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41st Meeting of the British Society for Paediatric Endocrinology and Diabetes 2013

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Speaker Abstracts

CME Session

CME1

Bone physiology or calcium and phosphate metabolism

J Allgrove
London, UK.

Bone has three main components: matrix, mostly made up of type 1 collagen, mineral, which is laid down on the matrix by osteoblasts, and bone cells: osteoclasts, which are derived from haemopoietic precursors, osteoclasts, which are of fibroblast precursor origin, and osteocytes, the most numerous, which are derived from osteoblasts.

Osteoblasts operate under the influence of several humoral factors including PTH, $1,25(OH)_2D$ and cytokines which act via specific receptors on the cell surface to stimulate osteoblast development and function with the aid of a number of other proteins such as LRP5, Sclerostin and Wnt signalling. Bone matrix formation is under genetic control by several genes including COL1A1, COL1A2, IFITM5, CRTAP, LEPRE1 and PPIB, mutations in any of which can cause OI.

Osteoclasts are controlled by osteoblasts under the influence of RANK and its natural inhibitor osteoprotegerin which acts via the RANK ligand on the surface of osteoclasts. Bone resorption is achieved by maintaining an acid environment using TCIRG1, CAII, OSTM1, CLCN7 and PLEKHM1 (mutations cause osteopetrosis), whilst cathepsin K removes demineralised matrix (mutations cause pyknodysostosis).

Osteocytes play a major role in maintaining phosphate mainly via the action of FGF23 which is under the influence of several genes including PHEX, DMP1, GALNT3, FGFR1c, Klotho and NaPi1. Mutations in any of these genes may cause either hypophosphataemic rickets or familial tumoral calcinosis.

This talk will give an overview of these processes and show how they link together and will concentrate on the newer aspects of phosphate physiology.

DOI: 10.1530/endoabs.33.CME1

CME2

Vitamin D and rickets

N Shaw
Birmingham, UK.

Rickets is a condition only seen in growing children due to disorders that result in impaired apoptosis of hypertrophic cells and mineralisation of the growth plate and osteoid. Although there are a variety of causes of rickets vitamin D deficiency remains the commonest cause worldwide with evidence of a resurgence in some developed countries.

There are several modes of presentation of vitamin D deficiency dependent on the age and growth rate of the child. These include hypocalcaemic symptoms, progressive leg deformities and muscle weakness. A variety of aetiological factors are important in the potential development of rickets including reduced sunlight exposure, dark skin pigmentation, atmospheric pollution and prolonged exclusive breastfeeding. An additional important factor is poor dietary calcium intake with evidence suggesting this needs to be present in conjunction with vitamin D deficiency to cause the development of rickets.

This talk will review the clinical presentation of vitamin D deficiency in children and adolescents, discuss aetiological factors and subsequent treatment.

DOI: 10.1530/endoabs.33.CME2

CME3

Osteoporosis in children and young people

N Bishop
Sheffield, UK.

What do we mean by 'osteoporosis'? Essentially, bone of reduced mass that is abnormal at a micro-architectural level, with an increased propensity to fracture. The detection of such abnormality is not straight-forward. Any bone will fracture given sufficient force, and it might be thought that restricting further investigation to those who fracture following mild or trivial trauma would be the way forward. Defining what level of trauma should be regarded as 'mild' or 'trivial' is difficult, however, given the anisotropic nature of bone and the problems of accurate recall in trauma settings.

Clear clinical signs of osteoporosis are vertebral crush fractures and buckle fractures of the distal femur or proximal tibia. These can have particular value in the differentiation of normal from fragile bone in the pre-mobile infant.

Bone densitometry by DXA can measure bone mass, but does not distinguish between bone compartments – cortical vs trabecular bone – and the measurements are strongly influenced by size. In children with chronic disorders who are small, account needs to be taken of this confounding element.

New imaging techniques – volumetric and peripheral high resolution QCT, and MRI are still research approaches that have not entered mainstream clinical practice. Bone biopsy can provide both static and dynamic information on bone, but is site-specific. Microindentation is still a laboratory technique currently; a handheld device used in adults might damage the thinner, less mineralised cortical bone of a child's tibia. Genetic panels for inherited bone fragility genes are improving diagnostic accuracy.

Current therapeutic interventions focus on anti-resorptive therapies, primarily bisphosphonates, as part of a multidisciplinary approach. Recent advances in the genetics of inherited bone fragility syndromes indicate alternative therapeutic targets in the canonical wnt-signalling pathway. There is still a need to provide clear advice regarding nutrition and exercise in all cases.

DOI: 10.1530/endoabs.33.CME3

CME4

Normal and abnormal variations of growth and puberty: how can the new RCPCH specialist childhood and puberty close monitoring charts help us?

G Butler
London, UK.

Growth through the pubertal progress is notoriously difficult to track and interpreting abnormal patterns is tricky. Current growth charts are unhelpful. I will present new analyses of understanding of growth patterns and the tempo of pubertal changes and how they all link together. The RCPCH has launched a specialist growth chart in June to help identify and diagnose abnormal growth patterns during puberty. These include growth centiles for extremes of stature and weight, and growth centiles for which the normal range varies according to the phase of puberty for tall, short or light children. I will present he new way of tracking puberty with stage lines which are on these new charts, and will show how they can be used to identify patterns of abnormal pubertal development.

DOI: 10.1530/endoabs.33.CME4

CME5

Puberty in SGA

A Hokken-Koelega
Rotterdam, The Netherlands.

Abstract unavailable.

DOI: 10.1530/endoabs.33.CME5

CME6

Precocious puberty

J Carel
Paris, France.

Abstract unavailable.

DOI: 10.1530/endoabs.33.CME6

Plenary Guest Lecture

PL1

Early intervention on type 1 diabetes

J Ludvigsson
Linköping, Sweden.

Most patients with type 1 diabetes, even children and adolescents, have residual insulin secretion at diagnosis. As long as this can be preserved blood glucose

fluctuates less, and the risk of acute and late complications decreases. Gradually the autoimmune process will destroy β-cell function unless immune intervention can stop the destructive process.
Several different interventions have been tried. The very first intervention with plasmapheresis may have had some effect, and lead to, as side effect, the discovery of the 64 kDa, later shown to be GAD. Cyclosporin proved the concept, but had, as several other broad immune suppressive agents, too serious adverse events.
Last decades the immune interventions have followed two different lines:
MABs have been used to block relevant receptors. AntiCD3 seems to be the most effective and certainly can preserve residual β-cell function, but high effective doses unfortunately lead to quite common and disturbing adverse event such as anemia, bleedings, cytokine release syndrome, etc. Phase III trials have failed, but one arm in the Teplizumab study with a moderate dose had significant effect and rather mild and acceptable adverse events, which encourages to further studies. AntiCD20 had also some effect, but short and transient.
Auto-antigen treatment to create tolerance is the other main and attractive approach. GAD-vaccination gave significant preservation of C-peptide in phase II studies in children and adolescents, but phase III did not reach primary endpoint. Efficacy in several pre-specified subgroups, however, support the concept and new studies are ongoing, when vitamin D and anti-inflammatory treatment is combined to improve the vaccination effect. Experimental studies suggest the use of insulin or pro-insulin/proinsulin peptides, and clinical studies are on their way. In addition to the main stream there are several other trials made to use, e.g. TNF-blocking agents, islet neogenesis associated protein (INGAP), DNA-vaccines, IL1 blocking agents, vitamin D, but further studies are needed.
Conclusion
Preservation of residual insulin secretion is crucial. Clinical intervention studies should be encouraged. Most probably combination therapies will be needed.

DOI: 10.1530/endoabs.33.PL1

Symposia 1 Care and controversies: present and future

S1.1

Preservation of fertility

R Anderson
Edinburgh, UK.

Fertility preservation is a rapidly advancing area of medicine. Its clinical potential in adult women was demonstrated by ovarian function and successful pregnancy following ovarian cortical tissue cyropreservation and replacement in the sheep in the 1990s with the first successful human pregnancy reported in 2004. Since then some 25 babies have been born to women who have had ovarian tissue cryopreserved and subsequently replaced, with most of these women having been treated for haematological malignancies. Much larger numbers of women have had embryo cryopreservation, which has long been a routine in IVF practice, and recent developments in oocyte vitrification have made that approach a much more viable option than was the case just a few years ago. For children however gonadal tissue storage remains the only option. Several case studies have been published showing its application to girls, and there are two reports of replacement of ovarian tissue to induce puberty in adolescent girls, although this indication is debatable. Options for boys remain experimental at present. Ovarian tissue harvesting requires a surgical intervention and therefore patient selection is of paramount importance. This is to ensure that only children at high risk of losing their fertility undergo such an additional procedure, and to minimise the risk of complications. Additional issues include the loss of a large proportion of the cryopreserved ovarian follicles following re-implantation, and the risk of re-implanting the original malignancies. Despite these significant issues it appears that this is a reasonable option at present for a small proportion of girls with newly diagnosed cancer.

DOI: 10.1530/endoabs.33.S1.1

S1.2

Cancer treatment late effects on the endocrine system

A Leiper
London, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S1.2

S1.3

SAGhe: GH safety and long term concerns

J C Carel
Paris, France.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S1.3

Symposia 2 Recent advances in CAH management

S2.1

CaHASE: a UK collaborative study on CAH in adults

R Ross
Sheffield, UK.

Congenital adrenal hyperplasia (CAH) is a genetic disorder arising from defective steroidogenesis resulting in glucocorticoid deficiency; the commonest mutation is in the gene encoding 21-hydroxylase. Lifesaving glucocorticoid treatment was introduced in the 1950s and there is now an enlarging cohort of adult patients; however, there is no consensus on management. To address this issue, the Congenital adrenal Hyperplasia Adult Study Executive (CaHASE) was formed in 2003 to study the health status of CAH patients in adulthood. Seventeen specialist Endocrinology centres around the United Kingdom recruited a cohort of 203 adult patients and gathered information on medical treatment, fertility, genetic analysis and quality of life (QoL). The CaHASE study found that adult patients are prescribed a variety of glucocorticoids including hydrocortisone, prednisone, prednisolone, dexamethasone, and combinations taken in either a circadian or reverse circadian regimen. Despite this variety in personalized treatment regimens biochemical control of CAH is only achieved in approximately a third of patients. There is evidence for poor health status in some patients with an increased incidence of obesity and osteoporosis, and impaired fertility and quality of life. The evidence suggests that these poor health outcomes relate to treatment rather than genotype. Patients receiving higher doses of glucocorticoids and the more potent synthetic glucocorticoids are more likely to suffer from obesity, insulin resistance and a reduced quality of life. Further research is required to determine whether improving management and treatment in CAH patients can improve their health.
References from CaHASE Cohort study: (1–4)
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4. Han TS, Krone N, Willis DS, Conway GS, Hahner S, Rees DA, Stimson RH, Walker BR, Arlt W & Ross RJ. Quality of life in adults with congenital adrenal hyperplasia relates to glucocorticoid treatment, adiposity and insulin resistance: United Kingdom Congenital adrenal Hyperplasia Adult Study Executive (CaHASE). *Eur J Endocrinol* 2013 **168** 887–893.

DOI: 10.1530/endoabs.33.S2.1

S2.2

Paediatric surveillance for CAH: informing newborn screening policy

R Knowles
London, UK.

Congenital adrenal hyperplasia (CAH) is a recessively inherited deficiency of cortisol production affecting an estimated 1 in 10 000–20 000 live births. The salt-wasting form, which is found in over half of all children with CAH, may present with a potentially life-threatening crisis in with the newborn period while associated excess androgen production may result in girls being incorrectly assigned as boys at birth. Early detection by newborn screening, combined with

cortisol and mineralocorticoid replacement can prevent life-threatening episodes, and ensure normal growth and sexual development in older children. Although some countries undertake screening for CAH as part of the newborn bloodspot programme, it has not been introduced in the UK, reflecting uncertainty regarding disease burden as well as the high false positive rate associated with the existing screening test. Prospective surveillance of all new diagnoses of CAH in British children was undertaken through the British Paediatric Surveillance Unit in order to determine the incidence of CAH and burden of disease, including short-term health outcomes, and to assess the potential benefit of introducing newborn screening for CAH in the UK.

Declaration funding
Department of Health – commissioned by the UK National Screening Committee.

DOI: 10.1530/endoabs.33.S2.2

Symposia 3 Present and future: novelty and goals

S3.1

Benefits of diabetes networks and beyond

F Campbell
Leeds, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S3.1

S3.2

Screening for diabetes related complications

R Amin
London, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S3.2

S3.3

What are the barriers of implementation to BPT

T Randell
Nottingham, UK.

The paediatric diabetes best practice tariff (BPT) was introduced in 2012, with the aim of standardising and improving paediatric diabetes services across England. In the first year, only about 50% of units were claiming the full tariff but this had substantially improved for 2013–2014. It is probably too early to see if there has been a positive impact on outcomes but data from the East Midlands will be presented to look at this in more detail. From 2014, the BPT will also include payment for in-patient stays and it is hoped that with more evidence we may be able to apply the tariff put to age 25.

DOI: 10.1530/endoabs.33.S3.3

Symposia 4 Debate: Pump vs MDI in all children with DMT1

S4.1

Pump therapy in all newly diagnosed T1DM

F Campbell
Leeds, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S4.1

S4.2

MDI in all newly diagnosed T1DM

T Hulse
London, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.S4.2

Diabetes professionals Meeting Programme

DP1

NPD implications for practice

F Campbell
Leeds, UK.

Abstract unavailable.

DOI: 10.1530/endoabs.33.DP1

DP2

Implementation of structured education

H Thornton
Prescot, UK.

Basic education about diabetes is a cornerstone to diabetes management but in the UK there was, until recently, no national recognised programme easily available in every Paediatric unit despite several being under development for considerable time.

Children in any age group vary considerably in their ability to learn and accept new responsibilities. Diabetes education, therefore, should be adapted to the individual child's level of development and understanding. There was a desperate need, at the time, for teams to be able to evidence this ongoing educational as part of best practice tariff.

The goals of diabetes was originally developed in 1996 in Denmark and was a nationally programme. Along with Industry partners, NovoNordisk, this programme was adapted for use in the UK in 2010–2011 and distributed to every paediatric clinic in 2012. The major key elements in its development demanded an evidence-based, structured curriculum which is flexible, quality assured, dynamic and auditable (DoH NICE 2005).

The journey of its development and implementation will be described giving delegated insight into how to utilise the materials and record sheets with practical examples of its use in clinical practice.

DOI: 10.1530/endoabs.33.DP2

DP3

Developing the role of diabetes educator in the UK

K Ross
Oxford, UK.

The multidisciplinary diabetes team consists of health care professionals (HCP) each with a profession specific role who are required to be competent to a basic level in all aspects of diabetes care. Working together, teams provide all the education required to manage this condition to children and families as they grow up. The amount and complexity of information is increasing making it difficult to deliver to all individually. Group education is a solution but introduces a range of new skills required by the HCP's to achieve the objectives of the education.

Teaching methods and teaching materials adapted from those used with individuals in diabetes education is no longer adequate. The best practice tariff requires the provision of structured education that meets rigorous standards, not least in its consistency and effectiveness for each child whilst also providing peer support and other benefits of children learning life and diabetes skills together and from each other. This requires the skills of a teacher.

In the USA, Australia, Canada and Europe children's diabetes teams often include a diabetes educator. These professionals have a variety of backgrounds however, the majority are nurses. The training to become a Credentialed Diabetes Educator is comprehensive with teaching skills just one component. This team member is

responsible for all the education and on going support of the child and family post diagnosis.
In the UK we are developing training courses to support the role of a diabetes educator which would enhance the skills of that professional and includes teaching skills. However, it will take time and further resources to fully establish this role so we need an interim approach using existing skills within the diabetes team with priority given to dedicated time to manage the structured education programme – the first responsibility of that teams 'diabetes educator'.

DOI: 10.1530/endoabs.33.DP3

DP4

Psychology: narrative theory

Abstract unavailable.

DOI: 10.1530/endoabs.33.DP4

DP5

Kids in control of food: results from the KICk-OFF randomised controlled trial

K Price
Sheffield, UK.

KICk-OFF is a 5 days structured education course for 11–16 years old with type 1 diabetes. It has been developed with input from school teachers, children and families and follows constructivist learning theory. A pilot study resulted in some changes to the curriculum.
From 2008–2013 a cluster randomised controlled trial, funded by Diabetes UK, has been undertaken, involving 396 participants from 31 UK NHS diabetes centres. Centres were randomised to deliver KICk-OFF courses or continue usual care and support. Courses were taught by three educators (two KICk-OFF employed and one from local team), to groups of up to nine young people. All educators attended a 5-day teaching skills course in advance of delivering KICk-OFF courses.
Primary outcomes are HbA1c and quality of life. Secondary outcomes include diabetic ketoacidosis, hypoglycaemia, fear of hypoglycaemia and self efficacy. Health economic analysis and modelling of future costs to the NHS has been undertaken. Courses were observed by independent educationalists to assess the standard and consistency of teaching and achievement of key learning points.
Attendance at courses was very good and feedback from participants and parents was excellent. The educationalists felt that the standard of teaching was high and the curriculum was appropriate for this age group. The mathematics involved in carbohydrate counting proved challenging for many young people and the educators needed to develop particular skills in supporting them with this.
Results will be presented for the primary and some of the secondary outcomes.

DOI: 10.1530/endoabs.33.DP5

DP6

Transition to adult services

H Gleeson

Abstract unavailable.

DOI: 10.1530/endoabs.33.DP6

DP7

How does the The National Paediatric Diabetes Audit help improve outcomes for CYP with diabetes?

J Warner
Cardiff, UK.

The National Paediatric Diabetes Audit (NPDA) has now been established for 9 years and collects data on standards of care as defined by the National Institute for Clinical Excellence (NICE). These include demographics of paediatric diabetes, care process completion rates and outcomes.
Since April 2011 the NPDA has been managed by the Royal College of Paediatrics and Child Health (RCPCH) which comprises a project board advised by specific working groups associated with the dataset and with experience measures and representing stakeholders.
Under the guidance of the working groups and the project board the RCPCH have been engaging with stakeholders to improve participation and data quality. In 2010/2011 there was an increase in 23.4% of patients submitted to the audit. With the development of the regional networks in England it has been possible to express the data at individual unit level and at regional and national level allowing valuable benchmarking to take place. Risk adjusted outcomes are being developed for 2011/2012 data which will attempt to adjust for confounding factors such as deprivation, ethnicity and age.
The first national Patient/Parent Reported Experience Measure (PREM) for paediatric diabetes reported in 2013 with approximately half the paediatric diabetes population participating. There is wide unit and regional level variation in patient experience which requires careful benchmarking and evaluation.
Data provided by the audit needs to be carefully reviewed by units and utilised as part of their peer review process to improve outcomes and quality of care by benchmarking against others and making changes to services where necessary.

DOI: 10.1530/endoabs.33.DP7

Endocrine Nurse Programme

EN1

Ipsen award 2012: managing children with symptomatic vitimin D deficiency; the role of the clinical nurse specialist

P Musson
Southampton, UK.

Over the past few years the number of children identified with vitamin D insufficiency/deficiency across the UK has increased. The Department of Health has recently reiterated the guidance for practitioners regarding at risk groups requiring surveillance and treatment recommendations. An audit in 2011 demonstrated that 30% of the children presenting to the paediatric orthopaedic service with musculoskeletal symptoms had vitamin D insufficiency or deficiency.
At the time management of these children was found to be inconsistent between practitioners, with children randomly being referred to the paediatric endocrine service, followed up in orthopaedic clinic or discharged to GP for management. Information given to parents by the orthopaedic service was also variable and 88% of parents were given no advice by their GP or hospital doctor on how to improve their child's vitamin D status.
The increasing number of referrals to the paediatric endocrine service were not manageable and were increasing the waiting times for all new appointments. Following discussion with the paediatric orthopaedic team it was agreed that the patient pathway for these patients was changed. Since January 2012 children with symptomatic vitamin D deficiency referred to the paediatric endocrine service are given an appointment with the clinical nurse specialist (CNS).
A standard operational procedure for clinic appointments was agreed to inform the structure and standards for the service. The CNS has undertaken further study and supervised practice to gain the necessary skills and expertise to manage this cohort of children. Standard guidelines for the management of vitamin D deficiency are followed and information provided to families in a way they can understand that promotes concordance with the suggested treatment. Once care is complete the patient is discharged to the care of the general practitioner with advice on maintaining optimum vitamin D levels in the future.
Challenges in establishing this service, benefits to the families and outcomes will be discussed.

DOI: 10.1530/endoabs.33.EN1

EN2

The advanced nurse practitioner in paediatric endocrinology; the journey and the reality

P Laing
Liverpool, UK.

The National Health Service and Nursing are currently facing challenging times. Continuing austerity measures combined with healthcare reform and a climate of professional uncertainty often results in nurses having to justify their existence. The quality, innovation, productivity and prevention (QIPP) initiative sets out how the National Health Service is to make efficiency savings whilst improving the quality of care that patients receive. With the appropriate training, competency, professional accountability and support advanced nurse practitioners are in a unique position to work across the clinical interface and are good value for money in terms of patient safety, quality of service and efficiency, which are all high on the agenda at both government and NHS Trust level.
This journey to advanced nurse practitioner presentation explores the concept of nurses developing their role in an innovative manner and explains how the step from clinical nurse specialist to advanced nurse practitioner can have a high impact effect on both personal and professional development and service delivery. The implementation of the advanced nurse practitioner role in endocrinology at Alder Hey Children's Hospital is a new initiative and has moved from an embryonic phase to impacting positively upon service delivery and has been achieved through working collaboratively with clinicians, nursing colleagues and other members of the multidisciplinary team.

DOI: 10.1530/endoabs.33.EN2

EN3

Multiple endocrine neoplasia (MEN) an overview

M Ahmed
Southampton, UK.

Multiple endocrine neoplasia type 1 (MEN1) and MEN) are distinct clinical and genetic entities.
This talk will cover the key clinical features and surveillance strategies for each of these conditions.

DOI: 10.1530/endoabs.33.EN3

EN4

Not another blood test! Parent/patient experience of MEN

J Russell-Winter & H Russell-Winter

Not another blood test !
Living as a teenager with multiple endocrine neoplasia type 1.
Brother and sister Joel (18 years) and Hope (14 years) Russell-Winter share their respective experiences of being diagnosed as teenagers with the rare condition multiple endocrine neoplasia type 1.
They believe that the needs and experiences of teenagers are sometimes forgotten during hospital testing, consultations and treatment. Their presentation would like to tell you more about their condition, how it effects them, what's it's like trying to come to terms with it – including how friends, girl/boy friends and other people react. They also want to let you know what has been helpful (and not so helpful!) from those professionals caring for them with the condition.

DOI: 10.1530/endoabs.33.EN4

Oral Communications

Oral Communications 1

OC1.1

GH testing: reducing the need for a second test for the diagnosis of GH deficiency

Zain Juma[1], Angela Casey[1], Jullia Prior[1], Jeremy Kirk[1] & Renuka Dias[2]
[1]Birmingham Children's Hospital, Birmingham, UK; [2]University of Birmingham, Birmingham, UK.

Background
The diagnosis of isolated GH deficiency (IGHD) is based on multiple factors: clinical, radiological and biochemical along with suboptimal peak GH levels demonstrated on dynamic testing. Recent guidance from the National Institute of Clinical Excellence (NICE; UK; 2010) advises that two GH stimulation tests must demonstrate a subnormal GH peak <6.7 μg/l (20 mU/l) to confirm the diagnosis of IGHD. In our centre, three different GH provocation tests are used: insulin tolerance, glucagon stimulation (1st line) and arginine stimulation (2nd line).
Objective and hypotheses
To see if other clinical and biochemical parameters can increase the sensitivity of GH provocation testing for the diagnosis of IGHD.
Methods
A retrospective case-review of all patients in a single centre from 2002 to 2012 undergoing two provocation tests, comparing those with two abnormal GH test results vs those with one abnormal result.
Results
107 children had two GH provocation tests; 41% with an abnormal 1st test had a normal GH response on retesting. Lowering the cut-off to 2.7 μg/l ($\sim$8 mU/l), missed 50% of children who would have otherwise met NICE GHD criteria. In patients who failed both tests, 35.3% had a low IGF1 and 30.0% had a delayed bone age (BA) >2 years vs 26.5% with low IGF1 and 20.5% with delayed BA in patients passing the 2nd test (P 0.44 and 0.45 respectively).
Conclusions
Many children failing a 1st GH stimulation test will have a normal GH peak on re-test with no absolute cutoff peak on the 1st test that predicts an abnormal 2nd test. Moreover, a significantly delayed bone age or low IGF1 does not improve the predictive value of GH testing. As currently GH stimulation testing costs $\sim$€1000, identification of other clinical or biochemical parameters are needed to reduce the necessity for repeat testing to diagnose IGHD.

DOI: 10.1530/endoabs.33.OC1.1

OC1.2

A single centre audit of the 2012 UK Newborn Screening Programme Guidelines for pre-term infants

Gemma Woods[1], Shirley Langham[2] & Catherine Peters[2]
[1]University of Cardiff Medical School, Wales, UK; [2]Great Ormond Street Hospital, London, UK.

Newborn screening of premature infants for congenital hypothyroidism (CH) may initially be normal despite the presence of thyroid pathology and therefore repeat TSH screening is required. The 2012 revised UK Newborn Screening guidelines for premature infants state that infants born <32 weeks gestation require a repeat TSH bloodspot at 28 days postnatal age or discharge home, whichever is earlier. Prior to this, repeat testing was required at 36 weeks corrected gestation for all pre-term infants born <36 weeks.
Method
We audited pre-term referrals to our centre pre and post guideline changes. Data were collected for gestational age, birth weight, bloodspot TSH concentration, venous free T_4 and TSH, age of referral and need for levothyroxine therapy.
Results
In babies born <32 weeks, we found an increase in referrals in the 1 year post policy change (17 referrals in 2012–2013 compared with an average of five referrals per year between April 2006 and 2012). The increase in referrals were mainly in infants with TSH concentrations <20 mU/l. 47 pre-term babies born at 32–36 weeks gestation were referred between 2006 and 2012. 14/47 had a venous TSH >20 mU/l and low free T_4 concentrations and were commenced on levothyroxine.
Discussion
Changes to the newborn screening of premature infants has increased the number of borderline referrals born at <32 weeks. Repeat screening at 28 days may detect a TSH surge that has resolved when repeat screening occurs later at 36 weeks. These false positive referrals need to be balanced by the potential neurodevelopmental benefit of earlier commencement of levothyroxine for those babies with confirmed CH. The new standards no longer require repeat screening in babies born at 32–36 weeks gestation and would have missed the 14 babies requiring levothyroxine treatment prior to the change in standards.

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OC1.3

The utility of AMH for predicting testosterone response to HCG stimulation in children with suspected DSD

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Introduction
In children undergoing investigation of testicular function the relationship between serum anti-Müllerian hormone (AMH) and the testosterone response to hCG stimulation test (HST) is unclear.
Methods
71 children (three females and 68 males) with a median age of 1.08 years (range: 0.003, 14.3) were investigated for suspected DSD by AMH on D1 and testosterone on D1 and D4, before and after 3-day HST. Of these children, 27 had an additional prolonged HST. Normal testosterone response to HST was defined as a testosterone greater than upper prepubertal limit or a testosterone increment (ΔT) greater than twice the baseline value. A low AMH was defined as below the 5th centile for age.
Results
The D4 testosterone response was normal in 61 with a median testosterone of 9.4 nmol/l (1.0, 40.7) and a median ΔT of 11.1 (0.8, 59.2) and abnormal in ten with a median testosterone of 0.55 nmol/l (0.5, 3.0) and a median ΔT of 1.0 (0.7, 1.8). AMH was low in 12/71 children and in 5 (42%) of these cases a low D4 testosterone was observed. An AMH $>$5th centile was associated with a low D4 testosterone in only 5/59 cases (8.4%) ($P<0.05$). Median AMH in the two groups of patients who responded and did not respond by D4 was 708 pmol/l (97, 1926) and 107.6 pmol/l (1.5, 256) ($P<0.0001$). The testosterone response after prolonged HST was normal in 23/27 children with a median testosterone of 15.0 nmol/l (0.8, 43.4) and a median ΔT of 18.2 (0.57, 62.0) and abnormal in four with a median testosterone of 0.55 nmol/l (0.5, 1.0) and a median ΔT of 1.0 (0.6, 1.2). AMH was low in six children and in 3 (50%) of these cases a low D22 testosterone was observed. An AMH $>$5th centile was associated with a normal D22 testosterone in 20/21 cases (95%) ($P<0.05$). Median AMH in children who responded and did not respond at D4 and D22 was 420 pmol/l (100, 1664) and 2.8 pmol/l (1.5, 214) ($P<0.05$).
Conclusion
A normal AMH may provide valuable information on overall testicular function. However, a low AMH does not necessarily predict a sub-optimal testosterone response to hCG stimulation.

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OC1.4

Abnormal glucose homeostasis in survivors of childhood acute lymphoblastic leukaemia treated with bone marrow transplantation and total body irradiation is associated with reduced β-cell reserve and pancreatic volume

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Background
Adult survivors of childhood acute lymphoblastic leukaemia (ALL) treated with bone marrow transplantation (BMT) and total body irradiation (TBI) have increased risk of impaired glucose tolerance (IGT) and diabetes mellitus (DM). Insulin resistance (IR) has been described, but effects of TBI on pancreatic growth and β-cell function have not been previously reported.
Method
Two groups of childhood ALL survivors were studied: Group 1, treated with ($n=21$, 11 M) and Group 2, without ($n=31$, 13 M) BMT/TBI. BMT/TBI survivors received 10–14.4 Gy TBI at mean age 9.3 (1.0–10.8) years. A control Group 3, was selected of obese subjects ($n=30$, 10 M). All were age 16–26 years

and had assessment of: pancreatic volume by abdominal MRI; IR by insulin composite insulin sensitivity index (ISIcomp) from oral glucose tolerance test (OGTT); β-cell function by acute-insulin-response (AIR) from Arginine intravenous glucose tolerance test (AIRarg). Data were logarithmically transformed if positively skewed and analysed by ANOVA with *post-hoc* Scheffé's multiple comparison tests, multiple regression and Pearson's correlations at 5% significance. Results are reported as mean (S.D.) or geometric means (range) as appropriate.

Results

Abnormal OGTT were reported in Groups 1 (DM = 2, IGT = 7) and 3 (IGT = 1). ISIcomp was lower in Groups 1 (1.7 (0.35–44.7), $P < 0.001$) and 3 (4.8 (0.75–9.6), $P = 0.001$) compared with Group 2 (2.2 (0.76–7.5)). β-cell function assessed in the context of IR was significantly lower in Group 1 [60.0 (CI: 43.8–76.7)) than Groups 2 (105.4 (CI: 79.8–138.4), $P = 0.003$) and 3 (83.8 (CI: 69.7–100.9), $P = 0.034$). Absolute pancreatic volume (cm^3) (PV) was lower in Group 1 (52.0 (14.2)) than Groups 2 (72.8 (23.5), $P = 0.003$) and 3 (72.8 (19.7), $P = 0.006$) and correlated with AIR ($r = 0.3$, $P = 0.01$). Pancreatic volume correlated positively with the size (represented by $height^2$) of participants ($r = 0.45$, $P < 0.001$). Regression analysis confirmed that PV adjusted for size remained lower in Group 1 (56 (47.4–65.1)) than Groups 2 (71.0 (63.8–78.2), $P = 0.014$) or 3 ((71.2 (63.2–79.3), $P = 0.016$). Absolute and corrected PV did not differ between Groups 2 and 3 ($P = 1.0$) and did not correlate with age at ALL diagnosis ($P = 0.9$), time from treatment ($P = 0.3$), age at BMT ($P = 0.7$), time from BMT ($P = 0.3$) or TBI dose ($P = 0.8$).

