

31st Meeting of the
**British Society for
Paediatric Endocrinology
and Diabetes**

19-21 November 2003
Royal College of Physicians
of Edinburgh, UK

**Programme
and
Abstracts**

This event, activity code number 20399 has been approved for external credit for the CPD scheme of the Federation of the Royal Colleges of Physicians of the UK.

31st Meeting of the
**British Society for
Paediatric Endocrinology
and Diabetes**

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of Edinburgh, UK

Benefactors:

**Disetronic Medical Systems, Eli Lilly & Co,
Ferring Pharmaceuticals, Novo Nordisk Pharmaceuticals,
Pfizer Ltd, Serono Pharmaceuticals.**
Also supported by the Child Growth Foundation
and the Turner Syndrome Support Group

**Programme
& Abstracts**

www.bsped.org.uk

Dear All,

Welcome to Edinburgh for the 31st Annual Meeting of the BSPED.

There can be no doubt that Edinburgh, the "Athens of the North", is one of the great capital cities of the world. It is a world-leading centre for business, finance and education, and is now home to the first Scottish Parliament in 300 years. Its magnificent architecture shifts from the lofty buildings of its medieval Old Town, which run down the spine of the Royal Mile, to the grace of the Georgian 'New' Town. Alleyways reveal ancient courtyards and wynds, and above it all, in its towering splendour, stands the Castle.

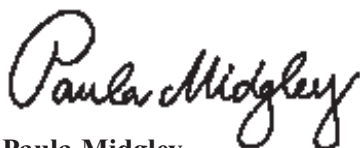
This year's meeting is being held at the Royal College of Physicians of Edinburgh, in Queen Street (hopefully not stirring too many unpleasant membership exam memories). This historic building has excellent facilities for the meeting, including a spacious lecture theatre. It has the advantage of being situated in the centre of Edinburgh, but consequently does not offer accommodation or parking facilities. The railway station is an easy walk, and shops, galleries and historic buildings are only a few steps away.

The programme is both exciting and varied. There will be a symposium on Perinatal Medicine exploring the thyroid, oestrogens and androgens in development. The programme symposia will also include hyoglycaemia, insulin resistance and androgen replacement. The 'meet the expert' session on Friday afternoon will be interactive, employing the electronic voting system in the lecture theatre. As is customary, however, the greater part of the programme is made up of oral communications and scientific posters. The latter will be attended during Thursday lunchtime, but will also be on display throughout the meeting. In addition, nursing members are holding their parallel symposium on Friday morning.

As participants will be scattered around the city, we invite you to meet up on Wednesday evening for a Welcome Reception in the beautiful Great Hall at the RCPE. Nibbles will be provided and a list of local restaurants will be available for those seeking more hearty fare. Do not miss the annual dinner and ceilidh at The Royal Museum of Scotland on Thursday night. This is a stunning venue where we will be dining and dancing, but with plenty of space to have a drink and talk if you prefer not to do the highland fling.

We look forward to seeing you all on Wednesday November 19.

With best wishes



Paula Midgley
Local Organising Chair
BSPED 2003, Edinburgh

Conference Secretariat

BioScientifica
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22 Apex Court
Woodlands
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Bristol BS32 4JT, UK

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Web site: <http://www.bioscientifica.com>

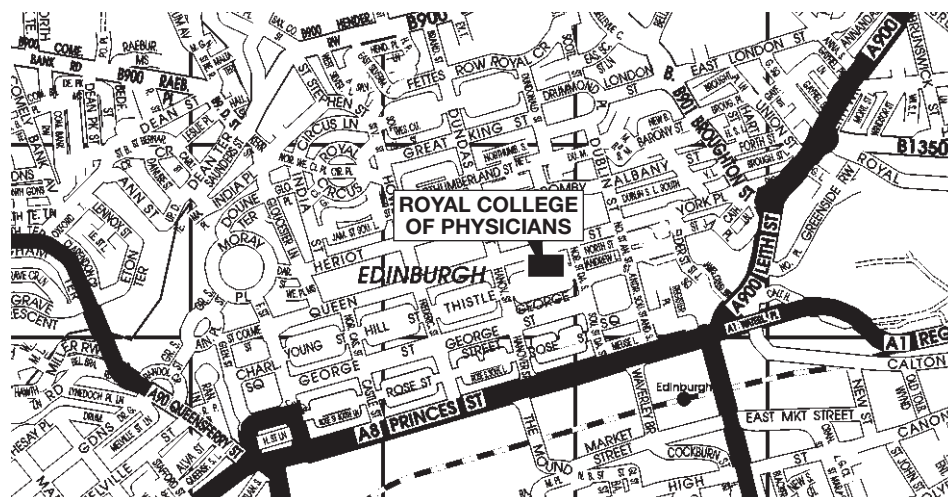
Venue

The 31st Meeting of the British Society for Paediatric Endocrinology and Diabetes will be held on 19-21 November 2003 at the Royal College of Physicians of Edinburgh, 9 Queen Street, Edinburgh, EH2 1JQ. Telephone number: +44 (0) 131 2257324 or fax: +44 (0) 131 2203939.

Edinburgh is the breathtakingly beautiful capital of Scotland, an exciting place to visit at any time of year. Edinburgh offers you superb sightseeing, historic buildings to explore, quiet galleries and museums to intrigue you, thrilling new attractions to discover, serious shopping and a vast choice of excellent restaurants, bistros, wine bars, pubs and cafés to suit all tastes. From Edinburgh Castle downward, historic houses, churches, galleries and museums surround you, each with its own history to share.

Venue Directions

Edinburgh is linked by the M8 if you are coming from the South off the M74. Also you can reach Edinburgh from most airports in Britain and Europe. Edinburgh International Airport is close to the city, only a bus or taxi-ride away, with car hire available at the airport. By rail, the East Coast line links Edinburgh's Waverley station with London and Europe. The West Coast lines link the city with Northern and Western Britain which is ideal for travellers from the English Lakes, Manchester or Bristol.



Registration fees

The registration fee for members is £150.00 and for non-members is £180.00. In addition nurses, trainees and students can register at the reduced rate of £90.00. This fee includes lunch on Thursday 20 November and Friday 21 November as well as entry to the Welcome Reception, but does not include the Annual Dinner.

Name Badges

Name badges will be provided at the registration desk and must be worn for admission to all scientific sessions.

Poster Sessions

Posters will be displayed from 12.30 to 14.00 on Thursday 20 November and 13.00 to 14.00 on Friday 21 November.

The Annual General Meeting of the BSPED

The Annual General Meeting of the BSPED will be held on Thursday 20 November at 16.30 to 17.30 in the main lecture theatre.

GROWING

INDICATIONS



Genotropin
is now licensed for
growth disturbance in short
children born Small for Gestational
Age (SGA) who have failed to show
catch up growth by age 4 and
whose current height is
lower than -2.5

Genotropin is the only GH
treatment licensed for children
born Small for Gestational Age,
Growth Hormone Deficiency,
Turner syndrome,
Prader-Willi syndrome and
Chronic Renal Insufficiency.

 **Genotropin**[®]
somatotropin (rbe)

Growing in so many ways

Genotropin[®] (somatotropin, rbe) Abbreviated Prescribing Information. Genotropin MiniQuick 0.2 mg. Genotropin MiniQuick 0.4 mg. Genotropin MiniQuick 0.6 mg. Genotropin MiniQuick 0.8 mg. Genotropin MiniQuick 1 mg. Genotropin MiniQuick 1.2 mg. Genotropin MiniQuick 1.4 mg. Genotropin MiniQuick 1.6 mg. Genotropin MiniQuick 1.8 mg. Genotropin MiniQuick 2 mg. Genotropin 5.3 mg. Genotropin 12 mg. **Presentation Genotropin MiniQuick:** Two-compartment cartridge in single dose syringe containing powder and solvent for injection together with an injection needle. Each device contains either 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg or 2 mg somatotropin (rbe). **Genotropin Cartridge:** Two-compartment cartridge for use in an injection device. Genotropin pen, or in a reconstitution device. The cartridges contain either 12 mg or 5.3 mg somatotropin (rbe). Each cartridge also contains 0.3% m-cresol as preservative. Instruction on reconstitution plus use of devices is supplied separately as are the Pen, Genotropin ZipTip and Genotropin Mixer devices and any necessary consumables. **Indications:** Children: Treatment of growth disturbance due to insufficient secretion of growth hormone (GH) or associated with gonadal dysgenesis (Turner Syndrome) or chronic renal insufficiency (CRI) or in short children born small for gestational age (SGA) with a birth weight and/or length below -2SD, who failed to show catch-up growth by 4 years of age or later. Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing. Adults: Replacement therapy in adults with pronounced GH deficiency defined as known pituitary pathology and at least one known deficiency of pituitary hormone not being prolactin. **Dosage and Administration:** Dose should be personalised for each individual. The subcutaneous injection site should be varied to prevent lipatrophy. **Insufficient secretion of GH in children:** 0.025–0.035 mg/kg/day. Higher doses have been used. **Prader-Willi Syndrome:** 0.035 mg/kg body weight per day. Daily doses of 2.7 mg should not be exceeded. **Gonadal Dysgenesis (Turner Syndrome):** 0.045–0.050 mg/kg/day. **CRI:** Approximately 0.045–0.050 mg/kg/day. Higher doses can be needed if growth velocity is too low. Dose correction can be needed after 6 months treatment. **Short children born SGA:** 0.035 mg/kg body weight per day until final height is reached. **GH Deficient Adults:** Start with low dose,

0.15–0.3 mg/day. The dose should be gradually increased as determined by the IGF-1 concentration. Clinical response and side effects may guide dose titration. Women (especially those on oral oestrogen) may require higher doses than men. **Contraindications, Warnings etc.** Genotropin should not be used when any evidence of tumour activity exists and anti-tumour treatment must be complete. Genotropin should not be used for growth promotion in children with closed epiphyses. Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with Genotropin. **Precautions:** Diagnosis and therapy should be initiated and monitored by suitably qualified and experienced doctors. Somatotropin may induce insulin resistance and in some patients hyperglycaemia. Patients should be observed for evidence of glucose intolerance. As thyroid function may be affected, it is advisable to test this after starting treatment with somatotropin and after dose adjustments. Signs of any relapse of malignant disease should be monitored. In patients with endocrine disorders, slipped epiphyses of the hip may occur. In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a funduscopy for papilloedema is recommended as some rare cases of benign intracranial hypertension have been reported and if appropriate treatment discontinued. In CRI, renal function should be below 50% of normal and growth followed for a year preceding therapy. Conservative treatment for renal insufficiency should have been established and be maintained during therapy. Discontinue GH after renal transplantation. Scoliosis is common in PWS and signs for scoliosis should be monitored. Experience of prolonged therapy in adults, patients with PWS and use in patients over 60 years is limited. In short children born SGA other medical reasons or treatments that could explain growth disturbance should be ruled out before starting treatment. Not recommended to initiate treatment in SGA patients near onset of puberty. In acute, critically ill adult patients, GH may increase mortality. **Interactions:** In diabetes mellitus, insulin dosage may need adjustment. Somatotropin has been reported to reduce serum cortisol levels, possibly by affecting carrier proteins or by increased hepatic clearance. The clinical relevance of these findings may be limited. Corticosteroid replacement therapy should be optimised before initiation of Genotropin therapy. **Pregnancy and Lactation:** There is no clinical

experience of use during pregnancy. Interrupt treatment if pregnancy occurs. It is not known whether peptide hormones pass into breast milk, but absorption of intact protein from the infant GI tract is unlikely. **Overdosage:** None known. **Side Effects:** In adult patients, common adverse effects related to fluid retention; such as peripheral oedema, arthralgia and myalgia. These effects are mild to moderate, arise within the first months of treatment and subside spontaneously or with dose reduction. Transient local skin reactions in children are common. Carpal tunnel syndrome is uncommon (< 1/100 & ≥ 1/1000) in adults. Formation of antibodies of low binding capacity in approximately 1% of patients; in vitro chromosome aberrations of unknown clinical significance. Very rare cases (< 1/10,000) of leukaemia have been reported in GH deficient children treated with somatotropin, but the incidence appears to be similar to that in children without GH deficiency. **Pharmaceutical Precautions:** Genotropin MiniQuick 0.2 mg x 7 E32.46 0022/0186. Genotropin MiniQuick 0.4 mg E64.91 0022/0187. Genotropin MiniQuick 0.6 mg x 7 E97.37 0022/0188. Genotropin MiniQuick 0.8 mg x 7 E129.82 0022/0189. Genotropin MiniQuick 1 mg x 7 E162.28 0022/0190. Genotropin MiniQuick 1.2 mg x 7 E194.74 0022/0191. Genotropin MiniQuick 1.4 mg x 7 E227.19 0022/0192. Genotropin MiniQuick 1.6 mg x 7 E259.65 0022/0193. Genotropin MiniQuick 1.8 mg x 7 E292.11 0022/0194. Genotropin MiniQuick 2 mg x 7 E324.56 0022/0195. Genotropin 12 mg x 1 E278.20 0022/0098. Genotropin 5.3 mg x 1 E122.87 0022/0085. **PL Holder:** Pharmacia Laboratories Limited, Davy Avenue, Milton Keynes, MK5 8PH, UK. Further information is available on request from: Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. **Date of preparation:** 22 September 2003. GEN042.



Awards

The BSPED, together with Pharmacia, are delighted to announce the ninth in a series of awards for clinical and laboratory research proposals in the fields of endocrinology, growth disorders and diabetes. A prize will also be awarded to the highest scoring submitted abstract and a further prize will be awarded to the best poster presentation.

CPD Approval

CPD approval from the Federation of the Royal College of Physicians of the UK has been given for this meeting. Delegates may claim 12 points for full attendance of the meeting. If you want to claim your CPD points you must sign the register on the registration desk at the meeting before 12.30 on Friday 21 November. You will need your GMC number.

Social Events and Catering

The Welcome Reception will take place on Wednesday 19 November in the Great Hall at the Royal College of Physicians, Edinburgh between 18.00-19.00. All delegates are welcome to join us for drinks in this beautiful building.

Conference Lunches

A buffet lunch will be served on Thursday 20 November and Friday 21 November in the Circulation Foyer of the conference venue. The cost of this is included in your registration fee.

Annual Dinner

The annual dinner will take place in the Main Hall of the National Museum of Scotland, Edinburgh, which has been described as one of the finest examples of Victorian architecture in the city. The evening will consist of pre-dinner drinks, dinner and ceilidh. Transport will be provided to and from the venue to the main hotels. The cost of dinner is £40.00.

Pfizer Satellite Symposium

The Pfizer satellite symposium 'Growth Hormone Treatment in Short Children Born SGA' will examine how long-term GH treatment can normalise final height in most children born SGA. Professor Martin Savage (St Bartholomew's Hospital, London) will talk about the paediatrician's response to approval of GH treatment in SGA and Professor Paul Czernichow (Paris, France) will discuss his own experience of treating short children born SGA. Professor David Dunger (Addenbrooke's Hospital, Cambridge) will chair the symposium.

Benefactors and Exhibitors

We are grateful to the following benefactors for their support of the BSPED. They will have display stands at the meeting:

Disetronic Medical Systems
Eli Lilly & Co
Ferring Pharmaceuticals
Novo Nordisk Pharmaceuticals,
Pfizer Ltd
Serono Pharmaceuticals
Child Growth Foundation
Turner Syndrome Support Group

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For use with Serono's recombinant human growth hormone Saizen® 8mg click.easy®

cool.click® comes in two colours, green for children and blue for adults. These two versions have all the same components and work in exactly the same way

Reference: 1. Murray et al: Today's Therapeutic Trends 2000, 18(4): 305-312
February 2003 Code: P3050203

Prescribing Information

SAIZEN® 8 mg click.easy® Somatropin

SAIZEN® 8 mg click.easy® Somatropin Phosphate is a powder, accompanied by a cartridge of solvent containing 0.3% w/v metacresol in water for injections.

Uses:

The treatment of short stature caused by decreased or absent secretion of endogenous growth hormone. Growth failure in girls with gonadal dysgenesis (Turner Syndrome). Growth failure in prepubertal children due to chronic renal failure. Replacement therapy in adults with pronounced growth hormone deficiency as diagnosed by a single dynamic test who fulfil the following criteria:
Childhood onset: Patients diagnosed as growth hormone deficient during childhood must be re-tested before treatment.
Adult onset: Patient must be growth hormone deficient as a result of hypothalamic or pituitary disease and at least one other hormone deficiency diagnosed (except for prolactin) before treatment.

Dosage and Administration:

The dosage must be individualised and given as a subcutaneous injection.

Inadequate secretion of endogenous growth hormone: 0.7-1.0 mg/m² body surface area per day or 0.025-0.035 mg/kg body weight per day.

Turner Syndrome: 1.4 mg/m² body surface area per day or 0.045-0.050 mg/kg body weight per day.

Chronic renal failure: 1.4 mg/m² body surface area per day, approximately equal to 0.045-0.050 mg/kg body weight per day.

Growth Hormone Deficiency in adults:

Doses of 0.15-0.3mg are recommended initially. Dosage should be adjusted stepwise, controlled by Insulin-like Growth Factor 1 (IGF-1) values. The lowest efficacious dose is recommended, this seldom exceeds 1.0mg/day. In older or overweight patients, lower doses may be necessary.

The injection site should be rotated to prevent lipatrophy.

Contraindications:

Epiphyseal fusion; recurrence or progression of an underlying intracranial lesion; active neoplasia (any anti-tumour therapy must be completed prior to starting somatropin treatment); known hypersensitivity to any ingredients. Do not use in critically ill patients.

Precautions:

Treatment should be carried out under regular specialist medical supervision. Use with caution in patients with diabetes mellitus, or a family history of diabetes mellitus. Concomitant corticosteroid therapy may inhibit the response to SAIZEN®.

There is limited clinical experience with growth hormone in pregnant women and experimental data in animals is incomplete. SAIZEN® treatment should be discontinued if pregnancy occurs. It is not known if exogenous peptide hormones are excreted into breast milk but absorption of intact protein from the GI tract of the infant is unlikely.

Previous history of intracranial lesions, or intra or extracranial neoplasia, requires regular monitoring. Thyroid function tests should be performed and any incidence of hypothyroidism should be treated. The patient should be monitored for insulin resistance.

There may be a slightly increased incidence of leukaemia in growth hormone deficient children however a causal relationship to growth hormone therapy has not been established.

In case of severe or recurrent headache, visual problems, nausea and/or vomiting, a fundoscopy for papilloedema is recommended.

If papilloedema is confirmed a diagnosis of benign intracranial hypertension should be considered and growth hormone discontinued.

If present there is insufficient evidence to guide clinical decision-making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted following resolution of intracranial hypertension, treatment should be discontinued following any recurrence.

In children with chronic renal failure, renal function should have improved to below 50% of normal before treatment. Conservative treatment (eg control of acidosis, hyperparathyroidism and nutritional status for one year prior to treatment) should be established and maintained during treatment. During treatment patients should be examined for progression of renal osteodystrophy. Treatment should be discontinued at the time of renal transplantation.

In persistent oedema or severe paraesthesia decrease the dosage in order to prevent carpal tunnel syndrome.

Adult growth hormone deficiency should be treated as a lifelong condition. Experience is limited in patients over 60.

Overdose:

Overdose can lead to hypoglycaemia followed by hyperglycaemia. Chronic overdose may result in clinical features of gigantism and/or acromegaly.

Side-effects:

Possible transient local skin irritation particularly when the subcutaneous route is used. Antibodies to Somatropin can form in some patients, the clinical significance of which is unknown. Intermittent dosage has been associated with the appearance of hypoglycaemia. Epiphyseolysis at the site of the hip joint may occur.

Pharmaceutical Precautions:

Do not store above 25°C. Store in the original package. Once constituted store at 2°C - 8°C, do not freeze, and use within 28 days.

