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**37th Meeting of the British Society for Paediatric Endocrinology and Diabetes 2009**

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Speaker Abstracts
S1
What the new UK-WHO growth charts mean to you
Charlotte Wright
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New UK growth charts using the new WHO standard for children from birth to four years should now be used for all babies born in England after May 11th 2009 (October 2009 in Scotland).

The WHO charts for the first time describe optimal rather than average growth, set breast feeding as the norm and are suitable for all ethnic groups. UK children fit the new charts well for length and height but will look appear relatively heavier by the age of one. This will mean that only around 0.5% children be below the weight 2nd centile and that weight centile falls will be much less common.

The new charts are going to look different and chart users need to familiarise themselves with the changes: there will be a disjunction at age 2 years when the WHO standard changes from length to height: parents tend to expect all healthy children to be on the 50th centile so this is no longer emphasised, but there are more subtle indicators of the 50th percentile.

The charts now include detailed instructions which draw on research evidence and UK policy on screening and referral. They define when a measurement or growth pattern is outside range of normality and advise when further assessment is advisable.

A new low birth weight chart is also available for very preterm and small infants. This uses a novel, simpler method of gestational correction and will be useful for all sick or vulnerable infants, as it is low reading and large scale.

The charts, educational materials and fact sheets are all freely downloadable from www.growthcharts.rcpch.ac.uk.

S2
New UK preterm growth charts
Tony Williams
London, UK.

Abstract unavailable.

S3
Current approaches to understanding the pubertal growth spurt
Tim Cole
UCL Institute of Child Health, London, UK.

The pubertal growth spurt involves a rapid increase then decrease in height velocity (HV), where both the timing and intensity of the spurt vary considerably between individuals. The analysis of such growth curve data is an ongoing statistical problem. Current approaches involve fitting say the Preece–Baines (PB) curve to each individual’s data, and summarising the curves by averaging the five fitted PB parameters across individuals. But this has two drawbacks: fitting lots of separate curves, and needing as many as five parameters per individual.

The talk will present an alternative model of pubertal growth, due to Bath and called SITAR, where just one growth curve is fitted that applies to all individuals. Growth curves for Individuals are matched to the average curve by shifting their curve up-down (representing differences in pre-pubertal size) and left-right (for differences in tempo or age at peak HV), and the age scale is also stretched or squashed (indicating how fast time passes in the individual, i.e. velocity). These three parameters per individual are estimated as random effects at the same time as fitting the average curve, and the goodness of fit of the model matches that of individually-fitted PB curves. The outcome is a cubic spline growth curve that applies to all subjects, plus triplets of parameters per individual (size, tempo and velocity) that summarise their departures from the mean curve.

Two datasets were used to demonstrate the method: N = 3245 boys from Christ’s Hospital (CH) School recruited 1939-68 and measured twice a term from 9 to 19 years (n=129,508), and N=92 Turner syndrome (TS) girls from the UK Turner Study measured 6-monthly from 9 to 16 years (n=1102). The TS girls randomised to receive oxandrolone from 9 years did not differ from the placebo group in terms of size or tempo, but their velocity was highly significantly increased (p<10^-3).

The SITAR growth curve model is a major step forward in the analysis of pubertal growth.


S4
Investigating peripubertal growth problems
Melul Dattani
UCL Institute of Child Health, London, UK.

The investigation of growth failure can be fraught with difficulties at all ages, but never more so than in the peri-pubertal period. The differential diagnosis at this period of life includes constitutional delay of growth and puberty (CDGP), hypogonadotropic hypogonadism (HH), GH insufficiency (GHD/GHB) and a physiological peri-pubertal reduction in growth velocity in addition to other organic causes of growth failure. Careful auxology and pubertal staging with assessment of growth velocity over a period of at least 6-12 months is usually required before making a decision to investigate a child. A decision is made to investigate a child if the height is more than 2 s.d.s below the mean, or if the child is more than 1.4 s.d.s below the mid-parental height, in conjunction with a poor growth velocity. The NICE guidelines recommend the performance of at least two tests of GH secretion, once other causes of growth failure have been excluded. Physiological tests lack reproducibility and are poorly validated, hence provocative testing remains the most widely used and accepted method of diagnosing GHD. A large number of provocative tests are available for use, and there is little or no consensus as to the most reliable tests. Lack of reproducibility, lack of normative data leading to the use of arbitrary ‘cut-off’ values, GH assay variability, and possible hazardous complications add to the controversy surrounding the tests and their interpretation. Obesity is associated with a reduction in GH secretion, often resulting in false positive results. Additionally, there is no consensus with respect to the use of sex steroid priming. The use of the GH-dependent growth factors IGF1 and IGFBP3 in isolation lacks sensitivity and specificity, but in combination with provocative tests of GH secretion, can be associated with acceptable sensitivity and specificity. More recently, the use of MRI to visualise the hypothalamo-pituitary axis has helped as an adjunct to the diagnosis of GHD, the presence of an ectopic posterior pituitary is highly predictive of GHD. The use of the GnRH test in combination with HCG stimulation may help in confirming a diagnosis of HH in isolation or combined with GHD. Finally, recent advances in molecular genetics may help in clarifying the diagnosis, with the identification of a number of genes implicated in the aetiology of GHD or HH. To conclude, the assessment of growth failure in the peri-pubertal period is associated with considerable diagnostic uncertainty, and likely requires a combination of GH provocation, measurement of IGF1 and IGFBP3 concentrations, neuroimaging and molecular genetics in order to achieve an acceptable sensitivity and specificity.

S5
Achieving the best growth at puberty in Turner syndrome
Malcolm Donaldson
Glasgow, UK.

Abstract unavailable.

S6
Insulin therapy at school
Julie Edge
John Radcliffe Hospital, Oxford, UK.

Diabetes control is poor in children in the UK with fewer than 20% of children achieving target HbA1c levels. Multiple injection therapy and insulin pumps produce the most physiological blood glucose control but both require the child to have blood glucose testing and insulin dosing at each meal and most snacks, and therefore at school. There are often huge obstacles to setting appropriate support in place in schools, particularly in children who are too young to perform their own injections and blood glucose testing, even under supervision. Many studies have now shown that glycaemic control is related to complications, even in young children, and that intensive insulin regimens result in improved control and reduced complication rates. We cannot therefore allow the fact that schools are reluctant to take on diabetes care, to be a reason for delaying the introduction of such regimens. Fortunately individual parents have started to lobby for change because of the problems they have encountered in school. Schools now have increasing obligations under various legislation to ensure that they do not discriminate against pupils or put them at a disadvantage because of their health. It is perhaps not widely appreciated how much of an adverse impact on education badly-controlled diabetes can have, and so this is indeed an educational issue. However there is no obligation on teachers to help with
administering medicines – this must be done by volunteers. Schools can employ a support worker with the role of administering insulin injections in the job description but this requires funding. The main obstacles to schools taking this on appear to be a lack of knowledge and understanding of the importance of diabetic control, and fear of adverse incidents and litigation, all of which can be overcome by explanation and education. Indeed, once the volunteers in schools understand the reasons for the injections and blood tests, and they have been adequately taught in the practical skills, schools are generally keen to help the individual child. Indemnity cover for all school staff can be provided by the Local Authority, which will insure all staff for their activities in administering medications. Education is the key, and we should all start now.

S7
Cystic fibrosis related diabetes (CFRD) in childhood and adolescents
Stephen O’Riordan
The Institute of Child Health, UCL, London, UK.

Life expectancy has improved for all children and adolescents with cystic fibrosis (CFAC); children now survive into adult life. Cystic fibrosis related diabetes (CFRD) is increasing1-3. The combination of CF and diabetes has a negative impact on survival. From 2002 to date, CFRD has been related to decreased survival3 and survival gender differences are also described4. Patients with CFRD have a sixfold increase in morbidity and mortality5. CFRD is usually asymptomatic and can remain undetected for up to 4 years prior to diagnosis. Recent International Society of Pediatric Diabetes Consensus Guidelines on CFRD highlight the use of continuous glucose monitoring (CGM) in the normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) stages may be important in early diagnosis of CFRD6. CGM has also been validated for use in children and adolescents with CF7. Early insulin therapy in CF improves growth, lung function and reduces the number of chest infections7. Diabetes is now the most common morbidity in CF patients, some reports estimate 50-75% will be diagnosed with CFRD by the age of 30 years. Early detection and identification of abnormalities in glycemia in CF is essential by all screening methods.

References:

S8
Sport for teenagers with diabetes
Francesca Annan
Liverpool, UK.

Abstract unavailable.

S9
Child protection issues in children and young people with diabetes
Sarah Steele
Southampton, UK.

Abstract unavailable.
Oral Communications
Oral Communications 1

OCI.1
Cholesterol and apolipoprotein levels in a cohort of girls with Turner syndrome, and the effect of GH therapy
Chris Gardner, Anne Gardner, Mohammed Didi, Paul Newland, Indi Banerjee & Jo Blair
Alder Hey Children’s NHS Foundation Trust, Liverpool, UK.

Introduction
Ischaemic heart disease occurs seven times more frequently in women with Turner syndrome (TS) than the normal population. Adult TS subjects have raised serum cholesterol (Ch). In our service we measure Ch, apolipoprotein A1 (AΠ) and B (AΠB) annually in TS patients aged >5 years as AΠ:AΠB in childhood is a strong predictor of cardiovascular risk in adult life. Little is known about lipid profiles or the effects of GH or oestrogen (Eq) in childhood TS.

Methods
Retrospective study of serum Ch, AΠ, AΠB and AΠB:AΠ collected at annual review.

Objectives
1) To describe serum Ch, AΠ and AΠB SDS in childhood; 2) to examine associations with GH and Eq treatment.

Results
Of 68 results from 34 subjects age (mean±1:sd) 13.3±3.87 years at sampling were analysed. Serum Ch SDS was significantly higher in subjects aged >12 years than younger subjects (1.39±0.63 vs 0.35±1.16, P<0.02), persisting after correction for body mass index. There was no significant difference in AΠ, AΠB or AΠB:AΠ SDS. In regression analysis (GH versus no GH), GH was associated with an increase in AΠ SDS (0.04±0.90 vs −0.85±0.69 R²=0.159, P<0.03) and reduction in AΠB:AΠ SDS (0.13±0.71 vs 1.12±1.82 R²=0.178, P<0.016) but not Ch or AΠ SDS (Ch 0.86±1.46 vs 0.85±1.39 R²=0.07, P<0.34, AΠB 0.17±0.86 vs 0.32±1.1 R²=0.055, P<0.475) when controlling for age, BMI SDS and treatment with Eq. In subgroup analysis, the association of GH with AΠ and AΠB:AΠ remained significant. Eq treatment was not associated with significant changes in lipid profiles.

Conclusion
The increase in serum Ch in adult TS subjects appears to have its origin in childhood. Treatment with GH is associated with a more favourable AΠB:AΠ SDS in childhood.

OCI.3
IGF1R gene expression in patients with idiopathic short stature according to GH and IGF1 status
Soraya Sader Milani, Rodrigo Custódio & Carlos Eduardo Martinelli Jr
Department of Paediatrics, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto/São Paulo, Brazil.

The aim of this study was to analyze IGF1R gene expression in patients with idiopathic short stature (ISS) and correlate it with their GH and IGF1 status. In a previous study, we reported lower final height in subjects with ISS and GH peak ≥ 40 mU/l (Group1, n = 16) compared to those with ISS and GH peak between 20 and 40 mU/l (Group2, n = 15), after stimulation test (ITT) before performed or during puberty. Patients were 16–24 (Group1) and 15–26 (Group2) years old when recalled for measurement of final height, BMI, serum IGF1 and biochemical determination. At these time whole blood sample were obtained for IGF1R gene expression analysis. While most of Group2 patients had serum IGF1 concentrations around the mean (±1:sd), Group1 patients had IGF1 mainly above >1:sd (Group1a) or below <1:sd (Group1b) (P<0.05). These 3 groups of patients (1a, 1b and 2) showed different BMI and lipid profile suggesting different status of GH–IGF axis.

Objectives
To study the expression of IGF1R gene in patients with idiopathic short stature (ISS) and correlate it with their GH and IGF1 status. In a previous study we reported lower final height in subjects with ISS and GH peak ≥ 40 mU/l (Group1, n = 16) compared to those with ISS and GH peak between 20 and 40 mU/l. It could reflect an up-regulation mechanism in attempt to compensate reduced IGF1 action due to either low GH levels or poor signaling.

Results
These findings reinforce the existence of different subgroups of patients under the label of ISS that must be better characterized to allow a better clinical approach.
frequency hearing loss, which is also a feature in DIO2 null mice. Normalisation of FSH levels following commencement of luteinising hormone treatment, was associated with improvement in linear growth, speech and neurodevelopment.

This unusual genetic disorder highlights the diverse roles of selenoproteins in biological processes and may also be a useful paradigm to model consequences of human selenium deficiency.

OC1.5
The primordial growth disorder 3-M syndrome connects ubiquitination to the cytoskeletal adaptor obscurin-like 1
D Hanson1, P G Murray1, A Sud1, S A Tentsy2, M Aglan3, A Superti-Furga1, S E Holder1, J Uraghat1, E Hilton1, F D C Manson1, P Scambler2, G C M Black1 & P E Clayton1
1University of Manchester, Manchester, UK; 2National Research Centre, Cairo, Egypt; 3University of Freiburg, Freiburg, Germany. Manchester Thames Regional Genetics Service, London, UK; 4Institute of Child Health, London, UK.