Conclusions

This study suggests that reduction in pancreatic size, and loss of β-cell compensation contribute, with increased IR, to the mechanism of abnormal glucose homeostasis in survivors of BMT/TBI in childhood.

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OC1.5

Novel genes affecting the timing of puberty

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Background

Disturbances of pubertal timing affect >4% of the population and are associated with adverse health outcomes. Studies estimate 60–80% of variation in pubertal onset is genetically determined, but few genetic factors are known. We hypothesise that causal variants will be low-frequency, intermediate-impact variants and will be enriched in populations at the extremes of normal pubertal timing. Families with constitutional delay in growth and puberty (CDGP) have pubertal onset delayed by >2 S.D., often with an apparent autosomal dominant inheritance pattern.

Methods

Seven highly informative families from our large, accurately phenotyped CDGP cohort were selected for whole exome sequencing. Annotation and filtering of variants produced an extensive list of potential causative mutations that segregate with trait. Variants were ranked on the basis of presence in >1 family, minor allele frequency <5% or novel, predicted effect on the protein and conservation. Pathway analysis was performed to identify genes with action within the hypothalamic–pituitary–gonadal axis or in linkage disequilibrium ($D' > 0.8$) with loci identified by genome-wide association studies (GWAS) of age-at-menarche.

Results

The 15 top-ranking genes identified all contained non-synonymous missense variants segregating an autosomal dominant pattern. Validation of these 15 genes through targeted re-sequencing in a further 288 CDGP individuals has identified a novel candidate gene, with variants in nine families. This gene has a predicted role in neural outgrowth and is expressed in nasal placode mesenchyme during embryogenesis, suggesting a possible function in GnRH neuronal development. Minimal overlap with GWAS loci was identified. Functional studies of these novel variants are in progress.

Discussion

We describe our strategy for identification of novel causal gene variants from next-generation sequencing data in this common condition. In addition to the exciting finding of a novel gene implicated in the timing of puberty, our results highlight the significant genetic heterogeneity seen in CDGP.

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OC1.6

Oral bisphosphonates as prophylaxis of steroid-induced osteoporosis in Duchenne muscular dystrophy

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Background

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy, resulting in death at a young age. Corticosteroids improve muscle function and slow disease progression. However long-term steroid therapy is a significant risk factor for osteoporosis.

Aim

To assess the effect of oral bisphosphonate (risedronate) treatment on bone mineral density in a cohort of steroid-treated children with DMD.

Method

Annual bone mineral density (DXA) scans were performed on boys with DMD treated with glucocorticoid under review at a National Muscle centre. Data prior to bisphosphanate initiation were compared with subsequent annual DXA assessments. Lumbar spine and total body bone densities were corrected for bone volume. Information about duration of steroid treatment and fractures was also collected. All patients received vitamin D supplementation.

Results

Data on 43 patients was analysed. The median duration of steroid therapy at the initiation of bisphosphanate therapy was 33 months (range: 0–87 months). The duration of bisphosphonate therapy ranged from 1 to 4 years (average 2 years). Total body adjusted density *Z* score increased post bisphosphonate therapy from −0.55 at baseline to 0.62 after 3 years ($P = 0.009$) whilst lumbar spine adjusted density (LSAD) remained stable with a baseline value of 0.11 and 0.21 at year 3 ($P = 0.97$). LSAD in those with an initial *Z* score < -1 increased from −1.44 to −0.49 ($P < 0.01$). Eight patients had documented fractures following a fall whilst on bisphosphonate therapy. Three of these involved lumbar spine and these patients all had a LSAD < -1 SDS at baseline.

Conclusions

The size adjusted lumbar spine BMD of steroid treated patients with DMD on bisphosphonates remains stable and particular benefit was seen in those with an initial LSAD < -1 SDS. The relationship between fracture and baseline LSAD highlights the need to consider ways of refining bone protection in these patients with more targeted therapy.

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OC1.7

A mutation in thioredoxin reductase 2 is associated with familial glucocorticoid deficiency

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Background

Novel pathogenic mechanisms involving replicative and oxidative stress have recently been described in familial glucocorticoid deficiency (FGD); including mutations in *NNT*. NNT supplies high concentrations of NADPH needed by the glutathione and thioredoxin anti-oxidant systems to detoxify mitochondrial H_2O_2. Six patients, from a consanguineous Kashmiri family, were diagnosed with glucocorticoid deficiency between 0.1 and 10.8 years of age and were mutation negative for known causes of FGD.

Methods

Whole exome sequencing was performed on three affected individuals followed by Sanger sequencing of all family members. A *TXNRD2*-knockdown human adrenocortical H295R cell line was established to investigate redox homeostasis.

Results

A novel homozygous mutation, p.Y447X in *TXNRD2* was identified segregating with disease in this kindred. TXNRD2 is a mitochondrial selenoprotein, dependent upon a c-terminal selenocysteine to maintain enzyme activity. *TXNRD2* knockout is described as embryonic lethal in mice due to cardiac

malformation and heterozygous mutations are described in humans with dilated cardiomyopathy. We find that *TXNRD2* is ubiquitously expressed in human tissues with high mRNA levels in the adrenal cortex. The predicted consequence of the mutation was premature truncation removing the selenocysteine residue, however RT-PCR of patient cDNA and western blotting of patient lysates revealed complete absence of TXNRD2 in patients homozygous for the mutation presumably as a result of nonsense-mediated decay of mRNA. In our affected homozygote individuals, with apparent absence of TXNRD2, we observe no evidence of cardiomyopathy or conduction disease. *TXNRD2*-knockdown in the H295R cell line leads to increased oxidative stress with pressure on the glutathione system and increased mitochondrial superoxide production.
Conclusion
A delicate balance of mitochondrial redox regulation controls steroidogenesis at the level of the adrenal gland. We report the first mutation in *TXNRD2* associated with a predominantly adrenal phenotype, indicating the importance of the thioredoxin system in maintaining redox homeostasis in the adrenocortical environment.

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OC1.8

The repressor activity of the Wnt/β-catenin effector Tcf3/TCF7L1 is required for normal hypothalamic–pituitary development

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Aberrant development of the pituitary gland can result in the clinical manifestation of hypopituitarism. The Wnt/β-catenin pathway has been shown to be involved in normal organogenesis, terminal differentiation and the aetiology of pituitary tumours. However, the specific developmental roles during hypothalamic–pituitary development of some of the Wnt/β-catenin effectors, such as *Tcf3*, have been hampered due to the early lethality of null embryos for this gene. To overcome this, we have conditionally deleted *Tcf3* ($Tcf3^{Fl/-}$;$Hesx1^{Cre/+}$) from the *Hesx1*-expressing cells within the early forebrain and developing pituitary gland. A low proportion of $Tcf3^{Fl/-}$;$Hesx1^{Cre/+}$ animals exhibit dwarfism indicating that deficiency in *Tcf3* can lead to hypopituitarism in mice. Analyses of $Tcf3^{Fl/-}$;$Hesx1^{Cre/+}$ mutant embryos reveals a mild hyperplasia of the pituitary gland, sometimes with the mis-location of the pituitary in the pharyngeal cavity. We show that *Tcf3* has a dual function and it is required in both the ventral diencephalon (VD) and anterior pituitary gland (AP). In the VD, absence of *Tcf3* results in aberrant VD signaling with rostrally expanded *Fgf10* and *BMP4* expression domains, leading to a broader region of the oral ectoderm being specified into Rathke's pouch. Within the developing AP, absence of *Tcf3* results in increased mitotic index of periluminal Rathke's pouch progenitors, further exacerbating the AP-hyperplasia. To assess if TCF3 is required to mediate transcriptional activation or repression of Wnt/β-catenin pathway, we studied a second murine mutant ($Tcf3^{\Delta N/\Delta N}$) expressing a mutant TCF3 lacking the β-catenin interacting domain, and therefore acting as a constitutive repressor. Interestingly, $Tcf3^{\Delta N/\Delta N}$ embryos exhibit normal development of both the prospective hypothalamus and the pituitary gland throughout all developmental stages, indicating that TCF3-repressing activity is essential for hypothalamic–pituitary development. Providing a translational impact to this research, we report the identification of a novel mutation in *hTCF3* that compromises TCF3-repressing activity in a patient with septo-optic dysplasia (SOD), suggesting a contributory role of *TCF3* in SOD. In summary, our research demonstrates a critical role for the Wnt/β-catenin effector *Tcf3* during early development of the pituitary-hypothalamic axis in mice and humans.

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OC1.9

Genetic characterisation of short children with potential defects of GH action by single gene sequencing

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Background
GH resistance or primary IGF1 deficiency (PIGFD) presents with growth failure, low serum IGF1 and normal/elevated serum GH. PIGFD comprises a spectrum of phenotypic and biochemical abnormalities for which genetic GH–IGF1 axis defects may be causative.
Objective
Genotyping of PIGFD patients referred for sequencing of candidate genes.
Methods
From 2008 to 2013, 62 patients (42 males and 20 females), median age 6.9 years (range 0.4–17.0) with short stature (mean height SDS −3.4; range −9.4 to −1.1) were referred for genotyping. Depending on the phenotype, coding exons/intron boundaries of *GHR*, the *GHR* pseudoexon, *STAT5B, IGFALS, IGF1* and *OBSL1* were amplified by PCR from genomic DNA and the products purified and sequenced on an automated DNA sequencer (ABI 3700).
Results
Median serum IGF1 levels were 32.9 ng/ml (range 1.4–95.0; below the normal IGF1 range for age), with 15 patient samples being below the lower limit of the assay. GH secretion was normal or elevated: median peak GH 19.0 μg/l (range 6.0–119.0). Seven patients did not have GH provocation tests, basal GH being elevated (median 45.0 μg/l; range 12.3–398.0). Seventeen patients (27%) had mutations in GH–IGF1 axis genes: homozygous *GHR* ($n=13$; including six pseudoexon and two novel IVS5ds+1 G to A), homozygous *IGFALS* ($n=3$; 1 novel c.1291delT) and a novel heterozygous *STAT5B* ($n=1$; p.A478V). Heights in these subjects were −6.9 to −2.0 SDS. Two homozygous mutations were identified in the *OBSL1* gene (height SDS −4.9 and −5.7). Two other patients had hypomethylation in imprinting control region one in 11p15 or maternal UPD for chromosome seven consistent with Silver–Russell syndrome (SRS) (height SDS −3.7 and −4.3).
Conclusions
Genotyping is advised in short children with PIGFD. In 27% of PIGFD patients, all with heights <-2.0 SDS, a genetic abnormality demonstrated a major contribution to pathogenesis. Diagnoses with similar phenotypes included SRS and 3M syndrome. In 65% ($n=41$) of patients no diagnosis was defined justifying further genetic investigation.

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Oral Communications 2

OC2.1

Whole Exome Sequencing as a diagnostic tool in adrenal insufficiency

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Introduction
In recent years a growing number of gene mutations have been identified which cause a myriad of syndromes having adrenal insufficiency as a core characteristic. The evolution of each syndrome is dependent on the variant and the particular gene affected. Common practice is for candidate genes to be sequenced individually, which can be time consuming and is complicated by overlapping clinical phenotypes. The increasing availability and cost effectiveness of whole exome sequencing (WES) is proving to be a powerful alternative, especially in disorders where a large number of causative genes need to be sequenced to gain a definitive diagnosis.
Methods
WES was performed on 38 probands referred to our unit with a clinical diagnosis of familial glucocorticoid deficiency. All had been screened for mutations in *MC2R*, *MRAP* and *STAR* and most for mutations in *GPX1* and *NNT*, the five genes linked to FGD.
Results
We made a genetic diagnosis in 14 probands plus two of their affected siblings, identifying mutations in the following genes; *NR0B1* in four patients, *CYP11A1* in five patients plus a sibling, *AAAS* in two patients, *MC2R* in one patient, CYP11B1 in one patient and *AIRE* in a pair of brothers, most mutations were novel. Genetic diagnoses were confirmed by direct sanger sequencing of the index case and other family members.
Conclusion
A genetic diagnosis was therefore readily achieved more than a third of patients that underwent WES. It is feasible that many of the other cases are caused by novel gene defects. WES as a diagnostic tool offers rapid accurate screening for disease variants, thus reducing erroneous clinical diagnoses and enabling targeted treatment plans that should result in better long-term clinical outcomes. We believe that the evolution of WES into a diagnostic tool offers a rapid cost effective way of screening patients for monogenic diseases.

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OC2.2

Increased bone area without reduction in volumetric bone mineral density in children treated with glucocorticoids for nephrotic syndrome

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Background
Glucocorticoids are frequently used to treat childhood inflammatory disorders, and may cause increased fracture predisposition with reduced bone mineral density (BMD), particularly from trabecular bone loss. The contribution of the underlying inflammatory disease processes to these outcomes is poorly understood. Childhood nephrotic syndrome (NS) is a useful model to investigate the effects of steroids on bone, as recurrent courses are often required, but systemic inflammation is low during remission.
Methods
Children with NS were compared to age- and sex-matched controls. Body composition and areal BMD were assessed by DXA. Peripheral quantitative computed tomography (pQCT) scans were obtained at the tibial metaphysis (4%) and diaphysis (66%) to determine volumetric BMD and bone geometry. Lifetime cumulative glucocorticoid exposure was calculated from medical records.
Results
29 children with NS (55% male, age 10.7 ± 3.1 years) were compared to 29 healthy controls (55% male, age 11.0 ± 3.0 years). Children with NS were of similar height SDS to controls ($P=0.28$), but were heavier ($P=0.02$) with greater % body fat SDS ($P=0.008$). Tibial trabecular and cortical vBMD were similar between the two groups but cross-sectional area (CSA) was significantly greater in children with NS at the metaphysis (954 ± 234 vs 817 ± 197 mm^2, $P=0.002$) and diaphysis (535 ± 163 vs 463 ± 156 mm^2, $P=0.014$). Cortical thickness was lower in the children with NS (2.4 ± 0.7 vs 2.8 ± 0.7 mm, $P=0.018$), but cortical CSA was similar to controls ($P=0.22$). The differences in geometry were no longer significant when adjusted for weight. Cumulative steroid exposure was not associated with bone outcomes.
Conclusions
Tibial bone CSA is increased in children with NS. We speculate this is a compensatory response to increased body weight. Reductions in vBMD were not identified in this cohort of children with NS.

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OC2.3

Clinical phenotype of patients with MCM4 mutation suggests pubertal delay in males

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Background
We recently reported the first human mutation in mini-chromosome maintenance homologue 4 (MCM4) in a cohort of patients with adrenal failure. We now report the endocrine phenotype of 14 patients with MCM4 mutations.
Methods
Patients case notes were examined and investigations performed to fully assess adrenal function, pubertal development, gonadal function and growth.
Results
13 of 14 patients have developed isolated glucocorticoid deficiency with age of diagnosis ranging from 0.5 to 12 years. Five patients initially had normal adrenal function. All patients have undetectable DHEAS levels and low androstendione levels. Clinically all children >8 years have absent adrenarche. Renin and aldosterone levels were normal.
Children had low birth weight (average -2.3 SDS) and subsequent short stature (-2.6 SDS). Boys showed lack of a pubertal growth spurt and final height was significantly shorter than girls (males -2.8 SDS, females -1.8 SDS, $P=0.01$). All children who have reached final height were significantly shorter than their mid-parental height. The GH and IGF1 axis was normal.
Four girls were of pubertal age; all entered and progressed through puberty normally and have normal menstrual cycles. In contrast all five boys of pubertal age had severe delay of growth and puberty and one required testosterone injections to induce puberty. Initially LHRH stimulation tests showed a pre-pubertal response. Subsequently two boys showed evidence of endogenous testosterone production with normal gonadotrophins and morning testosterone levels.
Conclusion
Patients with MCM4 mutations have isolated glucocorticoid deficiency with no evidence of mineralocorticoid deficiency. Both clinically and biochemically children have no evidence of adrenal androgen production suggesting failure of development of the zona reticularis. In addition boys have evidence of a significant delay in pubertal development. This potentially indicates a role for adrenal androgen priming in male puberty or a novel function of MCM4 in pubertal development.

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OC2.4

FGF21 causes GH resistance in human chondrocytes through activation of SOCS2 and inhibition of IGF1 expression

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Background
Fibroblast growth factor 21 (FGF21) is a key metabolic regulator in the adaptation to fasting. In food-restricted mice, inhibition of skeletal growth appears to be mediated by the antagonistic effect of FGF21 on GH action in the liver and in the growth plate (Kubicky *et al*. 2012, Yu *et al*. 2012). The role of FGF21 in growth regulation in humans is currently unknown.
Objective and hypothesis
To provide mechanistic insights into the reduced caloric intake associated with GH insensitivity and growth failure we hypothesized that FGF21 inhibits GH action in human chondrocytes by blocking post-receptor GH signaling.
Methods
We established chondrocyte primary cultures from costal cartilage of pediatric patients undergoing reconstructive surgery. We first assessed the integrity of the GH-receptor and IGF1 receptor signaling by western blotting, and expression of the FGF21 receptor complex by RT-PCR. Next we tested the effect of recombinant FGF21 on basal and GH-induced suppressor of cytokine signaling 2 (*SOCS2*) expression, basal and GH-induced *IGF1* expression by qPCR, and basal and GH/IGF1-induced cell proliferation by Methylene Blue assay.
Results
Human chondrocyte cultures expressed GH-receptor and responded to recombinant to GH and IGF1 through phosphorylation of ERK1/2, AKT and STAT5, and expressed the complex FGFR1c/βKLOTHO, the preferred FGF21 receptor. FGF21 significantly up-regulated basal and GH-induced *SOCS2* expression. FGF21 also inhibited GH-induced *IGF1* expression and cell proliferation, but did not affect IGF1-induced cell proliferation.
Conclusion
FGF21 blocks GH action in human chondrocytes by inhibiting post-receptor signaling involving induction of *SOCS2* and inhibition of *IGF1* expression. These data provide a new mechanistic insight into GH resistance secondary to reduced caloric intake.

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OC2.5

Continuous s.c. infusion of parathyroid hormone reduces PTH requirement in patient with activating mutation of the calcium sensing receptor

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Background
Activating mutations in the calcium sensing receptor can result in severe hypoparathyroidism with symptomatic hypocalcaemia. Complications of treatment with calcitriol or alfacacidol include hypercalciuria, nephrocalcinosis and renal failure. The use of synthetic parathyroid hormone (PTH 1–34, teriparatide)

provides a more physiological treatment option and reduces the risk of hypercalciuria. Intermittent injections of PTH have been used with some success but we report our experience of the first UK child treated with a continuous s.c. infusion of PTH (CSIP).
Presenting Problem
A 1-year-old girl presented with hypocalcaemic convulsions and was found to have hypoparathyroidism due to an activating mutation of the calcium sensing receptor (CaSR) (c.2528C>A, p.A843E). She was initially treated with alfacalcidol but continued to have episodes of symptomatic hypocalcaemia. After informed discussion, eucalcaemia was successfully achieved with twice daily s.c. injections of PTH. Her requirements slowly increased and after 3 years, she was requiring 75 μg daily in three divided injections, almost twice the recommended adult dose. To reduce the total dose of PTH and the need for multiple daily injections, CSIP was commenced using an insulin infusion pump to deliver the PTH at a constant rate throughout the day and night.
Clinical management
Baseline plasma calcium was 2.2 mmol/l. PTH 1–34 was infused initially at a rate of 72 μg/day (equivalent to the dose being received by injection) but she rapidly became hypercalcaemic. 72 h after starting the infusion, her total dose had been reduced by 50% and her calcium stabilised.
Discussion
PTH administered via CSIP significantly reduced the total daily dose, indicating that this more effective than multiple s.c. injections. She no longer required multiple injections and only needed to change her giving set every 3 days. We recommend that this is the treatment of choice in cases such as these.

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OC2.6

Review of the clinical scoring systems in Silver-Russell syndrome and development of modified diagnostic criteria to guide molecular genetic testing

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Background
About a half of all children with a clinical diagnosis of Silver-Russell syndrome (SRS) have a detectable molecular genetic abnormality (maternal uniparental disomy of chromosome 7 or hypomethylation of H19). The selection of children for molecular genetic testing can be difficult for non-specialists because of the broad phenotypic spectrum of SRS and the tendency of the facial features to mitigate during late childhood. Several clinical scoring systems for SRS have been developed by specialist researchers but the utility of these for guiding molecular genetic testing in routine clinical practice has not been established.
Objective and hypotheses
To evaluate the utility of four published clinical scoring systems for genetic testing in a cohort of patients referred to a clinical service laboratory.
Methods
Individuals with suspected SRS referred for molecular genetic testing of H19 methylation status or mUPD7 were scored according to published criteria. Anthropometric measures and clinical features were requested from the referring clinician using a custom-designed questionnaire.
Results
36 of 139 (25.9%) patients referred for testing had a genetic abnormality identified. Comparison of four published clinical scoring systems demonstrated that all included subjective criteria that could be difficult for the general clinician to assess. We developed a novel, simplified, scoring system utilising four objective, easily measured parameters (low birthweight, postnatal growth failure, relative macrocephaly and asymmetry) that performed similarly to the most sensitive and specific published scoring system (~80%).
Conclusions
Effective utilisation of genetic testing by clinicians without specialist clinical genetics training will be facilitated by the development of targeted testing protocols that are based on robust objective clinical features and that are designed for use in a busy clinical practice rather than a research setting.

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OC2.7

Novel lethal form of hypopituitarism associated with the first recessive *LHX4* mutation

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Background
LHX4 encodes a member of the LIM-homeodomain transcription factor protein family that is required for development of the pituitary gland. To date, only incompletely penetrant heterozygous mutations in *LHX4* have been described in patients with variable combined pituitary hormone deficiencies (CPHD).
Objective/hypothesis
To investigate a cohort of patients with congenital hypopituitarism for mutations in *LHX4*.
Method
We screened 150 patients with CPHD (the vast majority having an ectopic posterior pituitary (EPP)) using PCR and direct sequencing analysis. Upon identification of any variants, 100 ethnically-matched controls were screened and control databases (1000 genomes, dbSNP) consulted.
Results
We identified a novel homozygous missense mutation (c.377C>T, p.T126M) in two deceased male patients of Pakistani origin, born to non-consanguineous parents, with panhypopituitarism. The parents also had a daughter with a depressed nasal bridge and cleft palate. The second son had panhypopituitarism and was born small for gestational age with a micropenis, underdeveloped scrotum, and mid-facial hypoplasia. In spite of rapid commencement of hydrocortisone and thyroxine, all three children died within the first week of life. DNA analysis confirmed the presence of a homozygous p.T126M mutation, located in the LIM zinc-finger binding domain 2, predicted to alter protein–protein interaction. Additionally, we identified a novel heterozygous missense mutation (c.1009A>C, p.N337T) in a Caucasian female patient with isolated GHD (peak GH: 1.47 μg/l) learning difficulties, obesity and an EPP. The mutation is in the C-terminal domain, possibly affecting protein folding. Both mutations are located at highly conserved residues.
Functional studies are currently underway.
Conclusion
We report for the first time to our knowledge a novel homozygous mutation in *LHX4* associated with a lethal phenotype; recessive mutations in *LHX4* may be incompatible with life.

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OC2.8

Establishing a national audit of paediatric GH prescribing

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Introduction
GH therapy is prescribed to UK children for a variety of indications. However, no central record exists, making follow-up studies difficult.
Aim
To establish an ongoing audit of UK children and adolescents newly-prescribed GH in order to i) monitor trends in prescribing practice and ii) facilitate future long-term follow-up.
Patient population
UK children aged ≤16.0 years newly starting GH therapy.
Methods
Consultants prescribing paediatric GH (BSPED members/non-members) can participate. The following anonymised data are recorded: partial postcode, diagnostic category, sex, month/year of birth, age, GH dose, injections per week, ongoing prescription (GP/hospital). Data are submitted and collated centrally quarterly. Audit ID numbers are allocated and sent to participating centres for local linkage to NHS, CHI or H&C numbers.
Results
Eighty-four centres are participating; for the first quarter (Jan/Feb/Mar 2013), 75 submitted returns (89%), of which 22 had no patients to report. The remaining 53 centres reported 250 patients (M/F: 138/112) treated at a median (range) age of 8.2 (0.2–22.6) years for the following indications.

'Other' included short stature (16); syndromes (6) & constitutional delay of growth (2). GH dose is usually calculated as mg/m^2 per week or μg/kg per day (both 90), with mg/kg per week less common (68; Table 1). The majority (248) receive daily injections and most ongoing prescribing is via the GP (152 vs 95 hospital).

Table 1 Indication for GH therapy (*n*).

GHD	TS	PWS	CRI	SGA	SHOX	Other
134	23	9	7	39	4	34

Conclusion
Early indications are that a national audit of paediatric GH prescribing is feasible. Most treatment is for a licensed indication and initiated at all paediatric ages. Ongoing challenges include maintaining the initial high return rate and auditing local data linkage; fundamental to future follow-up studies.

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OC2.9

A comprehensive next generation sequencing-based strategy for genetic diagnosis in congenital hypothyroidism

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Introduction
Less than 20% of congenital hypothyroidism (CH) has a known genetic aetiology; thyroid transcription factor mutations (*PAX8, Nkx2.1, Nkx2.5, FOXE1*) or biallelic *TSHR* mutations cause <5% of thyroid dysgenesis (TD), whereas mutations in genes mediating thyroid hormone biosynthesis (*TPO, TG, DUOX2, DUOXA2, IYD, SLC5A5, SLC26A4*) account for most dyshormonogenesis cases. Increased CH frequency in consanguineous populations, relatives of TD cases, and in conjunction with extrathyroidal anomalies suggests involvement of hitherto unidentified genes.
Although genetic diagnosis is not routinely undertaken, establishing the molecular basis of CH may inform treatment, anticipate extrathyroidal features and confirm recurrence risk to facilitate genetic counselling. Prediction of genetic basis from clinical phenotype is unreliable, precluding implementation of selective candidate gene analysis; accordingly, a comprehensive genetic screening strategy has been developed.
Method
Compared to conventional sequencing, next generation sequencing (NGS) technologies increase sequencing capacity and speed, with molecular 'barcodes' enabling multiplex analysis of samples, to improve throughput and efficiency. 11 known and 20 putative CH-associated genes were screened using NGS in 49 families. This genetic diagnostic strategy aimed to identify mutations in known and predicted CH-associated genes and to delineate a 'mutation-negative' cohort in whom novel genetic causes can be sought.
Results
Ten families harboured mutations in known causative genes, of which five were known (*DUOX2*: Q686X, R354W, *TPO*: R665Q, R491H, *TG* R277X) and six were novel (*DUOX2*: Q570L, *TG*: S509X, R140X W1031L, C707Y, T1397RfsX30, c.638+5 G>A); two families harboured compound *TG* mutations.
Conclusion
NGS enables efficient screening of multiple genes simultaneously, facilitating genetic diagnosis in CH. Such comprehensive screening will identify mutations in known genes associated with atypical clinical phenotypes, and in putative CH-associated genes identified from animal models. Identification of 'mutation-negative' cases defines a population in whom whole exome sequencing may identify novel genetic aetiologies for CH, elucidating novel pathways in thyroid development and physiology.

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OC2.10

A new approach to the definition and diagnosis of adrenal insufficiency during inhaled corticosteroid therapy for asthma

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Background
Up to 50% of children treated with inhaled corticosteroids (ICS) have biochemical evidence of adrenal insufficiency (AI). Episodes of adrenal crisis (AC) are extremely rare.
To address the discordance between the prevalence of biochemical AI and AC, we re-examined the biochemical definition of AI during ICS therapy. We then investigated the utility of early morning salivary cortisol (EMSC) and cortisone (EMSCn) for the identification of patients with AI using standard and revised diagnostic criteria.
Patients and methods
Cases of AC during ICS therapy in childhood were identified on PubMed. Data from these cases were used to inform a revised definition of AI on the LDSST. subjects (160 M), median age 10.0 (5.1–15.2) years collected saliva samples for 3 consecutive days and underwent the LDSST (Synacthen 500 ng/1.73 m^2) on D3. The relationship between EMSC and EMSCn and peak cortisol (PC) on the LDSST and was examined using standard and revised definitions of AI.
Results
Fifty cases of AC were identified in PubMed. Dynamic function tests were reported in 34 subjects: PC (mean) was 44 (maximum 387) nmol/l on standard dose short Synacthen stimulation test (n=29), 127 and 107 nmol/l on LDSST (n=2) and 150 (312) nmol/l on glucagon stimulation test (n=3). The modified definition of AI was defined as PC <350 nmol/l on LDSST.
In our cohort, PC was <500 nmol/l in 101/269 subjects (37.5%) and <350 nmol/l in 12/269 subjects (4.5%) on the LDSST. EMSC and EMSCn had no predictive value for PC <500 nmol/l. EMSCn cut-off value of 12.5 nmol/l gave a negative predictive value of 99.2% and positive predictive value of 30.1% for PC <350 nmol/l.
Discussion
Screening subjects using EMSCn, followed by a LDSST using PC <350 nmol/l define AI, may enable a meaningful and practical method of identifying subjects at greatest risk of AC during ICS therapy.

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Oral Communications 3

OC3.1

Catch up growth and insulin sensitivity in adolescent children born preterm

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Background
Preterm infants represent around 10% of births worldwide and have increased risk of adverse metabolic outcomes in later life. The approach to feeding preterms must balance the need to promote brain growth by providing adequate nutrients whilst avoiding potentially harmful excess nutrition.
Objective
To investigate the association between patterns of weight gain in infancy and childhood with later insulin sensitivity in adolescents who were born preterm.
Design, setting and participants
Growth was assessed at regular intervals during the neonatal period, and early childhood. Subjects were reassessed in adolescence and underwent a short oral glucose tolerance test and assessment of fat mass using dual X-ray absorptiometry. Earlier growth parameters were compared with body compositional data and insulin sensitivity derived using the homeostatic model assessment.
Results
153 children were reviewed, 102 consented to venepuncture at a median age of 11.5 years. Median birthweight was 1365 g and mean gestation was 30.8 ± 2.2 weeks. Neither gestation nor birthweight SDS were associated with adolescent insulin sensitivity. Increase in weight SDS between birth and discharge was positively associated and increase in weight SDS between discharge and term negatively associated with later insulin sensitivity. In both periods, the association only remained significant for those born small for gestational age (SGA). Increase in childhood weight SDS and current fat mass index were negatively associated with subsequent insulin sensitivity.
Conclusions
Enhanced weight gain at a critical stage in early life may improve insulin sensitivity in adolescence. Although higher rates of pre-discharge weight gain do not appear harmful in SGA infants, rapid weight catch-up immediately following hospital discharge is associated with decreased later insulin sensitivity. The interactions between fetal, neonatal and infant weight gain and subsequent markers of the metabolic syndrome are complex, but suggest the potential for early nutritional care to modify later chronic disease risk.

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OC3.2

GAD and IA2 autoantibody positivity is associated with a requirement for insulin treatment: results of the UK national paediatric Type 2 Diabetes cohort

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Objectives
To establish the frequency of islet cell autoimmunity in children with a clinical diagnosis of type 2 diabetes (T2DM) and describe associated clinical and laboratory findings.
Methods
We recruited children with: paediatrician diagnosis of T2DM; BMI above 85th centile for age and sex; children with other confirmed diagnoses such as monogenic and type 1 diabetes (T1DM) were excluded. Clinical data was collected into a national database. Blood was taken for diabetes auto-antibody status to exclude diagnoses of T1DM. Autoantibodies were measured using standardised radio-binding assays; GADA and IA-2A with 35-S labelled antigens and IAA with I-125 labelled insulin in the reference laboratory in Bristol.
Results
Of the 130 recruited to the UK national cohort who have had antibody testing to date, 14 (11%) were positive for either GAD2 or IA2 antibodies (AAb positive). Of these, 8 (6%) were positive for a single antibody, and 6 (5%) were positive for both antibodies. Children were not classified as AAb positive if they were only positive for insulin autoantibodies, as this is likely an indicator of previous insulin treatment. Diabetes autoantibody positivity was significantly associated with a reduced pooled C-peptide (median 530 vs 1270 $P = 0.016$), and previous insulin treatment (86 vs 31% $P < 0.001$). There was a trend towards differences in sex, BMI-SDS and HbA1c between the groups, with more girls being antibody negative, the AAb positive group having a lower BMI-SDS, and higher HbA1c.
Conclusion
Approximately 11% of patients presenting with T2DM are in fact autoantibody positive, suggesting a masked diagnosis of T1DM. This is associated with insulin treatment and a reduced C-peptide. This suggests the need to do autoantibody testing on all children with a diagnosis of diabetes, even if it suspected T2DM, and predicts the need for insulin treatment 2 years after diagnosis in AAb positive patients.