Legal Category:

DOM*

Pack size and basic NHS cost:

Each carton contains 1 vial of SAIZEN® 8 mg and 1 solvent cartridge. Cost: £183.001.

Product Licence/Authorisation Number:

SAIZEN® 8mg click.easy® PL 03400/0079
lactriostatic solvent PL 03400/0076
SAIZEN® 8mg click.easy® and solvent PA 285/5/4

Name and Address of Licence Holder:

Serono Pharmaceuticals Limited
Bedford Cross
Stanwell Road
Uxbridge, Middlesex
W14 8NX
United Kingdom
Telephone: +44(0)20 8818 7200

Name and Address of Distributor in Ireland:

Alphar Services Limited
Pharmaceutical Agents and Distributors
Belgard Road
Gallagher
Dublin 24
Tel: (01) 404 1600

Date of Preparation:

September 2002
Different prices may apply in Ireland please consult Alphar Services Limited

UK Status

cool.click®

saizen®

somatropin (rDNA) origin

Wednesday 19 November 2003

	MAIN LECTURE THEATRE	CIRCULATION FOYER
12.00		
12.15		
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15.15		
15.30		
15.45		
16.00		
16.15		Registration
16.30		
16.45		
17.00		
17.15	Pfizer Satellite Symposium: Growth hormone treatment in short children born SGA	
17.30		
17.45		
18.00		
18.15	Welcome Reception <i>'THE GREAT HALL'</i> ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH	
18.30		
18.45		
19.00		
19.15		
19.30		
19.45		
20.00		

Thursday 20 November 2003

	MAIN LECTURE THEATRE	CIRCULATION FOYER
08.30	Oral Communications 1: Pituitary, adrenal and bone	
08.45		
09.00		
09.15		
09.30		
09.45		
10.00		Tea and coffee
10.15		
10.30	Symposium 1: Perinatal	
10.45		
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12.30		Lunch and Posters
12.45		
13.00		
13.15		
13.30		
13.45		
14.00	Symposium 2: Hypoglycaemia in diabetes	
14.15		
14.30	Oral Communications 2: Fetal and early life	
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16.45	AGM	
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19.30		

Annual Dinner at the National Museum of Scotland

Friday 21 November 2003

	MAIN LECTURE THEATRE	CIRCULATION FOYER	MEETING ROOMS 1 & 2	
08.30	Symposium 3: Puberty/diabetes			
08.45				
09.00				
09.15				
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10.45			Tea and coffee	Nurses' Session
11.00	Oral Communications 3: Glucose homeostatis and thyroid			
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12.45				
13.00				
13.15			Lunch and Posters	
13.30				
13.45				
14.00	Expert Session Combined case presentations in <i>Hypoglycaemia</i> and <i>Intersex</i> with interactive (voting) participation			
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TURNER SYNDROME SUPPORT SOCIETY

Registered Charity 1080507

The TSSS aims to offer support, social contact and information on all aspects of Turner syndrome to girls and women with TS and their families. The Society also works closely with health professionals involved in the care of those with TS, especially members of the BSPED.

The TSSS would like to take this opportunity to thank the BSPED and its members for allowing them to launch their extremely successful and well-received book

TURNER SYNDROME
lifelong
guidance & support

at last year's meeting.

Please visit the TSSS stand at any time during the conference to view the book and see other information the Society has to offer of interest to you and/or your patients. Members of the TSSS Committee will be on hand and pleased to discuss all aspects of Turner syndrome with you.

The TSSS looks forward to continuing its close working relationship with the BSPED for the benefit of girls with Turner syndrome and their families.

Turner Syndrome Support Society
12 Irving Quadrant
Hardgate
Clydebank
G81 6AZ

Tel 01389 380385 Fax 01389 380384
e-mail Turner.Syndrome@tss.org.uk website:- www.tsss.org.uk

Wednesday 19 November 2003

16:00 – 17:00 **Registration** - CIRCULATION FOYER

17:00 – 18:00 **Pfizer Satellite Symposium** - MAIN LECTURE THEATRE

Growth hormone treatment in short children born SGA

Chair: David Dunger (Cambridge)

Paediatricians' response to approval of GH treatment in SGA

Martin Savage (London)

Treating short children born SGA

Paul Czernichow (Paris, France)

18:00 – 19:00 **Welcome Reception** - THE GREAT HALL

Think ZomaJet®!

for all

GHD & TS children

requiring GH therapy

 **ZomaJet²**
Vision



Visit us on
stand 4

Take it
EASY
No-Needle

Zomacton® 4mg Injection (Somatotropin, INN). **Presentation:** Vials containing Somatotropin, 4.32mg, supplied with an ampoule of diluent. **Uses:** The long-term treatment of children who have growth failure due to inadequate secretion of growth hormone and for the long-term treatment of growth retardation due to Turner's syndrome confirmed by chromosome analysis. **Dosage and administration:** Zomacton® 4mg Injection is administered as a subcutaneous injection. Growth Hormone Deficiency: The dosage and schedule of administration should be individualised for each patient. Generally a dose of 0.17 - 0.23mg/kg bodyweight per week (approximating to 4.9 - 6.9 mg/m² body surface area) divided into 6 - 7 subcutaneous injections is recommended (corresponding to a daily injection of 0.02 - 0.03mg/kg bodyweight or 0.7 - 1.0 mg/m² body surface area). The total weekly dose of 0.27mg/kg bodyweight or 8mg/m² body surface area should not be exceeded. The duration of treatment will depend on maximum achievable therapeutic benefit. Turner's Syndrome: Generally a dose of 0.33 mg/kg bodyweight per week (approximating to 9.86 mg/m² body surface area) divided into 6 - 7 s.c. injections is recommended (corresponding to a daily injection of 0.05 mg/kg bodyweight or 1.40 - 1.63 mg/m² body surface area). **Contraindications:** Use in children with closed epiphyses. Evidence of tumour activity or if anti-tumour therapy is ongoing. Known sensitivity to benzyl alcohol. Zomacton® 4mg Injection should not be used during pregnancy or lactation. **Special**

warnings and precautions for use: Therapy should be under the supervision of a qualified physician, experienced in the management of patients with growth hormone deficiency. Patients should be observed for evidence of glucose intolerance. Use with caution in children with diabetes mellitus or a familial predisposition to the disease. In children with growth hormone deficiency and diabetes mellitus glycaemic control must be carefully monitored and insulin needs adjusted accordingly. Patients with growth hormone deficiency secondary to an intracranial lesion should be monitored frequently. Therapy should be discontinued if progression or recurrence of the lesion occurs. Fundoscopic examination for papilloedema is recommended at the initiation and periodically during the course of treatment, especially if the patient reports recurrent headache, visual problems, nausea and/or vomiting which may indicate intracranial hypertension. Hypothyroidism may develop during treatment with growth hormone and inadequate treatment may prevent optimal response to growth hormone. Leukaemia has been reported in a small number of patients treated with growth hormone. **Side effects:** Injection site reactions and transient headache have been reported. Infrequently, a slight transient oedema may occur during treatment. Formation of antibodies against Somatotropin or E.coli has not yet been observed. In individual cases a benign intracranial hypertension has been reported. Symptoms usually are headache, nausea and/or vomiting and visual problems. **Interactions:**

Glucocorticoid therapy may inhibit the growth promoting effect of Zomacton® 4mg Injection and patients with co-existing ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted. High doses of androgens, oestrogens or anabolic steroids can accelerate bone maturation and inhibit an increase in growth. **Overdose:** Acute overdosage may result in an initial hypoglycaemia followed by a subsequent hyperglycaemia. Long term effects of Zomacton® 4mg Injection in doses exceeding those recommended are unknown. Such use may produce signs and symptoms consistent with excess human growth hormone. **Pharmaceutical precautions:** Store at 2 - 8°C and protect from light. After reconstitution it is stable for 14 days when stored in the refrigerator at 2 - 8°C and protected from light. **Legal category:** POM. **Package quantity:** Carton containing one vial of Zomacton® 4mg Injection and one ampoule of diluent. **Basic NHS price:** £87.44. **Product Licence number:** Zomacton® Injection PL 03194/0052. Diluent PL 03194/0054. **Product Licence holder:** Ferring Pharmaceuticals Ltd., The Courtyard, Waterside Drive, Langley, Berkshire SL3 6EZ. **Date of preparation:** August 2001. Zomacton is a registered trade mark. © Ferring Pharmaceuticals Ltd. Full Prescribing Information is available from Ferring Pharmaceuticals Ltd., The Courtyard, Waterside Drive, Langley, Berkshire SL3 6EZ.

FERRING

PHARMACEUTICALS

Further Information is available from:

Ferring Pharmaceuticals Ltd., The Courtyard, Waterside Drive, Langley, Berkshire SL3 6EZ. Tel: 01753 214800 Fax: 01753 214801

Zomacton and ZomaJet are registered trademarks.

Z/503/10/03

Thursday 20 November 2003

08:30 – 10:00 Oral Communications 1 - MAIN LECTURE THEATRE

Pituitary, adrenal and bone

Chair: Mahul Dattani (London)

- 08:30 OC1 Reassessment of growth hormone status is required at final height in children treated with growth hormone replacement following radiation therapy
Gleeson HK, Gattamaneni HR, Smethurst L, Brennan BM & Shalet SM
- 08:45 OC2 Functional and endocrine outcome in adult survivors of medulloblastoma cranially irradiated before 5 years of age
Marr TJA, Alston A & Spoudeas HA
- 09:00 OC3 ACTH insufficiency: a diagnostic dilemma
Mehra A, Hindmarsh PC & Dattani MT
- 09:15 OC4 Familial Cushing's syndrome in a Danish family secondary to a novel mutation of the regulatory subunit type 1-alpha of the protein kinase A (PRKAR1A) gene
Storr HL, Metherell LA, Main K, Savage MO & Clark AJL
- 09:30 OC5 Phenotypic variability in a family with Adrenal Hypoplasia Congenita due to a novel DAX-1 mutation
Ahmad I, Adlard P, Duncan P, Harvey J, Tolmie J & Donaldson
- 09:45 OC6 Partial loss of function mutations (delF54) in *CYP17* can present with micropallus
Alexander S, Rumsby G, Honour J, Hakeem V, Dattani M & Achermann J
- 10:00 OC7 Bone mineral density in children and adolescents with galactosaemia
Kershaw MJR, Crabtree N, Chakrapani A, MacDonald A, Elias E & Shaw NJ

10:00 – 10:30 Tea & coffee - CIRCULATION FOYER

10:30 – 12:30 Symposium 1: Perinatal - MAIN LECTURE THEATRE

Chair: Mandy Ogilvie-Stuart (Cambridge)

- 10:30 S1 Oestrogen, androgens and sexual differentiation
Richard Sharpe (Edinburgh)
- 11:10 S2 Hormonal and metabolic dysfunction in infants
Robert Hume (Dundee)
- 11:50 S3 Thyroid status in pregnancy
John Lazarus (Cardiff)

- 12:30 – 14:00** **Lunch and Posters** - CIRCULATION FOYER
- 14:00 – 14:30** **Symposium 2: Hypoglycaemia in diabetes** - MAIN LECTURE THEATRE
Chair: Peter Betts (Winchester)
- S4 Hypoglycaemia in children with diabetes
Brian Frier (Edinburgh)
- 14:30 – 16:00** **Oral Communications 2** - MAIN LECTURE THEATRE
Fetal and early life
Chair: Peter Hindmarsh (London)
- 14:30 OC8 Expression of insulin, glucagon and voltage-gated-calcium channel subunits in early human embryonic pancreas
Natarajan A, Grabowski P, Ruban L, Moore H, Andrews P & Dunne M
- 14:45 OC9 Further investigation of the IGF-I gene association with birth size small for gestational age (SGA) using haplotype analysis
Chan LF, Nugent T, Dahlgren J, Gelande L, Savage MO, Albertsson Wikland K, Clark AJL & Johnston LB
- 15:00 OC10 Do cord IGF-I, insulin, leptin and ghrelin levels reflect subsequent infant feeding behaviour and growth?
James RJA, Drewett RF & Cheetham TD
- 15:15 OC11 Height velocity from birth to 6 years in ex-premature infants and controls
Wales JKH, Carney S, Gibson AT & Wright NP
- 15:30 OC12 Multivariate analysis on factors affecting suppression of thyroid stimulating hormone in treated congenital hypothyroidism
Ng SM, Wong SC & Didi M
- 15:45 OC13 A clinical and molecular analysis in patients with the complete androgen insensitivity syndrome
Deeb A, Aboushafa U, Jaaskelainen J, Martin H & Hughes IA
- 16:00 – 16:30** **Tea and coffee** - CIRCULATION FOYER
- 16:30 – 17:30** **AGM** - MAIN LECTURE THEATRE
- 19:30** **Annual Dinner at the National Museum of Scotland**

Friday 21 November 2003

08:30 – 10:30 Symposium 3: Puberty/diabetes - MAIN LECTURE THEATRE

Chair: David Dunger (Cambridge)

08:30 S5 Androgen replacement: the issues and the options

Richard Anderson (Edinburgh)

09:10 S6 The metabolic impact of puberty on type 1 diabetes mellitus
- new therapeutic approaches

Carlo Acerini (Cambridge)

09:50 S7 Deteriorating diabetes control during adolescence: physiologic or
psychologic/psychosocial?

Denis Daneman (Toronto, Canada)

10:30 – 11:00 Tea and coffee - CIRCULATION FOYER

10:30 – 13:00 Nurses' Session - MEETING ROOMS 1 & 2

Chair: Barbara Wardhaugh (Edinburgh)

Patient held records in diabetes

Fiona Lamb (Diabetes Nurse Specialist, Yorkhill, Glasgow)

Type II diabetes? - an interesting case

Harmony Richardson (Diabetes Nurse Specialist, RHSC, Edinburgh)

Assessment of insulin resistance in obese children

Karen McCall (Medical Student, University of Edinburgh)

Case study: Adrenal insufficiencies in two siblings on high dose steroids

Ethel McNeil (Endocrine Nurse Specialist, Yorkhill, Glasgow)

Short brothers with learning disability

Diane Barstow (Endocrine Nurse Specialist, Newcastle)

Business meeting

Chair: Pauline Musson (Southampton)

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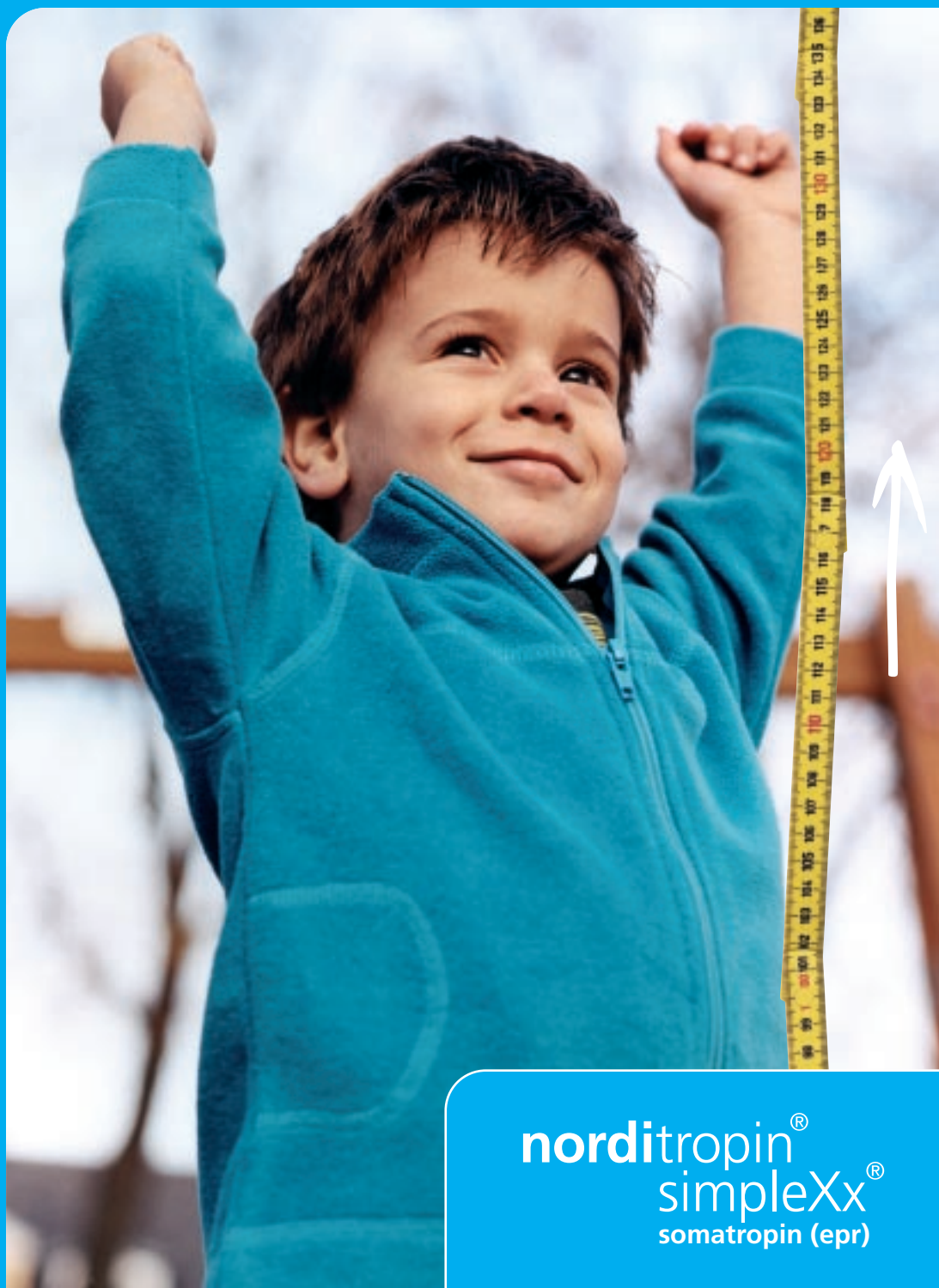


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11:00 – 13:00 Oral Communications 3 - MAIN LECTURE THEATRE

Glucose homeostatis and thyroid

Chair: Peter Smail (Aberdeen)

- 11:00 OC14 Insulin sensitivity in young women with Turner Syndrome
Amin R, Williams RM, Salgin B, Murgatroyd PR, Acerini CL & Dunger DB
- 11:15 OC15 Adult thresholds for obesity may not define metabolic risk in children: The Early Bird Diabetes Study
Voss LD, Jeffery AN, Metcalf BS, Perkins J, Mallam KM & Wilkin TJ
- 11:30 OC16 Development of an assessment tool to select children at risk of Type 2 diabetes for oral glucose tolerance testing
Ehtisham S, Casey AM, Hayes P, Shaw NJ, Kirk JMW & Barrett TG
- 11:45 OC17 Abnormalities of glucose homeostasis in obese children and adolescents
Viner RM & Segal TY
- 12:00 OC18 Compound heterozygote mutations in the glucose transporter (GLUT 2) gene are a novel familial cause of adolescent diabetes
Regan FM, Hattersley A & Betts PR
- 12:15 OC19 Novel homozygous glucokinase mutation in a Pakistani family causing permanent neonatal diabetes with preserved basal insulin release; does the mutation determine the phenotype?
Porter JR, Shaw NJ, Ellard S, Hattersley AT, Barrett TG & Gloyne AL
- 12:30 OC20 Early peripheral neuropathy identified in adolescents with type 2 diabetes
Karabouta Z, Barnett S, Shield JPH, Cowan FJ & Crowne EC
- 12:45 OC21 Block and replace therapy versus dose titration in the management of thyrotoxicosis
Cheetham T, Paterson W, Kelnar C & Donaldson M

13:00 – 14:00 Lunch and Posters - CIRCULATION FOYER

14:00 – 15:00 Expert Session - MAIN LECTURE THEATRE

Combined case presentations in Hypoglycaemia and Intersex with interactive (voting) participation facilitated by *Louise Bath (Edinburgh)* and *Paula Midgley (Edinburgh)*

Expert Panel:

Ieuan Hughes (Cambridge)

Tim Cheetham (Newcastle)

John Gregory (Cardiff)

15:30 Close of Meeting

S1**Oestrogen, androgens and sexual differentiation**

R Sharpe

MRC Human Reproduction Sciences Unit, Centre for Reproductive Biology, Edinburgh, UK

Abstract not available

S2**Hormonal and metabolic dysfunctions in infants**

R Hume

Maternal and Child Health Sciences, University of Dundee, Scotland.