3-M syndrome is an autosomal recessive primordial growth disorder characterized by pre- and post-natal growth restriction, facial dysmorphism and radiological abnormalities. Mutations in the gene CUL7 have been previously shown to cause 3-M syndrome. CUL7 is a member of the cullin family of E3 ubiquitin ligases involved in targeted protein degradation. We identified a large cohort of 3-M syndrome patients who did not carry CUL7 mutations but shared the same distinctive phenotypic features. Genome wide high density SNP mapping identified a second locus on chromosome 2q15-q36.1. Subsequent candidate gene analysis led to the identification of 7 distinct null mutations from 10 families within the gene encoding Obscurin-like-1 (OBSL1). OBSL1 is a putative cytoskeletal adaptor protein which we have shown localizes to the nuclear envelope and is homologous to the giant sarcoplasmic protein Obscurin. We have been able to demonstrate that OBSL1 interacts with CUL7 by co-immunoprecipitation of transiently expressed HEK293 cells. In addition knockdown of OBSL1 by siRNA in these cells leads to the concomitant loss of CUL7. Morpholino (anti-sense oligonucleotide) induced knockdown of the Obsl1 ortholog in Xenopus tropicalis causes significant growth restriction but otherwise phenotypically normal tadpoles at embryonic stage 50 (14 days).

To our knowledge we report the first identification of mutations in OBSL1 and first involvement of a cytoskeletal adaptor protein in a human growth disorder. Our findings imply that CUL7 and OBSL1 are involved in the same molecular pathway and this pathway is a key regulator of human growth. A small cohort of 3-M syndrome patients with neither CUL7 nor OBSL1 mutations has also been identified suggesting a third gene is likely to be involved in the CUL7/OBSL1 pathway.

OC1.6
Influence of JAK2 and PI3 kinase genotypes on growth response to GH therapy
A Omokane, M Solomon, R Morjaria, P Murray, A Whatmore, L Patel & P Clayton
Endocrine Science Research Group, University of Manchester, Manchester, UK.

Carriage of the exon 3 deletion in the GH receptor (GHR) gene has been reported to enhance growth response to GH therapy. JAK2 and PI3K are involved in signal transduction from the GH JAK2/PI3K and IGF1 (PI3K) receptors. We have investigated whether a single nucleotide polymorphism within these genes influences growth response to GH therapy. DNA was taken, with ethical approval, from 104 children treated with GH therapy. Diagnoses were: GHD (n=44), TS (n=23), SGID (n=15), PWS (n=9), ISSN (n=4), SD (n=4) and CT (n=5). Clinical and auxological data were obtained from case records. We examined the 9734G/A polymorphism in exon 19 of JAK2 and the 73167G/A polymorphism in exon 15 of PIK3CA catalytic subunit α (PIKCA), by PCR and subsequent restriction enzyme digestion. Factors influencing change in height SDS over 2 years were assessed by backwards linear regression (independent variables: genotype, mean parental height SDS, birth weight SDS, age at start of GH treatment, starting height SDS, starting BMI SDS, starting GH dose, and mean GH dose over 2 years). Genotype frequencies for JAK2 were AA=23, AG=76 and GG=5. Genotype frequencies for PIKCA were AA=30, AG=54 and GG=50. JAK2 and PI3K genotype did not feature in prediction models during analysis of all patient data, irrespective of diagnosis. However, PI3K genotype did feature in the prediction model for the GHD cohort. In the absence of genotype this prediction model accounted for 36% of the variability in growth response. By including genotype an improved model, accounting for 51% of the variability, was derived. The PIKCA 73167G/A polymorphism appears to influence growth response to GH in GHD patients. A systematic approach to assess the effect of multiple genes related to GHI/GFGI signalling pathways should be undertaken to evaluate their genetic contribution to growth response for patients receiving GH therapy.

OC2.1
Final height in Turner syndrome after Oxyandrolone and delayed pubertal induction: results of a UK randomised, double-blind, placebo-controlled trial
Emma-Jane Gault1, Rebecca Perry2, Sarah Casey2, Tim Cole3, Wendy Paterson2, Peter Hindmarsh1, Peter Bett5, David Dunger5 & Malcolm Donaldson1
1University of Glasgow, Glasgow, UK; 2Royal Hospital for Sick Children, Glasgow, UK; 3UCU Institute of Child Health, London, UK; 5Southampton University Hospitals NHS Trust, Southampton, UK; 6University of Cambridge, Cambridge, UK.

The UK Turner Study examined in girls with Turner syndrome (TS) the impact on final height (FH) of Oxyandrolone (Ox) and/or delayed pubertal induction (14y). Methods. Girls with TS aged 7–11y receiving GH were randomised to Ox (0.05 mg/kg per day, max. dose 2.5 mg/day) or placebo from 9y (or from enrolment if >9y). Girls requiring oestrogen were further randomised to begin oral Ethinylestradiol (E2) (1.2 g/day, Y2–4 g/day, Y3–4 months each of 60/10 g/day at 12y or 14y). Analysis was by multiple regression. Results. From 1999 to 2003, 106 girls were recruited at 36 UK hospitals. Fourteen withdrew, and 75 have reached FH. The table gives characteristics of girls by randomisation and outcome.

<table>
<thead>
<tr>
<th></th>
<th>1st randomisation</th>
<th>2nd randomisation</th>
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<tr>
<td>Age (y)</td>
<td>10.3 (1.6)</td>
<td>10.3 (1.6)</td>
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<tr>
<td>Height (cm)</td>
<td>126.7 (7.8)</td>
<td>126.7 (7.9)</td>
</tr>
<tr>
<td>Age at GH start (y)</td>
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<td>6.9 (2.3)</td>
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<tr>
<td>At final height (n=35)</td>
<td>154.0 (4.8)</td>
<td>148.9 (6.2)</td>
</tr>
<tr>
<td>Age at 14y (1.5)</td>
<td>16.4 (1.3)</td>
<td>16.6 (1.3)</td>
</tr>
<tr>
<td>FH (cm)</td>
<td>149.3 (7.0)</td>
<td>153.2 (4.4)</td>
</tr>
</tbody>
</table>

Ox and 14y-induced puberty both increased FH, by 5.0 cm (P=0.0002, n=75) and 3.7 cm (P=0.03, n=42) respectively. The interaction between them was negative and close to significance (P=0.06, n=42) with these FH effects: Ox vs no Ox (E2 at 12y), 8.2 cm; E2 at 14 vs 12y (no Ox), 6.4 cm; Ox/E2 at 14y vs no Ox/E2 at 12y, 8.4 cm. No significant adverse events such as voice deepening or clitoromegaly were reported.

Conclusions. Ox and pubertal induction at 14y both have a positive effect on FH in TS but the effects are not additive so there is little advantage in using both. Ox is a realistic alternative to late pubertal induction for increasing FH.

OC2.2
Recombinant human GH improves linear growth in children with inflammatory bowel disease: results of a randomised controlled trial
S C Wong1, P Kumar1, D H Casson1, A M Dalzell2, J C Blair3, M Didi4, K Hassan4, P McGrogan5 & S F Ahmed1
1Bone and Endocrine Research Group, Royal Hospital for Sick Children Yorkhill, Glasgow, UK; 2Department of Endocrinology, Royal Liverpool Children’s Hospital Alder Hey, Liverpool, UK; 3Department of Gastroenterology, Royal Liverpool Children’s Hospital Alder Hey, Liverpool, UK; 4Department of Gastroenterology, Royal Hospital for Sick Children Yorkhill, Glasgow, UK.

Background. Despite optimal management, children with inflammatory bowel disease (IBD) may suffer from growth retardation. The role of rGH in these children is unclear.

Table 1
<table>
<thead>
<tr>
<th>Case number</th>
<th>Ox</th>
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</tr>
<tr>
<td>Height (cm)</td>
<td>126.7 (7.8)</td>
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<td>Age at GH start (y)</td>
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<tr>
<td>At final height (n=35)</td>
<td>154.0 (4.8)</td>
<td>148.9 (6.2)</td>
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<tr>
<td>Age at 14y (1.5)</td>
<td>16.4 (1.3)</td>
<td>16.6 (1.3)</td>
</tr>
<tr>
<td>FH (cm)</td>
<td>149.3 (7.0)</td>
<td>153.2 (4.4)</td>
</tr>
</tbody>
</table>
Design
Randomised controlled trial of rhGH (0.067 mg/kg per day) for 6 months.

Subjects
Twenty-two children with IBD and HtSDS < -2 or HtSDS < -1 and HVSDS < -1. Eleven were in the control group (C) and eleven in the treatment group (Rx).

Methods
HtSDS, HV, HVSDS were compared between in Rx and C at baseline (T0) and 6 months (T6). HtSDS was adjusted for Tanner stage (TS) for girls ≥ 11 years and boys ≥ 12 years. Glucose homeostasis was assessed by fasting glucose, insulin and HbA1c. All data are expressed as median (10th, 90th).

Results
CA at T0 was 14.7 years (9.3, 16.2) and 13.7 (9.1, 15.5); median CA-BA at T0 was 1.7 years (0.3, 3.6) and 1.7 years (0.7, 4.1) for Rx and C. Pubertal progress was noted in 5/11 and 3/11 of Rx and C. HtSDS at T0 was in Rx and C: −2.8 (−4.1, −1.5) and −1.8 (−2.7, −1.3), (P = 0.001). Change in HtSDS at T6 in Rx and C was significantly different: 0.3 (0.1, 0.8) and 0.1 (0.3, 0.3), (P < 0.0001). HV at T0 was similar in Rx and C: 5.0 cm/year (0.8, 8.8) and 3.8 cm/year (1.6, 6.5) and so was HVSDS: −3.1 (−6.0, 4.4) and −2.4 (−6.2, 1.8). HV at T6 in Rx and C was 10.8 cm/year (6.1, 14.3) and 3.5 cm/year (2.0, 9.3), (P < 0.0001). HVSDS at T6 in Rx and C was 3.2 (−0.4, 16.4) and −2.0 (−6.3, 4.9), (P = 0.001). CRP, ESR, ABO, HB and cumulative prednisolone were similar between the two groups at T0. At T6, in Rx and C fasting insulin, was 7.0 mU/L (2.1, 15.7) and 3.8 mU/L (2.1, 6.6), P = 0.04 and HOMA index was 1.5 (0.3, 3.7) and 0.3 (0.2, 0.8), P = 0.05. Fasting glucose and HbA1c, were similar in both groups at T6.

Conclusion
rhGH in children with IBD and growth retardation can increase HV by over 100% without excessive skeletal maturation. It may be associated with a reduction in insulin sensitivity but there is no overt abnormality of glucose tolerance.

Oral Communications 3

OC3.1
Accuracy of 2.5 mg hydrocortisone doses from quatered 10 mg tablets
Kirby Heames1, Utpal Shah 2, Phil Riby 1, Jo Blazer & Jim Ford 1
1Liverpool John Moores University, Liverpool, UK; 2Cheshire, Merseyside and North Wales Medicines for Children Local Research Network, Liverpool, UK; 3Alder Hey Children’s NHS Foundation Trust, Liverpool, UK.

Introduction
In paediatric practice hydrocortisone (HC) is frequently prescribed in doses of ≤ 2.5 mg. HC tablets are only available in 10 mg strengths or as 2.5 mg Corlan pellets, a formulation designed for oro-mucosal delivery. Thus, tablets need to be segmented to obtain an appropriate dose. This study examines the accuracy of 2.5 mg HC doses from quartered tablets.

Materials and methods
Of 10 mg Hydrocortone tablets were studied. Weight uniformity of whole and quartered tablets was assessed. Tablets were quartered using a tablet cutter to mimic the manipulations undertaken prior to drug administration. HC content of each quarter was determined by HPLC.

Results
The mean intact tablet weight was 245.9 ± 0.55 mg, CV 29.7%. The mean quartered weight was 56.7 ± 0.55 mg, CV 29.7%.

Discussion
Hydrocortone tablets were oval in shape with a central score line. Limited disintegration occurred during halving but accurate quartering proved impossible. Tabletbrittleness resulted in quarters being gathered from tablet debris; increasing the risk of under- or over-dosing. The USP limits of weight variation (CV) of 1.0% was met by the intact tablets but by only 67% of the quarters against the target 61.5 mg weight.

Conclusions
Splitting Hydrocortone tablets into quarters produced unacceptable variation in weight uniformity and HC content. Oral dosing with Corlan (2.5 mg) would be more reproducible but its pharmacokinetics taken orally are unknown. The data highlight the need for appropriate paediatric strengths and formulations of HC.

OC3.2
Adrenalf function in children and adolescents with Prader–Willi syndrome attending a single centre from 1991 to 2009
Natalie Connell, Malcolm Donaldson & Wendy Paterson
Department of Child Health and Biochemistry, Royal Hospital for Sick Children, Glasgow, UK.

Introduction
There has recently been a suggested link between central adrenal insufficiency and the high rate of sudden death in children and adolescents with Prader–Willi syndrome (PWS). This finding has important implications for PWS management, since steroid cover could exacerbate the existing tendency towards obesity. We have retrospectively examined our data for both mortality and pituitary–adrenal axis status in subjects attending the dedicated PWS clinic at the Royal Hospital for Sick Children in Glasgow since 1991.

Methods
Case-note review of all patients in whom pituitary testing was carried out and cortisol responses to hypoglycaemia (insulin tolerance test) or synthetic ACTH recorded. A stimulus cortisol level of < 500 nmol/L was considered indicative of adrenal insufficiency.

Results
Of the 69 patients who have attended the Glasgow clinic since its inception in 1991 7 have died, median (range) age of death 25.3 (14.8–40.8) years of which only one was unexpected (following pneumonia in a woman aged 40 years). Twenty-five patients (19M:6F) have undergone anterior pituitary stimulation testing, median (range) age 7.16 (0.43–16.27) years. Median (range) basal and peak cortisol were 328 (105–851) nmol/L and 915 (479–1481) nmol/L respectively. There was no statistical difference between hypoglycaemia-induced or synacthen-induced basal (P = 0.64) or peak values of cortisol (P = 0.72). One patient showed a peak cortisol of 479 nmol/L in response to hypoglycaemia, while the remainder showed an adequate rise in cortisol.