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OC3.3

Successful treatment of four patients with severe hyperinsulinaemic hypoglycaemia with a novel therapy using mTOR inhibitor

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Introduction
Hyperinsulinaemic hypoglycaemia (HH) is the most common cause of severe and persistent hypoglycaemia in neonates. The treatment of diazoxide unresponsive HH involves pancreatectomy. Mammalian target of rapamycin (mTOR) is a protein kinase that regulates cellular proliferation. We aimed to evaluate the efficacy of mTOR inhibitor Sirolimus and assess mTOR expression in the pancreas of infants with severe HH.
Methods
Four infants with severe, persistent HH were recruited. Treatment with maximal doses of diazoxide and octreotide (35 μg/kg per day) was unsuccessful in all infants who required high concentrations of intravenous dextrose and intravenous glucagon to maintain normoglycaemia. We commenced treatment with Sirolimus and the dose was gradually increased based on serum concentration. Morphoproteomic analysis was performed on the tissue from two patients with diffuse HH to understand the role of mTOR in the pathogenesis of HH.
Results
Genetic testing suggested diffuse disease in three infants due to homozygous or maternally inherited heterozygous *ABCC8* mutations, but no mutation was identified in the fourth case. Following treatment with Sirolimus, all patients showed good glycaemic response over the following weeks. Intravenous dextrose fluids and glucagon were discontinued and oral feeds were established. Hematoxylin–eosin and insulin-staining showed β-cell hyperplasia in the exocrine pancreas. Overexpression of (p)-mTOR on the plasmalemmal compartment consistent with mTORC1 was noted in acinar elements.
Conclusion
We report, for the first time, the successful use of mTOR inhibitor Sirolimus in four infants with a severe form of diffuse HH. Our preliminary data suggest that mTOR inhibitors are a novel therapeutic option, individually or as adjuvant, for the severe forms of HH thereby averting the need for surgery and its associated complications. Morphoproteomic and histopathologic findings favour acinar-islet transdifferentiation as a key process and suggests a role for a constitutively activated and overexpressed mTORC1 pathway in the pathogenesis.

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OC3.4

Successful Use of Long Acting Octreotide in Treatment of Congenital Hyperinsulinism

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Introduction/Aim
Congenital hyperinsulinism (CHI) is a cause of severe hypoglycaemia in infancy. Treatment of diazoxide unresponsive patients includes the use of somatostatin

analogues (octreotide given either as four s.c. injections daily or via a pump). We aimed to evaluate the use of a long acting somatostatin analogue (Lanreotide) in children with CHI, switching them from daily oral diazoxide or s.c. Octreotide injections to 4 weekly Lanreotide injections.

Methods

Children with diffuse CHI on high dose diazoxide or daily octreotide injection were recruited. Lanreotide 30 mg was injected by deep s.c. route and the daily diazoxide/octreotide was weaned after the first dose of Lanreotide as per standard protocol. Each patient had height/weight, baseline USS abdomen, TFT, IGF1/IGFBP3, liver function, HbA1c and continuous glucose monitoring pre and post-Lanreotide therapy. Quality of life questionnaire was completed. Lanreotide levels for all the patients were measured.

Results

Four boys and four girls have been started on Lanreotide in the ongoing study. The mean age is 6.4 years (3.5–14 years). Three of them are currently being weaned off their continuous overnight feeds. Results as below.

	1	2	3	4	5	6	7	8
Treatment	Diazoxide 6.7 mg/kg per day	Octreotide 7.6 μg/kg per day	Octreotide 12 μg/kg per day	Octreotide 10 μg/kg per day	Diazoxide 13.5 mg/-kg per day	Octreotide 24 μg/kg per day	Octreotide 22.7 μg/ kg per day	Octreotide 29 μg/kg per day
Genetics	None	Homozyg-ous mutation *ABCC8*	Homozyg-ous mutation *ABCC8*	None	None	None	Heterozy gous mutation *ABCC8*	Homozyg-ous mutation *ABCC8*
Previous pancrea-tec-tomy	No	No	No	No	No	No	Yes	Yes
Time to come off above treatment (in weeks)	8	4	4	12	12 (on 5 mg/kg per day diazox-ide)	4	4	4

Conclusion

Lanreotide is a safe and effective alternative to octreotide/diazoxide therapy in patients with CHI, offering an improved quality of life. Long term follow up is required. The preliminary data on quality of life does suggest that both parents and children are very satisfied with the response.

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OC3.5

Loss of the tumour suppressor micro-RNA 34a, and anti tumour cellular immunity in paediatric obesity – is obesity increasing the future risk of cancer in children?

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There is strong epidemiological data linking obesity to an increased risk of various cancers. It is associated with immune dysregulation and chronic low grade inflammation, however little is known about its impact on anti-tumour immunity. Whether childhood obesity is an independent risk factor for future malignancy is not fully established. We hypothesized that alterations in key immune anti-tumour mechanisms begin prior to adulthood in paediatric obesity. MicroRNA-34a (miR-34a) is a transcriptional target of p53 that is down-regulated in some cancer cell lines. Natural killer cells and cytotoxic T cells are vital to tumour rejection. Invariant natural killer T cells are important bridging cells between the innate and adaptive immune system.

Peripheral blood mononuclear cells were isolated from 61 patients aged 6–18 years. The expression of microRNA 34a (miR34a), a target for tumour suppressor gene p53 was quantitatively measured. Cytotoxicity assays determining natural killer (NK) cell activity and immunophenotyping were performed.

Parameter	Obese ($n=40$)	Non-obese ($n=21$)	*P* value
CD8 cytotoxic T cells (%CD3+T cells)	25.3±7.1	30.3±6.6	**0.03**
Invariant natural killer T cell (%CD3+T cells) iNKT	0.32±0.03	0.54±0.02	**<0.001**
NK cytotoxicity (K562 tumour cell death)	201±88	615±122	**0.01**
miR 34a expression (relative quantification)	0.72±0.1	1.8±0.2	**<0.001**

Data expressed as mean±S.D. *P* values calculated using independent-samples *t*-test.

The age and BMI *Z*-score of obese participants were 12.9±3.0 years and 3.3±0.4 respectively and non-obese participants were 12.2±2.9 years and 0.4±0.9.

A reduction in cytotoxic cell capacity and targets of potent tumour suppressor gene expression occurs from an early age in obese children and may be contributing to future cancer risk in this population.

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OC3.6

A feasibility study of intra-gastric balloons (supported by a lifestyle programme) for the treatment of severe adolescent obesity – the (BOB) Study.

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Rationale

Although many adolescents meet the NICE criteria for bariatric surgery there is a reluctance to undertake or commission such irreversible procedures in young people. Balloons are temporary, reversible, safer and more acceptable and in adults have been shown to promote a clinically significant change in BMI of 4.0–9.0 kg/m^2 But due to subsequent weight regain, bypass surgery is preferred. This is a feasibility study of endocsopic intragastric balloon placement for 6 months supported by a lifestyle management programme.

Objectives

i) To assess the efficacy of the intragastric balloon s supported by a lifestyle intervention to promote weight loss in severely obese adolescents.

ii) To assess the effect of the weight loss on biomedical outcomes such as glucose metabolism, lipid profiles, bone density and architecture and psychosocial health.

Methodology

A cohort study of 12 adolescents (BMI >3.5 S.D., Tanner stage 4 or above) with a 2-year follow-up. All the young people took part in a comprehensive medical assessment including OGTT's, measurement of basal and stimulated incretins, bone turnover markers, DEXA scans and high resolution peripheral quantitative CT scans.

Results

Nine young people (four girls) currently recruited. Average age, weight, BMI and BMI SDS are 15.5 years, 139.8 kg, 47 kg/m^2 and +4.0 respectively.

Average weight loss at 4, 8 and 12 weeks is 6.3, 7.7 and 8.4 kg (Figure 1).

First balloon removals are in August 2013.

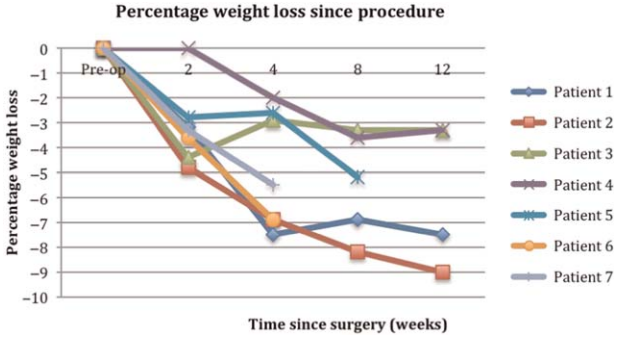

Figure 1 Graph depicting percentage weight loss over time.

Conclusion

Interim data suggests that the young people will experience clinically significant weight loss. The balloon has been well tolerated. Some data on impact of weight

loss on BP, OGTT and safety issues including skeletal health will be available at time of presentation.

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Oral Communications 4

OC4.1

Risk factors for emergency hospital admission for diabetic ketoacidosis in children and young people: national cross-sectional analysis

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Objectives
To identify patient and clinical factors associated with emergency hospital admission with diabetic ketoacidosis (DKA) in children and young people with type 1 diabetes attending specialist NHS outpatient clinics in England and Wales.
Design
Cross-sectional observational analysis of linked data from the National Paediatric Diabetes Audits (NPDAs) in England and Wales, and Hospital Episode Statistics and Patient Episode Database for Wales. We selected 12 potential independent variables from NPDAs including patient, care process and metabolic control factors. We imputed missing data and fitted Poisson Generalized Linear Multilevel Models with the Paediatric Diabetes Unit (PDU) of treatment as the random effects level.
Setting
PDUs in England and Wales.
Participants
2944 children and young people with type 1 diabetes with at least one DKA hospital admission between 2008 and 2010.
Interventions
Regular diabetes care provided by PDUs.
Main outcome measures
DKA hospital admissions between 2008 and 2010.
Results
In all age groups girls had a higher average number of DKA admissions over the 3 years than boys. Boys and girls aged 15–19 years had the highest DKA admission rates of any age group (342.3 and 627.3 per 1000 respectively). In the multivariate regression model, deprivation (quintile 5 IRR 1.20, 95% CIs 1.09–1.32), Black/Black Caribbean ethnicity (IRR 1.20, 95% CIs 1.02–1.41), female sex (IRR 1.11, 95% CIs 1.04–1.18), haemoglobin A1c (IRR 1.07, 95% CIs 1.05–1.09), and age (incidence rate ratio (IRR) 1.03, 95% CIs 1.01–1.04) were associated with significantly higher DKA admission rates.
Conclusions
Children from Black/Black Caribbean ethnic groups, those residing in deprived areas, young people aged 15–19 years and those diagnosed with diabetes at an earlier age are all at greater risk of being admitted with DKA. The strong association of admission rate with HbA1c level, but not other intermediate outcomes, shows the impact of HbA1c on short-term as well as chronic complications in diabetes. Our analysis points to the need to understand the determinants of the health inequalities identified and to explore interventions to reduce DKA admissions in these groups.

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OC4.2

Maturity-onset diabetes of young 5 (MODY5) with Gallbladder duplication cyst: a novel case

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Maturity-onset diabetes of young 5 (MODY5) is a type of monogenic diabetes involving multiple organs including pancreas and kidneys. This is caused by mutation/deletion of the hepatocyte nuclear factor-1β (*HNF-1β*) gene located in the chromosome region 17q12.
We report a 10-year-old, non-obese girl who was diagnosed with diabetes with features of insulin resistance. She was found to have a heterozygous whole gene deletion of *HNF-1β* and was diagnosed with MODY5. She was antenatally diagnosed with gallbladder duplication cyst, which could now be explained by the same genetic defect, as HNF-1β is expressed in the liver and biliary system and conditional *HNF-1β* knockout mouse showed similar features. She also had developmental delay, learning difficulties and autistic spectrum disorder. Interestingly these features could be explained by the contiguous gene deletion in the long arm of chromosome 17 within band q12 which included the *HNF-1β* gene found by further Microarray analysis. Following her genetic diagnosis, she was screened for other known associated features and was noted to have renal cyst and bicornuate uterus. She was treated with Metformin initially but soon she needed insulin treatment to maintain normoglycaemia.
We report this first case of MODY5 with gallbladder duplication cyst and to our knowledge this association has not been reported in the literature so far. This case highlights the importance of genetic testing which was very useful in finding an explanation for all of the problems and to plan the management appropriately. Although the biochemical features and the initial management might be similar to patients with type 2 diabetes, it is very important to understand the need for insulin treatment earlier in the course of the disease and to screen for other associated problems.

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OC4.3

The incentive trial: do financial rewards improve glycaemic control in teenagers with poorly controlled type 1 diabetes?

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Introduction
Adolescence is recognised as a period where compliance to diabetes treatment is challenging and adolescents assume increasing responsibility for their diabetes self-management. In this study we investigated whether giving modest financial rewards motivated teenagers with type 1 diabetes to improve glycaemic control.
Methods
Population; young people with type 1 diabetes, age 13–16 years at entry, duration of diabetes of >2 years and sustained HbA1c level of $>9\%$ for >6 months. Retinal screening and an educational refresher on hypoglycaemia was provided. At each clinic visit patients received a £10 gift voucher for every 0.5% drop in HbA1c. This reward was summative until an HbA1c of 7.5% was achieved. A maintenance voucher of £10 was given if HbA1c continued to be $<8.0\%$. If the HbA1c increased participants were only eligible for further financial rewards after they returned to their previous best HbA1c level. The patients were eligible for payments for one year and data was collected over the following year to assess for sustained improvements.
Results
The study included 17 participants (ten males and seven females) aged 13–15 years (median 14 years). Mean HbA1c at the start of the study 10.4% (range 9–12.1%) and at 2 years 10.4% (range 7.7–14.9%). At 9 months the cohort reached the lowest mean HbA1c (9.6%, $P=0.03$) however this was not sustained. No patients received a maintenance payment. Receivers of vouchers ($n=11$) showed an overall fall in HbA1c (10.8–9.8%) and for non-receivers ($n=6$) the HbA1c increased (9.6–11.6%).
Conclusions
In this cohort financial incentive did not improve HbA1c. In current practice good education at diagnosis and throughout is important as when glycaemic control deteriorates it can be difficult to instigate behaviour change.

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OC4.4

Special features of neonatal diabetes in a series of Arab patients from the Gulf region

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Advances in molecular genetics revealed various causes for neonatal diabetes (ND) Wider clinical awareness led to recognition of different phenotypes. In areas like the Gulf, it is expected that the incidence of ND to be higher due to the high frequency of consanguinity. The different ethnic background might result in different causes and phenotypes of ND compared to data reported from the west.

We report 19 patients from 11 families with ND. All patients were pancreatic autoantibody negative and 16 presented before 6 months of age. All patients were born at term and were small for gestational age. All were born to first degree relative parents. 12 patients were on multiple daily injections and seven on insulin pump therapy. Eight had liver impairment, five skeletal dysplasia and one had pancreatic agenesis. Four patients died at ages 3, 6, 7 and 15 years and one had liver failure requiring transplant.
Genetic analysis was carried out in all patients. KCNJ11, ABCC8, INS genes were sequenced in all patients while EIF2AK3, GCK, IPF1, PTF1A, GATA6, RFX6 were done based on specific clinical features.
Ten patients (five families) had Wolcott Rallison syndrome due to mutations in the EIF2AK3 gene; W430X, G956E, E524X, deletion exon 9–13, and I650T (novel). All parents were confirmed to be heterozygous carriers. Four siblings were homozygous to a novel mutation in insulin gene; INS c-331C > G. The same mutation was later found in another unrelated patient. One child had a kATP mutation and was successfully switched to sulphonyleurea and one patient had a novel heterozygous H410Y ABCC8 variant.
ND is an important cause of diabetes in areas like the Gulf countries. The main causes of ND vary in different ethnic groups. Phenotype related to age at presentation, organ involvement and disease severity may vary within the same family of affected children.
– WRS as the commonest cause of neonatal diabetes in this cohort with various ages at presentation of liver impairment.
– Death due to liver failure occurs regardless of age of presentation of liver disease.
– First patient reported to undergo liver transplant due to liver failure of WRS.
– Different phenotype and age at diabetes presentation in siblings of the same family with insulin gene mutation (6 weeks, 3 months, 13 years, 18 years).
– Relative difficulty to switch from insulin to sulphonylurea in a previously reported kATP channel mutation.

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OC4.5

Peer Review: A tool to improve Paediatric Diabetes services

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Peer Review programmes (PRP) help organisations to improve the quality of clinical services in a developmental and supportive way. The West Midlands Paediatric diabetes network (WMPDN) consists of 15 National Health Service (NHS) Trusts looking after 2800 children (aged 0–18 years). 2010/2011 National Paediatric diabetes audit (NPDA) data showed that the median HBA1c achieved in the region was 69 mmol/mol. In order to improve the metabolic control and quality of care, the network embarked on a PRP.
Method
Following development of network quality standards and formal training of members of the diabetes multidisciplinary team, parents and commissioners as reviewers, all the NHS Trusts carried out a self assessment of compliance against the quality standards. This was followed by review visits (September 2012–march 2013) assessing all aspects of the patient journey. During the visit of facilities, patients, parents, medical, nursing, dietetic are interviewed. Results of visits are sent to Trust chief executives and will be made public.
Results
14/15 Trusts have had visits. 48 reviewers trained. The median level of compliance following visits was significantly lower than self-assessment of compliance (61 vs 81%) ($P < 0.001$). The level of compliance amongst the Trusts varied from 38 to 86%, There was a significant positive correlation between level of compliance following peer review (CPR) and percentage of children in the unit with HBA1C < 58 mmol/l ($r = 0.63$, $P = 0.028$). 64% did not have adequate specialist nursing /dietetic staff for the number of children in their caseload. 65% did not offer regular robust structured group patient education on an ongoing basis.57% did not have robust arrangements for ensuring all children received all care processes as defined by NPDA. Transition arrangements were judged inadequate in 50%.
Conclusion
PRP has enabled the network to identify areas of service that need improvement. 88% of reviewers report using the experience to improve their services.

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OC4.6

Increased urinary megalin and cubulin excretion in children with type 1 diabetes mellitus: an association with low molecular weight protein loss

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Nephropathy remains a major diabetes related complication despite improvements in metabolic control. Current interventions are based on the appearance of albuminuria. Whether earlier detection and treatment might be beneficial is unclear. The reabsorption of low molecular weight (< 70 kDa) plasma proteins in the renal proximal tubule is mediated by an endocytic receptor, megalin, and its coreceptor, cubulin.
Using label free quantitative proteomics we measured megalin, cubulin, vitamin-D binding protein, retinal binding protein and albumin in the urine of ten children with type 1 diabetes mellitus (T1DM) and ten controls. The T1DM children displayed normal glomerular filtration rates with no evidence of microalbuminuria. Urinary megalin (T1DM 300 pmol/mmol creatinine; controls 110 pmol/mmol creatinine) and cubulin (450 vs 50 pmol/mmol creatinine; $P = 0.05$) values were elevated compared to controls. Excretion of vitamin-D binding protein and retinal binding protein were increased in T1DM (100 and 6.2 pmol/mmol creatinine respectively) compared to controls (40 and 1.0 pmol/mmol creatinine respectively; $P = 0.05$). Albumin excretion was not increased significantly. No correlation with HbA1c was observed.
Increased urinary excretion of low molecular weight proteins such as megalin and cubulin in children with T1DM may presage microalbuminuria.

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Oral Communications 5

OC5.1

Joint BPSU-CAPSS Surveillance Study of Childhood Gender Identity Disorder

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Aims
The incidence of childhood/adolescent gender identity disorder (GID) is unknown. GID is an important condition where gender identity differs from biological sex. It is associated with significant distress, particularly with puberty, with much controversy internationally over the optimal timing of hormonal treatment. We examine the incidence and clinical presentation in UK/Irish children and adolescents.
Methods
Study population: UK/Irish children/adolescents aged 4–15.9 years. Design: Joint British Paediatric Surveillance Unit (BPSU) and Child and Adolescent Psychiatry Surveillance System (CAPSS) study. New cases of GID reported by clinicians over a 19-month reporting period (01 November 2011–01 June 2013) are validated against the authoritative DSM-IV-TR (2000). Exclusions include disorders of sexual differentiation and major psychosis. Primary outcome: incidence of childhood/adolescent GID, calculated by dividing the number of validated cases by the base population of children/adolescents aged 4–15.9 years. Sources of denominator data: UK Office of National Statistics and the Central Statistics Office in Ireland. Statistical analysis: descriptive statistics and comparisons using two-sample *t*-tests/Mann–Whitney *U* tests for continuous data and χ^2/Fisher's exact tests for categorical data.
Results
Preliminary data from the first 15 months' surveillance ($n = 138$ cases, 69 males) indicate that similar numbers of males/females are affected by this condition. Early estimates suggest UK and Irish incidences of 1:80 000 and $<$1:200 000. There is a substantial lag between median (inter-quartile range) onset of symptoms (7 years (4–12 years)) and presentation to Paediatricians or Psychiatrists (14.5 years (11.9–15.2 years)). Only 25% of cases ($n = 35$) were $<$12 years old at reporting. There are high levels of psychiatric co-morbidity at presentation, with ≥ 1 other mental health diagnosis in 45%, and ≥ 2 other diagnoses in adolescents aged ≥ 12 years.
Conclusions
We present the first ever population-level data on the incidence, clinical features and presentation of childhood/adolescent GID. These data will inform clinical management, including the highly controversial debate around early pubertal suppression in this group.

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OC5.2

Clinical, biochemical and neuroradiological characterization of a cohort of patients with septo-optic dysplasia and multiple pituitary hormone deficiencies

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Introduction
Septo-optic dysplasia (SOD) is characterized by a combination of midline forebrain, pituitary and eye abnormalities. We aimed to evaluate the clinical, neuroradiological and endocrine features of patients with SOD and multiple pituitary hormone deficiencies (MPHD).
Design
Retrospective data were collected from 76 patients with SOD and 26 with MPHD, followed at a single centre. SOD patients were divided into two groups: i) with pituitary hormone deficiencies (SOD+, $n=64$) and ii) with normal pituitary function (SOD−, $n=12$).
Results
Mean age of diagnosis was similar in all three groups (Table 1).
Endocrinology
Onset of first pituitary hormone deficiency was similar in both groups. The most prevalent deficiency in SOD+ was GH deficiency, whilst TSH deficiency was the most prevalent deficiency in MPHD. Of patients with ACTH deficiency, all MPHD patients achieved adrenarche, whereas only 66.7% of SOD+ had adrenarche. Undervirilised external genitalia at birth were more frequent in MPHD patients, whereas spontaneous puberty and diabetes insipidus (DI) were more frequent in the SOD+ cohort. In three SOD+ patients, DI evolved after the age of 7.3 years.

Table 1 Clinical, biochemical and radiological features of patients with: i) septo-optic dysplasia (SOD) with pituitary hormone deficiencies (SOD+), ii) SOD with normal pituitary function (SOD−) and iii) multiple pituitary hormonal deficiencies (MPHD).

	SOD + ($n=64$)	**S0D−** ($n=12$)	**MPHD** ($n=26$)
Clinical details			
Gender (M/F)	34/30	7/5	12/12
CA at SOD/MPHD diagnosis (years)	2.1±0.4	3.7±1.5	2.2±0.7
Endocrinology			
CA at first pituitary deficiency diagnosis (years)	2.6±0.4	–	2.2±0.6
Undervirilised external genitalia (%)	29.7	33.3	65.4
Spontaneous puberty (%)	83.3 (*n*:6)	100 (*n*:1)	57.1 (*n*:7)
DI (%)	18.75	–	11.58
CA at DI diagnosis (years)	2.5±1.1	–	0.1±0.0
CA at GHD diagnosis (years)	3.4±0.4	–	3.1±0.6
CA at TSHD diagnosis (years)	1.9±0.4	–	3.1±0.9
CA at ACTHD diagnosis (years)	2.1±0.5	–	3.4±1.0
Associated clinical features			
Hypoacusis (H)	9.4	33.3	3.9
Neurodevelopmental delay (%)	60.9	66.7	15.4
Autism (%)	32.8	8.3	7.7
Sleep disturbances (%)	40.6	16.7	15.4
Neuroimaging			
Anterior pituitary hypoplasia (%)	78.1	75.0	80.8
Ectopic posterior pituitary (%)	35.9	–	65.4
Pituitary stalk abnormalities (%)	50	16.7	42.3

M, males; F, females; CA, chronological age; DI, diabetes insipidus; GHD, GH deficiency; TSHD, TSH deficiency; ACTHD, ACTH deficiency.

Associated clinical features
Neurodevelopmental delay, microcephaly, hypoacusis, autism and sleep disturbances were more prevalent in SOD patients.
Bilateral optic nerve hypoplasia was the most prevalent optic abnormality in SOD patients, although other eye abnormalities, e.g. coloboma and retinal dystrophy were also identified.
Neuroimaging
Anterior pituitary hypoplasia was the most common finding in all groups. Ectopic posterior pituitary was present in 35.9% of SOD+ and 65.4% of MPHD. Pituitary stalk abnormalities were more frequent in patients with hormone deficiencies,. Other brain abnormalities were more frequently identified in SOD patients.
Conclusions
Our data suggest striking differences between SOD+, SOD− and MPHD patients. Further understanding of the aetiology and the natural history of these conditions may aid in their clinical management.

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OC5.3

Hypoglycaemia success during the insulin tolerance test: a two centre comparison

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Introduction
The insulin tolerance test (ITT) is the gold standard method to assess GH and/or ACTH deficiency. Safety concerns with the use of this test were raised more than 20 years ago from overtreatment of hypoglycaemia and consequent cerebral oedema, resulting in some centres using alternative tests. We have re-appraised use of the ITT in a contemporary setting and evaluated: i) timing of the glucose nadir, ii) time to resolution of hypoglycaemia, iii) adverse events and iv) staffing levels.
Methods
Data from ITTs in two regional UK paediatric endocrinology centres (A and B) were collected retrospectively during 2012. Both centres use 0.1 unit/kg i.v. actrapid with samples taken at −30, 0, 30, 60, and 90 min. Centre A also samples at 20, 45 and 75 min whereas B samples at 15 and 120 min. Successful hypoglycaemia was defined as laboratory glucose <2.2 mmol/l and/or $>50\%$ reduction from baseline.
Results
49 patients (A, $n=23$ and B, $n=26$; 80% male) aged median (interquartile range) 14.8 (11.2–15.6) years were included. Patients from Centre A were older (median 15.0 vs 12.3 years, $P=0.04$) but had a similar BMI SDS ($P=0.19$) and gender ($P=0.30$). Hypoglycaemia occurred in 100% (23/23) patients in Centre A and 73% (19/26) in Centre B, $P=0.01$). The 7/26 patients from Centre B who did not become hypoglycaemic tended to be older, although this did not reach significance (median 14.0 vs 11.6 years, $P=0.59$). The glucose nadir was lower in Centre A (1.5 vs 1.9 mmol/l, $P=0.007$), occurred later (20 vs 15 min, $P=0.04$) and resolved more quickly (time to BM >4 mmol/l: 45 vs 60 min, $P=0.006$). None of the patients required i.v. treatment or hospital admission. Two healthcare professionals were present during each ITT. Centre A had two specialist endocrine nurses (EN) for the majority (87%) of the ITTs, whereas B always had one EN and one doctor present.
Conclusions
Successful hypoglycaemia was more likely if samples were taken at 20 min. The ITT is safe when performed under specialist endocrine nurse supervision. This has important resource and safety implications.

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Poster Presentations

P1

Plasma cortisol levels and adrenal weight in cases of death in childhood

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Introduction
The incidence of adrenal insufficiency in cases of unexplained death in young children is unclear. It is also unclear whether there is a relationship between adrenal size and plasma cortisol concentration.
Methods
All post-mortem (PM) reports of sudden deaths in children in the West of Scotland between 2010 and 2012 were retrospectively analysed. Combined adrenal weight (g) was recorded and expressed as the percentage of total body weight (%TBW). Plasma cortisol was measured by immunoassay using a sample from the right atrium.
Results
Of 153 cases during the study period, 106 had data on adrenal weight and plasma cortisol. The median (5th, 95th) age was 5months (3 days, 11 years) with 70 cases (63%) under the age of 1 year. Median time to PM was 60 h (20, 144). There was no correlation between plasma cortisol and time to PM ($r=-0.06$, $P=0.6$). The median %TBW was 0.058 (0.025, 0.27) and the median plasma cortisol was 232 nmol/l (28, 1300). There was a positive correlation between total body weight and combined adrenal weight ($r=0.4$, $P<0.0001$). There was a weak positive correlation between %TBW and plasma cortisol levels ($r=0.2$, $P=0.03$), with a stronger correlation seen in children over 1-year-old ($r=0.5$, $P=0.003$). The lowest and highest plasma cortisol quartile had a median of 52 nmol/l (28, 95) and 946 nmol/l (477, 1973), respectively. In the lowest quartile, conditions associated with death included 17 cases (65%) of sudden unexpected death in infancy, three cases (12%) of drowning and two cases of seizure (8%). In the highest quartile cases included infection (six cases, 23%), sudden unexpected death in childhood (five cases, 19%) and hypoxic ischaemic encephalopathy (four cases, 15%) ($P<0.0001$).
Discussion
Although there is a relationship between circulating cortisol and relative adrenal size, there is substantial inter-individual variability. Cortisol levels are often low at PM but this is a less frequent finding in cases of infection.

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P2

A descriptive analysis and prevalence of congenital adrenal hyperplasia in Sri Lankan children

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Introduction
Congenital adrenal hyperplasia (CAH) is autosomal recessively inherited with a world-wide incidence of 1:10 000–1:20 000 births.
Objectives
To document the prevalence of clinically diagnosed CAH and describe the spectrum of the condition in Sri Lankan children.
Method
Request letters were sent to all paediatricians in state-sector hospitals to report details of children <16 years with CAH under their care. State-sector hospitals care for >90% of long-term childhood diseases in Sri Lanka. Questionnaires with a stamped self-addressed envelope were also sent and periodic telephone reminders were given. Data were collected over 6 months from October 2012.
The estimation of prevalence of CAH was done using the number of CAH cases as the numerator and the child population of Sri Lanka of the same age category as the denominator. Population data were from the provisional population data 2012 from the Department of Census and Statistics, Sri Lanka. The study was approved by the Ethical Review Committee, Faculty of Medicine, Colombo.
Results
Details were received of 95 (67 girls) children with CAH. Consanguinity was noted in 37 (38.9%) parents. Of the total, 62 (65.3%) children were diagnosed before they turned a year old and 35 (36.8%) were diagnosed during the 1st month of life.
Estimated prevalence of CAH was 0.181/10 000. A majority of 61 (64.2%) had salt-wasting form of 21 hydroxylase deficiency and 41 (67.2%) were girls.
Diagnosis was made on clinical features in all patients and 94.7 and 77.9% respectively had conclusive 17 OHP and serum electrolyte findings. Ultrasonography supported the diagnosis in 66.3%.
Conclusions
Spectrum of CAH in Sri Lanka is similar to other countries. The prevalence is lower than in Kuwait (1.1/10 000) and other Arabian countries and is higher than the in West (0.06/10 000; Great Britain).