The transition from intra-uterine to post-natal life is complex and involves significant changes in the expression of key genes, many of which are acutely regulated by co-ordinated and often inter-related actions of hormones, such as catecholamines, insulin, glucagon, cortisol and thyroid hormones. Hormonal dysfunctions are common in some infant groups.

Transient hypothyroxinaemia in preterm infants is associated with later neurodevelopmental deficits. Our aim is to determine the molecular bases of transient hypothyroxinaemia of preterm infants and to use this information to drive the development of novel preventative and/or therapeutic strategies.

The late second-early third trimester is a critical transition period in human fetal thyroid hormone metabolism. The 23-27 week group of infants are distinctive with a severely attenuated hypothalamic-pituitary-thyroid axis in response to delivery and are hypothyroxinaemic on serum T4 levels, yet FT4 levels are within the range expected equivalent to gestational age. Thyroid hormone levels are influenced by severe illness in extreme preterm infants and by maternal hypertension.

The temporal and spatial expression of selected thyroid hormone-dependent genes, thyroid hormones, iodothyronine deiodinases (D2 and D3), and sulfotransferases in developing human brain are crucial for local regulation of thyroid hormone bioactivity. The expression of iodothyronine deiodinases in liver and kidney shows markedly different ontogenic profiles during human fetal and neonatal development. Reversible sulfation is an important mechanism of regulation of hormones during early human development, for example modulating the biological activity of estrogens and thyroid hormone..

Approximately 40% of pregnant women from the Tayside Region, Scotland have an iodine intake that is less than half that considered adequate during pregnancy and lactation (c250µg I/day). Recommendations for parenteral iodine intake in infants require review. Iodine balance studies data show that preterm infants are in negative iodine balance at current recommended intakes (1mg/kg/day). Funded : CEC (QLG3-2000-00930), CSO Scottish Executive (K/MRS/50/C741).

S3**Thyroid disease and pregnancy**

J Lazarus

Department of Medicine, University Hospital of Wales, Cardiff, UK.

Thyroid function during pregnancy is characterised by changes in circulating thyroid hormone concentrations related to alterations in thyroxine binding globulin, human chorionic gonadotrophin and iodine status. The immunology of normal pregnancy shows a reduction in antibody titre during gestation and an increase in T helper-2 (Th2) immune responses. Fertility is reduced in hypo and hyperthyroidism. Accumulating evidence suggests a strong association between the presence of thyroid antibodies and fetal loss, although the data relating to recurrent abortion are not so convincing. Maternal hyperthyroidism during gestation may be associated with hyperemesis gravidarum but the commonest cause is Graves' disease. Management is safely achieved with antithyroid drugs (propylthiouracil PTU is preferred). TSH receptor antibodies should be measured to predict neonatal hyperthyroidism. The latter may occur even when the mother is receiving thyroxine substitution therapy following previous therapy for Graves' disease. Breast feeding may be permitted in women taking PTU. There is no evidence of deleterious physical or psychological effects of maternal antithyroid drugs on the neonate or child. Frank hypothyroidism in pregnancy is unusual as conception will be impaired. In contrast asymptomatic maternal subclinical hypothyroidism may occur in up to 2.5% of women. This condition is similar to thyroid dysfunction seen in iodine deficient areas; both are associated with a decrease in child IQ emphasising the critical role of adequate maternal circulating thyroxine concentrations for fetal nervous system development and maturation. Screening for maternal hypothyroidism with thyroid hormone intervention may be justified. Postpartum thyroid thyroiditis (PPT) occurs in 5-10% of women, thyroid dysfunction being recorded in 50% of anti TPO antibody positive women. Permanent postpartum hypothyroidism is found in 30% of these patients; antenatal screening for thyroid dysfunction should be evaluated as a public health strategy.

S4**Hypoglycaemia in children with diabetes**

BM Frier

DEPARTMENT OF DIABETES, ROYAL INFIRMARY, EDINBURGH EH16 4SA, UK.

Hypoglycaemia is common in children and teenagers with type 1 diabetes.

The usual definitions in adults for mild (self-treated) and severe (requiring assistance) hypoglycaemia can not be applied in children, so accurate quantification of the frequency and severity of hypoglycaemia is difficult. Many risk factors for severe hypoglycaemia are similar to adults, with higher frequencies during sleep, strict glycaemic control and with a previous history, and age <7 years significantly increases vulnerability. Nocturnal hypoglycaemia is very common.

The common causes of hypoglycaemia are too much insulin, inadequate intake of carbohydrate and strenuous exercise. Inappropriate dietary decisions and limited ingestion of food during intercurrent illness, and errors in insulin administration may precipitate hypoglycaemia; many episodes have a multifactorial cause. Changes in routine may provoke hypoglycaemia, and seasonal variations in frequency are recognised.

The metabolic responses to hypoglycaemia in children predispose towards rapid depletion of stored glycogen and inadequate gluconeogenesis. These differences are exacerbated by hyperinsulinaemia and are compounded by the counterregulatory hormonal deficiencies. The sympatho-adrenal response to hypoglycaemia may be influenced by puberty. Symptom classification in children has identified behavioural symptoms, with inability to differentiate between autonomic and neuroglycopenic symptoms.

Hypoglycaemia has a significant morbidity (and mortality), with coma and convulsions in very young children being associated with adverse longterm effects on intellectual development. It is unclear whether exposure to recurrent severe hypoglycaemia in older children causes a permanent intellectual deficit. Transient cognitive dysfunction may disrupt learning, affecting educational attainment. Studies of structural change in the brain and cognitive function in young adults with childhood onset of diabetes, have shown no relationship to previous severe hypoglycaemia.

Prevention of hypoglycaemia presents a particular challenge in children, but new insulin analogues and regimens may help to reduce the frequency, particularly during the night.

S5**Androgen replacement: the issues and the options**

RA Anderson

MRC Human Reproductive Sciences Unit; University of Edinburgh; Edinburgh; Scotland.

The potential use of testosterone for supplementation in older men has led to a resurgence of interest in androgen physiology. Testosterone is central to a wide range of physiological processes, including development and maintenance of sexual characteristics, the skeleton, muscle mass, behavioural and cognitive functions and of course fertility. Direct cardiovascular effects are also likely. Testosterone has been recognised for many years to be a pre-hormone in some tissues, notably the prostate where the androgen signal is amplified by conversion to dihydrotestosterone, but 'modulation' of its action by conversion to oestradiol is also crucial in a number of tissues including bone and the hypothalamus/pituitary. These effects are mediated by classical steroid hormone receptors, which are transcription factors acting directly on DNA to regulate gene expression. Alternative signalling pathways mediated by membrane steroid receptors offer an additional level of regulation of steroid action.

There is an increasingly wide range of therapeutic options for androgen replacement. Mixed testosterone esters remain the most widely used, although with little rationale compared to single ester preparations. Testosterone pellets remain popular for long-term replacement despite the need for a minor surgical procedure for insertion. Transdermal (including scrotal) patches are available, but have drawbacks particularly the high prevalence of inflammatory reactions to the excipients needed to increase testosterone absorption. Preparations about to become available include a transdermal gel and buccal tablets, and longer acting injectable esters will follow. An alternative approach is the use of synthetic androgens. One such, 7 α -methyl-19-nortestosterone, is 10 fold more potent than testosterone and is subject to aromatisation but not 5 α -reduction, thus may offer selective low activity at the prostate. The tools for optimising testosterone replacement are therefore becoming available, but what is not clear is how best to use them for our patients.

S6**The metabolic impact of puberty on Type 1 diabetes mellitus - new therapeutic approaches**

CL Acerini

Department of Paediatrics, University of Cambridge, Cambridge, UK.

For the young person with Type 1 diabetes mellitus (T1DM) adolescence is often a time of instability in terms of glycaemic control. Emotional and psychological factors are known to play an important part in the development of this phenomenon, although there is good evidence to suggest that the hormonal changes associated with puberty are also directly involved. In T1DM, the pubertal increase in insulin resistance is exaggerated and largely attributable to abnormalities occurring in the growth hormone / insulin-like growth factor-I (GH / IGF-I) axis. Typically, spontaneous GH secretion is greater than normal, whereas circulating bioavailable IGF-I is reduced. Both lead to direct and indirect effects on peripheral and hepatic tissues resulting in reduced insulin sensitivity, and may contribute to the risk for the later development of microvascular complications. Insulin deficiency, particularly within the portal circulation, plays a pivotal role in the development of these abnormalities, yet intensification of subcutaneous insulin therapy can only partially restore GH and IGF-I levels to normal, and does so at the risk of increased hypoglycaemia and excessive weight gain.

Achieving good glycaemic control remains a major challenge for the adolescent with Type 1 diabetes and a therapeutic goal for the future is to develop safe alternative treatment strategies that take into account the physiological changes of puberty as well as the emotional problems of adolescence. Several different approaches to restore insulin sensitivity have been explored and will be discussed in this presentation, including the use of adjunct therapies with direct effects on the GH / IGF- I axis and those with direct insulin sensitising effects on the tissues.

S7

Deteriorating diabetes control during adolescence: physiologic or psychologic/psychosocial?

Denis Daneman, MB BCh FRCPC

Division of Endocrinology, Department of Pediatrics, The Hospital for Sick Children and University of Toronto

The pubertal years are a challenging time for adolescents with type 1 diabetes. Both epidemiologic as well as intervention studies provide good evidence that, in general, metabolic control deteriorates in adolescents with diabetes compared to younger children and adults. This presentation will explore possible reasons for this.

A. "Physiologic" factors impacting on metabolic control during adolescence

- i) Insulin resistance of puberty;
- ii) Counterregulatory effects; and
- iii) Possible peripheral hyperinsulinism-induced appetite stimulation.

B. Psychosocial factors impacting on metabolic control

Most of the published literature regarding poor diabetes control during adolescence has focused on psychosocial factors as contributors to poor HbA1c.

- i) Impact of chronic disease – psychological function
- ii) Transition of care from parents to child – family functioning and autonomy issues
- iii) Experimentation behaviour - smoking, ethanol, drugs
- iv) Eating disorders in adolescent females with type 1 diabetes
- v) Inappropriate diabetes management: knowledge or technical deficits

C. Treatment Strategies

- i) Psychosocial; and
- ii) Pharmacologic: adjunctive therapies.

Both psychosocial and physiologic factors contribute to the deterioration in metabolic control in the adolescent with diabetes. How can we separate out the effects of these components? Likely, more often than not they coexist, and one must consider the individual patient and attempt to determine which factors impede their efforts to achieve excellent metabolic control.

OC1

Reassessment of Growth Hormone Status is required at Final Height in Children treated with Growth Hormone Replacement following Radiation Therapy

HK Gleeson, HR Gattamaneni, L Smethurst, BM Brennan & SM Shalet

Departments of Endocrinology, Clinical Oncology & Paediatric Oncology, Christie Hospital, Manchester, UK.

The most appropriate way to manage growth hormone replacement (GH) in the transition to adulthood in children treated with GH for GH deficiency (GHD) is controversial. The GH Research Society suggest that retesting of GH status at final height (FH) is unnecessary in the presence of 'severe organic GHD' and cranial irradiation falls into this etiological category. This recommendation has never been validated.

To investigate whether patients diagnosed in childhood as GHD secondary to irradiation require retesting after FH, GH status has been reassessed in a large cohort of irradiated children treated with GH during childhood.

73 children underwent biochemical assessment of GH status after irradiation and again at FH after GH had been discontinued; 67 of the 73 patients underwent two provocative tests at each time point. The characteristics of the cohort are:- median (range) age at irradiation 5(1-11)y; median biological effective dose (BED) of irradiation to the HP axis 54(23-82)Gy.

During childhood patients with peak GH<20mU/L to provocative testing are treated with GH whereas in adulthood only those with severe GHD, peak GH<9mU/L, are considered. GH status in childhood has been grouped as follows:- peak GH<9mU/L to both tests ie severe GHD (group 1); one test with a peak GH<9mU/L and the other >9mU/L or peak GH of 9-20mU/L to both tests ie moderate GHD (group 2). In childhood 33 & 39 patients were in group 1 & 2 respectively. At retesting severe GHD was diagnosed in 64%(21/33) and 44%(17/39) of those diagnosed in childhood as group 1 & 2. In total 48%(35/73) of the cohort did not fulfill the severe GHD biochemical criteria for GH replacement in adulthood. Using multiple linear regression, GH status at retesting is predicted by BED, age at irradiation and use of chemotherapy.

In conclusion the diagnosis of radiation induced GHD in childhood should not be taken as irrefutable evidence of permanent 'severe organic GHD' and our recommendation is that retesting of GH status at FH is mandatory.

OC2

Functional and Endocrine Outcome in Adult Survivors of Medulloblastoma Cranially Irradiated Before 5 Years of Age

TJA Marr, A Alston & HA Spoudeas

London Centre for Paediatric Endocrinology, Great Ormond Street and University College Hospitals, London, UK.

OBJECTIVES:

Craniospinal irradiation is considered unacceptably neurotoxic before 3-5years of age. We retrospectively ascertained the functional status of adult (>16years) survivors treated with neuraxial radiotherapy for medulloblastoma under aged 5years.

PATIENTS AND METHODS:

We identified 13(5F) long-term [19.4(14.6-25.4)years] survivors, aged 21.1(17.4-30.1)years, treated in 1976-1989 aged 1.1-4.9years. All received >30Gy neuraxial radiotherapy (3 with chemotherapy) and biannual neuroendocrine review. Education, employment, growth, treatment history and details of adult endocrine status were collected. Z scores for adult BMI, height, midparental height and bone mineral density (BMD) were calculated.

RESULTS:

All underwent spontaneous, early puberty aged 9.1(F) and 11.0(M) years, receiving r-hGH therapy 4.2(1.2-10.2) years from diagnosis for 7.1(1.8-10.6)years. All had adult GH deficiency. Only one patient, being investigated for panhypopituitarism, required cortisol replacement. 6/13 have primary hypothyroidism. Adult height [-1.8 (-5.6 to -1.4)sds] was reduced for midparental height [-0.7 (-2.5 to 1.3)sds] but BMI [0.7 (-3.3 to 3.3)sds] was not excessive; BMD t-scores at hip(n10) [-2.2 (-4.7 to 0.7)] and spine(n6) [-1.6 (-4.7 to -0.92)] were reduced.

Most (10/13) attended mainstream secondary schools, 54% with support, just 3 (23%) requiring special education. 5 (40%) are employed fulltime. Median VIQ (n8) 11.1years from diagnosis was 89.5 (59-110) and PIQ was 82 (52-99). Those <3years old (n6, 3F) at diagnosis were shorter adults than those 3-5years old (n7, 2F) [-1.7 vs -1.9sds; p<0.05] and attended special school more frequently (p<0.05) but puberty, employment status, length of r-hGH treatment and BMD t-scores were similar.

CONCLUSION:

Despite high dose neuraxial radiotherapy in infancy (<5years), most '20-year' survivors of medulloblastoma have isolated pituitary GH deficiency and are potentially fertile; half also have primary hypothyroidism. Despite childhood r-hGH therapy, the adult height deficit is significant with reduction in BMD, but normal BMI. Importantly, with support, many can achieve employment and fulfil a useful place within society. These functional outcomes form a basis against which newer therapeutic regimens substituting chemotherapy for irradiation, can be compared.

OC3**ACTH insufficiency: a diagnostic dilemma**

A Mehta, PC Hindmarsh & MT Dattani

London Centre for Paediatric Endocrinology and Metabolism and the Institute of Child Health, London, UK.

ACTH deficiency is life-threatening but the optimal method for establishing the diagnosis remains unclear, particularly in neonates and infants in whom a circadian rhythm is not established. A standard synacthen test (SST) has been the mainstay for diagnosis although few studies have compared it with spontaneous cortisol secretion. We aimed to assess the usefulness of the SST in diagnosing ACTH insufficiency by retrospectively analysing SST-stimulated [peak; delta (peak-basal)] and 24 hour [2-hourly measurements] spontaneous serum cortisol concentrations in 23 patients [M:F ratio 9:14; mean age 0.74 (range 0.03-2.26) yrs] with optic nerve hypoplasia (n=5), septo-optic dysplasia (SOD) (n=15) and isolated hypothalamo-pituitary defects (n=3). A normal SST was defined as a peak serum cortisol concentration >550nmol/L and/or a delta >200nmol/L. Based on the mean spontaneous cortisol concentrations, patients were arbitrarily divided into those with mean <100, mean 100-250 and mean >250 nmol/L. Data are expressed as mean (SD). Mean spontaneous, SST-stimulated peak and delta serum cortisol concentrations were 139 (79), 587 (329) and 454 (296) nmol/L respectively. The spontaneous serum cortisol concentration correlated significantly (p=0.01) with both, SST-stimulated peak and delta cortisol concentrations. The SST was abnormal in 6/23 patients, all of whom had spontaneous serum cortisol concentrations <100nmol/L. Of the patients demonstrating a normal SST (17/23), the spontaneous cortisol concentration was >250nmol/L in 2 patients, 100-250nmol/L in 11 patients and <100nmol/L in 4 patients. These 4 patients had SOD with other pituitary hormone deficiencies and responded symptomatically to hydrocortisone treatment. Our data for the SST yields a sensitivity of 60% and a specificity of 100% as compared with spontaneous cortisol secretion. A subnormal response to SST therefore does not require further investigation, but a normal SST does not rule out cortisol deficiency and measurement of spontaneous cortisol secretion may be required to determine physiological cortisol secretion and exclude ACTH insufficiency.

OC4**Familial Cushing's syndrome in a Danish family secondary to a novel mutation of the regulatory subunit type 1-alpha of the protein kinase A (PRKAR1A) gene**

HL Storr [1], LA Metherell [1], K Main [2], MO Savage [1] & AJL Clark [1]

[1] Department of Endocrinology, Barts and London School of Medicine and Dentistry, London EC1A 7BE UK.; [2] Department of Growth and Reproduction, Copenhagen University Hospital, Copenhagen, Denmark.

Introduction: Cushing's syndrome, due to primary pigmented nodular adrenocortical disease (PPNAD) may be associated with an autosomal dominant multiple neoplasia syndrome resulting from mutations in the regulatory subunit type 1-alpha of protein kinase A (PRKAR1A) gene in 40-50% cases. We report a case of familial Cushing's syndrome due to a novel mutation of PRKAR1A. Case Report: A 10.5yr old male presented with weight gain, acne, depression and virilisation. His mother and maternal grandmother had been diagnosed with Cushing's syndrome and both were treated and cured by bilateral adrenalectomies, histology revealed bilateral nodular adrenal disease. Primary adrenal CS in our case was diagnosed on the basis of: elevated urinary free cortisol >1300 nanomoles per litre (NR 40-340) and failure of serum cortisol to suppress after low and high dose dexamethasone suppression tests. Plasma ACTH was undetectable <1 picomoles per litre (NR 10-50). Serum androstenedione 10.7 nanomoles per litre (NR <1.0; prepubertal) and testosterone 1.8 nanomoles per litre (NR <0.8; prepubertal) were elevated. MR scan of the adrenals was normal. Echocardiography was also normal. These findings are consistent with PPNAD in 5 other paediatric patients we have studied. Method: PCR of the 10 coding exons of the PRKAR1A gene was performed on genomic DNA, using primers directed to intronic sequences and the products sequenced directly. Results: Sequencing of the patient's DNA revealed a novel heterozygous mutation (IVS3 as+1 G to T) at the junction of intron3/exon 4A of the PRKAR1A gene. This mutation leads to a failure to splice exon 4A and the resulting transcript will encode a truncated, non-functional protein. Conclusion: We predict that this novel mutation will cause haplo-insufficiency of the PKAR1A gene product and subsequent de novo defects in the normal allele in adrenal cells are likely to lead to hyperplasia and development of PPNAD/CS. Mutations in PKA represent the principle genetic cause of familial CS.