Conclusion
In contrast to Roderick et al who reported an inadequate ACTH response to metyrapone in 60% of 25 patients, we found one patient with a borderline stimulated cortisol response. Given that steroids cause significant weight gain and that obesity is a major contributor to morbidity and mortality in PWS we caution against ad hoc steroid cover during intercurrent illness in this patient group.

OC3.3
Mutations in the SLC29A3 gene encoding the human equilibrative nucleoside transporter-3 protein (hENT3) is associated with pigmentary hypochromic, insulin dependent diabetes mellitus (PHID); short stature and hypogonadism
Raja Padidela1, Chela James 1, Raoul Hemnekam1, Simon Cliffe2, Tony Roscioli1, Michael Buckley 3 & Khalid Hussain1
1Developmental Endocrinology Research Group, Institute of Child Health and Great Ormond Street Hospital for Children, London, UK; 2Department of Haematology and Genetics, South Eastern Area Laboratory Services, Sydney, Australia; 3Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Background
PHID syndrome has been recently described as a unique syndrome characterised by pigmented hypochromic, non immune mediated insulin dependent diabetes mellitus (DM). Other associated features of the syndrome include pancreatic exocrine insufficiency, short stature and hypogonadism.

Aims
To identify the genetic basis of PHID syndrome in six patients from five unrelated families and to characterise the endocrine features associated with this syndrome.

Methods
Homozygosity mapping was performed in all five families followed by candidate gene sequencing in our cohort of six patients. Functional studies were performed on the diseased fibroblasts. Combined pituitary function test was performed to assess GH and pituitary–gonadal axis in 2 patients.

Results
Homozygosity mapping identified a single common 1.4 Mb region of shared homoygyosity within cytogenetic band 10q22.1. Five loss of function mutations were found in SLC29A3 gene (three nonsense, one frameshift and one nonsense). Functional studies from the diseased fibroblasts revealed a 34% reduction in the hENT3 mRNA and defect in cellular trafficking of residual protein. Oral glucose tolerance test showed undetectable insulin secretion in the face of high blood glucose concentration. Investigation of short stature revealed adequate GH response to glucagon stimulation test however patients failed to generate an IGF1/IGFBP3 response to GH treatment suggestive of GH resistance. GHRH test
revealed features of hypogonadotropic hypogonadism in a female with failure to attain puberty at 16 years of age.

Conclusion

Inactivating mutations in the human SLC29A3 gene causes a novel Mendelian disorder associated with insulin dependent DM; pigmented hypertrichosis; short stature and hypogonadism. Mutations in SLC29A3 lead to alterations in cell size/number possibly via the insulin signalling pathway. Further studies are required to understand the role of HEN3 protein in pancreatic endocrine and exocrine tissues and in the pituitary gland.

OC3.5

Pituitary function at least 4 years after traumatic brain injury in childhood

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Introduction

Post-traumatic hypopituitarism (PTHP) is a recognised sequel of traumatic brain injury (TBI), occurring in 25-69% of adult patients, but there are few data on the prevalence or natural history in childhood. Our aim was to determine pituitary function in children at least 4 years after TBI requiring paediatric intensive care unit (PICU) admission. At the same time body composition was evaluated.

Methods

Children discharged from the regional PICU with TBI from 1999 to 2004 (n = 127) were recruited. Clinical markers of TBI severity were obtained from case notes. Height, weight, waist circumference, and body fat percentage by skinfold thickness (SFT) and bioelectrical impedance (BIA) were measured. Blood and urine samples were collected for baseline pituitary function testing. Body composition was compared to age and sex matched controls.

Results

Eighteen patients (mean age 16.5 ± 3.8y, 16 independently mobile) agreed to participate. Age at injury (10.0 ± 4.4y) and gender (67% male) were similar to the whole cohort. Participants had longer duration of PICU admission (6.2 ± 5.5d vs 4.9 ± 6.1d, P=0.001) and notropic support (4.0 ± 3.1d vs 1.5 ± 4.6d, P<0.001) and lower GCS on arrival (7 ± 3 vs 10 ± 4, P=0.005). Mean interval from injury to assessment was 6.5 ± 1.6y. Standard deviation scores for height (−0.21 ± 1.16), weight (0.21 ± 2.22) and BMI (0.35 ± 1.31) and body fat percentage (SFT 24.2 ± 7.1%; BIA 21.1 ± 7.7%) were not significantly different from controls. Mean difference from mid-parental height SDS was 0.02 ± 0.80. Biochemical evidence of hypopituitarism was identified in only one case but this may have been caused by other confounding factors.

Conclusion

Pituitary dysfunction was less prevalent than published studies, despite the recruited patients having more severe injuries. However, as the time from injury to endocrine assessment was longer than previous reports, recovery of early pituitary dysfunction might have occurred.

OC3.6

Melatonin secretion in children with sleep disturbance and septo-optic dysplasia

Emma A Webb1, Michelle O Reilly1, Jane Orgill2, Naomi Dale1, Alison Salt1, Paul Gringras1 & Mehul Dattani2

1Institute of Child Health, London, UK; 2St Thomas Hospital, London, UK.

Introduction

A previous case-report described one individual whose significant sleep disturbance in association with septo-optic dysplasia (SOD) was corrected with melatonin administration. Subsequently a trial of melatonin treatment in children with SOD and sleep disruption has become accepted clinical practice in many centres. There are however no published data describing melatonin secretion in these individuals.

Methods

We studied six children with sleep disturbance associated with SOD (characteristics in table below), all of whom were on adequate hormonal replacement at the time of investigation. All children wore an actiwatch-mini for two weeks and were admitted to hospital for a 24 h period during which hourly measurements of serum melatonin were taken. Sleep data were analyzed in conjunction with a detailed sleep diary completed by the children’s parents over the 2-week period. Ethical approval was obtained for these studies.

Results

Actigraphic studies showed reduced sleep efficiency in all children, mainly due to frequent and often prolonged night awakenings. Only one child (t) presented with a free-running sleep pattern with incremental asynchrony suggesting a non-24-h sleep–wake disorder. Melatonin profiles of all children showed a normal circadian rhythm with mean serum levels being lowest in the day (mean 56 pg/ml) and peaking overnight (mean 380 pg/ml).

Conclusions

These findings indicate that abnormalities in timing and amount of melatonin secretion do not account for the significant sleep abnormalities observed in these children, suggesting that other as yet unexplored factors are contributing to their abnormal sleep patterns.

Table 1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Degree visual impairment</th>
<th>Hormonal abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.27</td>
<td>M</td>
<td>Severe</td>
</tr>
<tr>
<td>2</td>
<td>6.12</td>
<td>M</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>6.40</td>
<td>F</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>1.62</td>
<td>M</td>
<td>Severe</td>
</tr>
<tr>
<td>5</td>
<td>1.87</td>
<td>M</td>
<td>Moderate</td>
</tr>
<tr>
<td>6</td>
<td>1.67</td>
<td>F</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Severe, some form vision (non-light reflecting); moderate, worse than 6/18.
OC3.7
Heterogeneous tissue in the thyroid fossa on ultrasound in infants with proven thyroid ectopia on isotope scan: a diagnostic trap
Iez Jones1, Mirag Attia2, Sanjay Maroo2, David Neumann3, Rebecca Perry4 & Malcolm Donaldson1
1Royal Hospital for Sick Children, Glasgow, UK; 2University Hospital, Hradec Kralove, Czech Republic.

Introduction
Thyroid imaging is of proven help in establishing a diagnosis of congenital hypothyroidism in newly referred infants. Radio-isotope and/or ultrasound imaging is commonly used; each has weaknesses but have complimentary strengths and thus have been used in combination in our centre since 1999. We undertook a retrospective review and analysis of ultrasound imaging in infants with proven thyroid ectopia to re-examine the diagnoses.

Patients and Methods
Eighteen infants with proven thyroid ectopia on radio-isotope scanning were reassessed. Fifteen were found to have usable images. Thyroid biochemistry at the time of diagnosis was also reviewed.

Results
All infants showed the presence of tissue bilaterally in the thyroid fossa. This tissue was deemed to be non-thyroidal in nature since, apart from being non-functional on isotope scan, it exhibited some or all of the following typical features: hypochogenicity, heterogeneity, significantly smaller size than normal neonatal thyroid (P≤0.001), poor vascularity and anechoic and/or hypoechogenic cystic areas. A striking and consistent ultrasonographic finding was the extension of this tissue behind and around the great vessels of the neck – a previously unreported feature. Quantitative thyroglobulin measured at diagnosis was highly variable (2.6-612 μg/l) although the median value was 181.5 μg/l.

Conclusion
Considerable experience is required to interpret ultrasound data in neonates with abnormal thyroid function. We caution against diagnosing dysplastic thyroid in situ on the basis of ultrasound alone, particularly if the tissue exhibits any of the features we describe which are associated with non-thyroidal, cervical tissue found in situ in proven thyroid ectopia. A combination of initial venous thyroid function, including thyroglobulin measurement, and dual ultrasound and isotope scanning enhances diagnostic accuracy.

OC3.8
Determinants of remission and relapse in a cohort of children with thyrotoxicosis treated with dose titration of carbimazole
Indi Banerjee1, Rakesh Amin1, Elizabeth Okecha1, Anbu Subbarayan1, Mars Skae2, Catherine Hall1, Helena Gleeson3, Sarah Ehitsham1, Leena Patel4 & Peter Clayton2
1Royal Manchester Children’s Hospital, Manchester, UK; 2University of Manchester, Manchester, UK.

Introduction
Factors determining remission and relapse in children with thyrotoxicosis include ethnicity, age and thyroid hormone levels at diagnosis. We investigated if similar factors in pituitary development.

Methods
Forty-seven children (39 females) with thyrotoxicosis, treated with carbimazole, were followed up for ≥2 years. Initial remission was defined as first cessation of carbimazole and long term remission was defined if remission lasted >2 years.

Result
First remission was achieved in 28 (60%) children after a median (range) of 1.5 (0.3, 3.1) years after diagnosis, while long-term remission was achieved in 8 (17%) children, while remission after relapse was rare at 14%. Treatment with surgery or radiotherapy was given to 22 (46%) children. In survival analysis, risk of relapse was associated with a lower body mass index at diagnosis (hazard ratio (HR) (95% confidence interval) 14.5 (9.6, 26.2), P=0.002) and a higher dose of carbimazole 6 months after diagnosis (HR 1.17 (1.0, 1.3), P=0.03) but not with non-Caucasian ethnicity, younger age or high serum free thyroid levels. In linear regression (R²=0.68, P=0.002), time between initial remission and relapse was negatively correlated with time to achieve initial remission (P=0.002) and initial dose of carbimazole (P=0.01), when controlling for ethnicity, age, sex and weight, suggesting an association of greater disease severity with a higher risk of relapse.

Conclusion
Most children with thyrotoxicosis treated with dose titration of carbimazole relapse after remission, especially if they are thin at diagnosis and remain on high treatment doses at 6 months after diagnosis.

ORAL COMMUNICATIONS

OC4.1
Parahippocampal aberrations in children with GH deficiency: a diffusion tensor imaging study
E A Webb, M O’Reilly, K Seunarine, J Clayden, N Dale, A Saht, C Clark & M T Dattani
Institute of Child Health, London, UK.

Introduction
There is a large body of evidence to suggest that the GH axis plays an important role in brain myelination. However, results from studies in humans with an abnormal GH axis have varied and therefore there remains no consensus as to whether the GH/IGF1 axis plays a significant role in neural development. No previous studies have used diffusion tensor imaging (DTI) a sensitive magnetic resonance imaging (MRI) technique for studying brain white matter tracts, to address this question.

Methods
Fifteen children (mean 8.5 years) with isolated GH deficiency (IGHD) (peak GH to provocation <6.7 μg/l (mean 4.5 μg/l) plus a pathologically low IGF1 concentration for age (mean –2 s.d. for age and sex)), and twelve children (mean 8.3 years) with isolated short stature (ISS) (peak GH to provocation >10 μg/l (mean 14 μg/l), normal IGF1 measurements and growth rate) were studied. All underwent MRI imaging of the brain (DTI sequences acquired) and a comprehensive neuropsychological assessment including the Weschler Intelligence Scale for Children (WISC-IV) and the Movement-ABC (M-ABC) test. The fractional anisotropy (FA) images were processed using tract-based spatial statistics, and automated, observer-independent, voxel-by-voxel whole-brain between-group analysis performed.

Results
Children with IGHD had significantly lower FA (reduced white matter integrity) in the parahippocampal region and temporal lobes bilaterally and performed significantly worse on the perceptual reasoning component of the WISC-IV (P<0.05) and the M-ABC (P<0.009), compared to the ISS control group.

Conclusions
These preliminary findings show that white matter abnormalities are present in specific brain regions in children with IGHD, who are impaired compared to controls in perceptual reasoning and motor performance. Currently the main aim of GH treatment in children is to optimise final height and maintain bone mass; if GH also has a significant impact on neural development and cognition, then this may have important implications for clinical practice.

OC4.2
First report of a de novo heterozygous SOX2 deletion associated with a large hypothalamo-pituitary tumour gives further insights into the role of SOX2 in pituitary development.
Kyraki S Alatzoglou1, Maria Cristina Arria2, John Crolla3, Juan Pedro Martinez-Barbera4, Martin Roubicek5 & Melul T Dattani1
1Developmental Endocrinology Research Group, UCL Institute of Child Health, London, UK; 2Hospital Privado de Comunidad, Mar del Plata, Argentina; 3National Genetics Laboratory, Salisbury District Hospital, Salisbury, UK; 4Neural Development Unit, UCL Institute of Child Health, London, UK.