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P3

Diagnosing congenital adrenal hyperplasia. Radiologist rather than biochemist.

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Introduction
The male child with congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency classically presents with salt-wasting and the female with genital ambiguity. 17-OHP measurement is a key investigation but the assay takes time to perform and is not usually available at weekends. We have examined the role of renal/adrenal ultrasonography in the above clinical scenarios.
Method
An abdominal ultrasound focussing on adrenal anatomy was performed following the presentation of a baby with suspected CAH (March–June 2013). The images were viewed jointly by radiologist and paediatric endocrinologist. The radiological diagnosis (CAH or not) was compared with the final diagnosis made on the basis of a range of indices including 17-OHP values.
Results
There were four babies with suspected CAH. Cases 1–3 were male infants, 2–5 weeks of age, with a salt wasting picture (sodium 119, 120 and 128 mmol/l, potassium 6.7, 7.2 and 6.5 mmol/l). Case 4 had genital ambiguity noted at birth. A diagnosis of CAH was made in infants 1, 2, and 4 on the day of presentation on the basis of a normal renal tract but characteristically enlarged, irregular, echogenic adrenal glands. Grossly elevated 17-OHP concentrations were identified 2–5 days after the initial presentation (2681, 2882, and 2159 nmol/l). Imaging was normal in infant 3 and 17-OHP concentrations were age appropriate. He was diagnosed with pseudohypoaldosteronism on the basis of his biochemistry and urine steroid profile.
Conclusion
Adrenal ultrasonography is a key diagnostic tool when investigating suspected CAH with high sensitivity/specificity. It can be undertaken in the first hours following presentation, the images are easy to interpret and the test means that CAH can be diagnosed promptly out of hours. In two of the above cases the diagnosis was made at the weekend. UK guidance should highlight the role of adrenal ultrasonography in greater detail.

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P4

Subnormal Synacthen testing in infants <6 months age: a review of diagnoses and outcomes

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Background
The standard dose Synacthen test (SDST) is commonly used to identify glucocorticoid deficiency. A subnormal SDST in young infants raises the possibility of adrenal insufficiency (AI) due to pathology such as congenital adrenal hyperplasia (CAH). A physiological delay in maturation of adrenal glucocorticoid secretion may be another explanation especially in asymptomatic infants with a transiently subnormal SDST.
Aims
To review the diagnoses and outcomes of infants <6 months who had a subnormal SDST at a single regional centre.
Methods
Data from 45 infants <6 months age who had a SDST over a 2-year period was reviewed. A SDST with cortisol level <550 nmol/l at 30 min was defined as subnormal. Hyponatraemia and requirement for fludrocortisone indicated salt

wasting AI. Clinical outcomes were reviewed at 6 months after presentation.
Results
The SDST was normal in 23 (51%) and subnormal in 22 (49%) (15 males) infants. Among the latter, the subnormal SDST was associated with hypopituitarism (3/22), 21-hydroxylase CAH (1/22), salt-wasting primary AI of unknown aetiology (1/22), persistent glucocorticoid deficiency necessitating replacement with hydrocortisone but aetiology not identified (9/22, 41%) and transiently impaired SDST (8/22, 36%). Of the eight infants with a transient abnormality, two were born small-for-gestational-age, three were premature and none received steroid treatment antenatally. Their median (range) 30 min cortisol at initial SDST was 416 (266; 431) nmol/l which normalised by age 4 (1; 9) months. They were asymptomatic until follow-up SDST results normalized. No infant presented with an adrenal crisis.
Conclusion
A significant proportion of infants <6 months age have persistent AI, the aetiology of which can be primary, secondary or unascertained. A third of infants are asymptomatic and have a transiently subnormal SDST. This is suggestive of a physiological delay in maturation of adrenal glucocorticoid secretion.

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P5

Primary glucocorticoid deficiency presenting as cholestatic jaundice in a neonate

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Introduction
We report the case of a term neonate born with dark skin to Caucasian parents, who presented with severe hypoglycaemia on the postnatal ward. He went on to develop prolonged cholestatic jaundice, hypertransaminasaemia, pale stool and hepatosplenomegaly.
Case report
Thorough investigation led to a diagnosis of primary glucocorticoid deficiency. Hydrocortisone replacement therapy resulted in resolution of the cholestasis, improvement in liver function and pigmentation suggesting a causal relationship between cortisol deficiency and cholestasis.
Conclusion
On literature review we find several case reports of neonates presenting with cholestasis as a result of hypopituitarism, however in this case pituitary function was intact. Primary adrenal insufficiency as a cause for neonatal cholestatic jaundice is rarely reported in Caucasian populations. We explore potential pathological mechanisms from experimental models linking cortisol levels with bile synthesis, transport and flow rate. We conclude with the recommendation that neonates with unexpected hyperpigmentation, hypoglycaemia and cholestasis should alert paediatricians to the possibility of cortisol deficiency. Prompt investigation of adrenal function should be undertaken as this is a completely reversible cause of cholestasis.

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P6

Severe 21-hydroxylase deficiency congenital adrenal hyperplasia and congenital hypothyroidism due to thyroglobulin mutations in a single family: two distinct genetic disorders with phenotypic variability within a single family

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Background
21-Hydroxylase deficiency due to mutations in *CYP21A2* represents the commonest form of congenital adrenal hyperplasia (CAH). Dyshormonogenetic congenital hypothyroidism (CH) may be due to *TPO, TG, DUOX2, DUOXA2, IYD, SLC5A5* and *SLC26A4* mutations.
Case report
Two of six children born to unrelated parents presented in the neonatal period with salt-losing CAH due to compound heterozygosity in *CYP21A2* (maternally derived intron two splice mutation, paternally-derived p.Ile172Asn). Congenital hypothyroidism was diagnosed in both by neonatal screening. Next generation sequencing recently demonstrated compound mutations in the thyroglobulin gene (*TG*): p.R277X and p.T1397Rfs*30. A third sibling presented with pubic hair and body odour since 7 years of age, and had a simple virilising form of CAH (normal plasma renin, aldosterone and thyroid function; genetic analysis awaited), treated with hydrocortisone.
The oldest sibling, a female now aged 17, has learning difficulties and is short (height SDS −2.60) with severe obesity (BMI 52.5), insulin insensitivity, severe virilisation with marked hirsutism, primary amenorrhoea and voice changes, and polycystic ovarian disease, due to poor compliance with medication (currently on dexamethasone, 9-α-fludrocortisone, metformin, flutamide and thyroxine). Pelvic ultrasound and abdominal MRI revealed bilaterally enlarged adrenals with a probable right adrenal adenoma, probably due to chronic ACTH stimulation. Her 13-year-old brother is currently on hydrocortisone, fludrocortisone and thyroxine (height SDS −0.90, weight SDS +1.39, and BMI SDS +2.63). His compliance is also erratic, and he is being treated with GnRH analogue for gonadotrophin-dependent precocious puberty.
Conclusions
In this unusual pedigree, three siblings manifested two different forms of CAH, and the older siblings show inheritance of two distinct genetic disorders, namely CAH and CH due to *TG* mutations. Finally, this case illustrates the importance of optimal disease control in CAH; poor compliance with chronically elevated ACTH concentrations may have resulted in an adrenal adenoma in the older sibling.

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P7

Audit on the characteristics and management of patients in a large tertiary hospital paediatric adrenal clinic

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Adrenal insufficiency (Adr-I) and congenital adrenal hyperplasia (CAH) are important conditions requiring specialist attention and management. Recent CAH genotype–phenotype studies have linked mutations with enzyme functioning and disease severity. Accurate diagnosis for the cause of adrenal insufficiency and the genetic cause of CAH is vital as it impacts management and prognosis.
Methods
We audited patients with Adr-I and CAH seen in outpatients from January 2011 to May 2013. Data was collected on diagnosis, auxology and treatment from clinic letters and the specialist nurse database. Genetic reports were obtained from the Molecular Genetics Department.
Results
Of 129 patients with CAH (45% males), 119 had 21-hydroxylase deficiency. 22 patients (18%) were simple virilising and 97 (82%) salt wasting. 14 patients presented late ($M=4$ years, range 1–13). There were 184 patients with Adr-I which resolved in 47 during the audit period. 22 patients had primary Adr-I (13 Addison's, 1 AAA syndrome, four adrenoleukodystrophy). 74 patients had Adr-I secondary to exogenous steroid treatment (44 oral, 26 inhaled, four topical), 16 due to CNS pathology (four septo-optic dysplasia, eight CNS tumours, two hypopituitarism, one hypothalamic harmatoma, one meningitis), four had congenital adrenal hypoplasia, three pseudohypoaldosteronism, 19 were associated with prematurity and in 45 the cause was unclear. There was no adverse effect of steroid treatment on height (CAH mean HSDS $=-0.01\pm-1.96$; Adr-I $=0.85\pm1.96$) but it was associated with an increased BMI (CAH BMISDS mean $=1.14\pm1.42$, Adr-I $=0.89\pm2.00$). The distribution of genetic mutations for patients with CAH closely mirrored that found in other European studies. Hydrocortisone and fludrocortisone doses correlated with the severity of the genetic mutations ($P<0.02$) but BMI did not ($I=0.178$).
Conclusion
The patient cohort characteristics including genetic characteristics largely mirrored other European cohorts. Increased severity of CAH correlated with higher doses of hydrocortisone and fludrocortisone but had no effect on height or BMI.

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P8

Reliability of diagnostic tests for paediatric Cushing's syndrome

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Introduction
Cushing's syndrome is a rare and life-threatening paediatric disease, the diagnosis of which can be challenging given its heterogeneous clinical presentation and the investigation results which are frequently inconclusive.
Aim
To assess the reliability of the tests used for screening and for establishing the aetiology of Cushing's syndrome.
Design
We conducted a retrospective study analyzing cases of Cushing's syndrome that presented between 1983 and 2013 at two tertiary hospitals. Clinical, biochemical and radiological features are described.
Results
The study cohort included 30 patients (14 females) with a median age at presentation of 8.9 years (range 0.2–15.5) and a delay between onset of symptoms and diagnosis of 1.0 year (range 0.04–6). The most common presenting manifestations were weight gain (23/30), hirsutism (17/30) and acne (15/30). Other clinical features included psychological symptoms (13/30), weakness (12/30), growth retardation (11/30) and systolic hypertension (8/30). Median BMI SDS at presentation was +2.27 (range −6.5 to +4.6).
The table lists the investigations undertaken and their performance.

	Abnormal *n* (%)	Mean (S.D.)	Additional information
Urine free cortisol (nmol/24 h)	17/18 (94)	3314 (7116)	
0800 h cortisol (nmol/l)	10/27 (37)	740 (557)	
0800 h ACTH (ng/l)			
Pituitary tumours	7/13 (54)	48 (40)	
Adrenal tumours	8/10 (80)	14 (21)	
Ectopic ACTH	1/2 (50)	45 (8)	
Midnight cortisol (nmol/l)	27/27 (100)	661 (550)	
Midnight ACTH (ng/l)			
Pituitary tumours	5/10 (50)	40 (26)	
Adrenal tumours	6/7 (85)	22 (36)	
Ectopic ACTH	2/2 (100)	66 (20)	
24-h cortisol profile (mean value nmol/l)		555 (217)	
LDDS +48 h (nmol/l) (20 μg/kg per day only)	20/20 (100)	620 (369)	Suppression means cortisol at +48 h <50 nmol/l
HDDS +48 h (nmol/l) (80 μg/kg per day only)	Failure of suppression:		Suppression means cortisol at +48 h <50% of basal value
Pituitary tumours	1/10 (10)		
Adrenal tumours	6/6 (100)		
Ectopic ACTH	1/2 (50)		
CRH test	Rise in ACTH of cortisol		Response if: cortisol ↑ >20% ±ACTH ↑ >50%
Pituitary tumours	8/9 (89)		
Adrenal tumours	0/1 (0)		
Ectopic ACTH	1/2 (50)		

Urine Steroid Profile showed increased output of glucocorticoid metabolites in 20/30 (67%) patients and BIPPS was useful in the diagnosis of five cases of Cushing's disease and in one ectopic tumour.
All of the patients underwent surgery and final diagnosis were: 16 pituitary ACTH secreting adenomas, 11 primary adrenal diseases, two ectopic ACTH secretion and in one case the aetiology remains unknown. Complications included hormone deficiencies (28/30; including transient and persistent), incomplete resection (4/30), deep venous thrombosis (1/30), septic shock (1/30), CSF leak (1/30), chylous effusion (1/30), relapse (5/39) and second tumour (1/30).
Conclusion
Screening tests showed high sensitivity, with Urine Free cortisol, midnight cortisol and LDDS presenting the best performances. HDDS and CRH test reliably distinguished between pituitary and adrenal disease but performed less well in cases of ectopic ACTH secretion.

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P9

Enzyme-replacement therapy in life-threatening perinatal hypophosphatasia in a premature infant

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Hypophosphatasia (HP) is a rare inborn error of metabolism resulting from inactivating mutations in the gene for the tissue-nonspecific isozyme of alkaline phosphatase (*TNSALP*). Deficiency of alkaline phosphatase (ALK) activity leads to severe rickets. The perinatal form presents with extreme skeletal hypomineralisation at birth, and was a fatal condition until recently. We describe an 11-month-old infant who is one of the few surviving cases of a preterm infant with the perinatal form (homozygous mutation in *TNSALP* c.1336G>A) of HP. She has been treated with the recombinant TNSALP (Asfotase alfa) provided on a compassionate basis by Alexion (352 Knotter, CT 06410, United States).
A female infant was born preterm at 34 weeks of gestational age to consanguineous parents of Pakistani descent and required ventilatory support from birth for respiratory insufficiency. She was noted to have short limbs and hypotonia. Radiographs revealed severe skeletal hypomineralisation with features of rickets. Her serum ALK was low however, urinary phosphoethanolamine, serum calcium and serum inorganic pyrophosphatase (iPP) were elevated as expected in patients with HP.
Treatment with Asfotase alfa was commenced at 4 weeks of age. Infant remains on ventilatory support however, treatment has resulted in dramatic improvement in growth and mineralisation of bones, healing of rickets, normalisation of serum calcium and serum iPP, improved developmental milestones and pulmonary function.
Management of this infant has brought about unique challenges which have not been previously reported in medical literature. The dose of Asfotase alfa has been increased steadily (6 mg/kg per dose, three times a week) beyond the usual dose (2 mg/kg per dose) to allow adequate mineralisation of bones and normalisation of serum calcium concentration. Combination of lung disease of prematurity and respiratory comprise from HP has required on going ventilatory support. Nevertheless she is making good developmental progress and plans are underway to discharge her on home ventilatory support.

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P10

Case report: a novel PHEX mutation in a female with X-linked hypo-phosphataemic rickets

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Introduction
X-linked hypo-phosphataemic rickets is characterized by hypophosphataemia, vitamin D deficiency, poor bone and dental mineralization. Mutations occur within the PHEX gene. Currently 329 mutations have been sequenced[1]. We report a novel PHEX mutation in a female with hypophosphataemic rickets.
Case report
A 12-year-old girl presented with, genu varum, short stature and a previous dental abscess. Investigatons showed hypophosphataemia with a high urinary phosphate level, vitamin D deficiency, elevated parathyroid hormone, elevated alkaline phosphatase and normal calcium levels. Knee X-rays showed bilateral lucent lines and tibial growth plate defects. Dexa scan results were at the extreme lower limit of the expected range. The PHEX gene was analysed by Sanger sequence analysis of the coding and flanking intron regions by multiplex ligation-dependent probe amplification. Databases cross-referenced were: dbSNP, Exon Variant Server and locus specific database http://www.phexdb.mcgill.ca. DNA analysis of both parents was also performed. The patient was heterozygous for a novel, de novo PHEX mutation in the gene location c1501_1502ins24, exon 14 of PHEX gene. This resulted in an in-frame insertion of 8 novel amino acids in the protein p.Ala500Asp501ins8(p.A500_D501ins8).
Discussion
PHEX encodes an endopeptidase homolog mainly expressed in bone and teeth[2,3]. It has been proposed that PHEX acts directly or indirectly on fibroblast growth factor 23 (FGF23)[4,5]. FGF23 is produced by osteocytes[6,7] and acts on the sodium

dependent phosphate transporters within the renal proximal tubules to reduce phosphate reabsorption[8]. FGF23 also inhibits1-α-hydroxylase activity causing vitamin D deficiency[9]. PHEX mutations result in failure to cleave FGF23 to an inactive form, resulting in renal phosphate leak and low vitamin D levels[4,10]. FGF23 is considered a hormone, under the influence of PHEX as part of the bone-renal axis of phosphate homeostasis.

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P11

Succesfully modified intermittent i.v. calcium treatment in a patient with hereditary vitamin D resistant rickets with alopecia: presence of nonsense mutation in ligand binding domain of vitamin D receptor

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Hereditary vitamin D-resistant rickets (HVDRR) is a rare recessive genetic disorder caused by mutations in the VDR that result in end organ resistance to $1,25\text{-}(OH)_2D_3$ action. Here, we describe a patient with HVDDR with severe alopecia and rickets. Patient was 3 years old male presenting with gait disorder. He had hypocalcemia (8 mg/dl), secondary hyperparathyroidism (1232 pg/ml), and elevated serum alkaline phosphatase (661 U/l) and 1,25-dihydroxyvitamin D3 (>250 pg/ml). DNA sequence analyses of the vitamin D receptor (VDR) gene of ligand binding domain (LBD) showed that the patient had homozygous mutation for Q152X at exon five. This mutation was a C to T transition resulting in a premature stop at codon 152. Although his parents were non-consanguineous, both of his parents were found to be heterozygous for the mutation. The patient was initially treated with calcitriol (80 ng/kg per day) and high dose oral calcium (150 mg/kg per day) for 1 year. At the end of the first year, intermittent i.v. calcium therapy (5 days/month) was started, because of insufficient clinical and radiological improvement. After 2 years from intermittent i.v. calcium therapy, there was a clear clinical improvement based on clinical and X-ray findings as well as permenant improvement in biochemical findings. However, alopecia in our patient remained unchanged, despite treatment and improvement of rickets. We report the case of HVDRR with a mutation in the LBD and severe alopecia that was successfully treated with intermittent (5 days/month) i.v. calcium treatment.

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P12

Brown tumours caused by severe vitamin D deficiency: a report of two cases

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Brown tumours are benign osteolytic lesions of bone caused by high levels of serum parathyroid hormone (PTH). They are now rarely seen as a feature of primary hyperparathyroidism. We report two cases of brown tumour in adolescent girls caused by secondary hyperparathyroidism due to severe vitamin D and dietary calcium deficiency.

Case 1

14.5-year-old South Asian girl referred with a 1 year history of right hip pain. She had presented to the orthopaedic team with a low trauma fracture of her right fibula. X-ray and MRI scan of the hip which showed a brown tumour in the foot of her right acetabulum.

Case 2

13.6 year old South Asian girl referred by the orthopaedic team with a 2 year history of gradually worsening pain of the right knee but no history of trauma. X-rays and MRI scans showed a Looser's zone (insufficiency fracture) in the right distal femur and a 2.1 cm brown tumour in the right proximal fibula.

Both girls had low calcium intake and presented in Spring

	Case 1		Case 2	
Date	12/3/13	16/4/13	15/4/13	5/6/13
Calcium (2.2-2.7 mmol/l)	2.08	2.36	1.96	2.36
Alkaline phosphatase (170-460 IU/l)	716	660	1787	1570
Phosphate (0.9-1.8 mmol/l)	1.01	1.52	0.65	1.05
PTH (13-29 ng/l)	1430	83	–	19
Vitamin D (>50 nmol/l)	<4.5		<7.4	115

Investigations

Both patients were managed with daily oral supplementation vitamin D2 9,000 units and 500mg of calcium once daily.

Conclusion

Brown tumours, though rare, can be a manifestation of vitamin D deficiency. These cases highlight that dark-skinned adolescents are at risk of vitamin D deficiency and require vitamin D supplementation during the English winter and spring. Currently there are no national recommendations for vitamin D supplementation in this group.

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P13

In unexplained hypoglycaemia, is the presence of ketones (betahydroxybutyrate) a reliable indicator that insulin is suppressed, excluding hyperinsulinism and avoiding the need to assay insulin directly

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Introduction

In the majority of patients presenting to A&E with hypoglycaemia it is secondary to infection or stress and individuals exhibit a ketogenic response. A minority who first present with hypoglycaemia may have endocrine or metabolic disorders. For this reason a full 'hypoglycaemia screen' is undertaken. It is recommended by metbionet that before glucose administration, the following are measured: intermediary metabolites (glucose, b-OHB, free fatty acids, lactate), insulin, cortisol, GH, amino acids and acylcarnitines.

Insulin suppresses lipolysis and ketogenesis, thus in the presence of ketones, it would be expected that insulin should be appropriately suppressed.

Aims

To investigate whether the presence of ketones in unexplained hypoglycaemia is always associated with insulin suppression and whether specific measurement of insulin is required. If not, there is a modest potential cost saving.

Methods

Results were reviewed retrospectively on all patients that presented with unexplained hypoglycaemia over a 6-month period between 2012 and 2013.

The nationally accepted metbionet criteria was used for the definition of hypoglycaemia <2.6 mmol/l to select the samples. In addition, similar data from a historical study carried out between March 2006 and May 2008, were included. Inappropriate insulin at the time of hypoglycaemia was defined as >30 pmol/l.
Results
The study viewed 127 patients with glucose of ≤ 2.6 mmol/l. Two patients had insulin >30 pmol/l. Of the two patients, one had complex pituitary dysfunction; this patient had very high insulin (60.3 pmol/l) and low B-OHB (0.1 mmol/l). The second patient was a 1-month-old baby with high insulin (34.6 pmol/l) and high B-OHB (2.5 mmol/l); interestingly the plasma amino acids were also low indicating an anabolic (hyperinsulinaemic) state.
Conclusion
The study illustrates that suppressed levels of insulin cannot be inferred from the presence of intermediary metabolites. If insulin was only assayed if ketones are absent, complex and rare disorders may be missed.

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P14

Design and validation of a severity scale for use in congenital hyperinsulinism

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Introduction
Congenital hyperinsulinism (CHI) is an important cause of hypoglycaemia in infancy requiring intensive medical and surgical support. Carbohydrate requirement (CHO) represents a simple index of severity but does not predict the failure of medical treatment and hence the requirement for pancreatectomy.
Aims
To design and validate a severity tool for use in early onset CHI patients.
Methods
To design the Manchester CHI severity score (M-CHISS), frequency of blood glucose levels <3.5 mmol/l over 72 h (hypo), maximum dose of glucagon (max-glucagon) (μg/kg per h) and maximum dose of diazoxide (max-diazoxide) (mg/kg per day) as putative markers of severity, were tested for correlation with CHO (mg/kg per min) in a cohort ($n=9$) with early onset CHI. M-CHISS was validated in an independent cohort ($n=29$) with 4 years follow-up data, in whom 13 (45%) children had CHI-related mutations and 10 (35%) children underwent pancreatic surgery.
Results
Max-glucagon (standardised coefficient 0.9, $R^2=0.8$, <0.001) but not hypo or max-diazoxide correlated positively with CHO in the design cohort. To derive the M-CHISS tool, CHO and max-glucagon were each categorised into scores of one, two and three, and added together to form a composite score. In the validation cohort, M-CHISS, ranging between one and six, correlated positively with the need for surgery, indicating a severe outcome (odds ratio (95% CI) 3.7 (1.3; 10.6), $R^2=0.6$, $P<0.001$) in a logistic regression model controlling for age, gender and prematurity. For M-CHISS $=6$, the probability for requiring surgery was 80% (with a 75% probability of not needing surgery if M-CHISS <6). In contrast, for M-CHISS <3, the probability of not requiring surgery was 100% (with a 53% probability of requiring surgery for M-CHISS ≥ 3).
Conclusions
M-CHISS is a simple and practical tool to assess the severity of hypoglycaemia in early presenting CHI. Further validation is required in prospective cohorts to test the prognostic value of M-CHISS.

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P15

^{18}F-DOPA PET MRI as a new imaging modality for the precise localisation of focal congenital hyperinsulinism

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Introduction
Congenital hyperinsulinism (CHI) includes two major histological subtypes; diffuse and focal. Fluorine-18-L dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET/CT) has been established as a novel imagining technique to differentiate focal from diffuse CHI. However CT provides only limited soft tissue contrast and exposes the patient to a significant radiation dose. PET/MRI could provide images with an excellent soft tissue contrast, very good spatial resolution of the anatomy and very accurate temporal and spatial image fusion with no additional radiation exposure. We aimed to evaluate the feasibility of using ^{18}F-DOPA PET/MRI for the diagnosis focal CHI.
Methods
Five children with severe CHI underwent simultaneous ^{18}F-DOPA PET/CT and PET/MRI imaging. All medications including octreotide and glucagon were discontinued 48 h before the scan. The ^{18}F-DOPA was administered intravenously at a dose of 4 MBq/kg and iodine contrast media at a dosage of 1.5 ml/kg. Three regions of interest were drawn in the head, body, and tail of the pancreas to calculate the standardized uptake values (SUV max).
Results
PET/MRI in 4 children revealed diffuse CHI (SUV <1.3) and one child had focal CHI (SUV >1.5). The focal lesion was delineated clearly in accordance with the results from PET/CT images. In addition PET/MRI provided soft tissue and anatomical information of the adjacent structures that aided the precise surgical resection of the lesion.
Conclusions
In this preliminary study, we have demonstrated the feasibility of using PET/MRI as a novel imaging modality for diagnosing focal CHI. Further studies are needed to establish the accuracy and validity of PET/MRI. Given the potential of less radiation exposure and higher soft tissue clarity, PET/MRI is likely to become a preferred imaging modality for CHI management.

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P16

Increasing weight in children with congenital hyperinsulinism is linked to K_{ATP} channel gene mutations

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Introduction
Congenital hyperinsulinism (CHI) is a cause of severe hypoglycaemia due to insulin over-secretion. The medical management of CHI involves supplementary glucose, which combined with insulin excess, may be obesogenic. However, increased weight in CHI patients has not been reported. We have investigated if children with CHI increase in weight and if genetic or treatment factors influence the weight trajectory.
Methods
Weights were measured and expressed as SDS in children with CHI at birth ($n=70$) and at ages 1 ($n=51$), 2 ($n=44$), 3 ($n=30$) and 4 ($n=23$) years. Weight SDS at follow-up was tested for correlation with ATP-sensitive K^+ channel (K_{ATP}) gene mutation status ($n=65$) and with treatment variables, which included medical/surgical treatment, resolution of CHI, supplemental glucose and response to diazoxide, in a backward regression model.
Results
Weight SDS increased from birth (median (range) -0.2 (-4.4; 5.7)) to ages 2 ($+0.1$ (-3.7; $+5.0$)), 3 ($+0.5$ (-2.2; $+2.9$) and 4 ($+0.5$ (-3.3; $+3.1$)) years. The weight increment was most significant at age 2 years ($P=0.02$). K_{ATP} channel mutations, either heterozygous or homozygous, were present in 25 (39%) children. Children with mutations were heavier at birth ($P<0.001$) and remained so at 2 years ($P=0.02$). Mutation status, but not treatment variables were correlated with weight SDS at 2 years ($R^2=0.5$, $p=0.004$) implying that genetic factors alone may associate with an increased weight trajectory in CHI.
Conclusions
Weight SDS may increase in the first 2 years of life, which is correlated with K_{ATP} channel mutation status but not to the treatment of CHI. Further follow-up is required to assess if weight trajectory in later childhood leads to obesity.

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P17

Frequency of focal and diffuse congenital hyperinsulinism with paternally inherited mutations in *ABCC8* and *KCNJ11*

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Introduction
Congenital hyperinsulinism (CHI) causes severe hypoglycaemia, which can be either focal or diffuse in aetiology. Both forms are associated with paternally inherited mutations in *ABCC8*/*KCNJ11*. Lymphocytic DNA analysis alone is inadequate to diagnose focal CHI, as pancreatic maternal allelic silencing cannot be tested prior to surgery. Additional 18-fluorodopa PET–CT scanning (PET–CT) is required for definitive diagnosis; in this study, we have reviewed the diagnostic outcomes of scanning in children with paternally inherited *ABCC8*/*KCNJ11* mutations.
Methods
The diagnosis of focal/diffuse CHI was reviewed in children with paternally inherited mutations in *ABCC8*/*KCNJ11* ($n=23$) following PET–CT and confirmation by histology in those undergoing surgery. Severity of the CHI phenotype was assessed by maximum glucose requirement, maximum dose of glucagon and maximum dose of diazoxide at presentation.
Result
CHI was diagnosed with a mean (interquartile range) serum insulin 86.7 (110.2) mU/l and blood glucose 0.8 (1.4) mmol/l. The majority carried mutations in *ABCC8* ($n=17$, 74%). Focal CHI was present in 17 (74%) children, and was successfully treated surgically. Diffuse CHI was present in 6 (26%) children where a maternal allelic mutation was not identified. In this group, only two required subtotal pancreatectomy to achieve glycaemic stability. Three children were medically managed and one child achieved spontaneous resolution. The severity phenotype did not correlate with the diagnosis of focal or diffuse CHI following PET–CT.
Conclusions
A paternally inherited mutation in *ABCC8*/*KCNJ11* is associated with focal CHI in 74% children with CHI, requiring surgery. In those with diffuse CHI, the majority can be medically managed.

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P18

Altered plasma incretin concentrations in patients with non-typical forms of congenital hyperinsulinism

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Introduction
Congenital hyperinsulinism (CHI) may arise due to loss-of-function mutations in *ABCC8* and *KCNJ11* genes which encode subunits of ATP-sensitive potassium (K_{ATP}) channels. K_{ATP} channels couple nutrient metabolism with insulin secretion in pancreatic β-cells but are also located in enteroendocrine L- and K-cells and may play a role in the control of GLP-1 and GIP secretion respectively. More than 70% of patients with CHI have no identified mutations in known CHI-associated genes and this includes many patients with transient CHI which spontaneously resolves.
Aims
We hypothesized that CHI patients with K_{ATP} channel gene mutations may have altered plasma profiles of GLP-1 (7–36) and GIP compared with other groups of CHI patients.
Methods
Thirteen patients with CHI were recruited from a single referral centre. Fasting and post-prandial GLP-1 (7–36) and GIP were measured in patient plasma using ELISA. Data were compared between patients with *ABCC8/KCNJ11* mutation-positive CHI (CHI-F and CHI-D, focal and diffuse, $n=6$), mutation-negative persistent CHI (CHI-UV, unclassified variant, $n=2$), and mutation-negative transient CHI ($n=5$) using ANOVA and *post-hoc* tests.
Results
Our data revealed no differences in plasma incretin concentrations between transient CHI and *ABCC8/KCNJ11* mutation-positive patients, but demonstrated marked differences in plasma incretin concentrations in CHI-UV patients compared with all other groups ($P<0.05$).
Conclusion
These data provide evidence that measurement of plasma GLP-1 (7–36) and GIP may aid the identification and diagnosis of a novel sub-group of CHI patients, and suggest that K_{ATP} channels do not play a significant role in nutrient sensing in enteroendocrine cells.