OC 5

Phenotypic variability in a family with Adrenal Hypoplasia Congenita due to a novel DAX-1 mutation

I Ahmad [1], P Adlard [2], P Duncan [3], J Harvey [3], J Tolmie [4] & M Donaldson [1]

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The proband, a male, presented aged 2.1 years with a 6 week history of intermittent vomiting following an episode of croup, and a background history of recurrent fevers and increasing pigmentation. Investigation showed plasma sodium 123, potassium 6.0 mmol/l, cortisol 35 and 60 nmol/l before and 60 minutes after synacthen, with elevated ACTH (2333 ng/l) and renin (17 pmol/ml/hr). He responded dramatically to treatment and now aged 7.8 years he is well, on the 25th centile for height (10th at presentation), testes 3ml in volume. He is receiving hydrocortisone 13.4 mg/m²/day, and fludrocortisone 54 mcg/m²/day, having become hypertensive on 133 mcg/m²/day. A younger brother had a normal cortisol response to synacthen shortly after birth and remains well on no treatment.

Family history revealed that two paternal uncles died within minutes of birth despite normal birth weights and gestation. A third uncle failed to thrive during infancy but improved with a short course of cortisone treatment. He was then untreated until the age of 5 years when, following the death at 10 days of a further male sibling with urinary salt loss and small adrenal glands at post mortem, he was further investigated and found to have adrenal insufficiency. He went on to require pubertal induction, and is currently fit and well, receiving replacement therapy with testosterone, hydrocortisone 16.6 mg/m²/day, and fludrocortisone 56 mcg/m²/day.

A previously undescribed C to G substitution at nucleotide position 794 of the DAX 1 gene was identified in the proband, surviving maternal uncle, mother, and maternal grandmother but not in the unaffected brother. The phenotypic variability in this family is striking, the proband surviving untreated for over 2 years with low mineralocorticoid requirement and normal testicular size for age, while an affected uncle died within 10 days and two putatively affected uncles died soon after birth.

OC6

Partial Loss of Function Mutations (delF54) in CYP17 can Present with Microphallus

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Combined 17 α -hydroxylase/17,20-lyase deficiency is a well-recognized disorder of steroid biosynthesis resulting from mutations in the gene encoding cytochrome P450c17 (CYP17). Patients (46,XY) with this condition typically have a complete lack of virilization and develop hypertension and a failure of puberty with time. Milder forms of combined 17 α -hydroxylase/17,20-lyase deficiency have been described in 46,XY patients with ambiguous genitalia, but in most cases a female sex-of-rearing is chosen. Here, we describe an unusually mild form of combined 17 α -hydroxylase/17,20-lyase deficiency in a 17 day old baby with microphallus (0.5cm) born to consanguineous Asian parents. He had bilaterally descended testes and a meatal opening at the tip of the penis. Initial investigations revealed a 46,XY karyotype, normal electrolytes, elevated basal LH (basal 23.2 iU/l, 37.2 iU/l post-LHRH), poor cortisol response to a standard synacthen test (peak 203 nmol/l) and a poor testosterone response to hCG stimulation (basal 2.3 nmol/l; 3.3 nmol/l after 3 weeks). Adrenal androgens (DHEAS, androstenedione) were low and progesterone (12.4 nmol/l [0.4-5]), aldosterone (5229 nmol/l [1000-3800]) and ACTH (113 ng/dl [10-50]) were mildly elevated. Urine steroid profile showed a single abnormal peak of 16-hydroxypregnenolone. Following Ethical Review Board approval and informed consent, mutational analysis of the CYP17 gene revealed homozygous deletion of a single phenylalanine at codon 54 (delF54). This highly conserved amino-acid in the alpha-A helix is involved in membrane attachment and substrate entry. This case demonstrates that partial combined 17 α -hydroxylase/17,20-lyase deficiency can present with microphallus and careful biochemical and genetic evaluation is warranted in such cases. Indeed, even short-term treatment with hydrocortisone and testosterone has resolved the hyperaldosteronism and improved penile corporal volume, hopefully preventing development of hypertension, hypokalaemia and poor penile development in later life. Furthermore, we have now found this delF54 change in two other unrelated patients, suggesting a British Asian founder effect.

OC 7

Bone Mineral Density in children and adolescents with galactosaemia

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Previous research has demonstrated that bone mineral density in post-pubertal females with galactosaemia and premature ovarian failure is reduced. Two previous reports suggest bone mineral density is reduced in pre-pubertal children of both sexes. Failure to achieve normal peak bone mass has implications for bone health in later life.

Objective: To determine growth and bone mineral apparent density (BMAD) in children and adolescents with galactosaemia and compare with paediatric reference data.

Methods: Spinal and whole body DXA bone density measurements were performed in 20 children and adolescents (11 male, 9 female, mean age 13.0 years, range 5-22) with galactosaemia. BMAD Z scores were calculated using normative paediatric data established for the Lunar Prodigy scanner. Local ethical approval was obtained.

Results: This study demonstrates that although lumbar BMAD z scores were reduced for age (mean Z-score -0.62, SE=0.24, p=0.02) only one adolescent had a BMAD more than 2 standard deviations below the mean. The mean whole body bone density Z score was -0.93, SE=0.18, p<0.0001, with two individuals with Z scores < -2.0. There was no relationship between calcium intake and BMAD and only three individuals had an insufficient calcium intake. Height SDS scores were significantly reduced for this group of patients (mean Z-score -1.2, SE 0.23, p<0.0001) when compared to the 1990 UK standards. Pubertal status was appropriate for age in all but two patients. No significant gender difference in bone density was observed.

Conclusion: The results indicate that bone density in the majority of children with galactosaemia is within the normal range for age. Growth during childhood and adolescence may be compromised as indicated by the significantly reduced height SDS in this group. Factors influencing attainment of peak bone mass in galactosaemia warrant further research to facilitate avoidance of osteoporosis in later life.

OC 8

Expression of Insulin, Glucagon and Voltage-gated-calcium channel subunits in early human embryonic pancreas

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Background

Little is known about the timing of expression of hormones and ion channels in the embryonic human pancreas as it develops from its primitive hormone-negative state into the mature organ.

Aims: The aims of this study were to document the expression of mRNAs for insulin, glucagon and voltage-gated calcium channel subunits (VGCCs) in early human pancreatic tissues (5-13 weeks gestation), to quantify mRNA expression over time and to correlate mRNA expression with protein expression using immunohistochemistry.

Methods:

Human embryonic pancreas was obtained from patients undergoing first trimester termination of pregnancy (local ethics approval & informed consent). Samples were grouped by gestational age as 5-6, 7-8, 9-10, 11-12 and 13+ weeks.

Quantitative RT-PCR: RNA was extracted from tissues using TRIzol. cDNA was generated using Superscript II. Primer and probe sets were designed using Primer Express 2. Sequences of interest were amplified on an ABI 7700 using reagents from Eurogentec, Belgium. Target gene expression was normalised to fl-actin and calculated as an n-fold difference relative to the 5-6 weeks age group.

Immunohistochemistry- Indirect immunohistochemistry was performed on paraffin sections of the same tissues used for quantitative RT-PCR using primary antibodies to insulin and glucagon from Dako Ltd, USA.

Results

Insulin and glucagon mRNA expression rose significantly at 11-12 weeks. Insulin was 2878-fold (SD range 1987-4168; p<0.001) higher at 11-12 weeks and 5710-fold (SD range 2606-12510; p<0.002) higher at 13 weeks+ relative to 5-6 weeks (1, SD range 0.27-3.6), while glucagon was 1929-fold (SD range 853-4360; p<0.01) higher at 11-12 weeks, and 3066 (SD range 2123-4428; p<0.01) higher at 13 weeks+ relative to 5-6 weeks (1, SD range 0.23-4.3). In contrast, mRNAs for VGCCs were expressed at similar levels in all age groups. Elevation of insulin and glucagon mRNAs correlated with the immunohistochemical detection of these proteins in sections of pancreas after 10 weeks foetal age.

OC9

Further investigation of the IGF-I gene association with birth size small for gestational age (SGA) using haplotype analysis

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Objective

We have previously described the association of birth SGA with IGF-I genotype using microsatellite markers. The objective of the present study was to further explore the genetic region of association using single nucleotide polymorphisms (SNPs).

Subjects

Short SGA (n=124), SGA catch-up (n=57) and normal stature AGA (n=112) subjects were recruited in the Goteburg Pediatric Growth Research Centre. Subjects gave informed consent to genetic studies in accordance with Local Ethics Committee approval.

Methods

Eight IGF-I gene SNPs were selected from www.ensembl.org according to their genetic position and the availability of allele frequency data. Genotyping was performed using Amplifluor assays that were designed and run by KBioscience, Basildon, UK. Haplotypes were constructed using PHASE (1) and association analysis was performed using CLUMP software to undertake exact Chi squared tests (2).

Results

Four proximal markers spanning 50,648 base pairs were combined to form haplotypes (heterozygosity 0.73). There was no significant association with either SGA phenotype and the SGA phenotypes were not significantly different. Similarly there were no significant results when haplotypes were constructed from the three proximal markers spanning 18,867 base pairs (heterozygosity 0.70) were analysed.

Four different markers in the 3' region spanning 19,117 base pairs formed haplotypes (heterozygosity 0.64) that were not associated with either SGA group compared to controls. However there was a significant difference ($p=0.03$) in allele distribution when the two SGA groups were compared.

Conclusions

No haplotypes were identified which associated with birth size SGA. However the significant difference found in distal haplotypes between SGA subjects with and without catch-up suggest that IGF-I genetic variation may influence the pattern of postnatal growth in SGA subjects.

1. Stephens, M et al. (2001). *Am J Hum Genet* 68, 978—989.

2. Sham PC & Curtis D. (1995) *Ann Hum Genet* 59(1), 97-105.

OC10

Do cord IGF-I, insulin, leptin and ghrelin levels reflect subsequent infant feeding behaviour and growth?

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Background: Ghrelin stimulates appetite and weight gain in adults and leptin inhibits appetite and induces weight loss. Prevailing insulin concentrations may also influence human feeding behavior.

Objective: To determine whether there is a relationship between IGF-I, insulin, ghrelin and leptin concentrations in cord blood and milk intake, feed frequency (over the first six days of life) and growth up to twelve weeks of age.

Methods: 100 healthy term infants were recruited at birth. Milk intake was determined by difference weighting of bottles of formula milk. Infants were weighed at birth and at 12 weeks of age. Data was converted to SD scores using British 1995 growth reference data. 17 infants had slow weight gain (defined as a change in z score of -0.67) and were contrasted with the other 83 using logistic regression. Local Ethical Committee approval was obtained.

Results: IGF-I, insulin and leptin were related to birthweight ($p < 0.001$) but ghrelin was not ($p > 0.1$). Birthweight predicted mean milk intake day from day 1 to 6 ($p < 0.001$) and was inversely related to weight gain ($r = -0.25$, $p < 0.05$). Ghrelin was inversely related to insulin concentrations ($r = -0.32$, $p < 0.05$) and whilst there was no relationship between cord blood ghrelin, leptin or insulin and milk intake, insulin was negatively and independently associated with feed frequency ($p < 0.05$). After controlling for birthweight we found that ghrelin was associated with slow weight gain ($p < 0.01$) but leptin was not.

Conclusion: Our data suggests that low circulating insulin levels may be a stimulus for infant feeding. Infants with slower weight gain have lower basal ghrelin levels and may therefore have a reduced orexigenic drive.

OC11

Height Velocity from Birth to 6 years in Ex-premature Infants and Controls

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Introduction. As part of a larger growth and metabolic study, longitudinal height measurements were obtained at least yearly on a group of ex-premature babies and controls. All measurements were made by a single observer using standard methodology and equipment. Length was measured supine and age was conventionally corrected for prematurity until 2 years of age. Whole year height velocities were calculated for each individual and compared to the UK data first described by Tanner and Whitehouse in 1965.

Results. Full first year data was available on 167 children - 45 controls (26M; 19F); 87 children born 30-36w gestation (43M; 44F) and 35 children born 22-30w gestation (21M; 14F). By six years the numbers with complete longitudinal data had fallen to 126 - 35 (21M; 14F), 73 (41M; 32F) and 18 (9 M; 9F) for each group respectively.

Ex-premature infants grew faster than controls (mean 25.9 cm/yr; 3rd centile 18.3 to 97th centile 33.4 cm/yr) in the first year, (mean 33.4 cm/yr, 24.4. to 42 cm/yr for <30w : 31 cm/yr, 23.8 to 38 cm/yr for 30-36w). Thereafter the 50th, 3rd and 97th velocity centiles almost exactly matched the Tanner and Whitehouse data for both sexes apart from an observed wider variability of velocity in all groups between 2-3 years of age.

Discussion. The Tanner and Whitehouse data over this age range was calculated from longitudinal data on 80 randomly chosen central London children of each sex in the 1950's. Apart from the first year of life, when many ex-premature babies are demonstrating catch-up growth, and a wider range of velocities observed between 2-3 years of age these standards are still applicable to normal and ex-premature children from Sheffield more than 40 years later.

OC12

Multivariate analysis on factors affecting suppression of thyroid stimulating hormone in treated congenital hypothyroidism

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OBJECTIVE To determine the factors which influence the suppression of thyroid stimulating hormone (TSH) in infants with congenital hypothyroidism (CH) following treatment.

METHODS A retrospective study examining the patterns of TSH from diagnosis to 1 year of age in 112 neonates diagnosed with CH. Patients were classified into 3 groups on the basis of thyroid scans: athyreosis, dysgenesis and presumed dyshormonogenesis. Treatment was started with L-thyroxine (L-T4) at 25mcg/day at diagnosis and adjusted according to biochemical assessments of thyroid function. Adequate TSH suppression was defined as serum TSH concentration <6mU/l. The following factors were evaluated to assess their effect on the suppression of TSH at 1 year of age: confirmatory plasma TSH, confirmatory plasma T4, mean age of starting L-thyroxine(days), dose of L-T4 at diagnosis, 6 weeks, 3 months and 6 months and the aetiology of the CH.

Mean±SEM were used for data presentation. SPSS statistical package was used for data analysis. Fisher's exact and t-test was used for univariate analysis initially. Variables were then entered in a backward stepwise logistic regression model for multivariate analysis.

RESULTS All infants had radionuclide scans prior to treatment: athyreosis(n=32, dysgenesis(n=63) and dyshormonogenesis(n=17). Mean age (months) of TSH normalisation to <6 mU/l was significantly better in the dyshormonogenesis group: dyshormonogenesis 3.4±0.9, dysgenesis 14.5±1.4 and athyreosis 16.7±2.0 (athyreosis vs dyshormonogenesis p< 0.0001, dysgenesis vs dyshormonogenesis p< 0.0001). Logistic regression for factors affecting TSH suppression at 1 year of age found aetiology of CH to be the only significant factor(p=0.02).

CONCLUSION

1. The only independent factor which influences the suppression of TSH at 1 year of age is the aetiology of CH. There is a need to determine the aetiology of CH so that athyreosis and dysgenesis can be treated more vigorously for earlier normalization.

2. Pre-treatment TSH and T4, and initial L-T4 dose identified in previous studies using univariate analyses have not been identified in this study as an independent factor affecting TSH suppression at 1 year of age.

OC13

A clinical and molecular analysis in patients with the complete androgen insensitivity syndrome

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Androgen insensitivity syndrome (AIS) is caused by mutations in the androgen receptor (AR) gene, which comprises exon 1 for transactivation, exons 2-3 for DNA binding and exons 3-8 for ligand binding. The complete form (CAIS) manifests by a normal female phenotype.

We have studied 120 patients with CAIS. The majority presented with inguinal hernia (68 patients, 57%), of whom half were bilateral. Fourteen (12%) presented with primary amenorrhea; 34 (28%) were related to positive family history, and 4 were diagnosed antenatally (3%). An hCG stimulation test was performed in 27 patients; the median testosterone rise was 10.8 nmol/L. Androgen binding studies in genital skin fibroblast were performed in 37 patients: 24 showed negative binding, 7 abnormal, and 6 had normal binding.

A mutation screen was performed in 96 patients. 80% mutations were identified. The spontaneous mutation rate was 10%. The majority were missense mutations, the remainder comprising deletion, duplication, insertion and splice mutations. Most of missense mutations were in the ligand-binding domain; whereas 60% of nonsense mutations were in exon 1.

Two mutant receptors (Arg 855 His, Leu 907 Phe) with normal binding were created for functional studies in vitro. These showed marked reduction in receptor transactivation activity and in amino/carboxy (N/C) terminal interactions.

Based on an analysis of a large study group, we conclude that inguinal hernia is the commonest presentation of AIS in children; a karyotype is not currently routine for this surgical problem. We recommend an hCG test in support of the diagnosis, and to exclude an androgen biosynthetic defect. In addition to abnormal ligand or DNA binding, defective N/C interaction may explain the phenotype in CAIS. Exons 4, 5, 7 are preferential regions for missense mutations. The minority of patients with no gene mutation found may have an abnormality in RNA processing or in AR expression.

OC14

Insulin Sensitivity in Young Women With Turner Syndrome

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Background: Women with Turner Syndrome, 45XO, (TS) have a two to four-fold increased risk of impaired glucose tolerance and early onset type 2 diabetes. Insulin resistance may be an intrinsic feature of TS, but there are conflicting data in the literature.

Aim: To compare insulin resistance using a hyperinsulinaemic euglycaemic clamp in young women with TS and age matched healthy control women.

Methods: 16 women with TS, median (range) age 30 (21 to 43) yrs and 16 healthy control women age 30 (18 to 33) yrs were recruited. None had evidence of impaired glucose tolerance or type 2 diabetes. Following an overnight fast, a one step hyperinsulinaemic (0.5 mU/Kg/min insulin), euglycaemic clamp was performed between 0900 and 1100h and the mean glucose infusion rate for the final 30min (M-value; mg/kg/min) determined. DXA was used to assess body composition in a subgroup of 8 women with TS and 16 control women.

Results: Data are expressed as mean \pm SEM or median (interquartile range). Women with TS were shorter; 149.9 \pm 1.7 vs 166.1 \pm 1.6 cm ($p < 0.01$), had a greater BMI; 27.9 \pm 1.4 vs 22.9 \pm 0.9 kg/m² ($p < 0.01$) and greater percentage body fat; 38.4 \pm 1.8 vs 31.3 \pm 2.0 ($p < 0.05$) than control women. There was no difference in fasting glucose; 4.6 \pm 0.1 vs 4.6 \pm 0.2 mmol/l, but women with TS had higher fasting insulin; 67.8(26.9-121.2) vs 31.9(20.0-55.4) pmol/l ($p < 0.01$). HomaS was lower in women with TS; 78(45-196) vs 183(97-265) % ($p < 0.02$). During the hyperinsulinaemic clamp glucose; 4.2 \pm 0.07 vs 4.4 \pm 0.1 mmol/l and insulin; 258 \pm 51 vs 214 \pm 11 pmol/l concentrations were equivalent in the two groups, but even allowing for BMI, women with TS had a lower M value than control women; 2.9 \pm 0.5 vs 5.2 \pm 0.7 mg/kg/min ($F = 7.1$, $p < 0.02$).

Conclusions: Women with TS, with normal glucose tolerance are more insulin resistant than control women of equivalent age, independent of BMI.