Background
SOX2 is a member of the SOX family of transcription factors (SRY-related high mobility group (HMG) box). Heterozygous, de novo, loss-of-function mutations were initially reported in patients with bilateral anophthalmia/microphthalmia, developmental delay, male genital tract abnormalities, oesophageal atresia and sensorineural hearing loss. We have recently reported a number of SOX2 mutations in patients with anterior pituitary hypoplasia and hypogonadotropic hypogonadism. Additional features included the association with hypothalamic hamartoma and variable defects affecting the corpus callosum and mesial temporal structures. We herein report the first patient with a heterozygous SOX2 gene deletion associated with a large hypothalamo-pituitary tumour.

The proband is a female patient of non-consanguineous parents who presented at the age of 18 years with hypopituitarism. She had severe microphalniga, delayed motor milestones and severely impaired language development. At the age of 18 years, she had a height of $-3.12$ SDS, with a normal IGF1 (270.7 ng/ml) and GH concentration. Cortisol profile, thyroid function tests and prolactin were normal. Hypogonadotropic hypogonadism was diagnosed with a flat LH and FSH response to GnRH stimulation. Brain MRI demonstrated a large cystic tumour consistent with a craniopharyngioma, extending into the suprasellar region. However, at the age of 24 years, she progressed to develop spontaneous but incomplete pubertal development, without change on sequential MR imaging over time. Multiple ligation probe analysis (MLPA) revealed that this patient was heterozygous for a complete SOX2 deletion.

Conclusion

Heterozygous SOX2 mutations are associated with hypogonadotropic hypogonadism and anterior pituitary hypoplasia. We now describe loss of function of SOX2 associated with a cystic mass suggestive of a craniopharyngioma. In vitro, SOX2 represses β-catenin-TCF mediated transcription. Since β-catenin over-activation has been associated with craniopharyngiomas, the SOX2 deletion could be associated with β-catenin gain of function. The chance of this patient gives further insight in the role of SOX2 in pituitary development and tumorigenesis.

OC4.4
Pituitary adenomas presenting in children and young people: a single centre experience

Caroline Steele1, Jo Blain2, Mo Duí3, Mohtsen Javadpour1, Ian MacFarlane1 & Christina Diaxou1
1Aintree University Hospitals NHS Foundation Trust, Liverpool, UK; 2Alder Hey Children’s NHS Foundation Trust, Liverpool, UK; 3The Walton Centre for Neurology and Neurosurgery NHS Trust, Liverpool, UK.

Introduction

Pituitary adenomas are uncommon in childhood and adolescence and knowledge of long-term outcomes is sparse. We describe a large cohort of patients, now attending our adult clinic.

Patients and methods

Retrospective review of patients aged $\leq 18$ years at diagnosis of a pituitary adenoma.

Results

There were 24 patients (18 female), mean age at diagnosis 15.6 (range 11–18) years, current age 25.5 (14–47). Of 14 were prolactinomas (10 macroadenomas), 3 non-functioning adenomas (2 macroadenomas), 5 Cushings disease, 1 pituitary cyst and 2Alder Hey Children’s NHS Foundation Trust, Liverpool, UK; 3The Walton Centre for Neurology and Neurosurgery NHS Trust, Liverpool, UK.

OC5.1
Specialist nurse delivered emergency telephone service for children with type 1 diabetes

Hilary Linford, Trudy Tapson, Sanjay Gupta & Vergheese Mathew
Hull Royal Infirmary, Hull, UK.

Aim

To evaluate the paediatric specialist diabetes nurse (PDSN) delivered 24 h emergency telephone contact service for families with children and young people with type 1 diabetes within Hull and East Yorkshire Hospitals NHS Trust.

Methods

A prospective audit of telephone calls received by the 2 PDSNs over a 15-month period between 1 July 2005 and 30 September 2006 for out of hours advice. All the phone calls were logged into a database and details of type of inquiry, time and duration of phone call, advice given and outcome were recorded. A questionnaire about the use of this service was sent out to parents which included a satisfaction rating about their experience of this service.

Results

During the study period total number of children and young people with type 1 diabetes within our service was 220. Of 357 telephone calls were logged. 241 calls (68%) were made between 1700 and 2100 h. 250 calls (70%) lasted ten minutes or less in duration. The topics of discussion were intercurrent illness (32%), hyperglycaemia (19%), hypoglycaemia (11%), insulin dose adjustment (13%) and miscellaneous (23%). There were 20 admissions to the hospital following a telephone contact during the audit period (6% of the total phone calls). Of 95 questionnaires out of the 110 posted out were returned (86%). 75% of the families and young people who filled the questionnaire had used the emergency telephone contact. All the parents and young people contacting the PDSNs were either satisfied or very satisfied with the advice given.

Conclusion

A well established PDSN delivered emergency telephone service can improve patient/parent satisfaction and reduce the number of hospital contacts for families with children and young people with type 1 diabetes.

OC5.2
Survey on facilities in the local schools for children with type 1 diabetes (TID)

Bharathi Pai, Lizbeth Hudson, Simon Holmes & J Chizuo Agwu
Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK.

Introduction

Optimising management of diabetes in school is critical especially with more children being commenced on intensive insulin regimens. Partnership between families, school and caregivers is essential to enhance safety and satisfaction with the educational experience for students.

Methodology

We gathered information on facilities in schools for children with TID from our district hospital by telephonic questionnaire. The questions related to presence or not of a designated area at school for blood sugar monitoring (BSM), insulin administration (IA) and personnel present for supervision of IA.

Results

We have 78 school children with TID aged 5–16 years. 30 children attending 25 primary schools (PS) and 48 attending 23 secondary school (SS). 4 of twice daily injection, 1 on thrice daily regimen, 68 on basal bolus regimen and 5 on CSII. We obtained information on 33 schools and 61 children (23 in PS and 38 in SS). All children had individual care plans.

Conclusion

Facilities for children with diabetes in school is improving however, support for children who cannot self-inject is mainly provided by parents rather than school staff. Work still needs to be done to address local policies, funding for training to optimise this care.

OC5.3
Young persons’ weight management service: a service users’ evaluation

Marc Williams1, Debbie Kendall1, Helena Gleeson2, Rakesh Amin2, Indi Banerjee2, Leena Patel2, Peter Clayton1 & Catherine Hall2
1University of Manchester Medical School, Manchester, UK; 2Royal Manchester Children’s Hospital, Manchester, UK; 3University of Manchester, Manchester, UK.

Background

Obese young people are likely to suffer significant morbidity in adult life. Successful intervention during adolescence may have far-reaching benefits.
Evidence is emerging that patient-responsive clinical services may deliver improved outcomes.

Aims

To assess the perceptions of obese young people about weight and weight-management services.

Method

Anonimised, postal questionnaire survey of 116 obese young people (9-20 years), who had attended a clinic and/or participated in obesity research at our centre. Data was analysed using SPSS.

Results

Forty-four questionnaires were returned (38%). Respondent percentages are reported 98, 75 and 75%, respectively, ‘agreed’ or ‘strongly agreed’ that they were motivated to lose weight, change eating and exercise habits. 91, 68 and 75%, respectively, were ‘likely’ or ‘very likely’ to go walking, attend a gym or participate in exercise with similar young people. Of 51 and 47%, respectively, reported ‘always’ feeling anxious or sad about their weight. Of 53 and 32%, respectively, ‘agreed’ or ‘strongly agreed’ that their weight affected their sports activities and social life. Perceived causes for obesity were eating habits (22%), lack of exercise (20%), family history (14%) and stress (11%). 71 and 82%, respectively, ‘agreed’ or ‘strongly agreed’ that their obesity affects their current health and will affect their adult health.

Motivation to lose weight was correlated with impact on friendships and social activities (r=0.4, 0.3, respectively, P<0.05) and with impact on sports activities, sadness and anxiety about weight (r=0.5, 0.4, 0.6, respectively, P<0.01). There was no correlation between motivation and perceived impact upon health.

Young people would like to receive information from a personal trainer (59%), dietician (54%) doctor (43%), group discussion (40%). The most popular information delivery formats were leaflets (42%) and website (40%).

Conclusions

An adolescent weight-management service incorporating personal mentors, peer support and website may harness motivation more successfully than the conventional medical model.

OC5.4

Diabetes mellitus and hyperinsulinaemic hypoglycaemia (HH) due to dominant ABC6/KCNJ11 mutations

Ritika R Kapoor1, Sarah E Flanagan2, John McKiernan5, Julian P Shield4, Andrew Tinker1, Sian Ellard3 & Khalid Hussain3

1UCL Institute of Child Health and Great Ormond Street Hospital, London, UK; 2Peninsula Medical School, Exeter, UK; 3Bayne Institute, UCL, London, UK; 4Bristol Royal Hospital for Children, Bristol, UK; 5Cork University Hospital, Cork, Ireland.

Background

The pancreatic β-cell K<sub>ATP</sub> channel plays a key role in glucose stimulated insulin secretion and is encoded by the genes ABC6 and KCNJ11. Recessive mutations in ABC6/KCNJ11 cause severe medically unresponsive HH. Recently, dominant mutations in these genes have been described that cause mild, medically responsive HH. Controversy exists on whether these dominant ABC6/KCNJ11 mutations predispose to diabetes mellitus in adulthood or not.

Aim

To characterise the phenotype of the dominantly inherited ABC6/KCNJ11 mutations causing HH and study the prevalence of diabetes mellitus in the adult mutation carriers.

Methods

We studied the phenotype of ten families (fourteen patients with HH) with nine different dominant ABC6/KCNJ11 mutations. Functional consequences of six novel mutations were examined by reconstituting the K<sub>ATP</sub> channel in HEK293 cells and evaluating the effect of drugs (diazoxide, glibenclamide) and metabolic poisoning on the channels using Rh<sup>6G</sup> flux assay.

Results

HH was diagnosed at a median age of 1 year. The median birth weight was 4303 g at a median gestational age of 40 weeks. 12/14 probands responded to diazoxide, while the remaining two had transient HH that resolved spontaneously. Of the sixteen adult mutation carriers identified, only five have persisting or past symptoms of hypoglycaemia. Five adult mutation carriers have developed young onset diabetes mellitus, at a median age of 38 years whilst three others have developed gestational diabetes. When activated, wild-type K<sub>ATP</sub> channels showed significant Rh<sup>6G</sup> efflux whereas mutant K<sub>ATP</sub> channels showed no Rh<sup>6G</sup> efflux thus confirming the pathogenicity of the mutations.

Conclusions

Dominant mutations in ABC6/KCNJ11 cause a varying phenotype ranging from asymptomatic macrosomia to medically responsive HH in childhood. In adults, it may be an important cause of dominantly inherited early onset diabetes mellitus.
Rising incidence of type 1 diabetes mellitus in children and adolescents under 15 years in the Republic of Ireland in 2008

1Department of Paediatrics, University of Dublin, Trinity College, Dublin, Ireland; 2The National Children’s Hospital, Dublin, Ireland.

Objectives

To determine the incidence of type 1 diabetes in children and adolescents <15 years in ROI in 2008 and to establish a National Diabetes Register. To confirm the status of ROI as an area of high disease incidence, and ascertain if the incidence has increased. To act as the base year for the National Register.

Methods

Prospective national reporting of incident cases of type 1 diabetes <15 years as a primary diagnosis by Paediatricians and Paediatric Endocrinologists nationally was undertaken from January 2008. Following informed consent of children and parents further information was obtained using a standardised dataset. Completeness of ascertainment was assessed using the capture-recapture methodology. Intercensal estimates were used for calculation of (IR).

Results

Preliminary figures for 2008 indicate that the (IR) of T1DM within this population has increased an average of 6% per annum since 1997. This increase is across all years in ROI in 2008 and to establish a National Diabetes Register. To confirm the status of ROI as an area of high disease incidence, and ascertain if the incidence has increased. To act as the base year for the National Register.

Conclusion

The majority of respondents undertook microalbuminuria screening but only 30% follow nice guidance. There is wide variation in screening practice on method, type of specimen, repeating test on abnormal results and also seeking advice from Nephrologists. Detailed studies are required to ensure a National consensus on microalbuminuria screening, methodology and ongoing management for the paediatric diabetic patients.

Audit of paediatric diabetic eye screening

Navpreet Dhillon, Adele Farnsworth, Lesley Porter, Nick Shaw, Jeremy Kirk, Wolfgang Hoegler & Tim Barrett
Birmingham Children’s Hospital NHS Trust, Birmingham, UK.

Introduction

NICE recommends annual screening for diabetic retinopathy in children with type 1 diabetes aged over 12 years and/or with duration of diabetes over 5 years. This audit aimed to evaluate patient attendance for retinopathy screening, to identify the prevalence of retinopathy and maculopathy and to ascertain characteristics of patients.

Methods

This was a retrospective audit of patients attending for eye screening from January 2008 to April 2009, in a large paediatric diabetic clinic (n = 329). Data from the Twinkle database was used to identify patient attendance, socio-demographic information, HbAlc, duration of diabetes and microalbuminuria. Patients with retinopathy were compared to those without retinopathy.

Results

Of 145 /189 (89%) eligible patients attended screening, median (range) for age 13.5 (7.1–18.2) years, duration of diabetes 6.0 (0.5–13.8) years, and HbAlc 8.9 (5.8–14.%) Of 29/145 (20%) patients had stage one retinopathy (one or more haemorrhage and/or microaneurysms). Patients with retinopathy had a significantly higher HbAlc (9.9 vs 8.7%), longer duration of diabetes (8.1 vs 5.5 years) and higher microalbuminuria (10.1 vs 7.1 mg/mmol), (all P<0.05). There was no significant relationship of retinopathy to age.