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P19

6-Mercaptopurine linked with hyperinsulinaemic hypoglycaemia in two children with acute lymphoblastic leukaemia

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Introduction
Hypoglycaemia is a rare side-effect of 6-mercaptopurine (6MP) with unclear mechanism(s). The occurrence of hyperinsulinism accompanying the hypoglycaemia is reported here for the first time in children on 6MP for acute lymphoblastic leukaemia (ALL).
Case1
Caucasian female, diagnosed with ALL aged 4 years, was treated under UKALL2003 regime A. During an admission for neutropaenic sepsis, asymptomatic hypoglycaemia was noted pre-breakfast for 3 days. Laboratory glucose was 2.1 mmol/l with raised insulin 33.5 mIU/l on day 1. Full hypoglycaemic screen on day 3 showed glucose 2.3 mmol/l, insulin 36.7 mIU/l, and C-peptide 1087 pmol/l. Remainder of investigations (GH, cortisol, ammonia, lactate, acylcarnitine, free fatty acid, and 3-β-hydroxybutyrate) were normal. Synacthen stimulation test excluded primary adrenal disorders (peak cortisol 1124 mmol/l). Hypoglycaemia resolved after 6MP was discontinued. Two pre-breakfast hypoglycaemia (both 2.3 mmol/l), associated with reduced oral intake during illnesses, were recorded the following month while she was back on 6MP.
Case 2
Female of Bangladeshi origin, diagnosed with ALL, aged 4 years was treated under UKALL2003 regime A, modified to prednisolone due to dexamethasone toxicity. One year into treatment, she presented with symptomatic hypoglycaemia (dizziness, vomiting, and glucose 2.6 mmol/l) while fasted for a procedure under general anaesthesia. Continuous glucose monitoring revealed nocturnal hypoglycaemia (BM <2.6 mmol/l) which continued despite larger evening meals and slow release carbohydrate snacks pre-bed. Hypoglycaemic investigations showed glucose 2.6 mmol/l, insulin 11.5 mIU/l, and C-peptide 520 pmol/l. Remainder of investigations (as per case 1) were normal. Blood glucose levels normalised after switching 6MP administration to the morning. Five months later, she represented with hypoglycaemia after 6MP dosage increase, which resolved after reduction.
Discussion
Hyperinsulinism is a possible mechanism of 6MP associated hypoglycaemia. Paediatricians need to be aware of hypoglycaemic risk in young ALL patients on 6MP treatment. Glucose levels should be actively monitored during periods of fast or reduced oral intake.

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P20

18F-DOPA PET and enhanced CT imaging for congenital hyperinsulinism: Our experience of using oral sedation

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Introduction
Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycaemia in infants and children. Histologically there are two subgroups, diffuse and focal. Fluorine-18-L dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET/CT) helps to differentiate focal from diffuse CHI.
Objective and hypotheses
To evaluate the feasibility of using ^{18}F-DOPA PET/CT for the diagnosis of focal or diffuse CHI under oral sedation. To look into the protocol of performing these images.
Methods
27 ^{18}F-DOPA PET/CT and contrast enhanced CT imaging scans were performed on 22 consecutive patients with CHI (median age 2.1 years). All medications including octreotide and glucagon were discontinued 48 h before the scan. Single bed position PET/CT images over the pancreas were acquired under light sedation with oral chloral hydrate (dose 50 mg/kg). Four PET dynamic data scans were acquired at 20, 40, 50 and 60 min post injection for duration of 10 min each. Results were assessed by visual interpretation and quantitative measurements of standardized uptake values (SUVs) in the head, body and tail of the pancreas.
Results
Of the 22 patients, 16 showed diffuse and six showed focal ^{18}F-DOPA PET pancreatic uptakes. Six patients had an accumulation of ^{18}F-DOPA in the pancreas and a SUV ratio value of >1.5, indicating focal disease. The remaining 16 patients had diffuse accumulation of ^{18}F- DOPA in the pancreas (SUV ratio <1.3). All the children tolerated oral sedation well. All patients diagnosed with focal lesions underwent surgery and were cured eventually.
Conclusion
^{18}F-DOPA PET/CT offers excellent differentiation of focal from diffuse CHI and enhanced CT technique permits precise preoperative localisation of the lesion and anatomical land-marks. Also, excellent qualities of images were obtained after giving oral sedation (chloral hydrate) in all children without need of general anaesthesia.

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P21

Long-term endocrine and exocrine outcome of medically unresponsive diffuse congenital hyperinsulinism managed with near-total pancreatectomy: 18 years' experience

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Introduction
Diffuse congenital hyperinsulinism (CHI) is a major cause of severe hypoglycaemia. One treatment option is near-total pancreatectomy, which carries a risk of diabetes mellitus (DM) and pancreatic exocrine insufficiency.
Objective
We report our centre's experience on 36 consecutive medically unresponsive diffuse CHI children managed with near-total pancreatectomy.
Methods
Following near-total pancreatectomy, these children underwent regular 24-h blood glucose profile, controlled fast and oral glucose tolerance tests to assess glucose homeostasis. Clinical and biochemical evidence (faecal elastase 1) of pancreatic exocrine insufficiency was also evaluated.
Results
From 1994 to 2012, 36 children (male/female, 16/20) underwent near-total pancreatectomy for medically unresponsive diffuse CHI. The mean ($\pm$S.D.) birth weight (g) and gestational age (weeks) was 4080 ± 730 and 38 ± 2 respectively. The patients presented with severe hyperinsulinaemic hypoglycaemia at a median age of 1 day. Molecular genetic analysis revealed *ABCC8/KCNJ11* mutation in 31 patients. The median age at pancreatectomy was 0.17 years. The diagnosis of diffuse disease was reached either by pancreatic venous sampling or ^{18}F DOPA PET–CT. Histology confirmed diffuse disease in all patients. Hypoglycaemia persisted post-pancreatectomy in 16 patients (44%), necessitating either total-pancreatectomy, treatment with octreotide, diazoxide and/or frequent high carbohydrate feeds. Over a mean ($\pm$S.D..) follow-up period of 8 ($\pm$4.75) years, 18 children developed DM. The cumulative risk of DM after 5 and 10 years post-pancreatectomy was 74 and 86% respectively. Twenty-six patients (72%) showed biochemical evidence of pancreatic exocrine insufficiency, only seventeen (47%) of which developed clinical pancreatic exocrine insufficiency necessitating pancreatic enzyme replacement.
Conclusions
Near-total pancreatectomy for CHI is associated with high risk of DM, however not all patients with post-pancreatectomy go onto develop clinical or biochemical evidence of pancreatic exocrine insufficiency. There seems to be a poor correlation between biochemical and clinical pancreatic exocrine insufficiency.

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P22

Evaluation of Postprandial Hyperinsulinaemic Hypoglycemia in Children

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Introduction
Hyperinsulinaemic hypoglycaemia (HH) is characterized by dysregulated insulin secretion and is typically associated with reduced fasting tolerance. We aimed to evaluate the clinical and biochemical characteristics of children presenting with postprandial hyperinsulinaemic hypoglycemia.
Methods
Retrospective data collection on children who presented with symptomatic postprandial hypoglycaemia. Children with postprandial hypoglycaemia secondary to gastrointestinal surgery (such as dumping syndrome) were excluded. Prolonged OGTT was performed as per standard protocol.
Results
We identified six children with a mean age of 6.08 ($\pm$2.01) years who presented with symptomatic hypoglycemia occurring typically within 2-3 hours after a meal. The symptoms included lethargy, tiredness, hunger and shakiness. In one child seizures were noted during the hypoglycaemic episode. The family history included type two diabetes in two families, postprandial hypoglycaemia in one family and type one diabetes in another family. All children had a normal fast tolerance for age with a mean fast duration of 17.8 ($\pm$1.78) hours and appropriately suppressed insulin levels at the end of the fast ($<$ 2 mU/l). All children were noted to mobilize fatty acids at the end of the fast and also demonstrated normal glucocorticoid response. Metabolic screening did not reveal any abnormality. Prolonged OGTT revealed HH (mean blood glucose 2.78 mmol/l and mean insulin concentration 6.95 mU/l) occurring at an average time length of 170 ($\pm$36.3) minutes after the glucose load. Treatment with acarbose was noted to be beneficial in three children, diazoxide improved the glycaemic control in one child and two children were managed with frequent feeds.
Conclusion
We describe a group of children with symptomatic postprandial hypoglycaemia who demonstrated HH between 2-3 hours post glucose load. Prolonged OGTT is necessary to identify these episodes. Acarbose is beneficial in children with postprandial HH who do not respond to dietary modification. Further research is required to understand the molecular basis of this postprandial HH.

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P23

Can we prevent hypoglycaemic brain injuries in term babies with no risk factors of Hyperinsulinaemic Hypoglycaemia?

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Introduction
Hyperinsulinaemic hypoglycemia (HH) represents the most common cause of hyperinsulinism in neonates, often termed as congenital hyperinsulinism of infancy (CHI). CHI is characterised by inappropriate raised insulin secretion from the pancreatic β-cells in relation to blood glucose concentration. Insulin suppresses NEFA and BOHB production. Neurological damage is a known risk associated with hyperinsulinaemic hypoglycaemia (HH).

Aim
To describe the clinical course and neurological outcome of three term neonates with severe hypoglycaemic brain injury who have had delayed diagnosis of hyperinsulinaemic hypoglycaemia.
Methodology
We recruited three patients who presented in the neonatal period with biochemically confirmed HH and referred to a tertiary endocrine hospital. Detailed clinical information was collected including MRI brain scan reports.
Clinical presentation
All three patients were born by normal vaginal delivery and were discharges within 24–36 h of life.

Case	Gestation (weeks)	Birth weight (g)	Presentation	Blood glucose (mmol/l) on presentation	Medications	MRI/CT brain
Case 1	36+4	2730	On day 3 with history of poor feeding and jerky movements.	0.4	Diazoxide and Chlorothiazide	MRI: grossly abnormal with evidence of cortical necrosis
Case 2	39	3250	On day 4 with lethargy, poor responsiveness and seizures.	0.6	Diazoxide and Chlorothiazide	MRI and CT – subtle reduced attenuation within the cortex and white matter in keeping with generalised cerebral oedema related to hypoglycaemia
Case 3	38	3460	On day 3 with poor feeding, lethargy and seizures.	<0.3	Diazoxide and Chlorothiazide.	MRI – bilateral extensive parietal occipital lobe infarction with diffuse cerebral swelling and oedema, typical of hypoglycaemic brain injury

Conclusion
CHI leads to severe hypoglycaemia leading to severe brain injury and subsequent neurodevelopmental handicap. The identification, early diagnosis and prompt management of patients with hyperinsulinaemic hypoglycaemia are essential if brain damage is to be avoided. These infants are often difficult to identify due to the symptoms being non-specific.

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P24

Normoammonaemic Protein Sensitive Hyperinsulinaemic Hypoglycaemia: ? A novel syndrome

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Introduction
Hyperinsulinaemic hypoglycaemia (HH), characterized by unregulated insulin secretion from pancreatic β-cells, is an important cause of hypoglycaemia in children. Mutations in the K_{ATP} channel genes (*ABCC8/KCNJ11*) are the most common cause of congenital HH. The second common cause, hyperinsulinism hyperammonaemia (HIHA) syndrome caused by mutations in *GLUD1* gene, is associated with elevated serum ammonia and protein sensitivity. We describe four patients with severe protein sensitive hyperinsulinaemic hypoglycaemia (HH) with normal serum ammonia and no mutation in the *ABCC8/KCNJ11/GLUD1* genes.
Methods
Patients were investigated with 24-h blood glucose profile, controlled diagnostic fasting studies and protein load test. Molecular genetic testing for *ABCC8/KCNJ11/GLUD1* was undertaken on diagnosis of HH. Glutamate dehydrogenase (GDH; encoded by *GLUD1*) activity was measured in lymphoblasts and liver tissue in one patient.
Results
All four patients (three females/one male), born from non-consanguinous Caucasian parents, presented with symptomatic hypoglycaemia within first year of life. They had random episodes of hypoglycaemia, not necessarily related to fasting. Controlled fasting studies revealed appropriate suppression of serum insulin and elevation of β-hydroxybutyrate and non-esterified fatty acids. Serum cortisol, lactate, plasma aminoacids, acylcarnitine profile and urine organic-acids were normal. Serum ammonia was persistently normal in all patients. Oral protein load testing unmasked severe protein sensitive HH. Molecular genetic testing for *ABCC8*, *KCNJ11* and *GLUD1* was negative. Measurement of GDH activity was normal in lymphoblasts and liver tissue in one patient, not suggestive of mosaicism for *GLUD1*. All patients responded well to diazoxide treatment. Follow up testing of these patients showed persistence of protein sensitive HH.
Conclusions
We describe a case-series of four patients with normoammonaemic protein sensitive HH with negative molecular genetics for *ABCC8/KCNJ11/GLUD1*. These clinical and biochemical observations are suggestive of a possible new syndrome of protein induced HH with normal serum ammonia. Further research is required to understand the molecular basis.

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P25

Gene expression profiling reveals possible role of growth factors in beta cell hyperplasia in congenital hyperinsulinism

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Introduction
Congenital hyperinsulinism (CHI) is a clinically heterogeneous condition. Mutations in ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, UCP2 and HNF1A are known to cause CHI. There are two histological subtypes of CHI: diffuse and focal. Apart from the functional channel defect, β-cell hyperplasia has been observed in diffuse CHI. We aimed to understand the gene expression pattern in pancreatic tissue of patients with diffuse CHI when compared to normal controls and to compare the expression pattern in patients with known genetic aetiology of CHI with that of patients without a genetic aetiology.
Methods
Fresh frozen pancreatic tissue samples were obtained from six children with diffuse CHI who underwent near total pancreatectomy. RNA was extracted by standard techniques (TRIzol reagent). RNA Integrity was assessed by Agilent-derived RNA integrity number (RIN) and the presence of intact 18 and 28 s bands on the Agilent Bioanalyzer trace. Gene expression microarray (standard Affymetrix techniques) was undertaken on the six diffuse CHI (four with *ABBC8* mutation and two without any known mutation) and two normal RNA samples.
Results
We observed significant overexpression of growth factors and their regulatory proteins like IGF1, IGF2 and IGF2BP3 in diffuse CHI patients. Uncoupling proteins like UCP2 are up regulated in diffuse CHI patients. An anti-apoptotic factor OLFM4 is overexpressed in one of the diffuse CHI patients without any known mutation. Growth factor receptor-binding protein (Grb14) is significantly downregulated in the other diffuse patient without any known mutation possibly enhancing insulin-induced signalling. The markers of cellular proliferation Ki-67 and FOXM1 were significantly overexpressed in diffuse CHI.
Conclusions
The data, first of its kind in CHI, has suggested the potential role of growth factors and anti-apoptotic factors in the β-cell hyperplasia in diffuse CHI. Agents targeting IGF pathways can be a potential therapeutic option to ameliorate the β-cell proliferation in CHI.

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P26

Screening for Coeliac disease in children diagnosed with diabetes mellitus

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Background
Coeliac disease has higher prevalence in children with diabetes mellitus than in the general population, and can have significant impact on quality of life causing faltering growth, prolonged fatigue and recurrent abdominal pain.
Objective
To compare current practice in screening for coeliac disease in children with diabetes mellitus with recommended standards and to investigate the value of follow-up screening for coeliac disease in children previously diagnosed with diabetes mellitus.
Methods
One hundred and forty-six children under 19 years old who had been diagnosed with diabetes mellitus were retrospectively included. Results of coeliac screening at diagnosis (IgA Anti-TTG) and annual coeliac screening were analysed. Case notes of children who had positive results were analysed to see if symptoms were documented. Children with positive antibodies were referred to tertiary hospital and biopsy undertaken. Positive biopsy was taken as gold standard for diagnosis.
Results
In this retrospective study of 148 children diagnosed with diabetes mellitus, 7 were diagnosed with coeliac disease through screening, 6 of whom were on follow-up. 3 were symptomatic. We found the prevalence of coeliac disease to be 5%.
Conclusions
We recommend routine continued surveillance screening for coeliac disease after the diagnosis of type 1 diabetes in children.

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P27

Are paediatric patients attending their annual diabetic retinopathy screening?

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Background
Glycaemic control and duration of diabetes mellitus play an important role in delaying or preventing diabetic retinopathy. NICE guidelines state that for type 1 diabetes, those aged 12 years and over must be offered annual retinopathy screening. This audit aims to assess compliance with the guidelines and the prevalence of retinopathy.
Methods
This was a retrospective audit of paediatric diabetic patients registered to Good Hope Hospital attending diabetic retinopathy screening in 2011 and 2012. Data was obtained from the Retinal screening co-ordinators and the Optimize database. All children aged 12 at the start of the year of screening with type 1 or type 2 diabetes were included. Data collected included: demographic factors, screening attendance and results; HbA1c levels, and durations of diabetes.
Results
In 2011, of 79 eligible paediatric patients, 49 (62%) attended their annual retinopathy screening. 10 (20.4%) of patients had stage 1 retinopathy. Patients with retinopathy had a higher mean HbA1c (9.6 mol/l vs 9.3 mmol/l) and a longer duration of diabetes (8.6 years vs 5.8 years, P value <0.05).
In 2012, of 91 eligible paediatric patients, 63 (69.2%) attended their annual retinopathy screening. 14 (22.2%) of patients had stage 1 retinopathy. Patients with retinopathy had a higher mean HbA1c (9.9 mol/l vs 9.5 mmol/l) and a longer duration of diabetes (7.9 years vs 5.5 years, P value <0.05).
Conclusion
Glycaemic control varies widely within this cohort, but on average is higher than the recommended target level in paediatric patients both with and without retinopathy. Longer duration of diabetes is significantly associated with retinopathy. Retinal screening uptake in the community needs to be improved by patient education and better communication with primary care. The suboptimal glycaemic control may be improved by the use of intense insulin regimens and structured education programmes.

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P28

Resurgence of Lipoatrophy as a complication of treatment with insulin

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Background
Lipoatrophy (LA) was commonly associated with insulin use prior to the development of purified insulin in the 1970's, and then has virtually disappeared. In the last few years, however reports of LA among patients using analogue insulin preparations have increased. We report a case series of 4 patients from a tertiary paediatric diabetes unit presenting with LA while on treatment with analogue insulin via a continuous s.c. insulin infusion pump (CSII).
Methods
Four patients have presented within the last 2 years with LA, from our clinic population of 328 patients.
Results
All four patients were on insulin Aspart via CSII for the management of type 1 diabetes (T1DM) (Table 1).

Table 1 Demographic data (at time of diagnosis of LA unless otherwise specified.

Patient	Sex	Age (years)	Duration of diabetes (years)	Duration of CSII use (years)	Total daily dose of insulin (units/kg)	Site of LA	HbA1c 3 months prior to diagnosis of LA (%)	HbA1c at diagnosis of LA (%)	Follow up (months)	LA resolved: Y/N
1	F	12	3.3	3.25	0.8	Abdomen	8.3	7.8	3	N
2	F	3	1.5	1.3	0.7	Buttock	7.1	6.9	1	N
3	F	10	4.9	1.6	0.4	Abdomen	6.8	7	5	N
4	F	8	5.6	2.45	0.7	Thigh	8.9	7.7	19	Y

There was no statistically significant difference in HbA1c at the time of LA diagnosis compared to 3 months prior.
Conclusions
Lipoatrophy as a complication of insulin therapy in patients with T1DM is re-emerging. LA causes undesirable cosmetic appearances and may cause variable glycaemic control. We have not seen any cases with multiple injections, so it is possible that the continuous infusion of analogue insulin is an important factor. LA should be reported to drug companies and the Yellow Card system of adverse drug effects. This will facilitate observation of trend, and help monitor associations.

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P29

Prevalence and screening of thyroid and coeliac disease in type 1 diabetes mellitus

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Introduction
Children with type 1 diabetes mellitus are at increased risk of autoimmune thyroid and coeliac disease. Reported prevalence figures for thyroid and coeliac disease in this population has been reported in European studies as 3–8%[1] and 1–10%[2] respectively. Current NICE guidelines (June 2009) recommend screening for both conditions at diagnosis, and then screening annually for thyroid disease thereafter. We aimed to: i) estimate prevalence of these conditions in a British cohort; ii) determine whether NICE guidelines are being adhered to.
Methods
We ran a search on a web-based platform for paediatric patients with diabetes (*Twinkle .Net*) in a Greater London district general hospital trust for details of patients' thyroid function and anti-transglutaminase antibody tests during the past

year. Electronic clinical notes and correspondence were individually checked for diagnoses of autoimmune disease.
Results
Prevalence of coeliac disease was 4.29%, and 2.45% for thyroid disease ($n=163$). 76.07% of all patients had thyroid function tests in the last year and 70.83% of newly diagnosed patients had an autoimmune screen at diagnosis, in accordance with NICE guidelines.
Conclusion
Despite international variation in diabetes epidemiology, our prevalence figures are consistent with the limited literature. Screening for asymptomatic disease was sub-optimal, with poor patient compliance in adolescents playing a role. Untreated thyroid and coeliac disease can adversely affect glycaemic control, and therefore clinicians' awareness of their prevalence and regular screening is paramount.
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P30

GAD and IA2 autoantibody positivity is associated with a requirement for insulin treatment: results of the UK national paediatric type 2 diabetes cohort

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Objectives
To establish the frequency of islet cell autoimmunity in children with a clinical diagnosis of type 2 diabetes (T2DM) and describe associated clinical and laboratory findings.
Methods
We recruited children with paediatrician diagnosis of T2DM and body mass index (BMI) above 85th centile for age and sex. Patients with other confirmed diagnoses such as monogenic and type 1 diabetes (T1DM) were excluded. Clinical data was collected into a national database. Blood was taken for diabetes auto-antibody status to exclude diagnoses of T1DM. Autoantibodies were measured using standardised radiobinding assays; GADA and IA-2A with 35-S labelled antigens and IAA with I-125 labelled Insulin in the reference laboratory in Bristol.
Results
Of the 130 recruited to the UK national cohort who have had antibody testing to date, 14 (11%) were positive for either GAD2 or IA2 antibodies (AAb positive) . Of these, 8 (6%) were positive for a single antibody, and 6 (5%) positive for both antibodies. Children were not classified as AAb positive if they were only positive for insulin autoantibodies, as this is likely an indicator of previous insulin treatment. Diabetes autoantibody positivity was significantly associated with a reduced pooled C-peptide (median 530 vs 1270 $P=0.016$), and previous insulin treatment (86 vs 31% $P<0.001$). There was a trend towards differences in sex, BMI-SDS and HbA1c between the groups, with more girls being antibody negative, the AAb positive group having a lower BMI-SDS, and higher HbA1c.
Conclusion
Approximately 11% of patients presenting with T2DM are in fact autoantibody positive, suggesting a masked diagnosis of T1DM. This is associated with insulin treatment and a reduced C-peptide. This suggests the need to do autoantibody testing on all children with a diagnosis of diabetes, even if it suspected T2DM, and predicts the need for insulin treatment 2 years after diagnosis in AAb positive patients.

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P31

Growth and metabolic control in children and adolescents with type 1 diabetes mellitus associated with other autoimmune diseases

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Aim
To study the effect of type 1 diabetes mellitus (T1DM) and concurrent autoimmune condition (AI) on long term glycemic control and growth in children.
Methods
Twenty-eight children with T1DM and associated autoimmune condition were matched by sex and age at onset with two controls each. HbA1C, height SDS, weight SDS and BMI SDS were measured between 6 months and 5 years after developing T1DM.
Results
We included 28 children with T1DM and AI (10 males) and 56 (20 males) age and sex matched controls with T1DM. Out of the 28 patients with AI conditions, 21 (75%) had coeliac disease (CD), 8 (28%) had autoimmune hypothyroidism (AH) and 1 (4%) patient had both CD and AH. Development of an AI condition occurred at 2.3 ± 3.1 years after diagnosis of T1DM. There was no significant difference in growth parameters height SDS, weight SDS and BMI SDS between children in the AI group compared with controls from diagnosis to 5 years after diagnosis of T1DM. Children in the AI group had a significantly better HbA1c control 6 months after diagnosis, but no significance was noted at 1, 2, 3 and 5 years. Multiple logistic regression of factors showed no independent risk factors that affected the development of an AI.
Conclusion
Suboptimal therapeutic control of an autoimmune condition such as coeliac disease and T1DM is known to lead to impairment in growth and substantial morbidity. Our study shows children with T1DM developing a concurrent autoimmune disease were not at risk of worsening metabolic control or growth impairment long term.

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P32

Diabetes mellitus related to Williams syndrome: first report of childhood onset

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Introduction
Williams syndrome (WS) is a multi-systemic disorder caused by a deletion in the region 7q11.23. Childhood endocrine follow-up is mainly aimed to monitor hypercalcemia and thyroid function. A high prevalence (63–71%) of impaired glucose tolerance (IGT) and diabetes mellitus (DM) in young adults with WS is reported. WS guidelines recommend Oral Glucose Tolerance Test (OGTT) starting from 30 years of age. We demonstrate evidence of IGT and DM in WS at a much earlier age.
Case report
A 15.6 years old WS female presented with history of polyuria and polydipsia. She was never overweight and initially presented with glycosuria, moderate ketonuria and hyperglycaemia without acidosis, during a gastroenteritis at the age of 4.2. Subsequently diabetic ketoacidosis appeared, insulin was started but shortly stopped for persistent hypoglycaemia. Subsequent glucose monitoring was normal and remained off insulin. At the age of 10 nocturnal polyuria became evident. Glycosuria, without ketosis or hyperglycaemia, was confirmed and classified as 'renal glycosuria' due to WS renal impairment. Recent investigations confirmed glycosuria without ketonuria, and raised HbA1c (51 mmol/mol). OGTT confirmed DM ($T_0=7.8$ mmol/l; $T_{120}=15.3$ mmol/l). Insulin assessment was not available, C-peptide secretion was impaired ($T_0=<0.1$mmol/l; peak $T_{60}=0.32$ nmol/l). Autoimmunity is still pending. Type 2 like DM with β-cells impairment was considered most probable and diet modifications and Metformin treatment were started, improving glucose metabolism.
Conclusions
We describe the youngest patient with DM associated with WS. Main hypothesis for the underling etiopathogenesis suggest hyperinsulinism secondary to insulin sensitivity reduction linked to genes involved in deletion. Lack of studies in childhood raises the issue about the timing of onset of DM. It is possible that hyperinsulinism could be present for many years before IGT. Our finding demonstrates for the first time the need for studies aimed to assess the prevalence of glucose metabolism abnormalities in WS during childhood with appropriate intervention.

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P33

Transition of young people with diabetes: 3 years experience in a single centre

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Background
Transitioning of children with chronic illnesses into adult services is a major challenge. The diabetes transition process in our unit was being redesigned and this audit was performed to provide a historical benchmark relating to the previous setup. During the audit period, young people had a joint appointment in the paediatric service with an adult nurse specialist and then were referred by letter to the adult diabetes team.
Aim
We collected key data from the year before and after transition which included age, number of appointments offered and attended, average HbA1c, hospital admissions and whether patients had annual review before transition.
Methods
Data from patients transitioned over 3 year period ($n=46$) was collected retrospectively from case notes and laboratory database.
Results
The majority of patients were transitioned at the age of 17 years. Ninety-six percent were transitioned to adult services in the same trust. The number of appointments offered per year before transition was more than after. Attendance rates in the year before and after transition were 60 and 55%. Out of 46 patients, 7 did not attend any appointments in the year after transition, 6 of them were male and most had poor glycaemic control. Three were subsequently lost to follow up. Mean HbA1c before and after transition was 9.5 and 9.8% respectively. Hospital admissions were more in the year before transition.
Conclusions
This audit provided key information around the year of transition. Glycaemic control and clinic attendance is poor around transition. Following this audit, the transition process has been redesigned. We need to particularly target young boys with poor glycaemic control to engage with services to prevent them becoming lost to follow up.

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P34

Reduced acute complications, improved glycaemic control and reported quality of life in young diabetic patients on continuous s.c. insulin infusion (CSII)

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Objectives
The use of CSII in very young diabetic children was initially limited. The criteria for continued use are better long term glycaemic control and reduced hypoglycaemia episodes. The objective of this study was to evaluate the benefits of CSII on glycaemic control, acute complications and quality of life of diabetic patients.
Methods
Retrospective analyses of data from patients with type 1 diabetes from our database that were started on CSII from 2007 to 2012 were done. Their glycosylated hemoglobin (HbA1c), hypoglycaemic episodes, diabetic ketoacidosis and reported quality of life were documented in the year before CSII and compared post-CSII.
Results
There were 17 patients, 9 males, 8 females with mean age at diagnosis of diabetes at 5.1 (range 1.5–10) years. Mean age at CSII initiation was 9.9 (range 3–15) years and mean time taken for transferring a patient from MDI to CSII was 4.8 years.
Mean basal insulin dose before CSII was 0.45 units/kg, reduced to 0.3 units/kg at CSII initiation. At 1 and 3 years post-CSII, 0.33 units/kg and 0.38/kg respectively. Mean basal insulin was significantly higher in girls than boys (26.8 vs 16.8 $P=0.018$) before CSII initiation and not significantly different at start and 3 years post-CSII.
Mean HbA1c was 66 mmol at CSII initiation, decreased to 64.5, a month later and continued to improve 3 years post-CSII except in 3 patients >12 years with initial decrease but no significant difference 3 years post-CSII.
There was significantly less blood sugar excursions, diabetic ketoacidosis and hypoglycemic episodes post-CSII with improved quality of life measured by flexibility, autonomy, socialization and sleep.
Conclusions
CSII use was associated with improved reported quality of life. It is effective in providing lasting benefits such as optimizing glycaemic control and reducing acute complications in children with type 1 diabetes particularly in younger children and girls.

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P35

Tired, tachycardic, toxaemic, teenagers: fluids in severe DKA

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DKA guidelines aim to reduce risk of cerebral oedema. We present the outcomes of three young females with severe DKA with reduced conscious level at diagnosis that required deviation from these guidelines.
A. 12-year-old, pH 6.88 with DKA and sepsis. Received 20 ml/kg initial fluid bolus. CT head scan was normal. Hypotension required further fluid boluses, inotropes and an increase in fluids to 65% above the rate on DKA protocol. Although slow to wake after stopping sedation (4 days), she sustained no obvious neurological deficit. MRI head was normal.
B. 13-year-old, pH 6.72 with DKA, acute renal failure and candida sepsis. Received 20 ml/kg initial fluid bolus. Initial CT head scan was normal. Peritoneal dialysis was required days 7–11 as she was anuric. She was slow to wake from sedation. MRI brain showed severe diffuse ischaemic changes. She was discharged neurologically normal aside from right foot drop.
C. 14-year-old, pH 6.6 with DKA, peri-arrest, profound shock, candida sepsis and renal failure. Received 120 ml/kg fluid boluses and inotropes to gain cardiovascular stability. Initial CT head scan was normal. Poor perfusion led to necrotic skin lesions and caecal perforation. Haemodialysis was required. MRI head scan showed multifocal acute haemorrhagic striatal and leukoencephalopathic lesions. She is now making good progress with apparently normal cognitive function.
These cases demonstrate the challenges involved in treating those with severe DKA. In two of the cases, patients received large fluid volumes to restore circulating volume however did not develop cerebral oedema. The cases of severe renal failure were challenging as fluid and glucose management from a renal point of view can differ from diabetes management plans.

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P36

Insulin pumps for adolescents and young people; main problems observed in Macclesfield: United Kingdom

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Introduction
Continuous s.c. insulin infusion delivered via insulin pump has enabled patients with diabetes mellitus type 1 to improve metabolic control and lead healthier lives[1]. However some patients are experiencing problems with their pumps.
Aim and methods
A service review was carried out to look at the incidence of pump related problems using an online questionnaire survey.
Results
The response rate was 85% for the survey. 42 out of 85 (49.4%) children and young people are currently using insulin pumps. Different brands of insulin pumps are being used (Roche Combo, Medtronic and Animas vibe). 20 patients (56%) experienced some sort of problem with their pumps at some point. 16 patients (44%) did not experience any problem. 17 patients (85%) who had experienced problems with pumps contacted the pump company help line and found it helpful. The main problem was insulin administration failure/error (29.6%). Others were complete pump failure, battery and screen issues, bubble in tube and operational errors. Pump problems led to no clinical problems in majority but did lead to diabetic ketoacidosis on 4 occasions, hyperglycaemia in 5 cases and hypoglycaemia once which needed hospitalisation.
Conclusion
Insulin administration failure/error was the main problem reported by majority of our patients/parents. Most of our patients/parents found insulin pump company advice helpline is very useful.