OC15**Adult thresholds for obesity may not define metabolic risk in children: The EarlyBird Diabetes Study**

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Background: Paediatric cut-offs for overweight and obesity, corresponding to an adult BMI of 25 and 30, respectively, have been proposed by the International Obesity Task Force. Adult BMI thresholds for overweight and obesity relate to health risk. The centile equivalents proposed for children, however, were derived statistically, not according to risk. Insulin resistance, not fatness itself, poses the metabolic risk. We sought to establish whether cut-points defining overweight and obesity in young children embrace similar thresholds for insulin resistance as in adults.

Subjects and Methods: BMI, or centile equivalent in children, and insulin resistance (HOMA-IR) from fasting bloods, were measured in 300 healthy children (mean age 5y) and parents (mean age mothers 33y, fathers 36y).

Results: IR in mothers and fathers rose significantly according to BMI category. The pattern in children was similar, but levels of IR were much lower for equivalent 'fatness'. Mean IR for normal (BMI <25), overweight (BMI 25.0 - 29.9) and obese (BMI over 30) mothers was 1.23 (n= 92), 1.75 (n= 67) and 2.78 (n= 39); for fathers 1.29 (n= 68), 1.65 (n= 115) and 3.15 (n= 51); for children, 0.69 (n= 244), 1.01 (n= 44) and 1.24 (n= 12). In mothers and fathers, BMI accounted for 41% and 28% of the variance in IR, respectively (p< 0.001). In children, BMI accounted for only 6% of the variance in girls (p= 0.005) and just 2% in boys (p= 0.06).

Conclusions: The proposed BMI thresholds for overweight/obesity in young children are poor predictors of insulin resistance and, by implication, of metabolic risk. Furthermore, BMI tracks poorly from childhood to adulthood and undue emphasis on weight may stigmatise the fat child unnecessarily. Crucially, we now need to establish whether markers of metabolic disturbance track from early childhood, before extrapolating risk from adults to young children.

OC16**Development of an Assessment Tool to select children at risk of Type 2 Diabetes for Oral Glucose Tolerance Testing**

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Background:

Children are increasingly being referred to paediatric clinics with obesity. It is not clear which of these children are at risk of glucose intolerance, and it is not practical to undertake oral glucose tolerance tests on all referrals.

Aims:

We aimed to audit our own practice of oral glucose tolerance testing in children referred to clinic with obesity, acanthosis or suspected diabetes secondary to insulin resistance. We then aimed to refine our selection criteria for testing to minimise unnecessary tests.

Methods:

We undertook a case note review of all children who had undergone an oral glucose tolerance test (OGTT) during a 4 year period. Data collected included sex, ethnicity, age, reason for referral, family history of diabetes, height and weight, examination findings and laboratory results.

Results:

Of 66 OGTTs undertaken during the time period, 53 were normal and 13 (20%) were abnormal (4 children had diabetes, 8 had impaired glucose tolerance and 1 had impaired fasting glycaemia). Factors that predicted abnormal results were: age greater than 11 years, female sex, higher body mass index standard deviation score, ethnic minority origin, strong family history of type 2 diabetes and signs of insulin resistance.

Conclusions:

On the basis of these results we have revised our selection process for OGTT by developing an assessment tool, which uses clinical features to categorise children into low and high risk of having an abnormal OGTT. Testing only those children who fall into the high risk category picks up all 13 of the abnormal results but reduces the overall number of OGTTs undertaken to 36, giving a sensitivity of 100%, specificity of 57% and a positive predictive value of 36%, i.e. that 3 children need to be tested to identify one abnormal result.

OC17

Abnormalities of glucose homeostasis in obese children and adolescents

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Objectives. Little is known about the prevalence of abnormalities of glucose homeostasis (AGH) in obese children and adolescents, particularly in those from high risk Asian and Black ethnicities. There is also a lack of clarity regarding the extent of appropriate investigation for childhood obesity. We examined the prevalence of AGH in obese children and adolescents, and assessed the usefulness of fasting measures of insulin / glucose as predictors of AGH identified on an oral glucose tolerance test (OGTT).

Methods. We performed an OGTT (1.75mg/kg glucose) on 124 children and adolescents aged 2-18 years with simple obesity. None were known to have DM. All children were obese (BMI centile >99%). Abnormalities of glucose homeostasis were defined as: impaired fasting glucose (IFG) = fasting blood glucose (BG) \geq 6.0mmol/L; impaired glucose tolerance (IGT) = BG >7.0 at 120min; diabetes = fasting BG \geq 7.0 or BG >11.1 at 120min. Insulin resistance (HOMA-IR) was calculated from fasting values using the homeostasis model.

Results. 66% female; mean age 11.9 years. Ethnicity: White 60%, Asian 26%, Black 11%, mixed 3%. One subject (0.8%) had diabetes, 1 (0.8%) had IFG and a further 14 (11.3%) had IGT. Risk of AGH was associated with higher age (OR 1.3, p=0.02) but not with BMI, sex, family history, ethnicity, birth-weight or acanthosis. Neither fasting insulin nor BG were associated with risk of AGH. Forty-two (37%) had HOMA-IR \geq 4.5 (> 1 standard deviation above reference mean). Those with HOMA-IR \geq 4.5 were significantly more likely to have AGH (OR=4.1, p=0.017), a finding unchanged when controlled for BMI or age.

Conclusions. IGT and insulin resistance are concerning common in obese UK children and adolescents across ethnicities. Silent diabetes is rare. HOMA-IR calculated from fasting samples may be useful for identifying high-risk individuals who require further investigation.

OC18

Compound heterozygote mutations in the glucose transporter (GLUT 2) gene are a novel familial cause of adolescent diabetes

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Title:Compound heterozygote mutations in the glucose transporter (GLUT2) gene are a novel familial cause of adolescent diabetes
Fiona Regan, Andrew Hattersley, Peter Betts

The glucose transporter type 2 isoform (GLUT 2) is a low affinity transporter that ensures intra-cellular glucose reflects extra-cellular glucose. In conjunction with glucokinase it regulates both hepatic glucose uptake and insulin secretion from the pancreas. It is also expressed in intestinal and renal absorptive epithelial cells. Homozygous mice knockout models of GLUT 2 gene have demonstrated abnormal postnatal pancreatic development, loss of glucose induced insulin secretion and early development of type 2 diabetes. However in man diabetes has not been described and mutations of both copies of the GLUT 2 gene have only been associated with glycosuria and Fanconi-Bickel syndrome.

We present a pair of siblings who initially presented aged 5 months and 1 month with Fanconi-Bickel syndrome who had classical features of glycosuria, hepatorenal glycogen accumulation, fasting hypoglycaemia but normal glucose tolerance. On routine blood tests at the ages of 17 and 14 they were noted to have hyperglycaemia and subsequently raised HbA1C. They were asymptomatic and non-obese with BMIs of 21 and 20 respectively.

Investigation showed these children are compound heterozygotes for the 1363delG and 1405C-T GLUT 2 mutations. Beta cell antibodies were not detected.

Time

Sib 1

Glucose (mmol/L)

0 mins 9.7

60 mins 18.8

120 mins 18.8

Insulin (mU/L)

0 mins 1.8

60 mins 3.0

120 mins 12.6

HbA1c 9.6%

Sib 2

Glucose (mmol/L)

0 mins 4.5

60 mins 15.7

120 mins 17.8

Insulin (mU/L)

0 mins <0.8

60 mins <0.8

120 mins 2.1

HbA1c 8.6%

Oral glucose tolerance confirmed diabetes and showed minimal response despite marked hyperglycaemia

In conclusion we present the first report of mutations of GLUT 2 resulting in familial adolescent-onset diabetes. This emphasises the central role of GLUT2 in normal beta cell function and the need for thorough investigation of adolescent diabetes for an underlying aetiology.

OC19**Novel homozygous glucokinase mutation in a Pakistani family causing permanent neonatal diabetes with preserved basal insulin release; does the mutation determine the phenotype?**

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Heterozygous mutations of glucokinase cause maturity onset diabetes of the young (MODY 2). In white Europeans two families have been described with homozygous glucokinase mutations causing permanent neonatal diabetes. We present the first Asian infant with neonatal diabetes due to a novel glucokinase mutation.

A growth-restricted baby, birthweight 1.7 kilograms, was born to healthy consanguineous UK Pakistani parents. There was no gestational diabetes. The baby's blood glucose was 14.5 millimoles/litre with no ketonuria. Hyperglycaemia continued, and neonatal diabetes requiring insulin was diagnosed.

The insulin requirement remained after the neonatal period. There was an extensive family history of presumed type 2 diabetes. Investigation of the infant revealed no uniparental disomy of chromosome 6, but a novel homozygous glucokinase mutation R397L. Fasting blood glucose results in the asymptomatic parents were 5.8 millimoles/litre (mother) and 6.1 millimoles/litre (father); consistent with glucokinase heterozygous status. The infant remains on insulin (0.6 units/kilogram/day) at 9 months old and is thriving.

In Europeans glucokinase mutations are an uncommon cause of neonatal diabetes. Maturity onset diabetes of the young mutations have recently been described in Asians. Due to increased consanguinity in Pakistani families, glucokinase mutations may in fact be an important cause of neonatal diabetes in Pakistani infants.

Previously described cases (M210K, T228M) have negligible insulin secretion, and a persistently high insulin requirement. These mutations are close to glucokinase binding sites for glucose and adenosine triphosphate and are predicted to raise the threshold for insulin secretion to a blood glucose of 55 millimoles/litre or more. In contrast our patient had a c-peptide of 500 picamoles/litre, lower insulin requirement, and a mutation remote from the binding sites. We conclude that determination of the mutation in neonatal diabetes due to glucokinase may predict disease phenotype.

OC20**Early peripheral neuropathy identified in adolescents with type 2 diabetes**

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Aims: To examine the presence of microvascular complications in adolescents with type 2 diabetes.

Methods: Six adolescents with type 2 diabetes (insulin resistance was confirmed by oral glucose tolerance test) were assessed for early complications. All were on metformin, and one had additional treatment with insulin. Median duration of diabetes was 1.8 years (range 0.8-3.0 years) and HBA1c 7.2% (range 5.8-9.3%). All had blood pressure checked with a Hawksley random zero sphygmomanometer, an ophthalmologic examination for diabetic retinopathy, renal function tests, urine checked for microalbuminuria, and a ECG rhythm strip. An experienced podiatrist performed formal testing for peripheral neuropathy including: foot pulse palpation, tendo-achilles reflexes, large nerve fibre function (vibration and threshold for light touch/pressure) assessed by a 128 Hz tuning fork for a semi-quantitative measure of vibratory sense, and by the Semmes-Weinstein monofilament test using standard 10-gram monofilaments (for risk of ulceration and amputation), small nerve fibre function (pain) assessed by pinprick neurotip, and plantar callus test (if present, calluses are associated with a higher risk of ulcers).

Results: Three adolescents had evidence of peripheral neuropathy, with abnormal large and small nerve fibre function. Five out of six had plantar callus present, and weak but palpable posterior tibial pulses. All subjects had normal tendo-Achilles reflex, and normal response to vibration. None had signs of diabetic retinopathy. None were hypertensive. Renal function and ECGs were normal.

Conclusions: Unlike type 1 diabetes, microvascular complications in type 2 can be present soon after diagnosis. This is a well-recognised phenomenon in adults when hyperglycaemia has been present undiagnosed for a significant period of time. In our young population duration must be short but complications clearly occur early. Therefore, all children with type 2 diabetes need surveillance for complications from the time of diagnosis.

OC21**Block and replace therapy versus dose titration in the management of thyrotoxicosis**

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Introduction

There are two main approaches to the medical management of autoimmune thyrotoxicosis at presentation; blocking thyroid gland function with antithyroid drugs and replacing thyroxine or titrating the dose of antithyroid drug to maintain a euthyroid state. We have reviewed the notes of a group of thyrotoxic children to establish which treatment regimen provides greater biochemical stability.

Methods

The thyroid function tests of 12 children managed by the two treatment regimens in two endocrine units were reviewed. The mean age of patients managed by block and replace was 11.5 years (range 9.8 to 14.4) and those by dose titration was 12.0 years (range 6.5 to 14.4). We examined the time taken for the TSH to rise, biochemical stability as determined by the proportion of time that TSH levels were within the normal range once euthyroidism was established, the standard deviation of thyroxine concentrations and the interval between clinic appointments.

Results

The block and replace regimen group became euthyroid after 22 weeks (6 to 39) and the dose titration by 17 weeks (5 to 30). Patients managed with a block and replace regimen visited hospital outpatients every 16 weeks and those managed with dose titration every 13 weeks. The patients managed with block and replace were more stable than the dose titration group as reflected by a reduced number of occasions when TSH levels were outside the normal range (10 % versus 48%; $p = 0.04$) with a reduced FT4 Standard deviation of 3.0 versus 6.2 ($p = 0.03$).

Conclusions

In this small audit 'block and replace' antithyroid drug therapy provided greater biochemical stability once euthyroidism had been achieved. A more comprehensive study is planned under the auspices of the BSPED clinical trials unit to examine the two approaches in more detail.

Please note: the number in brackets beside the poster number, refers to the poster board location in the Circulation Foyer. A plan will be available on site.

P1 (13)

Transient neonatal secondary hypothyroidism and decompensating hyperthyrotropinaemia; further evidence of thyroxine transfer to the fetus in utero

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Introduction

The severe phenotype of the hypothyroid infant born to the hypothyroid mother and studies of the development of children born to mothers with mild thyroid dysfunction in early pregnancy illustrate the importance of thyroxine transfer from mother to fetus. We present two further clinical scenarios which reflect this process.

Scenario 1

A female infant was born at 33 weeks gestation to a mother with uncontrolled thyrotoxicosis. Mother had a TSH less than 0.01 milliunits per litre with free thyroxine concentrations greater than 83.4 picomole per litre throughout pregnancy. The infant had a TSH of 0.01 milliunits per litre and free thyroxine concentrations of 14.2 picomole per litre at birth. The TSH remained suppressed in the presence of low free thyroxine levels on day 3 and so the infant was commenced on thyroxine replacement. The TSH became measureable at 5 weeks of age. A transient central hypothyroid picture in this infant can be explained by thyroxine transfer from a profoundly thyrotoxic mother.

Scenario 2

Two term neonates were identified as borderline neonatal screening 'failures' with venous TSH values of 10.6 milliunits per litre and 5.9 milliunits per litre. Both mothers had normal thyroid function. 5 days later (infant 1) and 6 weeks later (infant 2) the TSH values had risen to 135 and 23.4 milliunits per litre with a free thyroxine of 7 and 11 picomole per litre respectively. Both were commenced on thyroxine replacement. The pronounced postnatal rise in TSH in these infants may reflect maternal thyroxine transfer.

Conclusions

The potential for hypothalamo-pituitary-thyroid suppression in the infant of the thyrotoxic mother and decompensation in the child with a mildly elevated TSH on neonatal screening are further illustrations of the significance of maternal thyroxine transfer to the fetus.

P2 (28)

Perceptions of body weight in seven year old children and their mothers: The EarlyBird Diabetes Study

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Background: Recognition of overweight is an essential first step in weight management and prevention. It would therefore be useful to know the extent to which children and their parents are aware of their body weight.

Aims: 1 To determine children's perceptions of their own weight. 2 To determine mothers' perceptions of children's weight. 3 To assess maternal concern about children's weight. 4 To investigate the impact of socio-economic factors on actual and perceived weight.

Subjects and methods: Questionnaire data from 230 healthy children (mean age 7.4y) and mothers. Outcome measures child: BMI, perceived weight from pictorial rating scale. Mother: BMI, perceived weight of child, level of concern about weight, social class, educational level.

Results: Children were significantly heavier than UK 1990 standards ($p < 0.001$) with 19% overweight (> 91 st centile). The accuracy of the child's perception was unrelated to BMI ($p = 0.66$), with 51% underestimating and 17% overestimating their own weight. Mothers of overweight, as opposed to normal weight children, were less likely to perceive their weight accurately ($p < 0.001$) and 71% underestimated it. Only where the child was obese (> 98 th centile) was the mother more accurate. Overweight and obese mothers (55%) were more likely to perceive their child's weight correctly than normal weight mothers ($p = 0.06$). Only one third of mothers with overweight children were concerned. Social class was unrelated to BMI in mothers or children, but children of mothers with lower educational attainment were more likely to be overweight ($p = 0.05$). However, neither social class nor educational level contributed to mothers' awareness of, or concern about, overweight in their children.

Conclusions: A substantial proportion of children and young mothers, from across the range of social and educational backgrounds, is overweight. That most mothers are unable to recognise an overweight child gives cause for concern and may reflect an insidious acceptance of overweight as normal.

P3 (5)**Audit of Investigation of Hypoglycaemia in Children**

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Introduction: Although guidelines exist, the investigation of children with hypoglycaemia is potentially problematic. Audits of such investigations are not well described - we found only one report that evaluated diagnostic fasts in a national referral centre.

Aims: To audit the investigation of both spontaneous and induced hypoglycaemia in children against existing guidelines in a regional centre.

Methods: Retrospective review was made in children who presented with spontaneous hypoglycaemia (blood glucose <2.6mmol per litre) or those admitted for starvation tests over a 5-year period. Neonates were included if hypoglycaemia resulted in measurement of insulin, growth hormone or cortisol. Children with type 1 diabetes mellitus and those undergoing growth hormone stimulation tests for investigation of growth disorders were excluded.

Results: Fifty-eight children were identified who presented with spontaneous hypoglycaemia (42 episodes) or who underwent controlled fasting (n=42). The diagnosis was unclear (including ketotic hypoglycaemia) in 21 children (36%). Twelve children had hyperinsulinism (6 transient, 6 persistent), six had adrenal insufficiency and one had methyl malonic aciduria. The clinical history was inadequately documented in 39% episodes (n=84). Substantial details of clinical examination were missing in 60%. Half the protocol investigations were omitted in 63%. The protocol was adhered to better in controlled fasts than at times of spontaneous hypoglycaemia with respect to recording growth data (p<0.001), overall performance of investigations (p<0.001) and follow-up arrangements (p=0.04). Hypoglycaemia occurred in 11 of 42 controlled fasts. One child who was fasted had hypoglycaemic convulsions, and another had altered consciousness needing intensive care.

Conclusion: Significant proportions of children presenting to a regional referral unit with hypoglycaemia have persistent hyperinsulinism (10%) and adrenal insufficiency (10%). Clinical history, examination and performance of investigations are currently below expected standards. Investigation of spontaneous hypoglycaemia might improve if a 'diagnostic kit' for blood samples is readily available in addition to a clear protocol.

P4 (1)**Pituitary macroadenoma causing cyclical hypercortisolaemia: an atypical presentation of paediatric Cushing's disease**

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Introduction: Paediatric Cushing's disease (CD) is generally caused by a corticotroph microadenoma. We present a case of cyclical CD secondary to a corticotroph macroadenoma, and review radiological and biochemical findings in our series of patients with CD microadenomas.

Case Report: An 11.9 yr old female had a 3 yr history of obesity (BMI SDS 2.47), growth failure (height SDS -1.97) and virilisation (Br1 AH3 PH5). CD was diagnosed from sleeping midnight cortisol (SMC) 389 nmol/l (N<50), urinary free cortisol (UFC) 507 nmol/24hr (NR 40-340), 09.00h ACTH 73.7 ng/l (NR 10-50), absent cortisol suppression after low-dose dexamethasone suppression test (LD-DST) 290 nmol/l (N <50), and suppression after high-dose DST to <50 nmol/l. Two months later SMC was 156 nmol/l, cortisol <50 nmol/l to the LDDST, UFC 76 nmol/24hr, and cortisol increased by 554% above basal (N<20%) after iv hCRH. Pituitary MRI demonstrated a macroadenoma (12 x 11 x 9 mm) with a suprasellar extension. Transsphenoidal surgery resulted in excision of the adenoma, histology confirming corticotroph adenoma staining for ACTH, with post-operative 09.00h cortisol x 3 < 50 nmol/l, consistent with cure.

