox, R P34 & P48
 Crabtree, N P8
- Craigie, R P44
 Croft, J P60
 Cropper, J OC3.3
 Crowne, E OC2.9, P29, P34, P37 & P48
 Cruickshank, JK P39
 Cruikshank, K OC1.5
- Daniel, A P11
 Daskas, N OC2.9 & P37
 Dattani, M OC1.6, OC1.8, P3, P32, P38, P6 & S1
 Dattani, MT OC2.8
 Davies, JH OC2.6 & OC4.2
 Davis, T OC1.8
 Dawnay, A OC2.1
 Dennison, EM OC2.6
 Denvir, L P56
 Dey, I P7
 Dias, R OC4.5
 Didi, M OC2.5
 Dimitri, P OC4.1
 Donaldson, M OC2.10, P42, P43, P54 & S5
 Donnelly, S P42
 Drake, A P64
 Drake, WM P2
 Dublon, V P52
 Duncan, AJ OC1.3
 Dunger, D OC4.3 & P50
 Dunkel, L OC1.3
 Dunnen, Jd OC1.8
 Dwyer, J OC2.4
- Edge, J OC4.2, P25
 Efsthathiou, E P16
 Ehtisham, S OC2.5, P33, P44 & P58
 Elder, C OC3.1
 Elson, R P34 & P48
 Emmett, P OC1.1
 Evans, H OC1.4
- Fallows, T P19
 Farmer, A P18
 Fenton, J OC4.4
 Ford, A OC4.3
 Ford-Adams, M OC3.3
 Freemont, T P10
 Frerichs, C P57
 Frystyk, J P8
- Galloway, PJ P51
 Gan, HW OC1.2
 Gault, EJ P42 & P43
 Gelder, C OC3.4
 Gemmell, I P39
- Gevers, E P38
 Gharanei, S OC4.4
 Gharavy, N OC1.8
 Glanville, T OC2.4
 Godfrey, K OC2.6
 Golding, J OC1.1
 Gopalakrishnamoorthy, M OC2.1
 Gou, P P59
 Govern, AM OC4.1
 Gray, Z OC4.3
 Gregory, LC OC2.8
 Grosser, S P28
 Guasti, L P1
 Gupta, K P7
 Gupta, S P26
- Hakeem, V P32
 Hale, J P55
 Hall, C OC4.1
 Hamilton-Shield, J OC4.3
 Hamilton-Shield, JPH P29
 Hankey, J P19
 Hanson, D OC2.7
 Harvey, NC OC2.6
 Hassan, K P51
 Hawton, K P6
 Heffernan, E P36
 Hennekam, R OC1.8
 Heslegrave, A P46
 Heywood, J OC4.3
 Hindmarsh, P P3
 Hogler, W P8
 Hollingsworth, K OC2.3 & P49
 Holloway, E OC3.5
 Holt, R S11
 Holzmann, J OC3.5
 Hopper, N P63
 Hughes, I P50
 Hughes, M P21
 Hulse, T OC3.3
 Hussain, K P21, P45, P46 & P47
 Hwa, V P8
- Ilsley, E OC4.3
 Inskip, HM OC2.6
 Isaac, A P64
 Ivison, F OC4.1
- Johnston, R P36
 Jones, J OC2.10, P33 & P58
 Kanchi, L OC3.3
 Kang, CY P56

- Katugampola, H OC1.3, OC5.2 & P16
 Kelberman, D OC1.6 & OC2.8
 Kendall, D OC4.1
 Khan, S OC1.5
 Kibirige, M OC4.1
 King, PJ OC1.3
 Kinmond, S P42
 Kinning, E P40
 Kirk, J OC2.7
 Kithany, H P22
 Kleta, R OC1.6
 Koppikar, S P36
 Kowalczyk, J P1
 Kubba, H P43
 Kumbattae, U P65
- Lamb, B P23
 Lambert, L P19
 Lance, C P44
 Lange, K S14
 Law, J P56
 Leonards, U P37
 Lescai, F OC1.6
 Lewis, G P35
 Lim, D P43
 Lokulo-Sodipe, K OC4.2
 Lovell, N S15
 Lyddall, A OC3.5
- Maffei, P P18
 Maghnie, M S2 & S9
 Makaya, T P24
 Makusha, L OC4.3
 Malik, S P61
 Marshall, M S16
 Martin, D P8
 Martinez, J OC1.6
 Mason, A P61
 Mathew, V OC4.1
 Matthew, V P26
 Matyka, K OC4.1
 Mavinkurve, M P59
 McAulay, A P22
 McCabe, MJ OC2.8
 Mccafferty, S P18
 McCarthy, A P36
 McGowan, S P42
 McGrogan, P P51 & P61
 McMillan, M P61
 McNay, DEG OC2.8
 McNeilly, J P61
 Mehta, A OC2.8
 Meimaridou, E P1
 Meredith, S P38
 Metherell, L P8
 Metherell, LA P1
 Miller, H P37
- Mitchell, RT P28
 Mlynarski, W P18
 Mohamed, Z P45