Reference
Michaud S & Geoffroy L. Malfunction of insulin pumps in children with diabetes mellitus type 1. *Pediatr Diab* 2012 **13** (114–115) 1399–543X.
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P37

Insulin pumps for adolescents and young people improve their quality of life

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Introduction
The study aimed to review the service provided for children and young people with type 1 diabetes mellitus focusing on their quality of life (QoL) before and after commencing insulin pump therapy.
Methods
An online survey using survey monkey was carried out. Each questionnaire had 10 questions and it was filled by either patients or their parents based on the age group.
Results
Forty-two patients are currently on insulin pump therapy. The response rate was 85% (36/42). The average length of insulin pump therapy was 33 months with a mode of 2 years. Fifty-three percent of our patients are using Roche Combo insulin pumps, 39% on Medtronic and 6% on Animas vibe.
All patients were on multiple daily injections (MDI) and carbohydrate counting before being commenced on insulin pump therapy. The QoL was classified into general, physical and moral states and each was ranked poor, medium or good. Significant improvement was noticed on all aspects of QoL after being started using the insulin pump. The general state improved dramatically in 75% of patients, moral state in 55% and better physical activity in 35% of them (Figure 1).

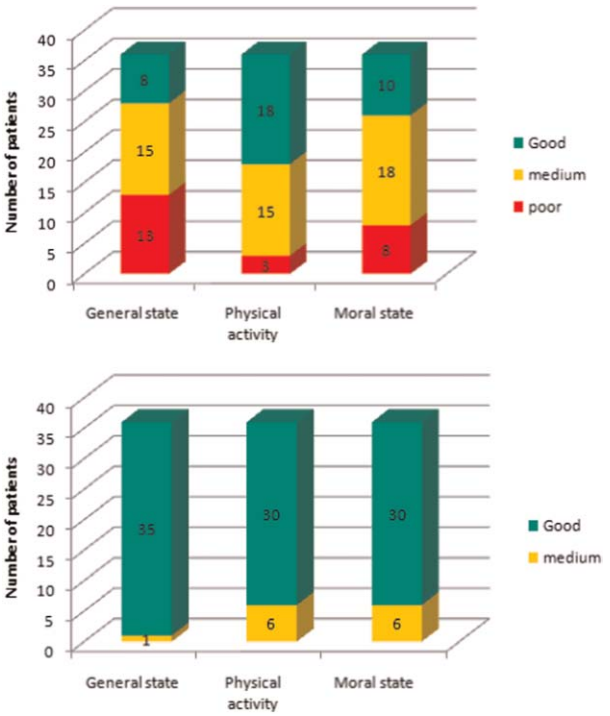

Figure 1 Quality of life for patients before (top chart) and after (bottom chart) using the insulin pump.

Conclusion
Continuous s.c. insulin infusion delivered via insulin pump has enabled children and young people with type 1 diabetes mellitus to have better quality of life in Macclesfield.
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P38

Three Families with Diabetes Mellitus and Sensorineural Deafness

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Background
Diabetes mellitus (DM) is one of the commonest chronic disorders of children, and Type 1 DM is the most frequent form of diabetes in children. Rarely DM is associated with other systemic features. DM and sensorineural deafness (SD) are features of rare syndromes like Wolfram syndrome, Rogers syndrome and Mitochondrial DM. Wolfram syndrome (also known as DIDMOAD syndrome) is caused by los of function mutations in the *WFS1* gene and the clinical features include diabetes Insipidus, DM, optic atrophy and SD. Rogers syndrome is caused by mutations in the *SLC19A2* gene and is characterised by the occurrence of megaloblastic anaemia, DM, and SD. Mitochondrial DM is caused by mutations in *MT-TL-1* and patients have DM with mitochondrial disease.
Patient/methods
We report three unrelated families (two consanguineous and one non consanguineous) with six affected children with DM and sensorineural hearing loss. These patients do not have any developmental or eye abnormalities; nor do they have any mental or neurological disorders, nor any learning disabilities. Genomic DNA was extracted and amplified using polymerase chain reaction and the exons and the exon–intron boundaries were sequenced for possible mutations in *WFS1, SLC19A2,* and *MT-TL1*.
Result
No mutations were identified in the coding regions of the genes *WFS1, SLC19A2, MT-TL1* to explain the clinical phenotype of these patients. This suggests that there might be another unidentified genetic aetiology in these patients to account for the phenotype.
Conclusion
In the three families, mutations in the known genes (*WFS1*, *SLC19A2*, and *MT-TL1*) which cause DM syndromes associated with SD have been excluded. This suggests that these patients may have other novel genetic causes for DM and SD. Further work including homozygosity mapping and whole exome sequencing are in progress to find the genetic mechanism of DM and SD in these patients.
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P39

Extreme hyperlipidaemia with poor glycaemic control in type 1 diabetes

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Background
Poorly controlled diabetes is associated with dyslipidaemia including high cholesterol and LDL concentrations. This increases the long term risk of atherosclerosis and cardiovascular complications. In children and young people with type 1 diabetes, management with lipid lowering agents is controversial and to date long term evidence of benefit is limited. We report a case of severe dyslipidaemia and the impact of improvement in glycaemic control.
Case
A 15-year-old female with type 1 diabetes was referred to a tertiary metabolic unit for advice on management of extreme hyperlipidaemia. At annual review, 8 years after diagnosis, she was found to have a triglyceride concentration of 43.9 mmol/l and cholesterol that was unmeasurable as the sample was too lipaemic. There was a family history of obesity and her father had been prescribed lipid lowering medication from his GP. The patients' weight was 55.8 kg with a BMI of 24.33. She was post pubertal and her HbA1c was 14.2%. The referring team commenced a bezafibrate, but this was not tolerated.
Initial management included intensive diabetes education with an improvement in HbA1c to 10.3% and a measurable cholesterol of 16 mmol/l. Insulin pump therapy resulted in further improvement (HbA1c 7.8%; cholesterol 6.7 mmol/l; triglycerides 1.96 mmol/l). 1 year following the start of insulin pump therapy, this improvement was sustained (Cholesterol 5.1 mmol/l; triglycerides 1.25 mmol/l). Molecular genetic testing was negative.
Discussion
This case of extreme dyslipidaemia in an adolescent with type 1 diabetes illustrates the close relationship between glycaemic control and lipid metabolism. Optimising the HbA1c will help identify individuals with dyslipidaemia who require further metabolic and molecular genetic assessment.
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P40

Sensor augmented insulin pump therapy in children with steroid induced diabetes (SID)

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Steroids are commonly used to treat many chronic illnesses and as part of chemotherapy regimen in children. The hyperglycaemia caused by steroids is poorly recognised and can lead to adverse outcomes. Early recognition and appropriate management of hyperglycaemia is therefore crucial. Fasting blood glucose (BG) levels can be normal and the most sensitive time to test BG is 2 h after lunch.

Steroids may also result in secondary adrenocortical insufficiency. In practice this means that steroids with shorter duration of action e.g. prednisolone given at breakfast may cause early morning hypoglycaemia the following day. This would have implications for the choice of insulin preparations and the timing of administration.

The increment of insulin dose is needed daily for several days until BG within the target range is achieved. With this approach in some patients BG levels remain outside the target range for many days. In others, severe insulin resistance secondary to steroids may demand more rapid increase in the insulin dose.

We report a child who was at high risk of developing SID and in whom tight BG control was desirable was commenced on sensor augmented insulin pump therapy (SAIPT). His BG levels were highest at lunch time. He was initially treated with prandial insulin but when commenced on longer duration of basal insulin analogue at breakfast, led to early morning hypoglycaemia the following day. SAIPT was useful in adjusting the dose of prandial and basal insulin and BG targets were achieved within 72 h with out subsequent hypoglycaemia.

This is the first case report of SAIPT in SID. We conclude that SAIPT can be used in patients at higher risk of developing SID, hyperglycaemia requiring rapid increase in insulin and who remain at higher risk of hypoglycaemia secondary to insulin treatment or adrenal suppression.

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P41

How to manage steroid induced diabetes in children

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There are no established guidelines on the management of steroid induced diabetes (SID) in children. Steroids are commonly used to treat many chronic illnesses and as part of chemotherapy regimen in children. The hyperglycaemia caused by steroids is poorly recognised and can lead to adverse outcomes. Early recognition and appropriate management of hyperglycaemia is therefore crucial. Fasting blood glucose (BG) levels can be normal and the most sensitive time to test BG is 2 h after lunch.

Insulin remains the main stay of treatment and has three components; basal, prandial and supplemental insulin requirements. As hyperglycaemia mainly occurs after meals; the prandial insulin is the primary need. Careful adjustment of insulin doses would then be required alongside calculation of carbohydrate-to-insulin ratios.

Administration of steroids may result in secondary adrenocortical insufficiency. The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration and duration of therapy. This would have implications for the choice of insulin preparations and the timing of administration and the weaning schedule.

If the BG remains persistently uncontrolled i.e. >10 mmol/l, i.v. insulin can be used. The use of i.v. insulin can also provide an estimate of the patient's 24-h insulin requirements. I.v. insulin should only be used on a temporary basis and need for continued use should be reviewed on a daily basis.

Patients will need to be monitored carefully if discharged on steroids. The discharge plan needs to include strategies to interpret BG trends and how to adjust the insulin dose with weaning schedule of steroids.

East of England Paediatric Diabetes Network has established guidelines on how to manage SID in the East Anglian region. Clinicians and health care professions should be aware of timely and appropriate management of SID.

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P42

'A retrospective audit to observe the effect of the use of bolus calculators and carbohydrate counting have on blood glucose control in children and young people with type 1 diabetes'

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Automated Bolus Calculators (ABC) were introduced into two inner city hospitals with a high deprivation index in August 2010.

Objective

To observe the change in HbA1c for 3–6 months after the introduction of ABC and carbohydrate counting. Also to explore the effects of age, gender, psycho-social circumstances on HbA1c as well as the uptake of insulin pump therapy after implementation.

Method

ABC were offered to all families who were carbohydrate counting or required a method of calculating a correction bolus. Two ABC were used: Accuchek Expert, Roche and Insulinx, Abbott. They were trained to use devices to give insulin bolus advice for meals and corrections as required. HbA1c was recorded at time of obtaining the meter and on average 167 days after implementation. Data was collected retrospectively. Patients using the meter within the year of diagnosis were excluded. Results were statistically analyzed using a paired *t*-test.

Results

Sample size 105. Mean HbA1c decreased by a small but statistically significant amount (0.41%) (2.54 mmol/l) $P<0.001$. 80% of the sample size carbohydrate counted all their meals whereas 15% counted only evening meals. Those reported to have no known psycho-social problems had an improved mean difference in the HbA1c compared to those who did.

Conclusion

ABC, whether used for a corrective dose, or with carbohydrate counting shows a statistically significant change in HbA1c over time. There were reductions in HbA1c when stratified by age, gender, difficulties, or carbohydrate counting. These were not statistically significant however the sample size was under-powered to detect significance in the different subgroups. This evidence supports the belief that regular usage of this meter alongside carbohydrate counting has a positive effect on HbA1c. Accurate advice is best obtained when using ABC alongside carbohydrate counting.

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P43

Challenges in Meeting Best Practice Guidelines at a District General Hospital in Yorkshire: a review of the changes that need to be made and the financial implications

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Introduction

It was recognised there was a need to improve the current diabetes service provision at a District General Hospital in Yorkshire to meet the payment by results (PBR) best practice tariff. This tariff is based on recommendations by NICE, the Department for Health and the regional tertiary centre.

Objective

The main change to be implemented by this district general hospital was the creation of a 24 h diabetes service staffed by trained professionals. This would allow the trust to meet the best practice tariff and aim to reduce the number and length of hospital admissions for young people with diabetes.

Method

The strengths and weaknesses of the current service provision were examined. The case for change looked at 7 specific aspects: risk management; productivity and cost effectiveness; recruitment and retention of staff; modernisation of service provision; patient choice and implementation of national guidance.

Three options for implementation of proposed change and their consequences were then examined: no change to current practice (option 1); a 24 h on call service staffed by specialist nursing staff (option 2) and a 24 h on call service staffed by a combination of trained medical staff and nurses (option 3).

Results

The additional cost to the trust of implementing option 2 was £30 560 versus a cost of £86 020 to implement option 3. The financial incentive for meeting the PBR best practice tariff would be £30 340. The additional savings that could be made by reducing admission rates and length of admissions was calculated to be between £21 846 and £159 552.

Conclusions

The most cost effective option would be option 2 which involved setting up a 24 h on call service staffed by specialist nursing staff. This service would meet current

government recommendations and the PBR best practice tariff. These options were presented to the trust and are currently under review.

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P44

Mealtime insulin carbohydrate ratios and intensive insulin therapy

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Background
Our practice is to commence newly diagnosed children and young people (CYP) with diabetes, over 5 years old, on multiple daily insulin (MDI), using fixed Insulin to Carbohydrate ratios (ICRs) with meals across the day. ICRs are subsequently adjusted according to blood glucose response, individualising insulin treatment. We know intensified insulin therapy includes use of varied ICRs, reflecting varying insulin sensitivity at different times of day. We do not know whether glycaemic outcomes are better if varying ICRs are introduced from diagnosis, or subsequently.
Aims
To retrospectively audit ICRs in children with newly diagnosed diabetes at diagnosis, 6 weeks and 3 months to identify evidence for individualised treatment.
Methods
Case note review of consecutive CYP presenting with diabetes, commenced on MDI between August 2010 and 2012, recording ICRs for each mealtime at diagnosis, 6 weeks and 3 months.
Results
MDI was commenced in 55 of 93 CYP presenting with diabetes, of which 48 records were retrieved for analysis (87%). Median age was 11.2 years (range 1.86–16.9 years). Carbohydrate counting and fixed ICRs were commenced in 45 CYP from diagnosis. Of three commenced on fixed mealtime doses, two were carbohydrate counting before 6 weeks. Two children had mealtime insulin temporarily discontinued by 6 weeks. One third of CYP were on the same ratios at 6 weeks and 3 months as they were at diagnosis, and the same ICR across the entire day.
Conclusion
Up to one third of our CYP had evidence of inadequately intensified or individualised insulin therapy at 6 weeks and 3 months. We are concerned this limits our ability to improve outcomes. We have adjusted our approach, utilising variable ICRs from diagnosis to avoid losing this important educational element, placing a greater focus on post-prandial glucose testing, frequent clinical reviews and greater emphasis on patient education.

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P45

Local factors influencing service improvements in median HbA1c in children and young people with diabetes between 2003 and 2012

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Background
HbA1c is a marker for the risk of long-term complications of Diabetes. Our unit cares for 349 children and young people (CYP) from a population with a higher than average prevalence of low-income families, ethnic minority families, and high unemployment. Over the last 10 years there have been service improvements, increased resources and changes in practice.
Aims
To review HbA1c outcomes achieved annually from 2003, compared with published national paediatric diabetes audit (NPDA) data, and to determine service factors impacting on this.
Methods
Data on HbA1c submitted to the NPDA from January 2003 to December 2012 was extracted from our patient management database to calculate the annual median HbA1c and the percentage of CYP achieving HbA1c $<7.5\%$. Clinical service changes were reviewed and mapped to these outcomes.
Results
Median HbA1c fell from 9.4 to 8.3%, between January 2003 and December 2011, compared with a national fall from 8.9 to 8.7% in the NPDA. We demonstrate a further reduction to 8.1% by December 2012. The proportion of CYP achieving HbA1c less than 7.5% rose steadily from 12% in 2004 to 25% in December 2011, compared with 14.7 to 15.7% in the NPDA. We have achieved a further increase to 29% in 2012.
Discussion
The fall in HbA1c and improvement in proportion of CYP achieving target HbA1c exceeds that observed nationally. The UK remains behind many European counterparts in securing reduced long-term risks. Changes to our clinical service resulting in improvement over this period include increased staff (2003), MDI introduction (2005/6), CSII introduction (2008/9), and increased promotion and recruitment to interventional and non interventional diabetes research studies (2009–2012). Services witnessing improvement in outcomes have a continuing responsibility to share strategies employed, with the aim of improving paediatric diabetes care across the UK.

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P46

'Bridging The Gap': improving glycaemic control for children of African descent in London

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Children and adolescents with type 1 diabetes treated at University College Hospital London (UCLH) from an African background have poorer glycaemic control compared to the British population (British mean HbA1c 7.8 (0.1), African mean HbA1c 9.4 (0.5) $P<0.001$).
Haemoglobin A1c is an element of the haemoglobin to which glucose is bound. The ideal range is between 6.5 and 7.5% and is considered to represent good glycaemic control. Patients who persistently have an HbA1c over 8.0% are at increased risk of the long-term complications of diabetes, retinopathy, neuropathy and nephropathy. The purpose of the study is to find appropriate educational methods to improve HbA1c.
We undertook an observational study over a 1 year period with patients self-allocated by attending the support group or not. The intervention was support groups involving translated education sessions, meeting with other children and families with good glycaemic control, culturally specific dietary advice and translated advice leaflets.
Data was available in full for 15 participants. One patient was lost to follow up. Four support groups were run with participants attending on average 2–3 of the sessions (intervention). In the intervention group the average HbA1c was 8.8% (2.3) before and 7.8% (1.5) $P=0.3$ after attending at least three support group sessions. In the control group the average HbA1c before was 9.0% (1.0) and after 8.8%(1.2) $P>0.5$.
This preliminary data suggests there may be an improvement in HbA1c due to a support group intervention. The sample size is small and due to the self-selection bias may have been introduced. Nonetheless the data suggest larger randomised trials of group intervention are warranted.

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P47

Factitious hypoglycaemia due to exogenous insulin 'Don't forget the skin'

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Introduction
Serum C Peptide is traditionally used to diagnose factitious Hypoglycaemia due to exogenous Insulin. However in our case we were able to initiate child protection work up on the basis of skin marks which were noted during child's admission in hospital.
Case report
2-year-old male presented with 3 days history of diarrhoea and vomiting. Past history and examination were unremarkable. Mother had gestational diabetes and was on insulin during pregnancy whilst Grandmother who died 1 month previously had type 2 diabetes managed with Insulin. He was admitted and commenced on ORS. His blood glucose (BG) dropped to 2.8 mmol/l. He had Hypoglycaemia screen and BG improved with sugary fluids. He continued good oral intake and was discharged the following day. He had 2 further repeat admissions with history of poor oral intake, floppy episodes, none of which were witnessed on the wards. On 3rd readmission he was kept in for prolonged observation during which he was noted to have low BG (2.6 mmol/l) with low

blood ketones of 0.3 mmol/l. He required >8mg/kg per minute of i.v. glucose to maintain euglycaemia. This was consistent with hyperinsulinism. Hypoglycaemia screen was repeated. Marks which matched imprints made by an insulin pen, were noted on the legs and arm of the child the next day. We instituted strict 1:1 nursing to ensure mother and other family members had only supervised access to child and his BG improved. Police Protection Order was put in place. Results showed insulin >100 mU/l, C Peptide <50 pmol/l, confirming exogenous insulin administration. Mother was arrested by the police. Child remained well and now is fostered.

Discussion

Presence of insulin pen imprints enabled us to suspect exogenous insulin administration prior to receiving hypoglycaemia screen results. We recommend thorough skin examination in any child with persistent hypoglycaemia.

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P48

Development of a next generation sequencing panel for disorders of sex development (DSDs)

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Disorders of sex development (DSDs) refer to a range of congenital disorders where the chromosomal, gonadal or anatomical sex is atypical. Patients typically present in the newborn period where ambiguous genitalia often prevents immediate gender assignment or during the adolescent period where atypical sexual development becomes apparent. Genetic testing is key in establishing the diagnosis allowing for personalised management of these patients, and can significantly reduce the period of uncertainty for families regarding the sex of rearing of their child. Cytogenetics may provide guidance on possible causes and if further investigations are indicated. However a definitive molecular diagnosis is only made in around 20% of cases. Current molecular testing strategies for DSDs are not ideal, as tests for only a few of the many associated genes are currently available and are tested sequentially. The development of next generation sequencing allows for multiple genes to be investigated in a single test at a reduced cost compared to current sequencing strategies. Such a test for DSDs would eliminate the long waiting times currently being experienced by patients due to sequential testing. A TruSeq custom amplicon panel has been designed encompassing 32 genes associated with DSDs including *WT1*, *SOX9*, *AR*, *ARX*, *ATRX*, *SRD5A2*, *CYP11B1* and *STAR*. Initial validation of the assay has been carried out with 30 patients carrying known mutations. Details of the panel and results obtained to date will be presented.

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P49

Precious puberty in an infant is not normal

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Background

A 5-month-old girl presented with a history of acute abdominal distension over several weeks. Three weeks previously she had developed pubic hair, and some early breast development. The GP had reassured parents on two occasions that this was normal. On examination she had Tanner breast stage 3 bilaterally, pubic hair stage 3, mild cliteromegaly, and gross abdominal distension.

Investigations

An ultrasound scan revealed a massively enlarged right ovary measuring 10 cm×6.7 cm×7.7 cm. The left ovary appeared normal. The uterus was adult in configuration with a thickened endometrium of 8 mm. There was ascites throughout.

Table 1 Baseline blood investigations.

Test (units)	Result	Normal range
Oestradiol (pmol/l)	2598	0–55
Testosterone (nmol/l)	3.3	1.0–2.5
Leutinising hormone (LH) (IU/l)	<0.1	0–1.0
Follicle stimulating hormone (FSH) (IU/l)	0.3	0–2
Human chorionic gonadotropin (HCG) (IU/l)	<2	0–4
Inhibin A (pg/ml)	284.2	<19
Inhibin B (pg/ml)	8856.2	<111
Alpha feto protein (AFP) (IU/ml)	74.3	Within normal range for age
Cancer antigen-125 (CA-125) (IU/l)	994	0–30

Bone age on TW3 scoring was not advanced.

Progress

Right salpingo-oophorectomy was performed (right ovary weighing 260 g). At operation the ovarian capsule was noted to be breached. Histology confirmed a Juvenile Granulosa Cell tumour. No tumour cells were reported in the peritoneal fluid. The tumour was staged as Stage 1c on account of there being a capsular breach and a mitotic rate of up to 23 mitoses per high power field but no evidence of distant metastases. Her baseline and post-op blood investigations are presented in Tables 1 and 2. In view of this she received postoperative chemotherapy.

Within 3 weeks tumour markers had normalised, and pubertal staging had regressed to Tanner stage 1.

Table 2 Day-3 post-op bloods.

Test (units)	Result	Normal range
Testosterone (nmol/l)	<0.4	1.0–2.5
Oestradiol (pmol/l)	<43	0–55

Conclusion

Precocious puberty in infancy must always be investigated promptly.

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P50

Early puberty in two girls with Prader–Willi syndrome

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Introduction

Prader–Willi syndrome (PWS) is characterised by hypotonia, obesity, short stature, and hypogonadism probably due to hypothalamic dysfunction (hypogonadotropic hypogonadism (HH)). Exaggerated adrenarche is however commonly noted in these patients. Early puberty is rarely described: we report two girls with PWS diagnosed with premature sexual maturation.

Case reports

Case 1: this 8-year-old girl was neonatally diagnosed with PWS (maternal uniparental disomy (MUPD)) of chromosome 15. At 2 years of age she started GH treatment to improve final height and muscle tone. At 6.5 years she was growing rapidly (height velocity 8.8 cm/year) and was B2 and PH3. On LHRH testing FSH increased from 6 to 39.3 U/l and LH from <0.2 to 7.6 U/l: compatible with her stage of puberty. Oestrogen was undetectable. Pelvic US showed 3.8×0.8×1.6 cm uterus; the right ovary was unidentified and the left ovary had a volume of 1 cc with a 6 mm follicle. GnRH analogue treatment was started for psychological reasons, and also to optimise growth potential. She has remained B2, P3.

Case 2: this 7-year-old girl was diagnosed with PWS due to MUPD of chromosome 15 at 2 years of age. GH therapy was commenced at 3.5 years to improve final height, tone, muscle mass and overall global development. At 6 years she developed pubic hair with no axillary hair or clitoromegaly. The height velocity was 7.5 cm/year. Investigations showed normal 17 OHP and adrenal androgens. Bone age was advanced by 1.8 years. She is currently PH3, Ax1 with B2: LHRH test and pelvic USS are ongoing.

Conclusion

Early puberty is uncommon in PWS, as patients characteristically have hypogonadotropic hypogonadism. Clinicians need to be aware that early puberty may also occur, although due to obesity initial signs of breast development may be masked.

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P51

NR5A1 Mutation – A Rare Cause of Pubertal Androgenisation

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Introduction
Steroidogenic factor-1 (SF-1) is encoded by the NR5A1 gene on chromosome nine and is a nuclear receptor involved in adrenal and gonadal development and differentiation. There is wide phenotypic variation in individuals with NR5A1 mutations, but little is known about the natural course of patients during puberty. This study reports the case of a phenotypical female who showed profound virilisation at puberty due to a mutation in the NR5A1 gene.
Case Report
A 14-year-old girl presented with facial and axillary hair, absent breast development and amenorrhoea. There was no history of ambiguous genitalia, but genital examination was refused. Her karyotype was found to be 46XY, with a high testosterone level (22.6 nmol/l) and raised testosterone:dihydrotestosterone ratio (14:1). A urine steroid profile was normal. Pelvic imaging showed inguinal gonads but no uterus. Examination under anaesthesia revealed extensive virilisation, with 6 cm clitoromegaly.
Genetic sequencing found no mutation in the androgen receptor gene, 17 HSD3 or SRD5A2 genes. Subsequent analysis of the NR5A1 gene revealed a heterozygous mutation within exon 5, resulting in a 'stop' codon, which was determined to be the pathogenic mutation.
After intensive psychological counselling the patient stated her desire for a female gender identity, and proceeded to laparoscopic gonadectomy, clitoral reduction, and oestrogen therapy.
Conclusion
This case highlights a rare presentation of NR5A1 gene mutations, in a patient with no genital ambiguity prior to puberty. The human SF1 protein, encoded by the NR5A1 gene, is one of the main regulators of enzymes involved in adrenal and gonadal steroidogenesis. It is expressed in undifferentiated gonads and there is wide phenotypic variation in XY patients with NR5A1 gene mutations. This case is a previously unreported presentation of this mutation, and highlights the variable presentation of SF1 protein mutations.

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P52

46,XX pure gonadal dysgenesis with tall stature due to an Xq21.2 deletion

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Introduction
46,XX gonadal dysgenesis without the phenotype of Turner's syndrome is described as 'pure' and is not usually associated with other anomalies with the exception of the rare Perrault syndrome (46,XX-GD with sensori-neural deafness). We describe a girl in whom tall stature was a dominant feature.
Case report
A girl was referred aged 15.6 years with primary amenorrhoea and slim build. Examination showed height 172.5 cm (+1.56 s.d.) (midparental height +0.1 SDS), bone age 13.1 years, weight 53.75 kg (−0.13 s.d.), Tanner stage B1P4A1, lax joints with subluxatable right hip. Investigations showed FSH 119 U/l, LH 33.7 U/l, AMH <4 pmol/l, pre-pubertal cylindrical uterus on ultrasound measuring 3.75 cm with small areas of mixed echogenicity in both adnexae consistent with ovarian dysgenesis. Puberty was induced with low dose ethinylestradiol and compliance was variable. At the time of adult transfer aged 19.5 years the girl measured 182.8 cm (+3.17 s.d.), weight 66.2 kg (+0.9 s.d.), Tanner stage B4P5A2. Genetic study showed a Xq21.2 microdeletion in one X chromosome in the girl but in neither parent.
Conclusion
The tall stature in our patient is not in keeping with parental heights and out of proportion to the compliance difficulties with estrogen treatment. We speculate that the Xq21.2 deletion has affected genes influencing not only ovarian genesis but also growth suppression.

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P53

Rapid molecular genetic diagnosis aiding personalised treatment of 5-α reductase type 2 deficiency

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Introduction
Steroid 5-α reductase type 2 deficiency causes 46,XY disorder of sex development (DSD) and is an autosomal recessive disorder resulting from mutations in the *SRD5A2* gene. SRD5A2 facilitates the conversion of testosterone to dihydrotestosterone (DHT), crucially required for masculinisation of external genitalia. Thus 46,XY individuals with *SRD5A2* mutations present with varying severity of undermasculinisation.
We describe the clinical presentation, investigations and management of two infants with novel *SRD5A2* mutations.
Cases
Two children presented in the neonatal period with ambiguous genitalia. Patient 1, born to non-consanguineous Indian parents presented with micropenis, bifid scrotum and penoscrotal hypospadias. Patient 2, born to consanguineous Pakistani parents presented with micropenis. In both patients, scrotal testes were palpated, karyotype was 46,XY and pelvic ultrasound did not reveal Müllerian structures.
Following three injections of chorionic gonadotrophin, plasma testosterone:DHT ratio was equivocal in both patients (15 and 14 respectively). Rapid molecular genetic analysis, performed within 3 days by direct DNA sequencing of the *SRD5A2* gene revealed novel mutations in both patients: patient 1 was compound heterozygous for the g.237_250 dup and g.264C>G genetic variants in the *SRD5A2* gene that results in a premature stop codon 150 bp downstream and predicted to result in an aberrant protein. Patient 2 had a homozygous mutation, c.598G>A in exon 4 of the *SRD5A2* gene that is also predicted to result in an abnormal protein, p.(Glu200Lys).
Topical Andractim gel (DHT 2.5%) applied once daily resulted in good phallic growth in both boys and surgical correction is planned at an older age.
Conclusion
Establishing the diagnosis of SRD5A2 deficiency is vital for personalised treatment and counselling. Rapid genetic analysis of the *SRD5A2* gene is recommended in suspected patients. Development of comprehensive rapid DSD assays will support such a diagnostic strategy, enabling timely diagnosis and institution of appropriate personalised treatment.

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P54

Causes of precocious puberty in children referred to an Endocrine Unit in the Northwest of Turkey

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Introduction
Although data from developed countries about precocious puberty (PP) are abundant, data from developing countries are scarce. The aim of our study was to analyze the frequency of the variants of PP in children who had applied to our department.
Patients and methods
Retrospective analysis of 367 children (349 girls and 18 boys) with features of PP referred for evaluation to our clinic between the years 2006–2012 was performed.
Results
Premature telarche (PT) was diagnosed in 117 (30.5%) girls with the mean age of 3.9±2.8 years. Their mean height SDS was 0.3±1.1 s.d. Premature adrenarche (PA) was diagnosed in 112 (30.5%) children (104 girls and eight boys), having the mean age of 7±1.2 years. Their mean height SDS was 0.9±1.0 s.d. Central precocious puberty (CPP) was diagnosed in 127 (34.6%) children (121 girls and six boys), with the mean age of 8.3±1.4 years. Of the patients with CPP, 95.3% (121 patients; 115 girls and six boys) were diagnosed as idiopathic. Organic causes for CPP were detected in only 6 (4.7%) girls. Of these six girls, two had hypothalamic hamartoma, one had astrocytoma, one had tuberous sclerosis, one had meningomylocele and one had traumatic brain injury. Peripheral precocious

puberty (PPP) was diagnosed in 11 children (seven girls and four boys), having the mean age of 7.3±2.2 years. Congenital adrenal hyperplasia (CAH) was diagnosed in four girls and two boys, and McCune–Albright syndrome in three girls.

Conclusion

The results of this study indicated that most of cases with PP are affected with CPP especially with idiopathic form of it, followed by PT. CAH might be the most frequent cause of PPP in our population as expected.

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P55

Diagnostic spectrum of female pubertal delay

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Introduction

Delayed onset of puberty is quite a common presentation in adolescent endocrine clinics, and the most common cause, particularly in boys is considered to be constitutional delay of growth and maturation. In girls, however, it is more likely that there is a significant underlying problem.

Aim

To review the aetiology of pubertal delay in female patients referred to a single tertiary centre.