25 paediatric patients with CD, 17 m, mean age 12.8 yr (6.6-17.0), had corticotroph microadenomas, visible on imaging in 14 (56%). Height SDS, mean (range) was -1.9 (-4.2 to 1.2), BMI SDS 2.5 (0.7-5.1), SMC 476 nmol/l (146-930), ACTH 47 ng/l (13-125), cortisol 314 nmol/l (55-842) during LDDST, >50% suppression during HDDST, 86% (53-93). Cortisol increment after iv CRH was exaggerated, 184% (119-319%).

Conclusion: In paediatric CD corticotroph macroadenoma is rare and was associated with atypical biochemical features. Pituitary imaging was generally unhelpful; however, this case demonstrates the importance of radiological and biochemical evaluation following an established protocol.

P5 (31)**Glucose Intolerance and Insulin Resistance In Obese Children**

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The prevalence of childhood obesity is increasing worldwide. This study aimed to determine the prevalence of glucose intolerance and insulin resistance in a cohort of obese children investigated at Royal Manchester Children's Hospital between 2000 and 2003.

METHOD: 42 obese children defined by Body Mass Index (BMI) greater than 98th centile for age, had an oral glucose tolerance test (OGTT) with fasting and 120 minute glucose and insulin measurements. Glucose results were categorized according to the World Health Organization criteria as normal, impaired glucose tolerance (IGT), or diabetic. Fasting insulin greater than 26 milli international units per litre was used as a measure of insulin resistance (IR).

RESULTS: Subject characteristics: 26 Caucasian (17 female, 9 male); 16 Asian (9 female, 7 male); 17 pre pubertal; 25 post pubertal; mean age 12.4 years (range 4.6-17 years); mean BMI standard deviation score 3.2 (range 1.7-5.1). 10 post pubertal girls had polycystic ovarian disease (PCO). OGTT results: 27 (64%) had a normal OGTT, 11 (26%) had IGT, and 3 (7%) were diabetic. 16 subjects had IR. Of those with IGT, 23% (95% confidence interval 9.3%-35.5%) had a normal fasting glucose. 56% with a family history of diabetes had an abnormal OGTT, compared to 18% no family history ($p=0.01$). 8/16 (50%) subjects with IR had an abnormal OGTT compared with 4/21 (19%) of those without IR ($p<0.05$). Fasting insulin measurements were higher in PCO compared to other post pubertal children, even when corrected for BMI ($p<0.03$).

CONCLUSIONS: 34% of obese children had an abnormal OGTT, with 71% having a family history of diabetes. An OGTT is more sensitive at identifying glucose intolerance than a fasting glucose alone. Girls with PCO are more insulin resistant than other post pubertal obese children. Asian children are over represented and appear to be at higher risk of developing obesity and its associated co morbidity.

P6 (23)**Endocrine and molecular investigations for GH insensitivity in patients with severe short stature**

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Background: Growth hormone insensitivity (GHIS) is characterised by severe short stature, increased GH secretion, and low serum IGF-I, IGFBP-3, ALS levels. Biochemical and molecular advances have demonstrated a spectrum of GHIS in children with severe short stature.

Patients: We investigated 3 prepubertal children from non-consanguineous pedigrees with a history of severe short stature. Patient 1, female, age 6.2 yrs, had a classical GHIS phenotype, height (Ht) minus 6.0 SD, IGF-I 8.5 nanograms per litre (N 58-318), IGFBP-3 0.4 milligrams per litre (N 1.5-10), ALS 2.2 milligrams per litre (N 7.9-30). Patient 2, female, age 12.2 yrs had no GHIS features, Ht -4.3 SDS, IGF-I 43 nanograms per litre, IGFBP-3 0.8 milligrams per litre, ALS 7.4 milligrams per litre. Patient 3, male, had mild GHIS features, Ht -7.4, IGF-I 27 nanograms per litre, IGFBP-3 0.8 milligrams per litre, ALS 6.8 milligrams per litre. In all 3, IGF-I failed to increase in an IGF-I generation test. All patients had normal or elevated peak GH concentrations (>75 , 138, 30 milliunits per litre respectively).

Results: Analysis of the GH receptor (GHR) demonstrated that Patient 1 had a novel homozygous mutation at the splice junction of exon 6/intron 6 (IVS6 ds+1G to A). Patient 2 had a heterozygous mutation at the splice junction of exon 9/intron 9 (IVS9 ds+2 T to C) in which exon 9 fails to splice. In patient 3 no mutation has been identified within the exonic sequences or splice junctions of the GHR. However, we cannot exclude a defect in the GHR without performing mRNA studies.

Conclusions: When GHIS in children with subtle clinical abnormalities in addition to severe short stature is confirmed, analysis of the GHR \pm the GH signalling cascade is indicated. Early identification of prepubertal children with GHIS is needed to allow the possibility of treatment with IGF-I.

P7 (16)**The limitations of biochemical testing in patients with suspected diabetes insipidus**

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Introduction. The sensitivity and specificity of endocrine testing is a source of much discussion. We would like to illustrate some of the limitations of biochemical testing when assessing children with suspected diabetes insipidus (DI).

Methods. Assessment of 6 cases (aged 1 to 11 years) investigated for suspected abnormal water homeostasis in the last 5 years. Four children have cranial diabetes insipidus (idiopathic, autosomal dominant, in association with Langerhans cell histiocytosis and as part of combined pituitary hormone deficiency), one child has nephrogenic diabetes insipidus (NDI) and one primary polydipsia. Arginine vasopressin (AVP) was assayed using florisil extraction from plasma followed by double antibody radioimmunoassay.

Results. 2 children with polyuria/polydipsia generated urine osmolalities greater than 600 milliosmols per kilogram (745, 732) at the time of normal serum osmolalities and yet both are now known to have had cranial DI (CDI). A child with primary polydipsia had unrecordable AVP levels (less than 0.8 picomols per litre) despite a urine osmolality of 936 milliosmols and a serum osmolality of 294 milliosmols. The diagnosis of CDI and NDI was delayed in two children because urine osmolalities were greater than 600 milliosmols. One further child had a baseline urine osmolality of 200 milliosmols and plasma osmolality of 311 milliosmols, with urine osmolality of 539 milliosmols and plasma osmolality of 299 milliosmols 6 hours later.

Conclusions. These cases illustrate the quantitative and qualitative nature of abnormalities of AVP production, the suboptimal sensitivity of deprivation testing, the limitations of AVP measurement, the importance of comparing urine with serum osmolalities, and the ability of patients with CDI and NDI to produce concentrated urine when in a volume contracted state. The assessment of children with polyuria and polydipsia can be difficult and an overdependence on any one test is unwise.

P8 (30)**Waist circumference and the prediction of metabolic health in primary school children (The EarlyBird Diabetes Programme)**

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Background: Visceral fat mass is a major contributor to insulin resistance in adults, for which waist circumference is a useful surrogate. Recently, waist circumference centile charts have been published for use in children, but their relationship to metabolic health has not been established. Our objective was to assess the value of BMI and waist circumference in the prediction of insulin resistance and lipid levels in primary school children.

Methods: A cross-sectional study of 206 children (115 boys, 91 girls) aged 7.0 to 10.5 years. Outcome measures: BMI SD score (BMI-SDS), waist circumference corrected for the proportionality effect of height as the data to create SD scores was not available (WC), and fasting bloods for insulin resistance (HOMA-IR), triglycerides and HDL-cholesterol. Local Ethical Committee approval was obtained.

Results: 1) In regression, BMI-SDS explained 10.7 % of HOMA-IR in the boys and 15.4% in the girls (both, $p < 0.001$). 2) The addition of WC improved the prediction of HOMA-IR to 16.3% in the boys (R^2 change, $p < 0.01$) and 20.4% in the girls (R^2 change, $p = 0.02$). 3) However this was not significantly superior to WC alone (boys 16.0% and girls 20.4%, both $p < 0.001$). 4) This pattern was repeated in the prediction of triglycerides and HDL-cholesterol although the predictive values were lower. WC alone explained 4.0% of triglycerides in the boys ($p = 0.03$) and 8.0% in the girls ($p < 0.01$), and 6.3% of HDL-cholesterol in the boys ($p < 0.001$) and 5.2% in the girls ($p = 0.03$).

Conclusion: Waist circumference is superior to BMI in the prediction of insulin resistance and lipid levels in primary school children, however neither explain more than 20% of the variation in these metabolic variables. Further studies are required to assess tracking of anthropometric and metabolic variables so that the value of simple anthropometric measures in screening for metabolic health can be assessed.

P9 (21)**Do longer courses of testosterone affect final height in boys with maturational delay?**

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Aim: The differential diagnosis of idiopathic hypogonadotrophic hypogonadism from extreme maturational delay can be difficult, so most boys receive testosterone (T) replacement until the diagnosis becomes clear. Standard 3 month T therapy for maturational delay does not diminish adult stature, so we set out to determine whether T treatment of greater than 6 months duration would have an adverse effect on final height (FH) in boys with the eventual diagnosis of extreme maturational delay.

Patients and methods: 18 boys demonstrating spontaneous testicular growth and progression in puberty were selected from the Yorkshire Region Endocrine Database. All had full auxology, pubertal staging and mid parental height (MPH) recorded. All boys received testosterone (oral or IM) in physiological replacement doses over 6-35 months until it was stopped when spontaneous testicular growth occurred. Auxology was compared with national and Leeds standards.

Results: 6/18 had reached FH mean 174.5 cm (-0.4 SDS), all within the Target Centile Range (TCR), MPHSDS - FHSDS range 0.2 to -1.0. Twelve boys were still growing but in 8 their last recorded height was within the TCR, and the remaining 4 were on target to reach this. In those who had stopped growing the correlation between SDS deficit and total time on T was poor ($r = 0.27$, $p = 0.66$) indicating that the duration of T therapy per se does not affect FH achieved.

Conclusion: This preliminary analysis suggests that longer term T therapy in a physiological dosage regimen does not appear to adversely affect the FH in boys with extreme maturational delay. FH outcome is not a function of the total time on T.

P10 (17)**Investigation of defects of urine concentration; A postal survey of protocols used by members of the BSPED**

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To evaluate current practice in the United Kingdom concerning the investigation of urine concentration defects in children.

METHOD

154 detailed questionnaires were mailed to BSPED members asking for information on the types of test used, criteria for initiation and cessation of tests, diagnosis and details of monitoring and safety. We also asked for a protocol to be returned if available.

RESULTS

58 replies were received (38%) but the vast majority of UK centres for Paediatric Endocrinology were represented in the study. Only 2 centres used the hypertonic saline test alone, the great majority of respondents used the water deprivation test, while 3 used both tests. The majority do not do a test if the early morning urine osmolality is greater than 600milliOsmols per litre but 19 (35%) use other criteria. Most centres undertook only 2-3 tests per year. Junior doctors perform the majority of tests and only 15 centres use their specialist endocrine nurses. The majority used 5% weight loss as the criteria for cessation. There was enormous variation in monitoring and safety features. Almost all respondents combine a water deprivation test with a DDAVP challenge if the test result is positive. 24 protocols were returned containing enormous variation in all aspects in the performance of the test.

CONCLUSION

This survey has revealed considerable variation in practice in the investigation of urine concentration disorders in children. The water deprivation test remains the test of choice. We have concerns about the safety of the protocols and 9 respondents have reported significant adverse effects. There is an urgent need for a standardised, evidence based protocol for the water deprivation test.

P11 (32)**Hypoglycaemia during prolonged oral glucose tolerance test (OGTT) in obese children and adolescents**

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Objective: Little is known about reactive hypoglycaemia in children and adolescents. Due to clinical concerns, we examined the occurrence of hypoglycaemia in children and adolescents with simple obesity undergoing oral glucose tolerance tests (OGTT).

Methods: 78 subjects (range 2-18yr, mean age 10yr, 31% male) underwent a 3 hour OGTT (1.75mg/kg glucose) after an overnight fast. Laboratory blood glucose (BG) and insulin were measured at 30min intervals. Insulin sensitivity was calculated from fasting values (homeostatic model assessment of insulin resistance (HOMA-IR)) and from OGTT data (whole body insulin sensitivity index (WBISI)).

Results: Hypoglycaemia (BG <4.0 millimoles per litre) occurred in 29 (37%). Eight (10%) had BG ≤3.0. Hypoglycaemia occurred at 120min in 1 (3%), 150min in 12 (41%) and at 180min in 16 (55%). Mean insulin at time of hypoglycaemia was 28.1 milliunits per litre. Insulin at the time of hypoglycaemia was higher than at baseline in 21 subjects (72%). While peak insulin values and time to peak were not different between groups, mean insulin levels were significantly lower in the hypoglycaemic group at 150min (p<0.05) and 180min (p<0.01). The decline in insulin from peak to the end of the test was 89% in the hypoglycaemic group compared with 56% in the non-hypoglycaemic group (p<0.001). The hypoglycaemic group had nonsignificantly lower HOMA-IR and higher WBISI. Hypoglycaemia was associated with lower birthweight (p<0.001) but not age, sex, ethnicity or BMI.

Conclusions: Hypoglycaemia occurred in 37% of obese children undergoing glycaemic challenge, with significant hypoglycaemia in 10%. Insulin levels at time of hypoglycaemia were inappropriately high even when accounting for raised basal insulin levels. Hypoglycaemia appears to be more common in those who are more insulin sensitive, and where insulin fell significantly from peak rather than remained high throughout the test. This may represent dysregulation of insulin secretion and requires further evaluation.

P12 (43)**Measurement of Glycosylated Haemoglobin (HbA1c) on dried filter paper blood spots and NycoCard reader in young people with Type 1 Diabetes**

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BACKGROUND. Near patient testing of HbA1c can improve management of diabetes and overall control. Devices for achieving this however vary considerably in price, often resulting in considerable ongoing costs per test.

OBJECTIVE. We evaluated two low cost methods of measurement of HbA1c which would enable results to be available at consultation, filter paper blood spots and the NycoCard reader (Axis Shield), for accuracy and reliability against the laboratory standard.

RESULTS. Following ethical approval, 42 subjects with Type 1 Diabetes, aged between 2 and 17 years, gave consent for extra samples to be taken by finger prick. From each subject, two samples were analysed on the NycoCard ; in addition two samples on untreated filter paper and an EDTA sample were measured on a Menarini HPLC analyser. Repeatability of the two tests was very good with Pearson's correlation coefficients of 0.92 and 0.96 for the NycoCard and Filter paper blood spots respectively (filter paper samples analysed up to 72 hours apart, with the first sample always within twenty four hours). Reliability of the tests compared to the laboratory standard was also assessed, showing correlation coefficient of 0.9 (p < 0.001) for NycoCard and 0.98 (p < 0.001) for filter paper.

CONCLUSIONS. Both dried filter paper blood spots and the NycoCard were more acceptable methods of assessing HbA1c for the patients, using lesser quantities of blood than the standard EDTA sample. They also proved accurate and reliable in a clinic setting, with the potential to allow results to be given at consultation. Both methods are also low cost compared to other near patient testing devices.

P13 (20)

Short-term overnight transdermal testosterone therapy results in a prolonged reduction in Sex Hormone Binding Globulin (SHBG) in boys with pubertal delay

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Aim: To assess changes in SHBG levels during Transdermal Testosterone (TT) therapy in children with pubertal delay and its relation to pubertal stage, plasma and salivary Testosterone.

Methods: 10 boys undergoing induction of puberty with different TT preparations (Viormone 5 mg n=7, Andropatch 5 mg n=2, Andropatch 2.5 mg n=1) applied overnight for up to 12 hours. Afternoon plasma SHBG and testosterone and morning saliva testosterone (salT) were obtained at baseline (BL), after 4 wks of run-in (RI) after 8 wks of Testosterone treatment (RX) and after 4 wks of wash-out (WO). Tanner stage was assessed at BL.

Results: There were 4 children in early puberty (T volume 4-6mls) and 6 prepubertal children. Median salT was higher in the pubertal (115 pmol/L, range <25-61) than the prepubertal children (37 pmol/L (range 80-67)) (p< 0.01). SHBG (median 99.8 (range 79.1-123) vs 94.2 (range 86-130) nmol/L) and plasma testosterone (median 1.39 (range 0.88-2.03) vs 0.7 (range 0.36-2.24) nmol/L) concentrations were not significantly different in pubertal vs prepubertal children. After 8 weeks of treatment with TT, there was a rise in salT (median 610 pmol/L, range 94- 5267) and a decline in SHBG concentrations but no significant change in plasma testosterone (median 1.47 nmol/L, range 0.77-5.79). SHBG at BL was significantly higher than at end of Rx and WO (p<0.02 and p<0.002). SalT returned to baseline levels at WO but plasma SHBG remained low. SHBG means and SEMs were BL 97.77 (6.65), RI 88.52 (5.87), RX 69.63 (5.55) and WO 63.76 (6.11) nmol/L. There was no difference in plasma testosterone and SHBG concentration between pubertal and prepubertal children at any time point. **Conclusion:** TT therapy leads to a reduction in SHBG in prepubertal and early pubertal children. This marker of androgen action and insulin sensitivity remains depressed despite cessation of androgen exposure.

P14 (14)

Growth Retardation Following Prenatal Glucocorticoid (GC) Exposure Is Associated With Raised Serum IGF-I and IGFBP-2

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The underlying pathophysiology of intrauterine growth retardation and the failure of catch-up growth in some small-for-gestational-age (SGA) infants is unclear. GCs retard growth pre- and postnatally in many mammals. Surprisingly little is known of the prenatal effects of GCs in mice though this species is optimal for genetic and transgenic studies. IGFBP-2 is the predominant prenatal IGF binding protein; its expression is regulated by IGF-II and it may inhibit IGF-I and IGF-II action. To determine the effects of prenatal GC exposure on fetal longitudinal growth, pregnant mice were exposed to dexamethasone (Dex)(100mcg/kg/d) for the last 6 days of pregnancy. Controls received vehicle injections. The crown rump length (CRL) and body weight were determined in 1-day-old mice (n=90). A sub-set of 1-day old mice (control:Dex,1:1) were injected with bromodeoxyuridine 1 hr before sacrifice, when blood was sampled and tibial length determined. Histological sections of tibiae were assessed for growth plate width and the chondrocyte proliferation rate. Dexamethasone treatment significantly decreased both body weight (11.1%; P<0.001) and CRL (7.0%; P<0.001) with female mice more severely affected. There was a strong relationship between body weight and tibial length (r=0.7, p<0.001). Median (10,90 centile) serum IGF-I & IGFBP-2 in the prenatal Dex treated groups were higher at 291ng/ml(282,297) & 3170ng/ml (3000,3209) than the control at 282ng/ml (281,284) & 2982ng/ml (2898,3282)(P<0.05); serum insulin was unaltered. A significant negative association was found between serum IGF-I and CRL (r=0.5, p<0.03). Histological examination revealed no significant differences in the number of proliferating chondrocytes within the growth plate or the width of the proliferating and hypertrophic zones. In conclusion, our studies show that prenatal GC exposure affects birth weight and length; this effect is more marked in the female offspring and is associated with raised IGF-I and IGFBP-2 levels raising the possibility of a state of IGF-I and, perhaps, IGF-II insensitivity.

P15 (15)**A TSH receptor mutation contributes to the excess prevalence of congenital hypothyroidism in Asian families**

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Congenital hypothyroidism (CH) is a common congenital endocrine disorder affecting 1 in 3000-1 in 4000 white UK newborns but 1 in 700 Asian newborns. This higher proportion has been attributed to genetic causes enhanced by the high degree of consanguinity within this ethnic group. We aimed to identify genetic factors contributing to the excess prevalence in our Asian population. Local ethical committee approval was sought and obtained prior to the commencement of this study. We undertook a genome-wide scan to identify homozygosity by descent in 5 unrelated consanguineous Asian families each with at least 2 affected children. We used microsatellite marker analysis of known candidate genes, and sequencing and restriction analysis of genes where linkage was shown. One large consanguineous family showed homozygosity for markers in the region of the TSHR gene. Sequencing the gene revealed a homozygous missense mutation, G1757A (A553T), in the 2 affected children and 3 affected uncles. The parents and unaffected siblings were heterozygous for the mutation. The same mutation was identified on both alleles in 1/13 unrelated children with CH of Asian origin, but absent in 50 healthy Asian controls and in 6 unrelated white children with CH. This mutation has been reported previously in a Moroccan family and is the first report in children of Pakistani origin. We conclude that this mutation is a factor in the excess prevalence of CH in this population.