 Monson, JP P2
 Moon, RJ OC2.6 & OC4.2
 Morrissey, S P43
 Mughal, Z P10, P11 & P12
 Murray, P OC2.7 & P15
 Mushtaq, T OC2.4, OC5.1 & OC5.3
 Mutair, AA OC1.6
- Nagy, Z OC4.4
 Neocleous, V P16
 Neylon, O P59
 Nicholas, S S24
 Nicholson, J OC2.5
 Nicola, T P25
 Noyes, KJ P28
 Ntani, G OC2.6
 Nunes, V P18
 Nutt, S P56
- O'Shea, E P33 & P58
 Omotade, O P39
 Ong, K P50
 Oostdijk, W OC1.8
- Padidela, R OC2.5, OC2.7, P10, P11, P33, P44 & P58
 Page, A P33
 Papadopoulou, M P47
 Paquis, V P18
 Parakkal, R P27
 Parkinson, K P18
 Patel, L OC2.5, OC2.7, P33, P44 & P58
 Paterson, W P42
 Pattman, S P9
 Peacock, A OC2.4
 Pemberton, P OC1.5
 Pereira, A OC1.8
 Perry, CG P54
 Persani, L OC1.8
 Peters, C P3
 Phylactou, LA P16
 Pickup, J S19
 Pokrovska, T OC2.10
 Prasad, R OC2.2
 Prentice, P P50
 Priesemann, M P22
 Pryce, M OC2.5
- Raffeeq, P P19
 Raine, J P6
 Rajput, S P62
 Randell, T P56
 Rayman, M OC1.1
- RCPCH Expert Working Group, C P52
 Regan, G S18
 Rigby, L OC2.5, P44 & S20
 Rogol, A S12
 Rose, S P8
 Rosenfeld, R P8
 Russell, R P61
 Russell, RK P51
 Ryan, F P41 & P62
- Sabin, HI P2
 Sakhinia, F OC2.7
 Sankilampi, U OC1.3
 Sardar, CM P42
 Savage, MO P2
 Say, J P16
 Schoemaker, M P50
 Schoenmakers, N OC1.8 & S4
 Senniappan, S P15, P21, P32, P45, P46 & P47
 Shah, P P15, P21 & P38
 Shah, S OC2.5
 Shaikh, G OC2.10
 Shaikh, MG P54
 Shailendra, R P25
 Shammas, C P16
 Sharples, P OC2.9 & P37
 Sharrard, M P60
 Shaw, N P66 & P8
 Shetty, A OC3.2
 Siddique, J P42
 Sik, A OC4.4
 de Silva, C P66
 Sinha, A OC1.7, OC2.3, P49 & P9
 Sinha, S S3
 Sinnott, R P18
 Skae, M OC2.5, OC2.7, P33, P44 & P58
 Skordis, N P16
 Slater, O P38
 Smith, JP P29
 Sowden, J OC1.6
 Spoudeas, H P3 & P35
 Spoudeas, HA OC1.2 & OC5.2
 Squire, Y OC3.5
 Srinivasan, R P20 & P30
 Steele, C P12
 Steer, C OC1.1
 Stevens, M P34 & P48
 Stirling, H OC4.1
 Stoneham, S P32
 Storr, H OC2.2
 Storr, HL OC1.3 & P2
 Stupka, E OC1.6
 Subbarayan, A P3
- Sun, Y OC1.8
 Sundaram, M P27
- Tapson, T P26
 Terrett, L P13
 Tetlow, L OC4.1
 Thomas, V P14 & P63
 Thornton, M P58
 Thyagarajan, M P34 & P48
 Tillman, V P18
 Tinklin, T P57
 le Tissier, P OC1.8
 van Tol, E P50
 Tomlinson, J P8
 Torpiano, J P38
 Tumba, M P16
 Towati, MAL P51
 van Trotsenburg, P OC1.8
 Turner, K OC4.3
 Turton, JPG OC2.8
- Vail, A OC4.1
 Varadhan, L P19
 Varughese, G P19
 Viner, R OC2.1
 Voshol, P OC1.8
 Vyas, A OC1.5
- Wales, J OC4.1, OC4.3 & P60
 Walker, J OC5.1, OC5.3 & P8
 Wardhaugh, B P64
 Warner, J OC3.2
 Wassef, M OC3.1
 Webb, E OC1.6
 Webb, EA OC2.8
 Wei, C P34 & P48
 Whatmore, A OC1.5
 White, A P38
 Whitehead, A OC5.1 & OC5.3
 Wilkins, J P19
 Wilkinson, D OC3.5
 Williams, G OC1.4
 Wit, J OC1.8
 Wong, SC P51
 Wood, D P32
 Woods, KS OC2.8
 Wright, C P52
 Wright, N OC3.1, OC4.1 & P24
 Wyatt, C OC4.5
- Yacoubian, C P40
 Yaw, SH OC5.3
 Zatyka, M OC4.4

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