Methodology

All female patients referred to the endocrinology clinic with delayed puberty, arrested puberty and primary amenorrhoea between January 2007 and December 2012 were identified using our clinic patient database. A review of medical case notes was carried out to identify the aetiology of pubertal delay, and information was also obtained on investigations, treatment and outcome. Patients with known conditions associated with pubertal delay, pituitary/gonadotoxic therapy or secondary amenorrhoea were excluded.

Results

Thirty-three patients were identified with a median age of presentation of 15.5 years. A total of 15 different reasons for pubertal delay were found in our population. The three most common causes were low BMI, constitutional delay (no abnormality found and no therapeutic intervention required for onset of menses) and idiopathic primary ovarian failure, but intracranial lesions (craniopharyngioma, prolactinoma), structural abnormalities of the genital tract (Mayer-Rokitansky syndrome) and genetic/chromosomal anomalies (androgen insensitivity syndrome, Turner mosaic) were all identified.

Conclusion

Although simple maturational delay can be a common cause of delayed puberty, in our study we found that a large number (88%) of our patients had a significant underlying aetiology. Seven girls (21%) had a marked eating disorder or other reason for a very low BMI. These results confirm the importance of thorough evaluation of all girls presenting with delayed puberty.

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P56

Review of the service for Turner syndrome patients at University Hospital of North Staffordshire

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Management of children with Turner's syndrome in the Paediatric Endocrine Service in the last 15 years were reviewed retrospectively. There were 19 children with age range from 2 to 16 years.

The age distribution at diagnosis showed 12/19(63%) diagnosed below 1-year-old of those 5/12 (42%) were diagnosed by amniocentesis. 4/19 were diagnosed between 1 and 5 years old, only 3/19 came to medical attention after 10 years of age. Two were mosaic karyotype

In terms of route of referral: the majority has been referred by neonatal consultant 11/19, seven patients has been seem by primary health care professionals for concern regarding short stature or failure to thrive. Only one girl with delayed puberty has been referred by school nurse.

Looking at Turner's syndrome features: only one girl had most of the clinical features of the syndrome, 2/19 suffer from cardiac problems, 7/19 had failure to thrive and short stature. 1/19 didn't had any clinical features and diagnosed by amniocentesis. Coeliac disease has been diagnosed in one of the patients, one child with dysplastic kidney and another one with hypothyroidism.

In the initial assessment in the endocrine service all the children had hearing test, echo cardiogram and renal ultrasound. The entire patients were seen 2–3 times/year and had annual blood tests.

11/19 patients (58%) on GH and most of the girls has been started on pubertal induction (5/7) before 13 birthdays.

Even though adolescent gynaecology service was mentioned to the child and family, only one patient was seen in that clinic.

Summary

Health care professional need to suspect and diagnose this condition early to provide appropriate support and treatment. There is a need to develop turner syndrome clinic and care pathway to improve transitional care service.

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P57

Middle ear disease in Turner syndrome: prevalence and risk factors

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Introduction

Middle ear disease in Turner syndrome (TS) is common, often resulting in troublesome temporary hearing loss, and more rarely to serious suppurative disease with cholesteatoma formation. We have examined the prevalence and pattern of middle ear disease in our TS clinic in relation to age and karyotype.

Methods

Case note review of all girls with TS attending clinic 1989–2012, scoring the most serious middle ear problem for each as: none (0), otitis media (OM) ± effusion (OME) only (1), OME requiring intervention (e.g. grommets) (2), suppurative OM/perforation/retraction pocket (3) and cholesteatoma (4).

Results

Of 173 subjects with TS, current median (range) age 25.6 (1.8–45.3) years, data were available in 155 as shown.

	45,X (n=70)	45,X/46,XiXq & 46,XiXq (n=35)	45,X/ 46,XY (n=10)	45,X/ 46XX (n=9)	45,X/ 47,XXX (n=11)	45,X/ 46,XrX (n=14)	Other (n=22)
0	23	13	6	6	6	7	11
1	13	5	2	0	3	3	2
2	17	8	2	0	0	3	2
3	6	3	0	0	2	0	5
4	4	3	0	0	0	0	0

Median age for girls with category 3 and 4 involvement was 9.25 (1.7–15.90) and 12.05 (7.1–15.2) years respectively, significantly older than the usual age of grommet insertion for OME (4–6 years).

Conclusion

The prevalence of middle ear disease in our TS population is at least 54%. Girls with 45,X monosomy and isochromosome of Xq and those who experience problems (e.g. ear discharge) beyond the age of 9 years are at high risk of serious disease.

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P58

Exploring the culture of listening amongst children's nurses in an outpatient department: A mini-ethnographic study

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Background

In the human communication process listening is often reduced to a passive, innate activity and often considered as 'just listening' (Wolvin 2010). Kilkelly & Donnelly (2011) advocates the promotion of a listening culture whereby children are able to voice and have their views listened to, not only to satisfy legal requirements. Much of paediatric services today are provided in the out-patient setting.

Objective

The study aimed to explore and describe the current listening culture and gain understanding of the challenges and difficulties that children's nurses face when listening to patients in an outpatient environment. The purpose of the study was to

provide a description of the current culture of listening, which could prompt other children's nurses to reflect on their own listening behaviour in practice, ultimately impacting on their clinical practice and patient care.
Methods
A mini-ethnographic approach was utilized and data collected using participant observation and unstructured interviews involving five children's nurses. Participant observation permitted participants to be observed in their natural environment. Interviewing participants involved clarification of events that occurred during data collection and discussions on listening in practice. Data analysis involved a grounded theorizing and a content analysis approach.
Results
Four sub-themes emerged from the data: connection, availability, rushing and pressure, and time. Two main themes emerged: dis-joined listening engagement and subjective temporal listening.
Conclusions
Dis-joined listening engagement refers to a mis-alignment between the purpose of listeners (nurse) and the goals of the speakers (children). Lack of time is frequently used by children's nurses as a reason for not being able to listen. On closer exploration, the research highlighted children's nurses are frequently referring to subjective time not objective time. Subjective time is needed for engaging and empowering patients. Improving the listening awareness of children's nurses could prove beneficial for patient care and compliance.

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P59

Screening log data can be used to inform protocol modifications, increasing patient recrutiment to a challanging clinical trial

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Background
Delivery of clinical trials to time and target is critical for studies to be financially viable and relevant. Feasibility studies are informative. However, protocol acceptability and recruitment rates can only be accurately ascertained once a study is open.
The SCIPI study (SubCutaneous Insulin: Pumps or Injections?), randomises patients to treatment with multiple daily injections (MDI) or pumps at diagnosis of type I diabetes (TID). A consent rate of 50% of eligible patients is required to achieve target recruitment (316 patients from 14 centres). We report how screening logs informed protocol changes to optimise recruitment.
Methods
The following data were recorded: time from diagnosis to i) screening, ii) information giving, iii) consent, iv) randomisation and v) start of randomised treatment. Reasons given for declining to participate, or not inviting a patient to participate were recorded. These data were used to inform changes to study protocol.
Results
Patients who consented were approached earlier than those who declined (median 3.0 vs 6.5 days). Most patients who declined stated a strong preference for MDI. The commonest reasons for ineligibility were: i) first degree relative with TID and ii) inability to complete study questionnaires. Eligible patients were not invited to participate when centres were unable to initiate pump therapy within protocol timelines. In response to these data research staff were encouraged to approach patients early. Eligibility criteria were refined so that patients with a parent, but not a sibling with TID could participate and families who were not fluent in written English could be supported to complete questionnaires. Protocol timelines were also revised. These interventions resulted in an improvement in recruitment rate from 44.7 to 56.6%.
Conclusion
Screening log data can be utilised to address the needs of research staff and families, invited to participate in a study at a time of great uncertainty.

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P60

Dumping syndrome an often unrecognised problem following post nissen fundoplication, gastrostomy in infants

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Background
Dumping syndrome in infants who have undergone gastrostomy or Nissens fundoplication is a recognised phenomenon. The pathogenesis is possibly due to a bolus feed causing an incretin effect and leading to hyperinsulinaemic hypoglycaemia. Continuous glucose monitoring (CGM) systems have not been used in the past to study this phenomenon. We report CGM findings which are almost identical on three such post surgical infants.
Case series 1: a 36-week infant with VACTERL association underwent a gastrostomy and was noted to have hypoglycaemic episodes, once established on bolus enteral feeds. CGM revealed a typical sinusoidal pattern of hyperglycaemia and hypoglycaemia re;ated to feed timings (18% of the time <3 mmol/l over a 3-day period).
2: a term infant with complex congenital heart disease and 22q11 deletion underwent Nissen's fundoplication and gastrostomy followed by post feed hypoglycaemia. CGM revealed hypoglycaemia (25% of the time) $\sim$2 h after the feeds. Continous feeds resulted in the reduction of this pattern (9%) on repeat CGM.
3: an ex-26-week infant with tracheal oesophageal fistula and gastrostomy was noted to have swings in blood glucose levels after commencement of bolus feeds. CGM revealed significant hypoglycaemia (45%) while on bolus feeds.
Continuous feeds corrected the hypoglycaemias and all infants were gradually established on full bolus feeds. Bolus feeds administered using a pump was better than gravity dependant feeding.
Conclusion
Dumping syndrome should be actively sought for, in post-surgical neonates presenting with spontaneous hypoglycaemia. CGM findings seem to be unique and we recommend it as a useful tool to demonstrate the relationship between bolus feeds and hypoglycemia. Further simple manipulation of feed delivery will result in resolution of abnormalities.

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P61

Disease- and treatment-related factors implicated in late neuroendocrine morbidity after paediatric optic pathway gliomas: a multivariate analysis of 166 patients over 30 years

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Introduction
Low-grade gliomas (LGGs) are the commonest benign childhood brain tumour and typically affect the optic pathway and diencephalon, thus potentially causing serious neuroendocrine deficits from tumour and/or treatment. We have previously presented a preliminary analysis of risk factors for neuroendocrine morbidity in our 30-year cohort of LGG patients at Great Ormond Street Hospital, and now present comprehensive results of the completed dataset.
Methods
Retrospective case note analysis of 166 patients with optic pathway and diencephalic LGGs diagnosed between 1980–2010 by multivariate regression.
Results
Patients were of median age 4.90 (range 0.18–15.37) years at diagnosis, and followed up for a median of 8.21 (0.04–29.70) years. 30-year overall, progression-free and endocrine event-free survival (EEFS) were 84.9, 49.0 and 20.8% respectively. EEFS continued to fall up to 15 years from diagnosis, being independently reduced by hypothalamic involvement ($P=0.00$), more recent treatment era ($P=0.00$) and radiotherapy ($P=0.02$). The number of deficits was increased by hypothalamic involvement ($P=0.02$), repeated surgery ($P=0.03$) and radiotherapy ($P=0.04$). GH deficiency was commonest (41.0%), followed by precocious puberty (26.6%), LH/FSH deficiency (20.4%), ACTH deficiency (14.5%), TSH deficiency (13.9%), posterior pituitary dysfunction (13.3%) and hyperprolactinaemia (10.8%). Posterior pituitary dysfunction occurred despite minor surgical interventions (17/29 events were post-shunt/ biopsy procedures), and was present at death in 6/10 patients. 32.5% were obese at last follow-up, particularly with more recent treatment strategies ($P=0.03$) and hypothalamic tumours ($P=0.04$).
Conclusion
This large long-term multivariate analysis of LGG survivors strongly suggests that hypothalamic involvement is more predictive of both the onset and severity of endocrinopathies than irradiation, and challenges the perception that surgery is less neurotoxic, as even minor, repeated surgical intervention can result in increased endocrinopathies and fatal posterior pituitary dysfunction. More recent treatment strategies have not increased overall survival in this cohort, at the expense of increasing the risk of earlier endocrinopathy and obesity.

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P62

Audit of obesity management in a tertiary endocrine centre

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Approximately 30% of children aged 2–15 years old in the UK are now either overweight or obese. There is some guidance on appropriate management within the UK for paediatricians, including a consensus statement by the Obesity Services for Children and Adolescents (OSCA) network. Obese patients referred to a tertiary paediatric endocrine clinic between January 2010 and December 2011 were audited retrospectively, with follow-up until the end of December 2012 included. Children with recognised syndromes, diabetes, underlying endocrine and oncology diagnoses were excluded. We looked specifically at investigations performed, medical interventions, follow-up and response to metformin. Twenty-nine new patients (55% females) were identified and followed up, with a median age at first clinic attendance of 13.5 (2.8–17.1) years. Median BMI was 35.0 kg/m^2. Ninety-seven per cent had BMI SDS ≥ 2 at presentation; 36% BMI SDS >3.5 (very severely obese). Ninety-three per cent ($n=27$) of patients had at least one blood investigation. All ($n=25$) thyroid function tests taken were normal. Seventy-nine per cent ($n=23$) of patients had either a fasting insulin level (16 patients) or an oral glucose tolerance test (seven patients): 74% had insulin resistance; 4% (one patient) had impaired glucose tolerance. Fourteen per cent were concomitantly diagnosed with polycystic ovarian syndrome. Forty-one per cent ($n=12$) were commenced on metformin. Six patients (20.7%) were discharged after the first visit. Eight patients (27.6%) were still under follow-up at the end of the study period; all of these were on metformin, with a median BMI change of -0.03 kg/m^2 (-3.6 to $+2.7$ kg/m^2). Our audit illustrates the significant patient load obesity currently has within a tertiary endocrine clinic and the variations in response to treatment. Management requires standardised guidelines advocating appropriate assessment and intervention in clinical management.

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P63

Serial 'body composition' measurements will help resolve the continued weight gain dilemma in children with PWS

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Introduction
PWS children have higher body fat content and lower lean muscle mass as compared to normal population. Bioelectrical impedance analysis (BIA) estimates lean muscle mass and total fat content separately and thus is more useful than BMI. Continued weight gain despite treatment, can be distressing to patients and parents. We hoped to resolve this dilemma through serial body composition measurements.
Materials and methods
Patients and families are given pro-active advice on calorie intake and consistent dietary practices to prevent unnecessary weight gain. Three-day food diaries are used to assess macro and micro nutrient intake. GH therapy is used in eligible children. Height, weight and BMI are recorded at each visit and body composition measurements by BIA annually after 4 years of age.
Results
Retrospective case note review identified 6 children who had at least 1 BIA measurement; mean age was 9 years; mean body fat was 42.3% and mean lean muscle mass was 19.6 kg (reference -28% and 25.9 kg respectively).
Three children had four serial measurements and two were on GH. Patient 1 had 6.1 kg weight gain over 36 months, but body fat percentage decreased by 0.5% (34.9 to 34.4%). Patient 2 had 29.1 kg weight gain over 40 months, but body fat percentage decreased by 5.5% (48.7 to 43.2%). Patient 3 had 10 kg weight gain over 24 months but body fat percentage decreased by 1.8% (44.7 to 42.9%).
Conclusions
PWS children have much higher body fat percentage and considerably lower lean muscle mass as compared to normal children. Unnecessary fat weight gain can be minimised or even reduced with pro-active management. When inevitable weight gain occurs in PWS children, serial measurements help distinguish clearly between unnecessary fat weight gain and healthy lean muscle mass gain. No increment in percentage body fat can be reassuring to patients and their parents.

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P64

Immune cell dysregulation – contributing to the risk of development of metabolic disease in childhood obesity

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Background
Although the association between obesity, chronic low-grade inflammation and immune dysregulation is well described in adults, there is a paucity of literature regarding this in children. We hypothesized that childhood obesity is associated with significant immune dysregulation.
Methods
Expression of cytokines and microRNAs (miR) involved in the pathogenesis of metabolic disease were assessed in 49 participants aged 6–18 years. Invariant NKT cells, NK cells, T cells and B cells were enumerated by staining with relevant antibodies and flow cytometry.
Results
The age and BMI Z-score of the obese participants were 12.9 ± 3.1 years and 3.4 ± 0.4 respectively and the non-obese participants were 12.2 ± 3.2 years and 0.2 ± 1.1. None had type 2 diabetes.

Parameter	Obese ($n=29$)	Non-obese ($n=20$)	*P* value
Fasting insulin (pmol/l)	149 ± 104	27.6 ± 20.2	<0.001
Invariant natural killer T cell (%CD3+T cells) iNKT	0.32 ± 0.03	0.54 ± 0.02	<0.001
Soluble CD163 (ng/ml)	135.7 ± 9.32	109.1 ± 7.55	0.03
IL1β (pg/ml) Post TLR4 stimulation of PBMCs	2108 ± 708.2	1518 ± 479.6	0.01

Data expressed as mean ± S.D. *P* values calculated using independent-samples *t*-test.

CD163 is a macrophage surface receptor that is shed into the circulation and is measured in its soluble form in serum. Serum concentrations of sCD163 were associated with an increased risk of development of T2DM in a prospective adult study.
INKT cells regulate the innate and adaptive immune system and are dysfunctional in obesity.
MicroRNAs (miRs) are post transcriptional regulators of gene expression. MiR-33a and MiR-33b play an important role in cholesterol homeostasis and insulin signalling, with expression of both greater than three-fold higher in the obese children ($P<0.05$ for both).
Conclusion
Immune cell distribution, tissue inflammation and metabolic gene expression are abnormal in obese children. This demonstrates the imperative to tackle obesity from an early age.

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P65

Modulation of mesenchymal stem cell differentiation by alterations in GH action and cell–matrix interaction

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Introduction
Mesenchymal stem cells (MSCs) are a type of multipotent cells readily found within the bone marrow, capable of undergoing self-renewal and giving rise to cells with different characteristics, such as, osteoblasts, adipocytes and chondrocytes. MSC differentiation requires optimal cell–matrix interaction and is also dependent on a number of growth factors.

Aim
To investigate the effect of GH, Rho-associated kinase (ROCK) and extracellular signal-regulated kinase (ERK) signaling on human MSC differentiation on nanoscale topography (NQ450) which represents a physiological *in vitro* model for cell–matrix interaction.
Methods
MSC were cultured on NQ450 and flat surfaces for variable durations and markers of adipogenesis, chondrogenesis and osteogenesis, were studied by immunofluorescence and qPCR. The model was then used to study the effect of GH, and JAK, ROCK and ERK inhibitor.
Results
An increase in bone formation markers, osteopontin (OPN) and osteocalcin (OCN) on NQ450 was observed in both 28- and 14-day cultures on immunofluorescence. qPCR showed significantly higher expression of BMPR2 and SOX9 genes on NQ450 than standard flat topography. The presence of GHR antibody did not affect BMPR2 expression on NQ450, but was associated with increased SOX9 levels, a marker of chondrogenesis. Although PPARG expression was not significantly higher on NQ450, an increase in PPARG expression was observed in the cells cultured on standard flat topography after GHR antibody exposure. The expression of OCN and OPN was stimulated with GH, reduced after inhibition of ROCK or ERK, and no cells were detected in the presence of JAK inhibitor.
Conclusion
ERK and ROCK signaling are important for topographically driven osteogenesis. Inhibition of GHR signaling shifted MSCs towards chondrogenic mode on NQ450 and adipogenic mode on standard topography. The interactive effect of GH and the ERK pathway on adhesion driven intracellular tension needs further study.

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P66

Chronic kidney disease: an uncommon cause of galactorrhoea in an adolescent

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Introduction
Hyperprolactinaemia may occur in 30% of adults with chronic kidney disease (CKD), although rare in paediatrics. The pathophysiology might be further complicated by pre-existing pituitary abnormalities.
Case
Symptomatic hyperprolactinaemia developed in this adolescent girl with CKD and hypopituitarism. History involved neonatal hypoxic ischaemic encephalopathy (HIE) and renal cortical necrosis. CKD Stage 3 ensued. Growth declined by 2.3 years (height −4.78 SDS) and GH therapy for CKD commenced aged 4.3 years. By 8 years, without dose increase, she maintained height velocity >97th centile. GH deficiency seemed a possible alternative (due to pituitary vasculature compromise during HIE). We identified additional anterior pituitary hormone deficiencies requiring replacement: TSH, ACTH, gonadotrophins, (TSH 2.5 mU/l, freeT4 8.8 pmol/l, synacthen peak cortisol 220 nmol/l and prepubertal by 13 years).
Aged 15 years, she developed galactorrhoea. Investigation showed prolactin 7530 mIU/l (normal <600 mIU/l). Over preceding months, renal failure had progressed to CKD5 (GFR 15 ml/min per 1.73 m^2) with peritoneal dialysis initiation, alongside ethinylestradiol dose increase from 10 to 20 μg daily. There were no further medications implicated in hyperprolactinaemia. Pituitary MRI excluded prolactinoma. The prolactin level remains unchanged by dialysis.
Discussion
Hyperprolactinaemia in CKD is predominantly a direct uraemic toxin effect on hypothalamic function (reducing inhibitory dopaminergic tonus increasing prolactin secretion). Reduced clearance provides a lesser contribution to elevated prolactin levels. Neither peritoneal nor haemodialysis correct hyperprolactinaemia. Ultimately, renal transplantation normalises prolactin. CKD progression is likely the main contributor to hyperprolactinaemia, although the pubertal oestrogen rise may amplify hyperprolactinaemia. Our patient's increase may have been more dramatic due to exogenous oestrogen requirement.
Prevalence of galactorrhoea (symptomatic hyperprolactinaemia) is unknown in the CKD population. This is the only known case of galactorrhoea in an adolescent with CKD and hypopituitarism. This case is more unusual as accompanied by other anterior pituitary hormone deficiencies. We can speculate whether the hypopituitarism contributed to altered prolactin inhibition, although the hyperprolactinaemia was a recent development.

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P67

Effect of latitude, summer daylight exposure and genetic background on growth response to recombinant human GH in GH deficient patients

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Introduction
Growth rate tends to be greater in children living at higher latitudes although the underlying mechanisms are unclear. The aim of this study was to compare height velocity (HV) in response to recombinant human GH (r-hGH) therapy in children with GH deficiency (GHD) living at different latitudes.
Design
Pre-pubertal children with GHD ($n=118$) were enrolled from the PREDICT long-term follow-up prospective study (NCT00699855). Data were submitted from 28 centres in 14 countries. Ethnicity background was consistent with country of origin. Absolute latitude was that of the study site.
Methods
Patients were categorized into three groups based on latitude site: high (>75th percentile: ≥45 °), intermediate (25th–75th percentiles: 34–45 °) and low (<25th percentile: ≤34 °). To look at mechanisms related to latitude effect, the average number of daylight hours during summer at each centre was recorded. First year treatment (Y1) HV (cm/year) was assessed. The effect on HV of summer daylight exposure (SDE) and carriage/non-carriage of nine single nucleotide polymorphisms (SNPs) previously associated with high growth response was analyzed, within *GRB10*, *IGFBP3*, *TGF-α, CYP19A1, SOS1, TP53* and *INPPL1*. The effect of SDE and SNP was assessed using a generalized linear model corrected for multiple variables: gender, baseline age, BMI, distance to target height, GH peak, r-hGH dose and birth weight.
Results
GHD patients from high latitudes had a better Y1 HV than from intermediate and low latitudes (median (Q1, Q3): 9.8 (8.5, 11.4) vs 8.0 (7.0, 9.7) and 8.0 (7.0, 10.5) cm/year, respectively; $P=0.015$). HV significantly correlated with SDE ($r=0.256$, $P=0.006$), but not with latitude ($P>0.05$). For seven growth-related SNPs within *GRB10*, *IGFBP3*, *TGF-α*, *CYP19A1* and *TP53,* HV was significantly affected by an interaction between carriage of the SNP and SDE ($P<0.05$).
Conclusions
Growth response to r-hGH in GHD is influenced by both the carriage of specific growth-related SNPs and geographical location, which may be explained by daylight exposure.

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P68

Multiple pituitary hormone deficiencies in two patients with arthrogryposis multiplex congenita

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Introduction
Arthrogryposis multiplex congenita is a rare congenital disorder characterised by multiple joint contractures. The association with hypopituitarism has only been reported once before. We report two further children with multiple pituitary hormone deficiencies (MPHD) and arthrogryposis.
Case reports
Case 1: this 12-year-old girl was born to consanguineous parents; a previously affected sibling had died. She was dysmorphic with multiple joint ankylosis, dislocated hips and right knee, multicystic dysplastic kidney, sensorineural deafness, optic nerve hypoplasia and hydrocephalus requiring ventriculostomy. Septum pellucidum was absent on MRI. Thyroxine was commenced at 2.1 years (free T_4 of 8.8 pmol/l (10.2–24.5) and TSH 15.4 mU/l (0.4–5)). IGF1 (2.4 nmol/l (4–20)) and IGFBP-3 (0.6 mg/l (0.5–2.9)) were both low. Glucagon stimulation test at 5 years showed low peak GH (3.4 mU/l) and cortisol (232 nmol/l). She was started on GH and hydrocortisone supplementation, the former was stopped after 1 year due to worsening of kyphoscoliosis requiring spinal surgery and instrumentation.
Case 2: this 3-year old boy with arthrogryposis had dysmorphism, contractures of hips, knees, shoulder, elbows, club feet, windswept deformity of hands, joint dimpling and finger webbing. He also had micropenis, undescended testis and hypoplastic scrotum. LHRH testing was normal but the synacthen response suboptimal (403 nmol/l). Hydrocortisone, thyroxine and testosterone (25 mg monthly for 3 months) were commenced with good response. He required herniotomy, bilateral orchidopexy, triceps release and Achilles tenotomy.

Microarrays and MRI scan performed at 16 months were normal. Glucagon stimulation test at 2.8 years for poor growth and low IGF1 (<3.3 nmol/l) demonstrated a peak GH response of 2.8 μg/l and GH therapy was commenced.
Conclusion
These cases illustrate an association between MPHD and arthrogryposis. The mechanism is yet to be elucidated. We plan to undertake further genetic studies to evaluate the causality of this association.

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P69

Congenital nasal pyriform aperture stenosis and pituitary abnormalities: case series of 20 patients and a management guideline for early identification of pituitary insufficiency

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Introduction
Congenital nasal pyriform aperture stenosis (CNPAS) is an increasingly recognised cause of upper airway obstruction associated with holoprosencephaly, of which solitary median maxillary central incisor (SMMCI) is the least severe form. Studies have described pituitary abnormalities in up to 40%. We aimed to determine the use of baseline endocrine investigations and MRI brain in assessing endocrine dysfunction.
Method
Retrospective casenote review of patients diagnosed with CNPAS between 2000 and 2013 in a tertiary paediatric unit.
Results
Twenty patients (65% females) were identified, with 80% diagnosed in the neonatal period at median age of 10 days (range 1–28), and four patients diagnosed late at age 2, 6, 11 and 60 months. 81% of neonatal diagnoses needed surgical correction and all late diagnoses were conservatively managed. SCMMI was detected in 60%.
Variable baseline endocrine investigations were performed in the neonatal period in 55% and MRI brain in 60%, with 45% having both. Hypoplastic/ectopic posterior pituitary was identified in one patient, who was also found to have panhypopituitarism. Two patients were referred later for evaluation of short stature and investigated at ages 3 and 5 years, of which one had an ectopic posterior pituitary together with abnormal baseline endocrine function (IGF1). The other patient had a normal pituitary but was also diagnosed with GH deficiency.
Available height SDS data at 1 year on 60% of our patients identified both the late-diagnosed GH deficient patients, with SDS of −2.6 and −3.6 respectively.
Conclusion
CNPAS management requires a multi-speciality and consistent approach in evaluation of the endocrine axis. All CPNAS patients at diagnosis should have MRI brain and baseline endocrine investigations which will allow early recognition and treatment of pituitary insufficiency. Growth monitoring for at least 1 year is recommended as height SDS at 1 year is a good predictive marker for pituitary function.

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P70

Growth hormone device change-over; is it beneficial?

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Recombinant growth hormone (GH) administration uses several different injection devices. Despite offering free patient choice at GH therapy start, ~20% of our patients subsequently change GH device.
Objective
To investigate reasons for GH device change, and evaluate the effect on adherence, height velocity standard deviation (HVSDS), and insulin-like growth factor-1 (IGF1).
Method
Retrospective study of extracted growth data and laboratory results of patients under our unit who changed GH device between January 2001 and January 2011.
Results
One hundred and nine patients (60 female) had a change in GH device (Table 1). Adherence data for 12 months before and after device change (based on ampoule counting) was available in 30 patients. 9 had 100% adherence before and after device change, 7 had an increase, and 14 had a decrease. IGF1 data was available for 41 patients 12 months before and after GH device change: 29 (71%) had an increase whilst 12 had a decrease. Fifty-four patients had full HVSDS data: 29 (54%) showed an increase, 24 a decrease and 1 no change in the 12 months following changeover. 22 patients had both IGF1 and HVSDS data available: of the 12 with an HVSDS increase, 9 (75%) had an increase and 3 had a decrease in IGF1. Of the 10 with decreased HVSDS, 5 (50%) had an increase, and 5 a decrease in IGF1.

Table 1 Reason for change

Reason	Number
Painful injection	9
Bruising	4
Problem with device	9
Unhappy with device	17
Non-adherence	18
To self inject	12
Wanted simpler device	15
Needle-free	4
Trial	9
Non-fridge	4
Other	12

Conclusions
Patients change GH device for a variety of reasons. GH adherence following changeover is variably altered, as are biological responses (HVSDS and IGF1).

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P71

GH neurosecretory dysfunction may be associated with structural abnormalities of the hypothalamic–pituitary axis

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Introduction
GH neurosecretory dysfunction (NSD) refers to children with abnormal auxology, normal GH responses to provocative testing, but with impaired spontaneous GH secretion over 24 h, leading to low IGF1 concentrations. It is thought to be due to abnormal hypothalamic function with aberrant GHRH and somatostatin secretion leading to impaired GH secretion and subsequently suboptimal growth.
Methods
We reviewed children admitted for spontaneous GH secretory profiles over the last 4 years. We aimed to identify children with growth failure who achieved adequate GH concentrations following stimulation but showed evidence of NSD on an overnight GH profile. We evaluated growth velocity and IGF1 before and after commencing GH treatment. All children diagnosed with NSD were further investigated using neuroimaging (MRI brain/pituitary).
Results
We identified four children with short stature (height <−2.5 SDS) and sub-optimal growth velocity who demonstrated inadequate endogenous GH secretion. These children had no or only one GH peak >7 μg/l over 12 h. All children had previously passed a standard GH stimulation test with stimulated GH concentrations ranging from 10.2 to 21.1 μg/l. However IGF1 concentrations were below −2 SDS in all children. All four children had structural abnormalities of the hypothalamic–pituitary axis including septo-optic dysplasia, anterior pituitary hypoplasia, ectopic posterior pituitary and abnormalities of the infundibulum. Two children subsequently developed multiple pituitary hormone deficiency. All children were commenced on GH treatment and showed normalisation of growth velocity and IGF1 concentrations.
Conclusions
Structural abnormalities of the hypothalamic–pituitary axis may be associated with NSD of GH secretion. Children with significantly abnormal auxology may therefore warrant further investigation in the form of neuroimaging and overnight GH profiling even if they achieve a normal GH peak following provocation. Children with GH deficiency secondary to NSD clearly benefit from treatment despite not being NICE approved; this may soon require discussion with commissioning groups.

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P72

Assessment of cortisol and thyroid hormone levels in neonates with myelomeningocele

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Background
GH deficiency has been reported widely in association with myelomeningocele and other pituitary hormone deficiencies occur less frequently. Following an episode of adrenal crisis in a newborn infant with myelomeningocele and multiple pituitary hormone deficiencies we introduced a policy of screening affected, newborn infants for pituitary insufficiency, focusing on thyroid function and cortisol levels.
Patients and methods
Data from 26 infants (13 males) were reviewed retrospectively. TSH sufficiency was assessed from an unstimulated measure of TSH and fT_4. ACTH sufficiency as assessed by the cortisol response to the low dose short Synacthen test (LDSST: Synacthen 150 ng). A peak cortisol $\geq$500 nmol/l was considered to be normal.
Results
- Thyroid hormone levels were normal in all infants.
- Median (range) basal cortisol was 313 ($<$50–618) nmol/l and peak cortisol 693 (375–1617) nmol/l.
- 4/26 infants (16%) had a suboptimal cortisol response and were treated with hydrocortisone during periods of stress.
- Peak cortisol was $>$500 nmol/l in 3/4 patients with an impaired response during the neonatal period at reassessment 6 months later.