P16 (2)**Warning: Thyroxine Can Seriously Damage Your Tan!**

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Introduction

Patients with hypothyroidism may also have other underlying associated endocrinopathies, which are important to exclude. We present the first report of a child presenting with hypothyroidism in whom thyroxine therapy unmasked Addison's Disease and precipitated an acute adrenal crisis. Following steroid replacement therapy her 'hypothyroidism' resolved.

Case History

A 15 year old girl presented to her GP with a 2 month history of general malaise, tiredness and lethargy. Thyroid function tests demonstrated a raised TSH (>100 milli units per litre) and a free T4 of <5.2 pica moles per litre, and a diagnosis of acquired hypothyroidism was made. She was commenced on thyroxine 75 micrograms a day, but 4 days later was admitted to hospital with severe abdominal pain and vomiting since commencement of thyroxine. She was clinically dehydrated, shocked and hyperpigmented.

Initial biochemistry showed hyponatraemia (plasma sodium 112 millimoles per litre) and a random cortisol of 62 nanomoles per litre. Addison's disease was subsequently confirmed on measurement of ACTH, renin/aldosterone and synacthen testing. Hydrocortisone and fludrocortisone were given in addition to her thyroxine. She was also found to be persistently positive for adrenal antibodies, but negative for thyroid antibodies. Her thyroxine replacement therapy was therefore discontinued and she remains well and euthyroid.

Discussion

Whilst autoimmune hypothyroidism is common in paediatrics, Addison's Disease is not. A raised TSH, in the presence of normal or low thyroxine levels, can also be a presenting feature of Addison's Disease, even in the absence of thyroid disease. Thyroxine increases the metabolic rate, and with no increase in cortisol production may precipitate an Addisonian crisis in a patient with adrenal insufficiency.

This case highlights the importance of not only excluding Addison's Disease at the time of diagnosing hypothyroidism, but also to ensure that the hypothyroidism is not itself secondary to Addison's Disease.

P17 (24)**Assessment of a direct School Nurse referral system for short stature in Glasgow**

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Following discussion with Community Paediatricians, a new referral system for children with short stature in Greater Glasgow, allowing School Nurses to refer directly to the Yorkhill Growth Clinic, was initiated in Autumn 1998.

Methods: Height screening is done at Primary School entry. Nurses also measure children of other ages if they are concerned about their height. Each School Nurse was supplied with a portable measuring device (Minimeter, Raven Equipment). All School Nurses attended an in-service training session on growth and measurement technique provided by WFP. The main referral criterion is height less than 0.4th centile.

Results: Since the inception of this system 109 [50 M: 59 F] children have been referred, of mean age 7.4 (range 4.8-12.5) years. Of these, 20 failed to attend clinic and were never reviewed, leaving a final cohort of 89 children. Biochemical investigations have been carried out in 17 (19%), including short stature screening in 9 and growth hormone provocation tests in 4. Final diagnosis has been ascertained in 71 children, as follows: genetic and/or constitutional short stature (67 (94%)); short stature secondary to known dysmorphic syndrome (2); short stature secondary to coeliac disease (1); normal stature (25th centile) (1). Intrauterine growth retardation was considered a contributory factor in 3 of the children with familial short stature.

Overall, of the original 109 children, 24 are still being followed up in the Growth Clinic, 31 in the Community, 27 have been discharged, 2 transferred to another speciality, while the remaining 25 are non-attenders.

Conclusions: As expected, we found a low incidence of pathology in children with short stature referred by School Nurses. However, given that there has only been one inappropriate referral in 5 years and a considerable number of children have merited investigation and ongoing follow up, we consider this referral system to be worthwhile.

P18 (26)**The Short Normal Child: Final Height - Catch-up Growth or Secular Trend?**

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Short normal children (SN) are reported to display spontaneous catch-up growth attaining adult heights within the normal range. Final height, however, is usually defined in relation to height centile at presentation. This may not be a true measure of catch-up growth as recent reports confirm a continuing secular trend in height. An increase in relative height may simply reflect an increase in population height.

The Wessex Growth Study has monitored the growth of a large number of SN children from age 5 years to final height together with 'average' height controls (C), allowing the extent of any secular increase to be determined. Final height was available for 103 SN (56 boys) and 114 C (62 boys).

At recruitment, the mean height of SN group was the 0.4th centile. Most had a height below parental target with 42% below target range. By comparison, mean height of controls was the 42nd centile and, as expected, 95% fell within target range. The mean adult height of SN group improved reaching the 3rd centile, and less were below target range. Significant improvement in relative height was also observed for control children who became relatively taller adults than their parents. The increase in height SD was greater for SN group (SN=0.69, C=0.29, $p<0.001$). No gender difference was observed in control group, but for SN children, the improvement was greater for boys (girls=0.50, boys=0.85, $p=0.005$). Consequently SN girls were more likely to attain a height <0.4th centile (girls=21%, boys=7%, $p=0.046$) and below target range (girls=24%, boys=7%, $p=0.026$).

The improvement in relative height of the control group with respect to initial and target height confirms a secular increase. However, height gain was greater for SN children, implying some degree of catch-up, especially for SN boys. Nevertheless, a substantial number of SN children fail to reach their genetic potential and remain short in relation to their peers.

P19 (6)**Effect of Saliva Collection Method on Cortisol Radioimmunoassay**

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BACKGROUND: Use of saliva for measurement of cortisol permits non-invasive study of adrenal function, but collection is technically difficult, particularly in small infants. Saliva collection can be assisted by citric acid to increase saliva flow, or by the use of cotton or polyester swabs in the mouth. The aim of this study was to determine whether different methods of saliva collection affect cortisol radioimmunoassay (RIA) performance. **METHODS:** Cortisol was measured in saliva collected from 16 adults using cotton swabs, polyester swabs, and citric acid, and was compared with saliva dribbled directly into a pot (plain saliva). Aspiration of saliva using citric acid as was also piloted in 10 infants. An in-house cortisol RIA without prior extraction, was used with an encapsulated sheep antibody (to cortisol 3carboxymethylxime ovalbumen).

RESULTS: Mean salivary cortisol in nanomoles per litre:

Plain Saliva 10.9

Citric Acid stimulated 10.4

Cotton Swab 25.3

Polyester Swab 27.9

Cortisol measurements in saliva collected using cotton and polyester swabs were significantly higher than cortisol measured in plain saliva ($p < 0.01$). Cortisol in saliva collected using citric acid was not significantly different from plain saliva ($p = 0.997$). Infants appeared to find the use of citric acid distressing. **CONCLUSIONS:** Use of cotton or polyester swabs for the collection of saliva can result in spuriously high levels of cortisol when measured by RIA. Although citric acid did not interfere with assay performance, its use as a sialogogue in infants may not be appropriate because of associated distress.

P20 (42)**Preliminary Results From A Randomised Controlled Trial Of Cognitive Behaviour Therapy (CBT) And Counselling For Adolescents With Type I Diabetes Mellitus (T1DM)**

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Background: Adolescents with T1DM are at increased risk of psychological problems but the role of psychological interventions has not been adequately defined.

Aim: To test the acceptability of CBT and counselling for adolescents with T1DM. We present these interventions, preliminary data on the themes raised in therapy and acceptability to these patients.

Methods: With ethical approval 11-16 years old patients were recruited from 4 centres and randomised to CBT (group 1) or counselling (group 2) in a 2 year prospective study, funded by Diabetes UK, to investigate impact on psychological well-being and glycaemic control.

CBT is a structured, time limited problem-orientated therapy. Non-directive supportive counselling provides the opportunity to express concerns.

Patients attended 6 individual sessions weekly and completed feedback forms. Issues explored during counselling and CBT were recorded and grouped into themes.

Results: At the host centre, 132 patients were approached, 49 were recruited. (37%)

We report on the results of 38 patients who have completed stage 1 of the study.

Group 1 n=19

Group 2 n=19

Acceptability: The majority recruited described their experience as positive and helpful.

Mean attendance

Group 1, 5.5 sessions

Group 2, 4.7 sessions.

Themes: Overall 11/38 (29%) did not raise diabetes related problems. 13/19 in group 1 and 14/19 in group 2 discussed diabetes related problems. In group 2 more general issues e.g., family and peer problems were raised than in group 1.

Conclusion: Recruitment was low principally due to concerns about the time commitment or not wanting psychological therapy. Those recruited found both interventions acceptable. The issues raised included those faced by young people generally and diabetes-related concerns. Both CBT, designed to achieve mutually negotiated goals; and counselling, with an open agenda; are acceptable and useful for identifying concerns. Longer-term follow up will establish their impact on psychological well-being and glycaemic control.

P21 (39)**Insulin resistant diabetes in children without obesity: an association with bone marrow transplantation**

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*[1] Birmingham Childrens Hospital, Birmingham, UK; [2] Birmingham Childrens Hospital, Birmingham, UK; [3] Birmingham Childrens Hospital, Birmingham, UK; [4] Birmingham Childrens Hospital, Birmingham, UK; [5] Queen Elizabeth Hospital, Birmingham, UK.***Aims**

Type 2 diabetes has been recognised in children in association with obesity and insulin resistance. Diabetes is also recognised as one of the long term sequelae of bone marrow transplantation. We aimed to characterise the nature of diabetes in a series of children presenting to our unit after bone marrow transplantation.

Methods

Children were identified from the diabetes database (1995 - 2002) of Birmingham Children's Hospital. Criteria for inclusion were: diabetes according to the WHO criteria and previous bone marrow transplantation. The data was then collected on a standard proforma and analysed.

Results

We identified five children aged 2.5 to 14 years. All patients were female and four were from ethnic minority groups. The median age of the children at transplant was 8 years ;indications were: Beta thalassaemia (n=2), acute myeloid leukaemia (n=1), acute lymphoblastic leukaemia (n=1), and myelodysplasia (n=1). Ablative radiation doses included total body irradiation (8-14 Gy). Cyclosporin was used in 4 of the 5 cases for Graft versus host disease prophylaxis. The median time from transplantation to diagnosis of diabetes was less than a year for the thalassaemia patients and 7 years (range 5 - 9.5 years) for the leukaemia group .None were obese (BMI > +2SDS) Insulin resistance was present in 4 of the 5 cases: 4 had acanthosis nigricans; of these, 2 had raised fasting insulin (210 and 911 pmol/l) and one had a raised C-peptide (1470 pmol/l).

Conclusion

Diabetes mellitus in 4 of the 5 children, following bone marrow transplantation, showed features of insulin resistance without obesity. These children constitute a special group with multisystem problems who have different needs from children with type 1 or type 2 diabetes.

P22 (9)**Pattern Of Bone Mineral Content Abnormality In Children with Chronic Renal Insufficiency (CRI) is Similar To That Observed In Children with Hypoparathyroidism (HPT)**

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To understand the pattern of skeletal disorder in CRI, we have studied the results of routine clinical investigations including DXA in 27 children with CRI(F:M,8:19) with a median age of 11yrs(P10,P90;4.3,14.2) and compared them to a cohort of 10 children with HPT and PseudoHPTIa(PHPT) (F:M-7:3; median age,13.7yrs(7,17)). Bone area (BAr) and Bone Mineral Content (BMC) of the total body (TB) and lumbar spine (LS) were measured by DXA (Lunar Prodigy). Actual BMC was compared to the predicted BMC for BAr and expressed as BMC SDS. In the CRI group, median GFR was 27.4ml/min/1.73m²(7.1,69.5) and the mean duration of illness was 9.3yrs(2.1,12.1). Out of the 27 children, 9 had received dialysis for a median duration of 2yrs(0.3,5.6). Median Ht SDS was -1.6(-2.7,0.3) and, as expected, median LS and TB pBAr, were low at 80%(69,97) and 75%(63,92), respectively. LS and TB BMD SDS, uncorrected for bone size, were -0.3(-2.4,1.2) and -0.6(-1.8,1.0). However, LS and TB BMC SDS were 0.4(-0.8,1.5) and 0.4(-0.2,0.9), respectively. There was no relationship between BMC SDS and duration of illness, GFR, serum intact PTH, Vit D dose or serum Calcium/Phosphate product. Median Ht SDS of the HPT and PseudoHPTIa cohort was -0.3(-2.9,0.3) and median LS & TB pBAr were 90%(66,99) and 91%(75, 98), respectively. Median LS & TB BMC SDS were 0.6(-0.4,1.8) and 0.7(0.3,1.1), respectively. There was no clear relationship with Vit D dose or serum PTH and one of the highest BMC SDS was recorded in a child with PHPTIa before she started on Vit D treatment. In conclusion, BMC as assessed by DXA is abnormally high in a number of children with CRI. This finding is similar to that observed in children who have an isolated disorder of PTH action. DXA bone densitometry may be a useful, non-invasive method of monitoring adynamic bone disease in children with CRI.

P23 (19)**Wolcott Rallison Syndrome: Clinical and genetic study of 3 children, novel mutation in EIF2AK3, and review of the literature**

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Background: Wolcott-Rallison syndrome is a rare autosomal recessive condition characterised by early infancy onset diabetes mellitus and multiple epiphyseal dysplasia. So far, 17 children have been described in the world literature. Recently, mutations in the gene encoding EIF2AK3 have been shown to segregate with the syndrome in 3 affected families.

Aims: We aimed to describe the clinical characterisation and mutation analysis of a further child, and full clinical and follow-up details on our first family including the longest surviving child.

Methods: Retrospective case notes review of 3 children presenting to the diabetic unit at our institution; mutation analysis of the EIF2AK3 gene in our most recent patient; and review of the literature on Wolcott-Rallison syndrome.

Results : Previously unreported phenotypic features in our patients included developmental regression after episodes of hepatic failure, and pachygyria on brain imaging. We have identified a novel 4 base pair deletion (np 3021-3024 del GAGA) in exon 13, that results in a frameshift and premature stop codon (R908 F/S +22X), causing premature truncation of the protein and abolition of the carboxy- segment of the catalytic domain.

Conclusions: Wolcott-Rallison syndrome should be considered in children with early onset diabetes who present with acute hepatic failure, which is manifest before epiphyseal dysplasia. Prenatal diagnosis may now be offered to affected families.

Keywords: Wolcott-Rallison syndrome, diabetes, hepatic failure, EIF2AK3.

P24 (37)**HbA1c and Islet cell antibodies at diagnosis - do they influence the timing of the honeymoon period?**

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HbA1c and Islet cell antibodies at diagnosis - do they influence the timing of the honeymoon period?

ABSTRACT

AIMS

1.To determine if there is any association between HbA1c at diagnosis and subsequent six months insulin requirements and thus the timing of the honeymoon period.

2.To ascertain if children who present in diabetic ketoacidosis have higher HbA1c levels at diagnosis.

3.To determine whether children with positive islet cell antibodies at diagnosis have a lower HbA1c at diagnosis and shorter honeymoon period.

METHODS

Retrospective analysis was undertaken of 74 paediatric patients. Data was available on 65 patients. Notes were examined and information extracted relating to diagnosis and treatment in the first six months. Insulin doses per kilogramme were calculated for each patient at discharge, 1 month, 4 months and 6 months following discharge. Throughout the study HbA1c values were expressed as standard deviations.

RESULTS

There is no correlation between HbA1c and insulin dose either at diagnosis or during the next six months. Children presenting in diabetic ketoacidosis (pH less than 7.3) did not have higher HbA1c than those with a normal pH at diagnosis (pH greater than or equal to 7.3) [mean S.D.15.87 vs 18.0, p = 0.5]. Positive islet cell antibodies did not effect the duration of the prediabetic phase. HbA1c values in children with positive antibodies were not significantly different from those with negative antibodies (mean S.D. 17.92 vs 14.02, p = 0.1).

CONCLUSION

HbA1c and islet cell antibodies have no influence on the honeymoon period.

It appears from this study that the length of the prediabetic phase, and thus HbA1c does not alter the subsequent course of diabetes.

P25 (3)**A local and national survey of glucocorticoid administration to patients with adrenal insufficiency at the time of inter-current illness**

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Introduction. A traditional approach to the management of inter-current illness in patient's with adrenal insufficiency is to recommend a doubling of the glucocorticoid dose although this may be relatively conservative given the responses of adrenal sufficient individuals. We wanted to sample the kind of advice given to families about the management of inter-current illness in the UK and to look at our patient's understanding of the recommendations provided locally.

Methods. fifty-two questionnaires were sent to specialist nurses and paediatricians involved in the care of adrenal insufficient children. We enquired about glucocorticoid dose adjustment at the time of illness and whether families were taught to administer parenteral hydrocortisone. fifty local families were asked about their treatment of inter-current illness including glucocorticoid administration. The families then had two education sessions and were asked identical questions six months later.

Results. Thirty-three questionnaires (64percent) from personnel at thirty different centres were returned. 44percent recommended a doubling and 35percent a trebling of the glucocorticoid dose. 70percent of families were taught how to give the injectable form of glucocorticoid if the child was unable to tolerate oral therapy. 50percent of local parents said they could not remember precise details about dose adjustment but 88percent knew the dose needed to be increased. Our practice is to teach families to administer IM glucocorticoid and 85percent felt equipped to do so. Families appeared to respond to education sessions with an improved awareness of illness management. Only 67percent of children wore SOS identification. **Summary and conclusions.** The impact of the different approaches to glucocorticoid replacement at the time of inter-current illness is unclear although we believe that clear guidelines linked to normal physiological responses should be developed. Regular education sessions should be held and a hard copy detailing the treatment regimen should be provided to all families

P26 (22)**The Role of Pelvic Ultrasound in the Investigation of Early Puberty**

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Introduction: The diagnosis of early puberty is based on clinical assessment and the gonadotrophin response to gonadotrophin- releasing hormone (GnRH) stimulation. However, it may be difficult to differentiate adiposity from breast tissue and the classical luteinising- hormone dominant response to GnRH is not always seen in pubertal children. This study evaluated the role of pelvic ultrasound (PUS) by assessing the relationships between PUS parameters, hormone tests and Tanner breast stage amongst girls investigated for early puberty.

Methods: A retrospective review of the case-notes of 109 girls was performed. PUS data included: uterine length (UTL, n=90), fundocervical ratio (FCR, n=38), presence of an endometrial stripe (EMS) and mean ovarian volume (MOV, n=68). Biochemical data included Luteinising Hormone: Follicle Stimulating Hormone ratios at 30 (R30, n=106) and 60 (R60, n=106) minutes post GnRH, and basal oestradiol concentration (n=104).

Results:

The girls were categorised into 4 groups according to Tanner stage, with those at stages 4 & 5 being pooled: BG1 (n=17), 2 (n=39), 3 (n=40), 4 (n=11).

Mean UTL, FCR and MOV increased across the Tanner groups. UTL increased from 3cm (BG 1) to 5cm (BG 4), $p=0.002$. FCR increased from 1.0 (BG2) to 1.5 (BG4), $p=0.01$. MOV rose from 2.2 (BG2) to 3.5 (BG4) cm^3 , $p=0.02$.

EMS was identified in 11 cases: BG1 (n=0), BG2 (n=3), BG3 (n=4) and BG4 (n=4).

Mean UTL correlated with R30, R60 ($p=0.01$, $r^2=0.12$ for both) and oestradiol ($p<0.005$, $r^2=0.35$).

FCR correlated with R30, R60 ($p=0.02$, $r^2=0.24$ for both) and oestradiol ($p=0.05$, $r^2=0.11$).

MOV correlated with R30 ($p=0.01$, $r^2=0.16$) and R60 ($p=0.04$, $r^2=0.13$).