Conclusion

There are significant differences in metabolic control in children with or without early retinopathy. Diabetic retinopathy is a common finding even within a paediatric clinic. Feedback of results to patients can be used as a motivational factor to improve glycaemic control. The significant rate of microvascular complications in this paediatric cohort stresses the urgent need to implement alternative strategies to improve glycaemic control with the goal to reduce long-term morbidity and mortality.
Poster Presentations
P1 Lipatrophy with insulin analogues in four children with type 1 diabetes
Amir Babiker, Nandu Thulange & Vipan Datta
Norfolk and Norwich University Hospital, Norwich, UK.

Introduction
Lipoatrophy (LA) was common before the advent of recombinant human insulin. More recently, insulin analogues have been widely introduced into paediatric practice. In the literature, LA has only been reported so far with insulin Lispro (Lilly, USA) (n = 4 adult patients and 3 children) and insulin Glargine (Sanofi-Aventis, France) (n = 1 adult patient). To our knowledge, this is the first report of LA with insulin Aspart (NovoRapid), biphasic insulin Aspart (Novomix 30) and insulin Detemir (Levemir) (Novo Nordisk, Denmark).

Case reports
Four children with type 1 diabetes were commenced on Novomix 30 (n = 2) or Novorapid/Levemir injections (n = 2). They developed LA at the injection sites after 2–3 years. One patient developed LA at the Novorapid site and the other at the Levemir site. The mean HbA1C ranged from 8.0–9.9%. Insulin antibody levels were high in 3/4. In 2/4, LA resolved by changing the injection site. It recurred at the new sites in 2 but resolved after changing the insulin preparation (Novomix 30 to Humalog mix25 and Levemir to insulin Glargine). HbA1C had steadily dropped to 7.4% along with the resolution of LA in one patient. LA resolved over a period of 1–2 years in all patients.

Discussion
The pathogenesis of LA is poorly understood. The suggested mechanisms are: repeated mechanical trauma from the injections, cryotrauma from refrigerated insulin or immune mediated. In 2/4, LA resolved after changing the injection site suggesting that local factors could be the cause of LA. It is our practice to examine the injection sites on each visit and this facilitated early detection of LA.

Conclusion
LA is a rare complication of treatment with insulin analogues. It may be sufficient to change the injection site to manage LA. If that is not effective, changing to an alternative analogue was successful in our experience.

P2 Scopes and Barriers for management of childhood obesity
Wayne Thornton1, Trupti DhoraJiwala1, Bratati Bose-Haider1 & Radhika Putha2
1Fairfield Hospital, Pennine Acute Trust, Manchester, UK; 2Royal Bolton Hospital, Manchester, UK; 3Royal Manchester Children’s Hospital, Central Manchester Foundation Trust, Manchester, UK.

Objective
The aim of our study is to evaluate the current practice, resources available and barriers to primary and secondary professionals providing care for children who are overweight or obese.

Methods
A questionnaire was sent to primary and secondary care providers including General Practitioners (GP), Practice Nurses (PN), Health visitors, school nurses and community nurses in a selected Primary Care Trust and hospital doctors in Pennine Acute Trust Hospitals.

Results
Ninety-Seven (40%) professionals replied. Height and weight was routinely measured by 96% of Paediatricians verses only 42.5% of Primary Care workers. Body Mass Index was calculated by 65% and 27% respectively. More than half the professionals (82%) followed-up patients solely within their own setting. Satisfaction scoring (out of 5) relating to ability to provide help and support to obese children were generally low especially with respect to training (1.88), self expertise (2.5), exercise programmes (1.88), family acceptance (2.22) and engagement (2.4). 15% and 3% of respondents referred to Dietitian and Psychology services respectively.

Only 70% of Senior Paediatricians and GPs were aware of NICE guideline. With respect to service availability 14% respondents were not aware of the local services, 32% had a dietitian service, 5% psychology access and only 10% had local exercise programme availability.

Conclusions
In spite of extensive campaigning by the government and the NICE guidelines, this study identified shortfalls and dissatisfaction in training, assessment, management and services available to help children with obesity. Improved training, assessment, service provision and collaborative working are needed between healthcare and non-healthcare services to help tackle Childhood obesity, an increasing epidemic with high morbidity and mortality.

P3 Use of clinic proforma as a tool has been shown to improve diabetic reviews
James Law & Dougie Thomas
United Lincolnshire Hospitals NHS Trust, Lincoln, Lincoln, UK.

Abstract withdrawn.

P4 Use of clinic proforma as a tool has been shown to improve diabetic reviews
James Law & Dougie Thomas
United Lincolnshire Hospitals NHS Trust, Lincoln, Lincoln, UK.

Acute and long-term complications attributable to diabetes are regrettably still common. To monitor for the development of such complications NICE recommend regular measurement of certain criteria to enable early intervention. A previous audit performed in our hospital looked at the adherence of paediatric diabetic reviews to NICE guidelines. As a consequence of this audit a detailed pro-forma to be used at all paediatric diabetic reviews was introduced.

This poster presents the results of a closed loop audit that has resulted in our service offering improved clinical care. Patients were selected randomly from a local database of paediatric diabetic patients and the notes reviewed retrospectively for evidence of meeting the NICE criteria.

It was found that thyroid and coeliac screening improved to 100% from an initial 86% and 87.5% respectively. Improvement was also noted in the documentation of foot reviews (up 29% from 0%), growth charting at every visit (up 40% to 50%) and blood pressure monitoring (up 50% to 75%).

The pro-forma allows individual targeted changes to be made or added with ease if areas for improvement are identified during the audit process. In this last audit it was identified that dental reviews continued to be poorly documented and therefore a designated space to document these has now been included; this will hopefully trigger a similar level of improvement as shown in other areas over the last year.

Other changes included a tick box for “growth chart plotted” and a line to state definitively whether microalbuminuria was present on urine dip (rather than just whether urine was checked).

In conclusion the introduction and use of a pro-forma can facilitate an improvement in the care of paediatric diabetic patients working toward standardised national targets. The resultant pro-forma has the potential to be used at a national level.

P5 Hyponatremia in Type 1 Diabetes: Pseudohyponatremia or presentation of autoimmune Adrenal Dysfunction
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Autoimmune destruction of adrenal gland is rare in the paediatric population and can present in type 1 diabetic mellitus (TIDM). Patients with TIDM are routinely screened for Autoimmune hypothyroidism and coeliac disease. We would like to present an unusual case of hyponatremia in patient with TIDM due to simultaneous developments of both glucocorticoid and mineralocorticoid deficiency.

Fourteen-year-old Type 1 Diabetic male presented with incidental persistent hyponatremia. He was clinically well and had poor diabetes control with few hypoglycaemic episodes. There was strong family history of autoimmune thyroid disorder. He had significant urinary loses of Sodium. He had a Suboptimal incremental rise in cortisol levels on short synacthen test. His Thyroid function test was normal. He had a markedly raised Adreno-corticotrophin hormone level (3172 pmol/L, Normal Range: 10-60)and also had positive anti adrenal antibodies. CT Scan of adrenal gland was normal. Oral Hydrocortisone only made minimal difference to plasma sodium levels and addition of fludrocortisone (50 Micrograms) normalised his plasma sodium.

There have been recent genetic studies identifying a gene which confers risk for auto-immune Addison’s disease and Type 1 Diabetes. The occurrence of multiple organ specific autoimmune disorders in the same patient have been well documented.It is therefore important to have a low threshold to investigate diabetic patients with hyponatremia and not to dismiss this an pseudohyponatremia.
P6
Growth, Final Height and Endocrine Sequelae post Bone Marrow Transplantation in a UK population of patients with Hurler Syndrome (MPS IH)
Chris Gardner, Nicola Robinson, Jean Mercier, Tim Meadows, Andrew Will, Robert Wynn, Ed Wraith & Peter Clayton
Royal Manchester Children’s Hospital, Manchester, UK.

Introduction
Hurler Syndrome (MPS IH) is an inborn error of metabolism which was previously fatal in childhood. Bone marrow transplantation (BMT) has transformed the prognosis for these children. First BMTs are preprovided with chemotherapy, and we have therefore put in place surveillance for endocrine sequelae. We present for the first time data on final adult height in children with MPS IH post BMT, as well as the endocrine complications seen in this cohort.

Methodology
Retrospective case note study and a prospective programme of growth and endocrine assessment.

Results
Twenty-two patients were eligible for inclusion, mean age at last assessment 12.2 yrs. Age at BMT 1.3 (s.d. 0.6) yrs. Conditioning for first BMT included busulphan and cyclophosphamide with 5 out of 10 second transplants receiving total body irradiation. Height SDS showed a progressive fall over time. Final height (FH) was attained in 7 patients: Male FH SDS -4.8 (s.d. 0.9). Female FH SDS -3.8 (s.d. 1.3). Assessment of the GH-IGF axis was undertaken in 13: 9 had evidence of GH resistance, I had GH deficiency. Adrenal and thyroid function was normal in all. 11 patients were peri or post pubertal. 2 females had pubertal failure requiring intervention, with raised gonadotrophins. All male patients had spontaneous, normally timed complete puberty; however 2 post pubertal patients have reduced testicular volumes implying germinal cell damage. Most importantly insulin-glucose status has been monitored with OGT testing. 5 out of 13 tested had an abnormality of glucose metabolism. Conclusion
Growth is impaired in this cohort primarily related to progressive skeletal dysplasia, but also associated with GH resistance. Full pubertal development may be compromised and abnormalities of glucose metabolism are common. We recommend endocrine surveillance for these patients.

P7
Increased Hypothalamic-pituitary-adrenal axis (HPAA) activity after childhood bone marrow transplantation (BMT) with total body irradiation (TBI) results in chronic hypercortisolidaemia associated with obesity
Nikki Davis, Ruth Elson, Claire Stewart, Andrew Moss, Wolf Wolthersdorf, Jacqueline Cornish, Michael Stevens & Elizabeth Crowne
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Introduction
Data on the impact of TBI on the HPAA are limited. This study investigates the HPAA in BMT-survivors and non-BMT controls using overnight serum cortisol profiles and midnight/9am ACTH levels.

Subjects & Methods
Subjects (N=35)
N=14, child (7), adult (7) controls, N=21 child (7), adult (14) BMT-survivors (TBI dose 12.0-14.4Gy). None had had treatment with corticosteroids in the last year.

Method
Subjects rested for 3 h after venous cannulation, then blood samples were taken every 20 min between 9pm-9am. Subjects slept at their usual time and waking time was recorded. Body composition was measured by DEXA. Cortisol profiles were analysed using Cluster and Autodeconvolution software.

Results
Median (range) age at and time since BMT were 5.8 (0.2–16.0) yrs and 3.5 (1.2–20.4) yrs respectively. Peak cortisol (r:0.003) and females versus males (83.0 vs 40.0 nmol/l/min, P<0.05). Covariate analysis identified the main determinant of trough levels (P<0.05). There was no difference in time of awakening, CAR, AUC, time of peak, or ACTH levels between BMT-survivors and controls. Time from BMT correlated with trough cortisol levels (r=0.478, P=0.03).

Discussion
Therefore age, gender, adiposity and BMT all influenced HPAA activity. Gender and adiposity were pre-eminent factors for peak cortisol whereas BMT influenced raised trough levels. This may relate to TBI or to chronic stress altering HPAA feedback regulation.

P8
The Current UK Experience of Recombinant IGF1 For Cases of Severe Primary IGF Deficiency
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Background
Severe primary IGF1 deficiency (SPIGFD) is defined in children as a height less than –3sd, low IGF1 levels with normal growth hormone levels. Recombinant IGF1 (rhIGF1, Mecasermin) given twice daily as a subcutaneous injection is the only therapy available to improve the height potential in this group of children. However it may have important side effects including hypoglycaemia, growth of lymphoid tissue and injection site lipo hypertrophy.

Aim
To accumulate the UK experience in implementing and monitoring therapy with rhIGF1 and to report short term data on response to treatment. The data from 5 centres (representing 6 of the 7 children on rhIGF1 for SPIGFD in the UK) was collected by a standardised questionnaire.

Results
All 6 children were of South Asian origin. The duration of treatment has ranged from 0 to 2 years (median 0.2 years). The median age of starting treatment was 10.6 years (range 6,11.7 years). The median dose limit of 0.12 mg/kg bd. Treatment was commenced in hospital in 4 children and blood sugars were mainly monitored at initiation and dose adjustments. 1 child had a reported hypoglycaemia one year into treatment. Injection site hypertrophy or pain was the most common reported adverse event (4 children).

Conclusion
Recombinant IGF1 therapy appears to be well tolerated in the short term with most adverse events involving the injection site. There are some early improvements in the height sds and scope for further dose increases still remain. Longer term monitoring remains essential to provide a safety profile and to assess clinical benefits.

P9
Improvement in growth of children with crohn’s disease following anti-TNFa: therapy can be independent of pubertal progress and glucocorticoid reduction
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Introduction
Treatment with anti-TNFa therapy such as infliximab may improve growth in children with CD but the extent of improvement in growth and its relationship to pubertal progress and changes in glucocorticoid therapy are unclear.

Aim
A retrospective study of growth, puberty and disease activity over the 6 months prior (T-6) to starting infliximab, at baseline (T0) and for the following 6 months (T+6) in CD. Results are expressed as median(10th, 90th).