Conclusion
Infants with myelomeningocoele undergo a number of medical and surgical interventions in the first year of life. In this group of patients it is particularly important to identify infants who may have an impaired cortisol response to stress. Our data suggest that routine assessment of the pituitary, possibly limited to assessment of ACTH, should continue.

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P73

Stopping desmopressin treatment in a child with hypopituitarism and epilepsy

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Case
A 10-year-old girl with panhypopituitarism and cerebral palsy secondary to Group B streptococcal meningitis as a neonate had full hormonal replacement therapy (hydrocortisone, thyroxine, DDAVP) since infancy. GH was started at 3 years of age. Sodium levels were always stable in the high normal range. She became epileptic aged seven and was started on sodium valproate. Recurrent chest infections occurred from age eight and she became colonised with *Pseudomonas* and required home oxygen. In the same year, she stopped feeding orally and became totally gastrostomy fed on a fixed volume of 1000 ml a day. Hydrocortisone was changed to prednisolone at aged seven to facilitate the effects of DDAVP through the day.
GH was stopped at aged nine when it appeared that she was not growing very well. She had been quite ill that year with recurrent chest infections. Her weight escalated despite a calorie reduction in feeds. Prior to stopping GH, her plasma sodium was 138 mmol/l. This fell to 129 mmol/l despite sodium supplements of 3 mmol/kg per day. Urine output was $<$3 ml/kg per h despite reduction of DDAVP dose. Urinary sodium peaked at 133 mmol/l.
Management
She was admitted for fluid assessment and a cortisol profile whilst hydrocortisone was reintroduced 6 hourly and DDAVP and sodium supplements stopped.
Hyponatraemia and natriuresis persisted till GH was reintroduced at 0.026 mg/kg per day. Urinary sodium fell to $<$10 mmol/l in the first week of treatment. Urine output was $<$3 ml/kg per h on no DDAVP. She is still off DDAVP 15 months later.
Conclusions
There are a number of reasons for this complex child to stop DDAVP. Hyponatraemia and reduced urine output implies that there is some endogenous ADH secretion, although vasopressin levels were never confirmed. GH has potent renal tubular antinatriuretic effects. This, coupled with the antidiuretic effect of valproic acid must not be underestimated. Six-hourly dosing of hydorcortisone ensures residual DDAVP works effectively.

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P74

Comparison of Glucagon vs Clonidine stimulation test to diagnose growth hormone deficiency

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NICE guidelines (2010) recommend two different GH provocation tests demonstrating subnormal peak GH levels to diagnose isolated GH deficiency (GHD). Choice of stimulation test varies in different units. In our centre, glucagon (GST) and clonidine (CST) stimulation tests are used to make a diagnosis of IGHD. IGF1 is done as part of the initial screening tests.
Purpose of this study was to compare the GST vs CST and to establish if IGF1 level provided any extra information. GH assay at our centre sets a peak GH level of $>$7 μg/l as normal.
44 children who underwent two GH stimulation tests were included. IGF1 levels measured in 42 children prior to GH tests. Whilst 33/44 (75%) had GST as first test, 11/44 CST as first test. Of the 33 children with subnormal GST (peak $<$7 μg/l), 21 (64%) had normal response to CST. Of the 11 children with subnormal CST, 1 (9%) subsequently had normal response to GST but 91% diagnosed to have GHD after GST. No difference in age group of the children in both groups (median age 8.3 years CST first test vs 10.7 years GST first test) was identified. Results of IGF1 did not provide any additional information. 74% (17/23) of those diagnosed GHD had low IGF1 levels (8/10 with GHD in CST group vs 9/13 in GST group).
Significant proportion who failed GST (first test) showed normal response in subsequent CST compared to those who had CST as first test. There were no predictors to choose either test as a first choice and hence avoid a second test if possible. Until a 'gold standard biomarker' of GHD becomes available, current NICE guideline recommendation of two GH tests to diagnose IGHD stands with no evidence of choice of GST or CST as first test.

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P75

How late is too late to treat with Growth Hormone? A case study

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Introduction
13.1-year-old boy referred for growth hormone (GH) treatment with extreme short stature.

Baseline investigations.

Insulin tolerance test	Peak GH – 29.3 mU/l
Cortisol	480 nmol/l (245–725)
24 h GH profile	4 peaks $>$20 mU/l
IGF-1	13.9 nmol/l (23–90)
IGF-BP3	1.6 mg/l (2.1–5.3)
Bone age	11 years
Skeletal survey	No evidence of dysplasia
Dual-energy X-ray absorptiometry (DXA)	L1–L4 'Z' score: −3.2 Total body 'Z' score: −3.1 Total body (%fat): 9.0 Android fat (%): 7.1, Gynoid fat (%): 19.2

Re-evaluation following 5 years of GH therapy at 19.3 years.

Height	159.3 cm (SDS: −2.51)
Tanner stage	G5 P5 TV 25/25mls
Height velocity	2.5 cm/year
Parental adjusted height SDS	−1.62 SDS
IGF-1	56.8 nmol/l (nmol/l)
IGF-BP3	6.77 mg/l (mg/l)
Bone age	17 years
DXA	L1–L4 'Z' score: −2.4 Total body 'Z' score: −3.0 Total body (%fat): 6.7 Android fat (%): 9.5 Gynoid fat (%): 11.4

Background
Born premature at 28 weeks gestation, fraternal twin, birth weight: 1.06 kg (−0.58 SDS). Neonatal course complicated by respiratory distress syndrome, grade 2 Intraventricular haemorrhage, grade 2 Retinopathy and failure to thrive. Although not born small for gestational age, he was small at term (1.67 kg (−4.18 SDS)).
Initial assessment at 13.1 years: Height: 125.2 cm (−3.86 SDS), Weight: 21.8 kg (−4.56 SDS), Tanner stage G1 P1 A1 TV 2mls. Parental Adjusted Height: −3.75 SDS. Height velocity for 0.9 years pre-GH treatment: 4 cm/year.
Management
GH treatment with Norditropin Simplex initiated at 14yrs (Height: 128.9 cm (−4.41 SDS)). GH doses ranged from 0.03−0.067mg/kg/day, titrated according to IGF levels. Pubertal development noted at 15.1 years.
Conclusions
GH therapy has improved this patient's height with notable change in his android/gynoid fat distribution. Little is known about fat mass distribution in SGA children and adolescents during puberty. Gynoid fat mass has been positively associated with several cardiovascular risk factors and warrants further investigation.

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P76

"Short But Not Sweet" – Panhypopituaritism in children presenting with hypoglycaemia as a recurring complication of gastroenteritis

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Background
In the human communication process listening is often reduced to a passive, innate activity and often considered as 'just listening' (Wolvin 2010). Kilkelly & Donnelly (2011) advocates the promotion of a listening culture whereby children are able to voice and have their views listened to, not only to satisfy legal requirements. Much of paediatric services today are provided in the out-patient setting.
Objective
The study aimed to explore and describe the current listening culture and gain understanding of the challenges and difficulties that children's nurses face when listening to patients in an outpatient environment. The purpose of the study was to provide a description of the current culture of listening, which could prompt other children's nurses to reflect on their own listening behaviour in practice, ultimately impacting on their clinical practice and patient care.
Methods
A mini-ethnographic approach was utilized and data collected using participant observation and unstructured interviews involving five children's nurses. Participant observation permitted participants to be observed in their natural environment. Interviewing participants involved clarification of events that occurred during data collection and discussions on listening in practice. Data analysis involved a grounded theorizing and a content analysis approach.
Results
4 sub-themes emerged from the data: connection, availability, rushing and pressure, and time. Two main themes emerged: dis-joined listening engagement and Subjective temporal listening.
Conclusions
Dis-joined listening engagement refers to a mis-alignment between the purpose of listeners (nurse) and the goals of the speakers (children). Lack of time is frequently used by children's nurses as a reason for not being able to listen. On closer exploration, the research highlighted children's nurses are frequently referring to subjective time not objective time. Subjective time is needed for engaging and empowering patients. Improving the listening awareness of children's nurses could prove beneficial for patient care and compliance.

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P77

Urinary gonadotrophins: role in assessment and management of disorders of puberty

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Introduction
With improvements in assays and the increasing need for non-invasive, out-patient based investigations, there is a renewed interest in the use of urinary gonadotrophins (UG) for assessing pubertal progress. This study aims to establish the correlation between serum and urinary LH and FSH in patients undergoing investigation or management of pubertal disorders.
Methods/design
Retrospective evaluation of eight patients undergoing investigation for pubertal delay (five males and three females) and 21 patients (six males and 15 females) for early puberty or suppression of puberty by GnRH agonist (GnRH-a) therapy. Median ages (range) for the boys and girls were 14.4 years (8.9–17.2) and 9.2 years (4.2–17.3), respectively. Non-timed spot urine samples were collected for all cases and 11 (five males and six females) of these were on GnRH-a. Of the 29 cases, matched serum gonadotrophins were available in 15 cases (seven males and eight females). UG were measured by chemiluminescent microparticle immunoassay and corrected for urinary creatinine.

	Groups	*n*	ULH:Creat (median, range)	UFSH:Creat (median, range)	ULH:UFSH (median, range)
Males	Pubertal	7	0.16 (0.08–0.28)	0.42 (0.16–0.63)	0.5 (0.2–0.7)
	GnRH-a	5	0.01 (0–0.02)	0.07 (0.04–0.09)	0.2 (0–0.28)
	Pubertal vs GnRH-a		$P=0.002$	$P=0.002$	$P=0.02$
Females	Pubertal	4	0.11 (0.1–0.33)	1.03 (0.39–1.56)	0.1 (0.1–0.28)
	GnRH-a	6	0 (0–0.026)	0.31 (0.09–0.33)	0 (0–0.125)
	Pubertal vs GnRH-a		$P=0.0002$	$P=0.0001$	$P=0.0000$

Results
In both pubertal males and females, UG were significantly higher than during-GnRH-a treatment:
For the 15 cases with matched serum and urine samples, median serum LH and ULH:creat were 1.5 U/l (0.1–21.9) and 0.16 (0–1.37), respectively. There was a strong correlation between these values (r^2, 0.92), independent of sex.
Conclusion
These preliminary data suggest that UG reflect serum gonadotrophin concentrations and the finding of low UG in patients on GnRH-a therapy suggest that this test may represent a useful non-invasive method of assessing and monitoring effectiveness of GnRH-a therapy.

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P78

How to improve the "gold standard" – the insulin tolerance test (ITT) revisited

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Background
The ITT has been said to be the gold standard for diagnosing GH deficiency (GHD) for 50 years. The original 0, 20, 30, 60, 90 and 120 min time points are still used in many but a survey of current UK paediatric ITT protocols identified several variations.
Objective and hypotheses
To identify optimal GH sampling time points to avoid over diagnosis of GHD.
Methods
Results of 502 paediatric ITTs using two different sampling protocols (P1 $n=459$ with time points: −30, 0, 30, 60, 90, 120 min and P2 $n=43$ with time points −30, 0, 20, 30, 45, 60, 75, 90 min). GH deficiency (GHD) was defined by peak GH <7 μg/l for paediatric or <5 μg/l in transition age-ranges.
Results
Hypoglycaemia was achieved in 97% of tests. With P1, peak GH was measured (in decreasing order of frequency) at 60, 30, 0, −30, 90 and 120 min (46, 20, 15, 13, 4 and 1% respectively) while with P2 at 45 (25%), 60, −30, 0, 30 min (16% each).
GH concentrations above the age related cut-offs at −30 min were seen in 21 cases and represented the maximum level in 16 of them. This precluded GHD in 3% of cases (16/502). Using the same criteria, GH was precluded with the 45 min sample in 2/43 tests (5%) and with the 75 min in 1/43 tests (2%). The 90 and 120 min samples did not preclude GHD.

Conclusions
GH peaks that preclude GHD can be seen in samples even before the administration of insulin in 3% of children. 45 and 75 min samples precluded GHD deficiency in an additional 5–10% of children, avoiding potentially inappropriate and costly GH treatment or repeat tests. 120 min sampling did not contribute to GHD diagnosis.

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Use of prolactin concentrations in disorders of pituitary function and optic nerve hypoplasia

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Introduction
Measurement of the anterior pituitary hormone prolactin is often performed in patients with pituitary pathology. Mild hyperprolactinemia occurs in subjects with hypothalamic disorders and/or pituitary stalk dysfunction, and is also described in patients with isolated optic nerve hypoplasia (ONH), this is proposed to be due to decreased dopaminergic tone.
Objective
To assess prolactin levels in patients with septo-optic dysplasia (SOD) (with/without hypopituitarism), multiple pituitary hormone deficiency (MPHD), isolated GH deficiency (IGHD) and isolated optic nerve hypoplasia (ONH).
Methods
Prolactin data were retrospectively analysed from our database of children with SOD, MPHD, IGHD and ONH. Prolactin was measured using the Immulite assay. 238 prolactin results were included: patients with SOD and hypopituitarism ($n=56$), SOD with normal endocrine function (19), MPHD (73), IGHD (76) and ONH (uni- and bi-lateral) (14). Prolactin concentrations were compared using analysis of covariance using SPSS.
Results
The mean prolactin levels in patients with SOD with hypopituitarism was 448.9 mU/l and in those with SOD and normal pituitary function was 339.1 mU/l. MPHD, IGHD and ONH patients had mean prolactin concentrations of 295.4, 185.2 and 284.6 mU/l respectively. Children with SOD and hypopituitarism had higher levels than those with MPHD ($P=0.008$) and IGHD ($P\leq0.001$). Four SOD patients (three with hypopituitarism) and two with MPHD had prolactin levels >1000 mU/l. Five children with MPHD had prolactin levels below the lower limit of the assay; one is known to have a POU1F1 mutation. Mean prolactin concentrations in children with ONH and SOD without hypopitutarism were similar to the other groups, although a greater sample size is required to report this with confidence.
Conclusion
Prolactin is often measured in patients with suspected pituitary dysfunction. Higher prolactin levels are found in SOD patients with hypopituitarism. Undetectable prolactin levels in MPHD patients should instigate investigation of genetic causes.

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Endocrine manifestations of CHARGE syndrome

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Introduction
CHARGE syndrome is a multi-organ disorder; 67% have mutations in the chromodomain gene CHD 7. Endocrine abnormalities are increasingly recognized and we report our experience in a tertiary endocrine unit.
Methods/Study design
Children with CHARGE syndrome attending endocrine clinic were identified and data collected retrospectively from medical notes.
Results
31 patients (13 females) were identified. Mean age was 10.5 years (range 0.67–21 years). Whilst all children presented neonatally with congenital malformations and dysmorphic features, CHARGE diagnosis based on clinical criteria was made up to 4 years of age. CHD7 mutations were identified in 22 (71%). Mean age of endocrine referral was 10 years (range 0.1–17 years). Endocrine causes for referral were: three with short stature only, seven with short stature and hypogonadotrophic hypogonadism (HH: delayed puberty, hypoplastic genitalia and/or undescended testis), 12 with HH and one with osteopenia. Mean height SDS was – 2.2 (range -0.43 to -5.8). GH provocation testing ($n=5$) showed a mean GH peak of 29.8 mU/l (range 21.9–45). Two patients received GH therapy. 19 patients (16/17 males, 6/13 females) had HH clinically; 17 (55%) were prepubertal. Of 14 (eight female) children in the pubertal age range, spontaneous puberty occurred in only three (all female). Puberty induction occurred in the remainder at a mean age of 14.3 years (range 12–17.5 years). Three patients had low bone mineral density on DEXA scan (BMAD SDS – 2.2 to -2.4). In one child low bone mineral density was associated with fractures and required treatment with bisphosphonates.
Conclusion
HH is the predominant endocrine problem in children with CHARGE syndrome, being more common in boys than girls (94 vs 46%), who consequently are more likely to require pubertal induction. These children may be at an increased risk of osteoporosis. Other endocrinopathies appear to be rare.

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The role of GH in early postnatal life in mice

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GH concentrations are high at birth but it is unclear whether and where GH signaling takes place at this time. We assessed the response to GH in young normal and GH-deficient (GHD) pups.
Transgenic M2-GRF mice were significantly GHD from birth. Weight and plasma IGF1 concentration were normal, but reduced at 6–8 day of age ($P<0.01$). 3 and 10-day-old GHD and normal (WT) mice were treated with bovine GH (bGH, 10 μg/g bw s.c. bd) or vehicle for 5 day ($n=5$–8/group). Ten day old GHD mice, but not WT mice, responded by increasing weight gain ($P=0.01$), tibial length ($P=0.02$) and plasma IGF1 ($P<0.05$). In contrast, these parameters were unaffected in response to bGH in 3-day-old GHD mice ($P>0.05$). A single mouse GH (mGH) injection (1 μg/g bw i.p.) in GHD mice induced Stat5 signaling in liver and growth plate 25 min later, at both 0 and 7 day of age. When 7-day-old GHD and WT mice were killed at various times, GHD mice ($n=12$) had undetectable plasma GH-concentration and no detectable pY-Stat5 in the liver. In 21 WT mice, GH-concentrations ranged from 4.1–55.2 ng/ml. Hepatic pY-Stat5 was detected in eight mice, and these mice had significantly higher plasma GH concentrations (24.4 ± 5.0 vs 9.1 ± 1.0 ng/ml, $P=0.001$), and pY-Stat5 staining was most intense in the mice with the highest GH-concentration.
In conclusion, 10-day-old but not 3-day-old GHD mice grow in response to 5-day bGH. In contrast, both 0 day and 7-day-old mice are able to respond to a single GH pulse by phosphorylating hepatic Stat5. This suggests that hepatic GHR signaling takes place from birth, but that this GHR activation does not result in growth acceleration or increased IGF1 production. The presence of hepatic pY-Stat5 in mice that have high GH-concentrations suggests that hepatic Stat5 phosphorylation follows an endogenous GH pulse as in older mice.

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The use of Radioactive Iodine in the treatment of childhood and adolescent hyperthyroidism

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Background
Treatment options for Graves' disease (GD) and multinodular goitre include antithyroid medication, near total thyroidectomy and radioactive iodine (RAI). RAI is an established treatment for GD in the adult population but is used less commonly in children and the adolescent population due to concerns with regards to safety.

Methods
A review of a series of 14 adolescent patients receiving RAI between 2007 and 2013 in our department was performed retrospectively. This was done via review of case notes, GP follow up details and direct patient interview.
Results
The group consisted of four male and ten female patients between the ages of 11 and 19 years. RAI dose received ranged from 419 to 803 MBq. Four of the patients underwent RAI due to large multinodular goitres. A further five of the 14 patients received RAI as they remained thyrotoxic clinically and biochemically despite oral antithyroid therapy. Additionally, three of the 14 patients had poor compliance whilst the remaining two relapsed following treatment with oral antithyroid therapy. All patients underwent a clinically significant reduction in goitre size after RAI with an improvement in quality of life soon after treatment. There was a marked improvement in thyroid function particularly in the thyrotoxic patients. Seven of the 14 patients developed hypothyroidism between 4 and 12 weeks after RAI whilst a second RAI dose was required in one patient. There was no report of malignancy in this group of patients.
Conclusion
RAI is an effective and well tolerated treatment in this age group resulting in a marked reduction in goitre size and improvements in quality of life.

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BSPED National thyrotoxicosis study: patient characteristics and initial response to antithyroid drug therapy

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Introduction
The BSPED UK thyrotoxicosis study has been running for 10 years. The primary objective is to assess biochemical control on block and replace (BR) and dose titration (DT) regimens. The final patient was recruited towards the end of 2011 and study will finish in 2015. We would like to describe the baseline characteristics of study patients and the initial response to anti-thyroid drug therapy (ATD).
Methods
We focused on patient age, sex, BMI and the initial change in levels of TSH and free thyroxine (FT_4) following initiation of anti-thyroid drug. We also examined the time taken for FT_4 and TSH to normalise according to local reference values.
Results
81 patients have been recruited (41BR, 40 DT). 77% were female, median age at presentation was 13 years (range 3–16 years) and 83% were aged 10–15 years. The median BMI SDS was 0.08 with a range from −1.92 to 2.4. The median baseline FT_4 was 48 (range 13.5–150 pmol/l). The percentage of FT_4 values in the range <25, 25–50, 51–75, 76–100 and >100 pmol/l was 6, 47, 15, 23 and 6% respectively. In 98% cases TSH was suppressed at diagnosis. The average starting dose of ATD (Carbimazole) was 0.65 mg/kg per day and FT_4 normalised in 60% of cases within 4weeks and in 95% patients within 16weeks. Only 12% achieved normal TSH values within 4weeks and 45% by 16weeks. There was no relationship between baseline thyroid function and time taken for FT_4 to normalise.
Conclusions
UK patients with thyrotoxicosis are not thin at presentation. Parents can be informed that FT_4 will be within the normal range or close to normal range within 4 weeks if a dose of Carbimazole between 0.5 and 0.75 mg/kg is administered. TSH levels cannot be used to guide therapy in this early phase of treatment.

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Incidence and clinical characteristics of dual thyroid ectopia in congenital hypothyroidism

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Thyroid ectopia is a frequent and severe form of congenital hypothyroidism and results from failure of the process of embryonic development and migration of the thyroid gland from the pharyngeal pouch to the anterior neck with the isthmus sited at the level of the cricoid cartilage. With improved technetium scanning techniques, cases of dual foci thyroid tissue are increasingly recognised. The incidence and clinical characteristics of this group of patients has not been established.
Methods
A review of clinical, biochemical, and radiological data from babies referred through the UK newborn screening programme to Great Ormond Street Hospital between 2006 and 2012 with identification of all cases of thyroid ectopia. Anterior and lateral views of the thyroid technetium scans were reviewed by a single consultant in nuclear medicine to establish the presence of one or two foci of thyroid tissue. Clinical and biochemical data from the single and dual foci thyroid groups were compared.
Results
143 cases were reported to demonstrate thyroid ectopia on technetium scan between 2006 and 2013. Of these 22 (15.4%) had dual foci ectopic thyroid tissue. The initial TSH was lower in the dual foci (177.5 mU/l) compared with single foci (252.1 mU/l) and free T_4 higher in the dual foci than single foci groups (10.38 vs 8.44 pmol/l). The male:female ratio in the dual foci group was 1:3.4 compared to 1:2.6 in the single foci groups. There was no difference in gestation or birth weight between groups. Related pathology was more frequent with single foci.
Discussion
Dual foci thyroid ectopia occurs in 15% of thyroid ectopia and presents with a slightly milder phenotype. It is more common than previously recognised and this divergence of two populations of cells in thyroid embryogenesis with failure of migration requires further genetic evaluation.

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Kocher-Debre-Semelaigne syndrome: a report of three cases

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Introduction
Kocher-Debre-Semelaigne sndrome (KDSS) is a rare association of muscular pseudohypertrophy and long standing moderate-to-severe hypothyroidism in pediatric age group. This report decribes three cases with KDSS.
Case 1
A 4-year-old girl was admitted to our department with growth failure and mental-motor retardation. She was diagnosed as primary hypothyroidism at the age of 15 days and was started on L-thyroxine but at the age of 6 months the therapy was discontinued by parents. Physical examination showed that her height SDS was −5.01, weight SDS −4.7. She had dry skin, psycomotor retardation, strabismus of the right eye and hypertrophy of both calf muscles. Laboratory findings revealed that TSH, >100 mIU/ml; fT_4, <0.3 ng/ml (normal range, 0.80–1.58) and creatinine phosphokinase (CPK) level, 621 U/l (33–211).
Case 2
A 11 years 6 months old girl was admitted to our clinic with history of growth failure and weight gain in the last 1 year. On examination her height SDS was −2.03 while weight SDS was +0.32. She had coarse facial feature, athletic build and hypertrophy of both calf muscles.
Laboratory findings revealed that TSH, 250 mIU/ml; fT_4, 0.13 ng/dl; antiTPO Ab, 383 IU/ml (0–35) and CPK level, 2502 U/l.
Case 3
A 10 years 9 months old girl was referred to our outpatient clinic with history of growth failure for 2 years. On physical examination her height SDS was −2.8, while weight SDS was +1.19. She had coarse facies and bilateral hypertrophied calf muscles. Laboratory values were TSH, 615 mIU/ml; fT_4, 0.3 ng/dl; antiTPO Ab, 1000 IU/ml and CPK level, 2096 U/l.
Conclusion
We emphasize that because KDSS may be develop due to untreated hypothyroidism, musculoskeletal system should be carefully assessed in hypothyroid children and adolescence.

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PTEN hamartoma syndrome: unravelling the complexities of childhood screening

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Background
PTEN hamartoma tumour syndromes (PHTS) are rare autosomal dominant inherited disorders characterised by macrocephaly, multiple hamartomas and an increased risk of several cancers, including breast, thyroid and endometrium. PTEN encodes a tumour suppressor phosphatase that regulates cell survival and migration. Published guidelines are available for adult patients but screening in children is currently not standardised. Moreover, there is poor genotype-phenotype correlation and age-related penetrance in PTEN mutations, making decisions around appropriate paediatric surveillance highly complex.
Aim
To examine the literature for existing guidelines and epidemiological data to produce a comprehensive screening plan for our paediatric PHTS patients.
Patients and methods
We manage two siblings with a confirmed germline truncating mutation in PTEN (R233X) inherited from their mother, who developed Hashimoto's thyroiditis and a compressing thyroid goitre requiring near-total thyroidectomy aged 28 years. Both children have macrocephaly and developmental delay with autistic-spectrum features but are otherwise asymptomatic (aged 7 and 6 years). A primary search of Medline via PubMed and secondary searches via national guideline databases were carried out.
Results
12 relevant papers and two published guidelines (NICE guidelines, National Comprehensive Cancer Network guidelines) were identified. The risk for tumour development in patients with PTEN mutations is considered low in childhood, and no screening guidelines were found for paediatric patients. Surveillance is recommended from 18 years unless there is a family history of cancer <23 years. However, a recent case series reported the development of thyroid nodules and cancer from early childhood.
Conclusions
Available guidance for the management in childhood of PHTS patients is limited. The lack of paediatric reports of PHTS-associated cancer may be explained by previous diagnostic limitations. We recommend yearly physical examination (particularly of skin and thyroid) and yearly thyroid ultrasound upon diagnosis. In view of the high lifetime risk of malignancy it is important to keep patients under close surveillance.

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Review of presentation and management of juvenile thyrotoxicosis at a single-centre between 2000 and 2010

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Introduction
Juvenile thyrotoxicosis is treated with anti-thyroid drugs using a block and replace or dose titration regimen. There is a high rate of relapse and majority require definitive treatment with surgical or radio-iodine ablation. Increasingly radio-iodine therapy is being used in children, particularly in the USA, but experience with this is limited in the UK. In our unit we have an experienced paediatric thyroid surgeon and we have always carried out surgery in children who relapse after medical treatment.
Objectives
To review presentation, management and outcome of juvenile thyrotoxicosis at a single tertiary centre.
Methods
Case notes review of all children aged 0–18 years diagnosed with thyrotoxicosis between January 2000–December 2010.
Results
Twelve eligible patients were identified. This gives an incidence of 0.7/100 000 per year. Figures may be higher due to difficulties in ascertainment. All patients were female aged 10–18 years, with a median peak at 14.4 years and presented with classical symptoms of thyrotoxicosis.
All patients were treated with carbimazole. The block and replace regimen was used in 83.3% and dose titration in 16.6%. Total duration of treatment varied from 9 months to 5 years.
Of the 12 patients, 6 (54.5%) proceeded directly to surgery due to goiter or difficult symptom control; medical treatment was discontinued in 5 (45.5%) patients of whom 3 (60%) relapsed and 2 (40%) remained in remission at 1and 2 years of follow up. All three relapsed patients underwent surgery. One patient remains on medical treatment after 5 years
Conclusion
Our findings are consistent with figures reported in the literature. In view of the high relapse rate and the developing experience of radio-iodine ablation definitive treatment may need to be considered earlier in our group of children.

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An unexpected diagnosis of follicular–variant papillary thyroid carcinoma in an 11-year-old male

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Introduction
Thyroid carcinoma in childhood is rare, but may present with distant metastases. We present an unexpected diagnosis of follicular–variant papillary thyroid carcinoma (FVPTC) presenting to acute services with cyanosis.
Case report
An 11-year old boy presented to A&E with a two month history of cyanosis, worse with exertion, but not associated with respiratory distress or limitation of exercise tolerance. He had peripheral cyanosis, clubbing and oxygen saturations 78% (air). CT chest showed bilateral, extensive miliary nodules, in keeping with interstitial lung disease. Differential diagnoses included sarcoidosis, tuberculosis and pulmonary alveolar microlithiasis. Following lung biopsy, histology showed FVPTC; subsequent neck examination then revealed a thyroid mass with bilateral cervical lymphadenopathy, confirmed on thyroid ultrasound and MRI neck. Thyroid function test (TFT) was normal (TSH, 4.4 mU/l and FT_4, 13.1 pmol/l). After radical thyroidectomy and neck dissection, histology confirmed FVPTC. Full lymph-node resection was not possible. MRI brain showed four distinct lesions; abdominal CT showed bilateral renal metastases. TFT remained normal post-operatively, but after one cycle of radio-iodine therapy, levothyroxine supplementation was introduced (75 μg once daily). Papillary thyroid cancer is the commonest differentiated thyroid cancer; FVPTC is a common subtype. Regional lymph-node involvement is common in young patients (60–80%), 10–20% have distant metastases. Females predominate; 12% have history of local irradiation; 10% have family history. Adult series have shown younger age and lung-metastases only are associated with good prognosis. A paediatric series of 83 patients aged under 21 at diagnosis of differentiated thyroid carcinoma with distant metastases showed 100% 10-year survival.
Conclusion
This case highlights the importance of considering unlikely causes of common presentations. FVPTC in young patients with widely metastatic disease tends to be extremely radio-iodine responsive, with high cure rate, however this case has more wide-spread metastases than previously reported and the reversibility of the lung disease is unknown.

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Low remission rates and high failure rate for medical treatment of thyrotoxicosis in childhood and adolescence: strategic implications for stopping antithyroid drugs

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Background
Paediatric thyrotoxicosis due Graves' disease (GD)and Hashimoto's thyroiditis (HT) disease is both more rare yet more severe than in adulthood. Antithyroid drug treatment (ATD) is with carbimazole or PTU either alone (dose titration (DT)) or with L-thyroxine ($L\text{-}T_4$) – block and replace (BR).
Methods
We have examined outcome of medical treatment in a cohort of patients treated from 1989 to 2012 according to whether medical treatment was given for <3 or >3 years.

Results

62 patients (8 M) with either GD (50) or HT (12), median (range) age 10.8 (1.8–15.8) years at diagnosis, received initial DT (42) or BR (20) treatment with ATD. Outcome was available in 36 patients receiving ATD for median (range) 5 (3–16.2) years and in 12 patients for 2 (0.3–2.8) years. In the <3 years group, seven patients had surgery and three radioiodine (RI) for poor control, while two (one GD and one HT) remitted when ATD was stopped. In the >3 years group 20 stopped ATD for possible remission of whom ten relapsed (all GD) and ten remitted (5HT),one had surgery and 12 had RI for failed therapy while three remain on ATD after 5.5–8.3 years.

Conclusion

Paediatric thyrotoxicosis may follow a protracted course with variable age of remission and high relapse rate as well as high rate of failure with ATD. We therefore recommend that patients on BR therapy do not discontinue their medication abruptly, but instead are weaned slowly off ATD according to thyroid function tests after stopping L-T_4 therapy, in the hope of anticipating incipient relapse.

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