Subjects & Methods
The growth and treatment details of 28 children (M:17) who were started on infliximab at a median (10th, 90th) age of 13.1y (10.15.7) were reviewed. In 20 children, pubertal data were also available at all time points. Data on disease...
markers (CRP, ESR, and Albumin), total Alkaline Phosphatase (ALP) and a physician global assessment were also collected. Results: Out of 28 cases, 21 (75%) demonstrated a clinical response to infliximab treatment. Overall, height velocity (HV) increased from 3.6 cm/year (0.4, 7.8) at T0 to 5.5 cm/year (2.1, 9.2) at T+6 (P = 0.003). In infliximab responders, HV increased from 1.9 cm/year (0.3, 7.1) to 6 cm/year (2.3, 9.1) (P = 0.003) and in the non-responders, HV remained static at 4.3 cm/year (2.5, 8.6) at T0 and 3.6 cm/year (2.0, 11.3) (NS) at T+6. HV also increased in the subgroup of 13 children who had remained prepubertal from 4.5 cm/year (0.4, 8) to 5.5 cm/year (3.3, 8.4) (P = 0.05). In the subgroup of 11 children who had a reduction (n, 2) or cessation in GC (n, 9), HV increased from 1.8 cm/year (0.3, 8.3) at T0 to 5.6 cm/year (2.9, 9.2) at T+6 (NS), whereas those children who did not receive GC over the 12 months had an increase from 3.7 cm/year (0.6, 6.5) to 6.4 cm/year (2.9, 9.0) (P < 0.05). HV at T0 and T+6 showed a significant association with the average ALP over the prior 6 months (r, 0.39, P < 0.05). HV didn't show any association with individual markers of disease activity. Conclusion: Clinical response to infliximab therapy is associated with an improvement in average ALP over the prior 6 months (P = 0.03 years (0.71). The mean percentage difference is 0.02% (6.2%). Overall 5 bone ages had a difference of greater than 1 year between the manual and automated scoring systems. Conclusion: An automated bone age scoring system may be a reliable and reproducible method to score bone ages utilising the TW3 system.

P11
Evaluation of an automated bone age scoring program against a single observer, using the TW3 scoring system
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Background: Bone age assessment is used in the management and monitoring of treatment effects in growth disorders. This may be associated with a considerable variability between reporters. This subjectivity has raised questions about acceptable levels of error in our current practice and has led us to search for other tools for assessing bone ages.
Method: A single observer was trained in reporting bone ages using Tanner Whitehouse 3 atlas and these results were compared to an automated bone age scoring system (BoneExpert).
Results: Currently this study includes 42 patients (21 male) with an age range of 7.1 to 16.4 years, who have had bone age assessments undertaken for clinical indications. The mean (±s.d.) age of the group was 11.6 years (3.7). The mean difference between the single observer and BoneExpert was −0.03 years (0.71). The mean percentage difference is 0.02% (6.2%). Overall 5 bone ages had a difference of greater than 1 year between the manual and automated scoring systems. Conclusion: An automated bone age scoring system may be a reliable and reproducible method to score bone ages utilising the TW3 system.

P12
The IGF system during acute hypoxia in children
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The hypoxia, associated to intra-uterine growth restriction, is related to high concentrations of IGFBP1 and unchanged concentrations of IGF1 in animals. Nevertheless, during threatening life events, low IGF concentrations and high IGFBP1 concentrations were reported. Furthermore, severe hypoxia increased the IGF1R expression of the neuronal growth cones in the ovine fetal brain. No information is available regarding the regulation of the IGF system by the acute hypoxia in humans. The aim of this study was to evaluate the effect of acute hypoxia on the IGF system in children. Twenty seven previously healthy children (14 boys and 13 girls) aged 15 days to 9.5 years were studied in 2 different situations: during acute hypoxia due to acute respiratory distress and after full recovering. In these two opportunities oxygen saturation was measured using pulse-oximeter and blood samples were collected for serum IGF1 and IGFBP1 determination and also for analyzing of IGFIR gene expression in peripheral lymphocytes. IGF1 and IGFBP1 were determined by specific ELSA. Lymphocytes were first isolated from other blood cells using Fycoll-Hypaque and then RNA was extracted. The levels of mRNA expression of the IGFIR gene were analyzed by quantitative real-time PCR. Data were pared compared by Wilcoxon non-parametric test. Oxygen saturation was 87.8 ± 3.5% in the fist evaluation (Hypoxy: state or HS) and 96.4 ± 1.2% after recovering (non-HS) (P < 0.0001). IGF1 levels were lower during HS compared to non-HS (median 12 vs. 56 ng/ml) (P < 0.0001) whilst IGFBP1 were higher during HS than in non-HS (median: 113 vs. 60 ng/ml) (P = 0.004). The expression of IGFIR mRNA, expressed as 2^-△△CT, were higher during HS than after it (1.28 vs 0.93) (P = 0.03). In conclusion, the above results showed during acute hypoxia a combination of alterations usually associated with decrease of IGF action. The higher expression of IGFIR mRNA may reflect an up regulation of the transcriptional process.

P13
Reduced growth hormone secretion in children and young adults following total body irradiation (TBI) for bone marrow transplantation (BMT) in childhood
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Introduction: Growth hormone deficiency (GHD) after cranial irradiation (CRI) is time, dose and fraction dependent. TBI (12-14 Gy) involves low dose CRI, and skeletal

irradiation causing further adverse growth effects. We present baseline data from a prospective study of GH treatment.

Subjects

We studied 13 BMT survivors (all had TBI, 3 also had CRI <18Gy), and 12 non-BMT subjects investigated for GHD. Both groups contained young GH-naive children and young adults having end of GH treatment rests and were well-matched for age, gender and pubertal status.

Methods

GH treatment was stopped >3 months before study if applicable 12 hr overnight GH profiles (GHP) were performed (20 min sampling 9pm–9am) and analysed by Cluster and Autodeconvolution software. Subjects slept at their usual time. 22 subjects also had an insulin tolerance test (ITT). Body composition was measured by DEXA.

Results

Median(range) age at and time since BMT were 5.8 (0.2–16.0) yrs and 3.5 (1.2–19.3) yrs respectively. Compared to controls, BMT survivors had increased % body fat (35.5(10.3) vs 25.5(12.8), P<0.05) and reduced peak GH levels in ITT (4.3(3.0) vs 7.2(5.0) mU/l, P<0.05) and their GHPs demonstrated reduced peak (3.5(1.5) vs 6.3(2.2) mU/l, P<0.05) and area under the curve (AUC) (7.0(3.4) vs 15.9(11.4) mU/l, P<0.05). Peak and AUC GH correlated with % body fat (r=−0.45, P<0.05 and r = −0.55, P<0.005). Covariate analysis showed that BMT had an additional effect on peak GH and AUC after adjusting for body fat, and that CBI had an additional effect to TBI. There was no gender effect. 7/8 adult BMT survivors were GH insufficient on retesting.

Discussion

These data indicate a significant reduction in GH secretion after BMT partly explained by increased adiposity. Additional TBI effects relate to hypothalamic-pituitary exposure and potentially altered feedback following skeletal irradiation. These data indicate a significant reduction in GH secretion after BMT partly explained by increased adiposity. Additional TBI effects relate to hypothalamic-pituitary exposure and potentially altered feedback following skeletal irradiation.

GHD was more pronounced in adult TBI survivors.

The presence of growth restriction with a proven reduction in growth hormone production in response to the glucagon stimulation test (peak 0.025 mg/kg/day) was introduced. After 4 months serum IGF1 was 34.2 nmol/l and IGFBP−3 35.8 mg/l (NR 0.8–3.4). GH dose was increased after 4 months to 0.035 mg/kg/day and after 8 months to 0.045 mg/kg/day. There has been no change in cardiac appearance or function and no reported adverse effects of GH therapy. 13 months after starting GH the patient has gained 0.6SD in height.

Conclusion

The growth response to GH treatment observed in this patient is similar to that reported in children with NS and less than might be expected given the biochemical features of GH deficiency. The efficacy of GH in this syndrome will only be elucidated in collaborative studies of patients with CFC.

P14

Growth restriction with insufficient growth hormone production in a child with variant Miller-Dieker syndrome

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Introduction

We describe a girl presenting with abnormal facial features, growth restriction with insufficient growth hormone production and learning difficulties. She has an unbalanced translocation between 17p13.3 and 10q26.13 causing a microdeletion at 17p13.3 and trisomy of 10q26.3.

Case report

At presentation at 3½ years of age, her height was 4 cm below the 0.4th centile with a weight of 10.1 kg (0.4th centile). Height velocity was on 0.6th centile. Investigations showed a bone age two years behind her chronological age, a poor increase in growth hormone production in response to the glucagon stimulation test (peak value 10.1 mU/l) and also a low Insulin-like growth factor 1 (IGF1). In the first year of treatment with growth hormone she grew 8 cm. Thereafter, her rate of growth steadied at 4 cm/year.

Chromosome 17p13.3 deletions are most commonly seen in Miller-Dieker syndrome associated with lissencephaly. This patient has facial features in keeping with Miller-Dieker syndrome but no lissencephaly. This may be because the 17p13.3 breakpoint is unusually telomeric sparing the LIS1 gene thought to be important in neuronal migration.

Conclusion

Growth restriction has been described in Miller-Dieker syndrome although there are no case reports describing growth hormone levels or supplementation in these patients. The presence of growth restriction with a proven reduction in growth hormone production in this case raises the question of whether there may be unidentified growth hormone defects in other patients with Miller-Dieker syndrome and/or 10q trisomy. Further research in this area has the potential to contribute towards future management of these patients.

P15

Growth hormone therapy in the treatment of short stature in cardio-facio-cutaneous syndrome

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Background

The term “neuro-cardio-facial-cutaneous (NCFc) syndrome” describes a group of phenotypically overlapping conditions that result from germline mutations in genes of the RAS-MAPKinase pathway. This pathway plays a role in growth factor signalling and short stature is a consistent feature of NCFc syndromes. This diagnostic group includes Noonan syndrome (NS) and cardio-facio-cutaneous (CFC) syndrome. Growth hormone (GH) has been used with good effect in NS. To our knowledge the effect of GH in CFC has yet to be reported.

Case report

A female infant was born at term, birth weight SDS = −0.34, following a pregnancy complicated by polyhydramnios. She was dysmorphic (posteriorly rotated low set ears, high forehead, depressed nasal bridge, antimongoloid slant of palpebral fissures). Cardiac assessment identified pulmonary artery branch stenosis and minor atrioseptal defect. A clinical diagnosis of NS was made. At 9.9yrs of age her height SDS was −3.15, bone age 9.2yrs, serum IGF1 12 nmol/l (normal range (NR) 15–101) and peak GH response to glucagon was 10.4 mU/l. At this time the phenotype was more consistent with CFC than NS. The diagnosis was confirmed by the identification of a BRAF mutation (c.770A>G). Treatment with GH (0.025 mg/kg/day) was introduced. After 4 months serum IGF1 was 34.2 nmol/l and IGFBP−3 35.8 mg/l (NR 0.8–3.4). GH dose was increased after 4 months to 0.035 mg/kg/day and after 8 months to 0.045 mg/kg/day. There has been no change in cardiac appearance or function and no reported adverse effects of GH therapy. 13 months after starting GH the patient has gained 0.6SD in height.

Conclusion

The growth response to GH treatment observed in this patient is similar to that reported in children with NS and less than might be expected given the biochemical features of GH deficiency. The efficacy of GH in this syndrome will only be elucidated in collaborative studies of patients with CFC.

P16

Two novel missense mutations in MRAP (p.Y59D and p.V26A) that lead to late onset Familial Glucocorticoid Deficiency (FGD) type 2

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Background

FGD is an autosomal recessive disorder causing glucocorticoid deficiency. Mutations in the ACTH receptor (MC2R) or the MC2R accessory protein (MRAP) cause FGD types 1 & 2 respectively. All the reported MRAP mutations result in abolition of a functional protein. This is reflected clinically as type 2 patients present early, no patient described to date has presented later than 1yrs. In contrast FGD type 1 mutations are usually missense and patients have a median age of onset of 2yrs.

Aim

To investigate the cause of disease in two families with late onset FGD. In family 1 the proband was diagnosed aged 5yrs. Family review revealed 2 older siblings with undiagnosed FGD. 1 sibling is well; the second has cerebral palsy secondary to hypoglycaemic seizures. In family 2 the proband was diagnosed aged 18yrs with symptoms of fatigue, weight loss and depression.

Methods and Results

Coding exons of MC2R and MRAP were sequenced. ACTH dose response curves were generated for MC2R when transfected with wildtype (WT) or mutant MRAP constructs. MC2R trafficking with mutant Y59D MRAP was investigated using an immunofluorescence assay. MRAP gene analysis identified 2 novel homozygous missense mutations, c.175T>G (p.Y59D) in family 1 and c.76T>C (p.V26A) in family 2. Both mutants caused a right shift in the dose response curve and showed reduced cAMP generation in comparison to WT, this reached significance for the Y59D mutant. Immunofluorescence studies showed normal trafficking of MC2R to the cell surface when transfected with Y59D mutant MRAP indicating the defect is in signalling rather than trafficking.

Conclusion

These results describing late onset milder disease resulting from missense MRAP mutations indicate that disease severity in FGD patients reflects the functional significance of the underlying mutations.

P17

Severe glucocorticoid deficiency in 17-hydroxylase deficiency – novel mutation in the CYP17A1 gene

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CYP17A1 is a key enzyme of human steroidogenesis, which is unique in that it catalyses two reactions, 17-hydroxylase activity and 17,20 lyase activity.
17-hydroxylase deficiency, a variant of congenital adrenal hyperplasia, results in hypertension and mild glucocorticoid deficiency. Loss of 17,20 lyase activity results in sex steroid deficiency, presenting with undervirilisation in boys (46, XY DSD) and lack of pubertal development in girls. Here we present the cases of two sisters with 17-hydroxylase deficiency presenting with severe glucocorticoid deficiency.

**Case 1**
A 4-week-old infant (46, XX) was assessed for prolonged jaundice and failure to thrive. A random serum cortisol was < 2.5 nmol/l. A Synacthen test (with peak cortisol < 25 nmol/l), normal 17-OH and raised ACTH confirmed severe primary adrenal insufficiency. Gas chromatography/mass spectrometry (GC/MS) analysis of the urinary steroid pattern revealed predominant excretion of pregnenolone metabolites suggestive of combined and complete absence of CYP17A1 activities. Genetic test confirmed novel homozygous mutation of the CYP17A1 gene yielding an early truncation of the CYP17A1 protein.

**Case 2**
A 6-week-old infant (46XX) and younger sibling of case 1 also presented with failure to thrive. Investigations confirmed primary adrenal insufficiency and genetic tests confirmed identical mutation as that of case 1. Their mother was identified to be a heterozygous carrier of the mutation.

Both girls are currently on Hydrocortisone supplements and doing well.

**Conclusion**
In 17-hydroxylase deficiency, relative increase of corticosterone with its glucocorticoid effect compensates for the lack of cortisol and hence rarely manifests with overt glucocorticoid deficiency. However in these two cases, very early truncation of the CYP17A1 protein explains the near total loss of activity with residual corticosterone secretion not sufficient to compensate for the loss of glucocorticoid synthesis in the early neonatal period. These cases further highlight the value of urinary steroid secretion analysis by the GC/MS in the differential diagnosis of adrenal insufficiency.
Adrenal hypoplasia congenita presenting as sudden death in the newborn: how should we manage subsequent siblings?  
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Introduction  
Adrenal hypoplasia congenita (AHC) is often difficult to differentiate from congenital adrenal hyperplasia in the early stages of life. Both can present with severe salt-losing crises, and in some cases, even sudden, unexpected death. In particular there tends to be no abnormalities of the genitalia in AHC thus delaying a possible diagnosis. In the autosomal recessive form of AHC, the absence of a recognised single gene mutation can cause significant difficulties in genetic counselling and in the immediate and longterm management of subsequent siblings.

Case Series  
We present three cases where the index child died suddenly, despite resuscitation, at 62, 12 and 19 h of age respectively. The diagnosis of AHC was made on post-mortem examination, based on adrenal size and histopathological appearance. From our experiences, we discuss potential difficulties that may be encountered, and we propose a management plan for dealing with future siblings. This plan includes re-evaluating a diagnosis when presented with unusual features is highlighted.

Conclusions  
Children with AHC can die suddenly and unexpectedly soon after birth. It is important that we devise a plan for further siblings of all children with AHC to ensure early detection and treatment.

P22  
Nepalese StAR  
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Introduction and Case report  
Congenital adrenal hyperplasia (CAH) is a heterogeneous group of conditions resulting from inborn errors of steroidogenesis, of which over 95% are due to 21-hydroxylase deficiency. We present a 15-year-old Nepalese female, who was referred to the endocrine clinic for management of CAH. This diagnosis had been at 11 months of age, whilst resident in Hong Kong, when she presented acutely with vomiting and seizures. She had since been treated with fludrocortisone and hydrocortisone. Despite admitting variable compliance with hydrocortisone, she reported seizures. She had since been treated with fludrocortisone and hydrocortisone.

The clinical importance of this case is two-fold. Firstly, the importance of re-evaluating a diagnosis when presented with unusual features is highlighted. StAR controls transfer of cholesterol across the mitochondrial membrane, and impairment results in severely compromised adrenal and testicular steroidogenesis. However, StAR-independent ovarian steroidogenesis can result in spontaneous puberty in affected 46,XX subjects. Premature ovarian failure and anovulatory cycles due to ovarian cholesterol deposition are well recognised, however successful pregnancy with fertility support has been recently reported. This emphasises the importance of establishing this diagnosis to allow appropriate fertility counselling.

Secondly, the G221D mutation of StAR has not previously been reported. Functional studies are underway, which could provide additional insight into the molecular mechanisms of LCAH.

P23  
The Androgen Status Of Young Women With Premature Ovarian Failure Depends On The Female Sex Steroid Replacement Regimen  
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Aims  
To compare the effect of a standard Sex Steroid Regimen (sSSR) with a physiological SSR (pSSR) on androgen status in young women with premature ovarian failure (POF).

Patient Population: Seven women with POF were evaluated for the study. The median age was 28 years (range 21–36) and the median duration of ovarian failure was 14 years (range 4–25).

Methods  
An open label randomised, controlled, crossover study over 28 months comparing the effect of sSSR and pSSR on androgen status. Treatment consisted of a 12 month period of 4-week cycles of pSSR (transdermal estradiol 100 mcg daily for week 1 and 150 mcg for weeks 2–4 and either 200 mg progesterone vaginal pessaries or progesterone 10 mg orally twice daily in weeks 3–4), or sSSR (Loestrin 30, Galen Ltd; ethinylestradiol 30 mcg and norethisterone 1.5 mg daily for weeks 1–3, followed by 7 pill-free days), separated by run-in and wash-out periods. Serum Testosterone (T), Androstenedione (A4), SHBG were measured and the Free Androgen Index (FAI= [serum T/SHBG] × 100) calculated at months 0/6/12.

Results  
At baseline in the sSSR group, median T, A4 and SHBG were not significantly different from those in the pSSR group. Median T at 6 and 12 months were 5.6 and 4.7 nmol/l (sSSR) and 5.4 and 6.4 nmol/l (pSSR). Median SHBG at 6 and 12 months were 105 and 110 nmol/l (sSSR) and 62 and 66 nmol/l (pSSR). Median A4 at 6 and 12 months were 105 and 110 nmol/l (sSSR) and 62 and 66 nmol/l (pSSR). Median FAI was significantly higher in the sSSR group at 6 months and 12 months (P<0.02). Median FAI fell in the sSSR group from 2.4 (2.2;7.4) at 0 months to 0.7 (0.5;3.1) at 12 months (P=0.02); this fall was not seen in the pSSR arm.

Conclusion  
pSSR, not associated with any further decline in free androgen levels, is an attractive treatment for long-term replacement in young women with POF.

P24  
Age at menarche and pubertal education in the London Borough of Islington  
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There is data suggesting that puberty is starting earlier than in previous generations. However, there is minimal information on menarche and its management in UK primary schools. We present a population study, performed in Islington: a London borough with wide ethnic diversity, conducted using written questionnaires to all primary schools. Data collected included: information on menarche, provision and disposal of sanitary towels and teaching on puberty. 22 questionnaires to all primary schools. Data collected included: information on menarche, provision and disposal of sanitary towels and teaching on puberty. 22 questionnaires to all primary schools. 22 questionnaires to all primary schools. 22 questionnaires to all primary schools. 22 questionnaires to all primary schools. 22 questionnaires to all primary schools. 22 questionnaires to all primary schools. 22 questionnaires to all primary schools.

Aims  
To compare the effect of a standard Sex Steroid Regimen (sSSR) with a physiological SSR (pSSR) on androgen status in young women with premature ovarian failure (POF).

Patient Population: Seven women with POF were evaluated for the study. The median age was 28 years (range 21–36) and the median duration of ovarian failure was 14 years (range 4–25).

Methods  
An open label randomised, controlled, crossover study over 28 months comparing the effect of sSSR and pSSR on androgen status. Treatment consisted of a 12 month period of 4-week cycles of pSSR (transdermal estradiol 100 mcg daily for week 1 and 150 mcg for weeks 2–4 and either 200 mg progesterone vaginal pessaries or progesterone 10 mg orally twice daily in weeks 3–4), or sSSR (Loestrin 30, Galen Ltd; ethinylestradiol 30 mcg and norethisterone 1.5 mg daily for weeks 1–3, followed by 7 pill-free days), separated by run-in and wash-out periods. Serum Testosterone (T), Androstenedione (A4), SHBG were measured and the Free Androgen Index (FAI= [serum T/SHBG] × 100) calculated at months 0/6/12.

Results  
At baseline in the sSSR group, median T, A4 and SHBG were not significantly different from those in the pSSR group. Median T at 6 and 12 months were 5.6 and 4.7 nmol/l (sSSR) and 5.4 and 6.4 nmol/l (pSSR). Median SHBG at 6 and 12 months were 105 and 110 nmol/l (sSSR) and 62 and 66 nmol/l (pSSR). Median A4 at 6 and 12 months were 105 and 110 nmol/l (sSSR) and 62 and 66 nmol/l (pSSR). Median FAI was significantly higher in the sSSR group at 6 months and 12 months (P<0.02). Median FAI fell in the sSSR group from 2.4 (2.2;7.4) at 0 months to 0.7 (0.5;3.1) at 12 months (P=0.02); this fall was not seen in the pSSR arm.

Conclusion  
pSSR, not associated with any further decline in free androgen levels, is an attractive treatment for long-term replacement in young women with POF.
P25
Diagnostic Challenges in Androgen Insensitivity Syndrome & 5 Alpha Reductase Deficiency
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Introduction
The clinical differentiation between androgen insensitivity syndrome (AIS) and 5 alpha reductase deficiency (5-ARD) can be difficult. Presenting features may be similar and initial investigations may still not be discriminatory.

Methods
Case notes on a total of ten patients with the initial diagnosis of AIS or 5-ARD were retrospectively reviewed.

Results
All ten children had a 46XY male karyotype. Four children were raised as male. Three of the six initial patients had AIS diagnosed, but subsequent re-evaluation revealed a diagnosis of 5-ARD. The age at diagnosis in the 5-ARD group ranged from birth to 12.4 years. A sibling pair who had had previous gonadectomies and negative androgen mutations on genetic analysis was re-investigated due to the development of clitoromegaly. A urine steroid profile (USP) and then genetic analysis confirmed the diagnosis of 5-ARD. A child whose sibling had complete AIS also subsequently had a diagnosis of 5-ARD on urinary steroid profile. Interestingly, one male infant presenting with microopenis had post HCG testosterone: DHT ratio of 7. A diagnosis of 5-ARD was subsequently made on urinary steroid profile and confirmed on genetic testing.

Conclusion
This series revealed that clitoromegaly and inguinal lumps were a common finding in females with 5-ARD. Thus females with a diagnosis of AIS were re-evaluated and subsequently 3 of them were reclassified as 5-ARD. Furthermore the post HCG testosterone: DHT ratio may not be diagnostic of 5-ARD. We reinforce the need to evaluate these children using a combination of USP, HCG test & genetics.

P26
Prevalence of congenital malformation in Scottish children with true congenital hypothyroidism 1979–2009
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Introduction
The prevalence of congenital malformations (CM) in congenital hypothyroidism (CH) is higher than expected, particularly for cardiac malformations, but the published data vary considerably - from 2.4% to 26% - in different series.

Methods
Using existing databases for CH and Scottish population statistics, we have retrospectively determined the prevalence of cardiac, non-cardiac and syndromic disorders in Scotland since the introduction of newborn screening.

Results
Five–hundred and six cases of true CH have been logged in Scotland since 1979 including 489 born between 1980 and 2008, giving a period prevalence of 1:3,617. Associated malformations were recorded to be present in 35/498(7%) cases, and 19(54%) of these had a karyotype performed. Comparing the two centres with the highest number of cases in the register, report of a karyotype was present in the register for 6/90(7%) cases from Aberdeen and 65/342(19%) cases from Glasgow. The median EMS scores of these cases in Aberdeen and Glasgow were 8.5 (1.11) and 7.5 (0.11), respectively.

Summary
These data represent the first attempt at benchmarking the decision to check a karyotype in infants with suspected DSD. Whilst this decision may be related to the complexity of the genital anomaly, there are other factors that may influence this, and these require further exploration through more rigorous systems for data collection.
Conclusion
In our diverse group of 46XY girls, only a small minority were picked up during the neonatal period. Many girls at presentation had clinical signs including palpable gonads, UGS or enlarged phallus. This emphasizes the importance of thorough neonatal genital examination for early diagnosis of DSD, especially in those with positive family history.

P29
46. XY DSD: A case of clinical and biochemical conflict
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Introduction
We describe a case of 17- beta hydroxysteroid dehydrogenase Type III (17bHSD3) deficiency in a girl from the travelling community. This case demonstrates how the clinical picture may not correlate with the biochemical results.

Case
A 4.7 year old girl presented for elective herna repair. Intraoperatively, what was felt to be a testis was palpated. Investigations revealed a 46, XY karyotype. Pelvic ultrasound demonstrated absence of Mullerian structures. Bilateral palpable gonads in the inguinal region with normal female external genitalia were found on clinical examination. Family history was very difficult to obtain as parents were reluctant for disclosure of information. However, it was revealed that two maternal first cousins had presented with delayed puberty and required bilateral gonadectomy.

Initial impression was that of complete androgen insensitivity syndrome (CAIS) or a defect in testosterone biosynthesis. However, testosterone was undetectable with only a small increment in androstenedione post HCG stimulation. Androgen receptor (AR) sequencing revealed no mutations in the AR gene thus eliminating CAIS. Serum inhibin and anti-mullerian hormone (AMH) were detectable at 63 mg/l and 22 pmol/l respectively indicating the presence of functioning testicular tissue. A 24 h urine steroid profile was reported as normal with no evidence of an androgen biosynthesis defect. Further ongoing DNA analysis revealed no mutations in the SF1 or SRY genes but a positive mutation in intron 3 of the 17bHSD3 gene.

Conclusion
Open communication is necessary for optimal investigation and management in 46, XY DSD individuals. However, confidentiality must be paramount. Ongoing research into molecular studies will allow for more precise diagnosis in these 46,XY DSD individuals. This case highlights the importance of continuously recalling the clinical picture despite conflicting biochemical results.

P30
Congenital hypothyroidism – A thirty year audit of the National Newborn Screening Programme in the Republic of Ireland
Ciara McDonnell, Aoife Carroll, Sylvia Dockey, Philip Mayne & Nuala Murphy
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Introduction
Congenital hypothyroidism (CHT) has a reported incidence of 1:3500 in Caucasian populations. Early detection by newborn screening and appropriate L-thyroxine treatment leads to normal or near-normal neurocognitive outcome. The National Newborn screening programme (NNP) was established in Children’s University Hospital, Temple St. in 1979. This study aimed to ascertain the incidence of congenital hypothyroidism in the Republic of Ireland (ROI) and to evaluate the screening programme with regard to time taken to diagnosis, initiation of treatment and the contribution of scanning to diagnosis.

Methods
An audit was performed of all positive screens for CHT between July 1979 and December 2008. Date of detection, clinical presentation, thyroid function tests and technetium scan results (from 1990) were reviewed.

Results
A total of 648 children have been diagnosed with CHT. The incidence of CHT was 1 case per 2296 live births in the Republic of Ireland (ROI) in the past decade with increasing numbers over recent years. Sixty five percent of cases were female (male = 221, female = 403, unreported = 24). A median of 22 cases were reported annually (range 14–44). The median time to sample collection was 5 days and median time to detection of an abnormal sample was 9 days. Scan information was available on 308/459 cases screened since 1990 discriminating between thyroid agenesis (n = 87), ectopic/small thyroid (n = 164), dyshormonogenesis (n = 58), and normally placed thyroids (n = 59). Mean TSH on screening card compared to scan results were 230 mU/l (agenesis), 162 mU/l (ectopic thyroid), 60mU/l (dyshormonogenesis) and 78 mU/l (normal thyroid).

Conclusions
The CHT screening programme has been successful in the early detection of affected cases. A target time of 10 days is been evaluated. Reasons for the increase in incidence of CHT in recent years require further investigation.

P31
Prophylactic Thyroidectomy in Children with Multiple Endocrine Neoplasia Type 2
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Background
The most common cause of death in patients with Multiple Endocrine Neoplasia type 2 is medullary thyroid carcinoma. All patients with MEN2 develop this cancer and Prophylactic Thyroidectomy (PT) is recommended to prevent malignant transformation.

Method
This study reviews our experience of treating children identified as carriers of a RET mutation diagnostic of MEN-2A. Data was collected by reviewing patient notes and hospital electronic databases.

Results
Between 1998 and 2009 15 children (8 boys; 7 girls) were identified by genetic analysis as having MEN 2. The commonest codon with RET mutation was 634V (n = 8), 2 siblings were positive for 891A, 2 further siblings were 790F positive and 1 child had codon 620G mutation. Of these, 13 underwent PT and 3 central lymphadenectomy (2 are awaiting surgery). Median patient age of those undergoing surgery was 7.5 years (range 3.5-15 years) and median hospital stay was 4 days. 10 children had transient hypocalcaemia following surgery and required oral calcium (n=10) and alfacalcidiol (n=3). There were no other post-op complications. Histology showed medullary carcinoma in 4 specimens (completely excised) C-cell hyperplasia in 8 cases, and 1 case showed non-specific thyroiditis only. There were no lymph node metastasis and all children but one have undetectable calcitonin levels.

Discussion
This is the first UK case series of children with MEN2 undergoing prophylactic thyroidectomy. We have shown PT to be a rare but safe procedure. We propose to conduct a UK audit of prophylactic thyroidectomy in children with MEN2.

P32
Has the change in Guthrie TSH cut off point made an impact in early detection & management of congenital hypothyroidism?
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Introduction
Neonatal thyroid screening commenced in the UK in 1981. The TSH cut off point has changed from 80 mu/l to 25 mu/l over the period for early detection and referral. From April 2006 in the West midland this has dropped to 20 mu/l as upper level and 10 mu/l as lower level.

Method
Retrospective audit was undertaken in our hospital on babies referred with an abnormal Guthrie test for a period of 13 years from April 1996 to April 2009.

Results
Results were compared between 1996–2006 and 2006–2009 to see the impact on the change in Guthrie TSH levels.

Results
There were 20 cases referred in 10-year period during 1996–2006, and 18 cases in 3-year period, during 2006–2009. Lowering upper cut off point from 25 to 20 µl picked up 4 additional cases.

Four cases were picked up by lower cut off point (> 10 µl/l), could have been picked up by the previous lower cut off point (> 13 µl/l) as all the values were above 13 µl/l. 3/18 cases (17%) have not required treatment but needed regular monitoring and follow-up.

Conclusion

Number of referrals has increased from 2 cases per year during 1996-2006 to 6 cases per year during 2006-2009.

4/18 cases (22%) were picked up by lowering high cut off point, but lowering the cases per year during 2006–2009.

Number of referrals has increased from 2 cases per year during 1996–2006 to 6 cases per year during 2006–2009.

There has been an increase in patient referrals and clinical workload following the change in recent TSH guidance.

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**P33**

**Is There A High Incidence Of Graves’ Disease In Doncaster And What Are The Potential Causes? A Retrospective Study**

James West & Amuja Natarajan

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Graves’ disease is the most common cause of hyperthyroidism in children. The incidence in the UK and Ireland is unknown but estimated to be 0.84 per 100,000 people (0–15 yr olds). Due to an apparent high local incidence, a retrospective study was conducted on patients diagnosed with Graves’ disease in a district general hospital in the locality.

Aim

To evaluate the clinical features, investigations and treatment of patients diagnosed from 2004 onwards and to identify possible causes.

Method

A proforma was designed prior to data collection. Case notes and investigation reports were reviewed.

Results

Seven patients were identified (6 females, 1 male) with a mean age at diagnosis of 13.9 years (range 12–15 years). This gives a local incidence of 2.43 per 100,000 people (0–15 yr olds). The most frequent symptoms were heat intolerance (71%), anxiety (57%), irritability (57%), palpitations (57%) and weight loss (57%). The most frequent signs were goitre (86%) and tremor (57%). Thyroid peroxidase autoantibodies were found in 86% of cases. All 7 patients received block and replacement therapy and 3 patients required propranolol for palpitations. Three patients achieved remission with a mean duration of treatment of 47.5 months. One patient had a total thyroidectomy.

Conclusion

Whilst considering the small sample size, the local incidence of Graves’ disease could be higher than the incidence for the UK and Ireland. Studies on monozygotic twins have demonstrated an environmental influence to the multifactorial aetiology with the susceptibility to the development of Graves’ disease due to non-genetic factors estimated to be 21%. Smoking is one factor that has been related to Graves’ disease and in our region there is a greater prevalence of smokers than the UK as a whole. Other potential factors include infection and high iodine intake.

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**P34**

**What skills do young people attending paediatric endocrine clinics feel they need before transfer to adult services?**

Keerthiga Yohanathan, Julie Jones, Elaine O’Shea, Rakesh Amin, Indi Banerjee, Catherine Hall, Leena Patel, Peter Clayton & Helena Gleeson

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Background

A key element of the transition process is encouraging young people (YP) to become more independent in their healthcare. However it is not known what skills YP feel they need before being ready for transfer to adult services.

Method

A simple questionnaire was designed for YP to rate out of 5 A. their current status in terms of 5 aspects of independence in healthcare (5 “yes, I do it all of the time” to 1 “no, my family does it for me”); B. how important they are at the time of transfer (5 “totally important”, 1 “not at all important”) and C. their preparedness to be seen alone. A signed rank test was performed between their current status and their ideal status at transfer and regression analysis was performed to identify which aspects were associated with feeling more prepared.

Results

The questionnaire was administered to 72 YP (37 male) with long term endocrine conditions. The mean age was 15.5±2.5 years old. 31% of YP were aware that transition or transfer had been discussed, however only 11% were aware of what the plan was. The following aspects of independence in healthcare were felt to be at least fairly important at the time of transfer (rate 3 +) were: organizing and taking medication in 79% of YP (75%); seeing the doctor alone in 72% (21%); asking questions in clinic, in 69% (63%); organizing and collecting prescriptions in 63% (29%); and phoning endocrine service with questions in 43% (14%)

Conclusion

To prepare for adult services YP have identified a need to increase independence in healthcare. Doctors and nurses should do more to encourage this, particularly by giving YP the opportunity to be seen alone in clinic.

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**P35**

**Point of care glucose monitoring on the Neonatal Unit: An audit project**

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Introduction

Assessment of hypoglycaemia in neonates is challenging due to limited blood availability, and lower glucose readings compared to adults. ISO criteria used to assess the accuracy of glucometers are based on adult needs where values below 4.2 mmol/l require intervention. National neonatal guidelines define an action threshold for hypoglycaemia as a glucose below 2mmol/l. We currently use a Radiometer ABL-735 blood gas analyser which uses 35 microlitres of blood. We trialled the Nova Statstrip glucometer (NSG), which uses 1.2microlitres of blood, and internally corrects for haematocrit.

Aims

To compare the accuracy of the NSG against the Radiometer and establish if the NSG could be a reliable alternative for gluco-analysis on the unit.

Method

We reviewed paired glucose readings from the NSG and Radiometer, collected prospectively between December 2008 and February 2009 from babies on the unit. We performed statistical tests to assess the accuracy and precision of the NSG compared to the Radiometer.

Results and Conclusion

We obtained 730 validated paired values. 166 had a value less than 4.2 mmol/l on the Radiometer, 10 below 2 mmol/l and 2 below 1 mmol/l. 98.80% of NSG values less than 4.2 mmol/l and 97.70% of values greater than 4.2 mmol/l met the ISO criteria. Bland-Altman and linear regression analysis showed good correlation between the readings (r-squared = 0.8259). An Error Grid showed that most infants would be appropriately managed as per our local guidelines when Radiometer values were below 2 mmol/l. The NSG performed well on statistical analysis compared to the Radiometer, and performed well across a wide range of haematocrits. We recommend its use on our unit.

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**P36**

**What do young people think about seeing the doctor alone in paediatric endocrine clinics?**

Helena Gleeson, Elaine O’Shea, Julie Jones, Leena Patel, Catherine Hall, Indi Banerjee, Rakesh Amin & Peter Clayton

Royal Manchester Children’s Hospital, Manchester, UK.

Background

Seeing the doctor alone has been associated with a better outcome following transition to adult services.

Methods

A simple questionnaire was designed for young people (YP) to enquire about being seen alone in paediatric endocrine clinics.

Results

The questionnaire was administered to 72 YP young people (37 male) with long term endocrine conditions. The mean age was 15.5±2.5. 10% of YP thought they should be offered the opportunity to be seen on their own at any age, 7% from the age of 11, 19% from the age of 14, 25% from the age of 17, 22% thought it depended on maturity not age and 14% were unsure. Of those that stated an age 40% of all the YP were the age that they felt they should be offered an opportunity to be seen on their own. 32% of YP were either totally or very confident to be seen alone.

P37

Pitfalls of the four hour wait: keeping alert to potential endocrine presentations in Accident and Emergency
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Background
Emergency staff are under pressure to assess and refer within tight targets. Two adolescents presented to A&E with psychiatric symptoms, were referred to Child and Adolescent Mental Health (CAMH), but fortunately came to our attention and were diagnosed with thyroid disorders.

Case 1
Fifteen-year-old boy presented with a two week history of disturbing auditory hallucinations. The A&E doctor did ask for a Paediatric opinion as he “was lacking facial hair”. OE Ht < 0.4th C, Wt >25th C, facial features of myxoedema, smooth goitre, sparse dry hair and bilateral hydroceles. Investigations: TSH > 150 mIU/l (0.25–5), FT4 4 pmol/l (9–23), TPO antibodies 1000 iu/l. The antipsychotic medication was stopped, he was treated with thyroxine and his hallucinations resolved.

Case 2
Fourteen-year girl presented with “panic attacks”, anxiety, auditory hallucinations and compulsive behaviour. CAMHs staff commenced Sertraline. At her psychiatric symptoms resolved.

Discussion
Although it is well recognized that adults presenting with acute psychotic symptoms may have thyroid disease, there does not appear to be the same recognition in children. Previous studies have indicated that the yield from “routine screening” TFTs in Paediatric Psychiatry patients is low and that no clear correlation appears to exist between psychiatric presentation and degree of severity in thyroid dysfunction. However, all health care professionals should be alert to patients who have additional symptoms and signs of thyroid disorders, particularly goitre. Appropriate treatment usually results in resolution of psychiatric symptomatology.

P38

Management of central diabetes insipidus in a paediatric intensive care unit
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Background
Central diabetes insipidus (CDI) is rare in infants and children. Up to 30 percent of cases are idiopathic and its clinical presentation is poorly defined. In critically ill paediatric intensive care unit (PICU) patient with CDI, there is increased risk of brain damage and death due to severe hyperosmolality, hypovolaemic shock, hyponatraemic seizures or complications of treatment.

Aim
To assess the causes, management and outcome of CDI in patients admitted to a tertiary PICU with a large neurosurgery and oncology service.

Method
Retrospective data were collected in PICU patients who required assessment of serum and urine osmolalities over a period of 3 years (2006–8).

Results
A total of 58 patients, 7/58 (12%) had CDI, 1/58 (1.7%) had nephrogenic DI and 10/58 (17.2%) had incomplete DI or solute diuresis. Brain tumours were the commonest cause of CDI. All patients with CDI received full maintenance fluids of: 0.9% sodium chloride (n = 5), 0.45% sodium chloride/5% dextrose (n = 1), or oral feeds (n = 1). Only 2 patients required replacement of fluid losses which were estimated as urine output plus 10% of body weight. An initial dose of intravenous DDAVP was required in 6 patients. One patient was treated with oral DDAVP and had developed SIADH during treatment. He had a hyponatraemic seizure and was treated with 3% sodium chloride infusion and 50% fluid restriction. All patients were monitored by hourly urine output and 4-hourly blood gases for electrolytes level. Repeated doses of DDAVP were required in 4 patients following breakthrough episodes. We discharged 3 patients home on regular DDAVP, transferred 1 to another hospital and 3 died because of their primary illness.

Conclusion
PICU patients with CDI need prompt fluid management, close monitoring of urine output and electrolytes as well as appropriate DDAVP doses to avoid serious complications of the disorder and management pitfalls.
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