Conclusions: UTL, FCR and MOV correlated well with Tanner stage and hormone tests. An expertly- performed and reported PUS is a valuable non-invasive tool in the investigation of early puberty. PUS may render biochemical testing unnecessary in some circumstances e.g. monitoring response to treatment.

P27 (45)**Thyroid function in 273 diabetic children tested annually: proposal for an evidence based screening protocol**

JC Blair & J Allgrove

*East London Centre for Paediatric and Adolescent Diabetes, Newham General Hospital and The Royal London Hospital, London, UK.***Introduction**

Thyroid abnormalities are thought occur in 3-5% of children with Type I diabetes. However, an evidence based protocol for thyroid screening in diabetic children has yet to be established. We present the findings of a retrospective study of thyroid function in 273 diabetic children and propose a screening protocol.

Patients and methods

Free thyroxine (fT4) and thyrotropin (TSH) were measured annually in 273 children. Of 247 children with Type I diabetes, 2 were thyrotoxic (TT) and 13 hypothyroid (HT). In 4 children (1 TT, 3 HT) thyroid dysfunction preceded diabetes. All children identified by screening were asymptomatic.

Thyroid auto-antibody titres were always significantly elevated when measured in subjects with thyroid dysfunction (5 / 13 HT, 2 / 2 TT).

Thyroid function was normal in children with Type 2 diabetes (n=20), or diabetes secondary to other pathology (n=6).

Conclusions

1. Thyroid dysfunction coexists with Type I diabetes in 5.5% of this cohort but not with Type 2 diabetes, or diabetes secondary to other pathology.
2. Screening identifies asymptomatic children.
3. Thyroid dysfunction is strongly associated with thyroid auto-antibodies.
4. Thyroid function should be assessed annually in diabetic children.

Recommendations

1. fT4 and TSH are measured at diagnosis and annually thereafter.
2. Thyroid auto-antibodies are measured at diagnosis, and repeated if TSH exceeds the reference range.

P28 (40)**Familial Remitting Diabetes: a New Syndrome?**

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We present a unique family with remitting diabetes. Diabetes was diagnosed in two asymptomatic brothers aged 3.6 and 1.5 years during investigation of failure to thrive in the older boy (random glucose values of 3.3-9.5 and 3.5-10 millimols per litre respectively). Due to concern about untreated early Type 1 diabetes, both boys commenced insulin (0.2 units per kilogram per day). HbA1c improved from 7.0% and 9.0% to 5.3% and 5.5%. The index case's linear growth did not change. After 1.6 and 2.3 years respectively, insulin was stopped as HbA1c and blood sugars were normal. Both children have normal OGTT (eldest 2hr glucose 2.0 millimols per litre suggesting possible dysregulation of insulin secretion) and normal HbA1c (5.4%, 5.5%). Investigation of the family showed father had mild hyperglycaemia (44 years, normal weight, Impaired Glucose Tolerance: 6.4 0 minutes, 10.4 120 minutes) and paternal grandmother has Type 2 diabetes on metformin (not overweight, no diabetes complications).

The transient hyperglycaemia in these boys remains unexplained. Type 1 diabetes may have an extended honeymoon however islet cell and GAD antibodies were negative and both boys have remained well off insulin for 2.3 and 1.6 years respectively. Transient neonatal diabetes presents within 3 months. Familial inheritance could suggest Maturity Onset Diabetes of the Young: a glucokinase mutation could potentially explain the father and grandmother's elevated blood sugars, this does not explain the children as neither had a fasting blood glucose greater than 5 mmol per litre, and improving glycaemia is not seen in this condition.

This family remains a conundrum, hyperglycaemia in the boys occurred in early childhood but resolved, while the two adults have hyperglycaemia of uncertain duration, which may indicate that the boys will relapse later. This clinical scenario has not previously been described, and may represent a new rare genetic form of diabetes.

P29 (18)**Familial neurohypophysial diabetes insipidus in two Welsh kindreds**

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An 18 month old girl was investigated for diabetes insipidus (DI) because of a strong paternal family history affecting 10 members over 4 generations. She was asymptomatic and an early morning urine specimen demonstrated an osmolality of 756 mOsm/kg. At the age of 3 years she had nocturnal enuresis and was drinking excessively and a water deprivation test (WDT) was interpreted as normal. By 6 years there was worsening of polyuria and polydipsia and she was drinking in excess of 6 litres / day but did not have consistent nocturnal symptoms. There were no symptoms suggestive of wider pituitary dysfunction and she was thriving. The result of a hypertonic saline test was consistent with partial cranial DI and she was commenced on desmopressin with symptomatic improvement.

Two children from a different family and from the same area presented with polydipsia and polyuria and a maternal family history of DI. A hypertonic saline test was performed and confirmed severe cranial DI in the more symptomatic child and was normal in the other.

DNA analysis of the index cases and affected parents in both families confirmed a new mutation (Cys98Ser) of the AVP-neurophysin II gene indicative of familial neurohypophysial DI (FNDI). This mutation adversely effects folding and / or dimerisation of the AVP-neurophysin II prohormone resulting in reduced AVP secretion. It is likely that this mutation accounts for the symptomatology of the other affected family members.

Establishing the presence of a mutation in familial cranial DI is particularly useful initially in asymptomatic individuals to determine the need for future treatment. Where this is not possible the use of the hypertonic saline test may delineate those with evolving disease. This case illustrates the variable age of onset of FNDI and the mechanism as to why this should occur will be discussed.

P30 (4)**Inhaled Fluticasone Propionate therapy in young children with asthma: Effects on hypothalamic pituitary axis**

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A higher than expected frequency of adrenal crisis has been reported in asthmatic children treated with inhaled Fluticasone Propionate (FP). FP is being increasingly prescribed, off license, to treat very young children with severe asthma. However, its safety in terms of effects on the hypothalamic pituitary axis (HPA) in this age group has not been established.

We prospectively studied 10 children (8M; median (range) age 10 (5-24) months who presented with recurrent wheeze and had a family history of bronchial asthma in a parent or a sibling. These children were commenced on FP (median dose 580microgram/m²/day) for 6 months as part of routine clinical management. Subjects received no other steroid treatment during the study. FP was delivered via spacer, following training by a specialist nurse. A short Synacthen test (125ug) was performed before and after 6 months of treatment. Cortisol was assayed at 0, 30, 60 minutes. Weight, height, and body mass index (BMI) were measured by a single observer.

Data are presented as median (IQR) or mean (SEM). Fasting cortisol (nmol/l) did not change following 6 months treatment with FP; 366 (153-462) pre vs 351.5 (205-421) post. Cortisol response to Synacthen was greater at 30 minutes; 663 (519-719) vs 682 (624-829), p=0.01 and 60 minutes; 649 (618-835) vs 806 (693-895), p =0.02 following treatment. There was no difference in the Z score of height; -0.11 (0.4) vs 0.07 (0.4), weight; -0.39 (0.3) vs 0.09 (0.3) or BMI; -0.26 (0.3) vs 0.09 (0.3) following FP treatment.

In conclusion, 6 months therapy with FP does not appear to have any adverse effect on HPA in young children with bronchial asthma. Long-term follow up is needed to assess the growth and the metabolic effects of FP treatment in this age group.

P31 (8)**An evaluation of the clinical utility of the GnRH stimulation test in the prediction of gonadal failure in survivors of childhood cancer**

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OBJECTIVE: We aimed to analyse the clinical effectiveness of the GnRH stimulation test in the prediction of gonadal failure in survivors of childhood cancer.

PATIENTS AND METHODS: Seventy eight children, 41 boys and 37 girls, aged 3.9 - 21.7 years at the time of combined pituitary function testing, who had undergone treatment for childhood cancer. Basal and peak gonadotrophin levels were selected from the GnRH stimulation test and the Area Under the Curve (AUC) was calculated. The results were compared with the clinical progression of puberty taken from the case notes.

RESULTS: The AUC, FSH and LH response to GnRH stimulation correlated positively with basal FSH and LH concentrations. A finding of delayed puberty on clinical examination in conjunction with an abnormally elevated (>10U/L) basal gonadotrophin measurement and an exaggerated response to GnRH stimulation (>10U/L rise from the basal measurement, according to the Tanner stage of sexual maturity) indicated primary gonadal failure. The response of FSH and LH to GnRH stimulation was significantly lower in male and female patients with apparently normal puberty and gonadal function. The Positive Predictive Value (proportion correctly identified as having gonadal failure on follow up) was 75% (male 81%, female 69%). The Negative Predictive Value (proportion correctly identified as not having gonadal failure on follow up) was 83% (male 73%, female 94%).

CONCLUSION: The GnRH stimulation test remains of considerable value in the detection of defects within the hypothalamic-pituitary-gonadal axis when used in conjunction with baseline hormone measurements. An abnormal response to GnRH stimulation is observed commonly in adolescents following treatment for childhood cancer.

P32 (47)**Role of oral Hypoglycaemics in the prediabetic stage of Cystic Fibrosis related diabetes(CFRD)**

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Introduction:The prevalence of cystic fibrosis related diabetes (CFRD) ranges between 5% and 10%.Diabetes in Cystic Fibrosis(CF) results from both insulin deficiency and insulin resistance. In patients with CF, progressive destruction of the pancreatic tissue leads to loss of islet cells. This results in varying degrees of glucose metabolism abnormalities.

We describe a patient who was born full term weighing 8lb 10oz. He was admitted aged 15months with failure to thrive. He continued to have poor weight gain and was diagnosed with CF aged 4 years following a sweat test Na of 112.Following introduction of routine medication, his weight was steady at the 50th centile, height at the 25th centile until the age of 11 years when his weight gradually fell to below the 25th centile and height to the 10th centile by the age of 15 years .His FEV1 also fell from more than 90% predicted (FEV1 predicted 1.9, measured 1.8) to 60-80% predicted (predicted 2.46 measured 1.62) over the same time. At age 13 years DNase was commenced but FEV1 remained less than 80% predicted. (predicted 2.6 measured 1.87).At age 15years a routine Hba1c was slightly raised at 6.1mmol(5.1 mmol in the past). A subsequent OGTT showed fasting sugar at 5.9mmol, and 4.3mmol at 2 hours.. He was commenced on oral glibenclamide 40mg twice daily. His weight improved to reach just below the 75th centile by age 17 ,his height improved to minus 0.6 sds and his FEV1 also increased within 4 months to more than 90% predicted (predicted 4.14 measured 3.82). He remained in this range until his transfer to adult services. His Hba1c remained less than 6.0mmol.Conclusion:It has been suggested that an insidious decline in lung function takes place years before the diagnoses of diabetes in cystic fibroses. Glibenclamide causes additional secretion of insulin from islet cells of Langerhans.We propose that a trial of sulphonylurea treatment be considered in patients with declining lung function and increasing HBA1c levels.

P33 (10)**Review of 12 years experience of paediatric craniopharyngioma:**

Diagnosis, management and long term endocrine sequelae

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We reviewed presentation, post-operative, and long-term endocrine function of children with craniopharyngiomas diagnosed and treated at the Royal Hospital for Sick Children Edinburgh. 12 patients (7 boys) were identified, diagnosed at median age 11.5 years (range 1.82 to 15.6 years) and under long-term follow up for median of 3.92 years (range 0.19 to 12 years).

The main presenting neurological symptoms were headache 50%, vomiting 42% and visual disturbances 25%, and endocrine symptoms were short stature 33% and delayed puberty 25%. The median age of patients presenting with short stature was 15.2 years. Although endocrine symptoms were infrequent as a presenting complaint, 58% had a history of poor growth.

Surgery for obstructive hydrocephalus (5) and / or concern regarding optic nerve compression (7) was indicated in 10, one is being monitored and the other received radiotherapy. 5 patients had subtotal resections, 1 radical surgery and 4 had cyst decompression. Surgical procedures were carried out within 1 month of diagnosis. Tumour progression occurred (within 1 year) in 6 patients and no progression in 4 patients who received radiotherapy (median follow up post radiotherapy 4.75 years). Postoperatively visual field defects improved in 3 and deteriorated in 3. Visual acuity improved in 5 and diminished in 2.

After surgery: 80% panhypopituitarism, 70% diabetes insipidus, 80% growth hormone deficient, 90% primary hypothyroidism and 80% ACTH deficient. All (4) who were peripubertal required sex hormone therapy. A smaller percentage (1 in 3) had diabetes insipidus after cyst aspiration.

We concluded that children with craniopharyngioma usually present with a non-endocrine main complaint with hydrocephalus and / or visual defect. Adolescents are generally referred with short stature and delayed puberty. The morbidity associated with treatment is high but limited by less aggressive surgery to preserve hypothalamic function, early radiotherapy and managed with appropriate hormonal replacement.

P34 (46)**Review of the effect of starting insulin or repaglinide on lung function and body mass index in children with cystic fibrosis and diabetes**

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Background:

Diabetes mellitus affects up to 20 percent of children with cystic fibrosis. Treatment with insulin or oral hypoglycaemic agent is thought to improve lung function, body mass index and decrease respiratory infections. However, the evidence for the beneficial effect of glucose lowering treatment is conflicting

Aims:

We aimed to review the effect of glucose lowering treatment on lung function (FEV1 SDS and FVC SDS) and body mass index (BMI SDS) for children with cystic fibrosis and diabetes.

Methods:

We undertook a retrospective study on 11 children with cystic fibrosis and diabetes presenting to Birmingham Children's Hospital between 1996 and 2003. Diabetes mellitus was diagnosed using WHO criteria. We calculated SDS scores based on national paediatric data for FEV1 and FVC (Rosenthal 1993) and BMI (British Growth Reference 1990). We collected data from 1 year before diagnosis, to 6 months after treatment was commenced.

Results:

The median age at diagnosis of diabetes was 11.77 years (range 6.5 to 15.3 years). In the 10 patients with available data from 1 year before diagnosis to 6 months the median change in FEV1 SDS was minus 1.7835 (minus 13.1229 to plus 0.6201) and FVC was minus 1.2262 (range minus 9.4431 to plus 1.5667). For BMI SDS the median change was minus 0.0091, range (minus 0.03858 to plus 1.36).

Conclusion:

There was great patient variability, but no clear improvement in the indices after treatment of diabetes. We conclude that the reasons we did not see a measurable benefit in lung function and BMI in our patients may include: intercurrent illness, steroid treatment, delayed diagnosis, inadequate treatment. Children with cystic fibrosis need to have diabetes diagnosed promptly and adequate treatment instituted in order to maintain lung function and BMI.

P35 (25)**Final Height after Growth Hormone Treatment in the Yorkshire Region: results of KIGS analysis in a single centre**

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Aim: To evaluate the efficacy of growth hormone (GH) treatment on final height using the KIGS Yorkshire Region database - a single centre with consistent diagnostic and treatment policies.

Patients and methods: 65 patients (34 males and 31 females) treated with GH for a variety of reasons from 1st January 1987 onwards who had reached Final Height (FH) by 1st April 2003 and who had MPH documented were included in this study. All patients received GH doses between 0.5-1.0 IU/kg/wk, on a minimum of 6 injections/wk, for at least 2 years.

Results: 62% of the patients achieved a final height within the target height range. No significant sex differences were found. All results were adjusted for MPH standard deviation scores, values indicating number, pretreatment SDS and FH SDS: Idiopathic GHD (17) minus 2.1, minus 1.1; Idiopathic SS (6) minus 2.1, minus 0.7; Medulloblastoma (7) minus 1.0, minus 1.1; Other CNS tumours (9) minus 0.7, minus 0.3; Turners Syndrome (5) minus 2.4, minus 1.9.

Conclusion: Overall, patients treated with GH in the Yorkshire region benefit from an increase in their mean height SDS, most groups of patients achieving FH within the normal adult range. The failure of patients with IGHD to achieve their target height is notable, especially as, by contrast, GH treatment in this group of ISS patients appears more successful and FH in patients with acquired GHD is greater than that documented in KIGS reports. Why a policy of early GH replacement using the optimum dosage regimen produces such different results requires further study.

P36 (44)**Use of Glargine Insulin in Adolescents: A Questionnaire Study**

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Aim: To study the benefits, disadvantages and efficacy of a basal-bolus regime of insulin (using glargine-insulin and rapid-acting insulin analogues) administration in adolescent type-1 diabetes.

Methods: Questionnaires were sent to 26 adolescents with type 1 diabetes who had changed from a twice daily pre-mixed insulin regime to a basal-bolus regime and had been on it for a minimum of three months. Case notes were reviewed retrospectively. We studied the changes in day and night time hypoglycaemic episodes, insulin dose, HbA1C, type of insulin, eating pattern, control of diabetes and confidence in controlling the insulin dose for adequate glycaemic control since start of glargine.

Results: 18 responded; 12 were on the glargine regime for three months, 3 for six months and 3 for more than six months. No daytime hypoglycaemic episodes were reported in 8, the frequency halved in 7 and was no different in 3. There were no night hypoglycaemic episodes in 8, halved in 7, was no different in 2 and worsened in 1 child.

13 youngsters decreased their total daily insulin dose by a mean of 18 units (range 10-34), 2 had an increase by 21 +/- 2 units.

HbA1c levels remained the same in 3, increased by 2% in one and decreased in fourteen patients by a mean of 1.7% (range 1-2.4%).

16 described a difference in their eating patterns. (8-miss meals, 7-alter food timings, 3-consume sugary food). 15 were confident in adjusting the dose of insulin. 17 adolescents preferred the glargine regime (flexibility 9, better control 5, increased confidence 1, better lifestyle 1 and flexible eating pattern 1).

Conclusion: A basal-bolus regime using glargine-insulin is well accepted by adolescents making a difference in the control of diabetes with decrease in day and night time hypoglycaemic episodes, increased flexibility, confidence and better lifestyle.

P37 (27)**Body Composition of Prepubertal Children**

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The rising level of obesity in children is causing concern but little is known of the amount of fat and lean mass children need to stay healthy and grow normally. The Wessex Growth Study is establishing a new community-based project to investigate the body composition of children. We report preliminary results from phase 1.

During the summer term 2003, 465 (214 boys) children in school years 1 to 4 were recruited from eight Southampton primary schools. The mean age was 7.8 (5.6 to 9.9) years. Height, weight, skinfold thicknesses, waist and mid-arm circumference (MAC) were measured and converted to SD scores where possible. BMI was determined from height and weight. Percentage body fat was calculated from triceps and subscapular skinfolds and lean and fat mass were derived.

No significant gender differences were found for height, weight, BMI or waist circumference but skinfold thicknesses, MAC and fat mass were greater for girls. Although the mean height was close to the 50th centile, the mean weight was significantly higher (64th centile, $p < 0.001$). Consequently, the mean BMI was significantly above the population mean (65th centile, $p < 0.001$). BMI was >91 st centile for 19% but <9 th centile for only 3% suggesting an upward population shift. The mean waist circumference was also higher than expected, lying on the 75th and 80th centiles for boys and girls, respectively. Percentage fat ranged from 8.4% to 45.5%.

The gender difference in body fat observed in adults is already evident in prepubertal, school-aged children. However, both boys and girls are heavier than expected with many having a waist circumference above the 50th centile. This may indicate that the observed increase in weight results from an increase in visceral fat. Excess fat accumulation, especially visceral fat, is associated with increased health risks. Future work will determine predictors of percentage fat.

P38 (29)**Are wheel chair bound physically disabled children more overweight than their independently mobile counterparts?**

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Aims:

1. To estimate the prevalence of overweight in physically disabled children.
2. Compare the prevalence of overweight between wheel chair bound (WB) and independently mobile (IM) children

Subjects and Methods:

Body Mass Index (weight (kg)/height (m) superscript 2) was estimated in those aged 4- 16 years in a special school for physically disabled children. Body Mass Index (BMI) was expressed as a standard deviation (SDS) using the 1990 British revised reference data. The frequency of overweight (>91 st centile) was determined. Children were categorised according to gender and further into WB or IM. BMI SDS was compared between boys and girls. BMI SDS was compared between WB and IM.

Results:

Sixty seven children (46 males) were studied. Nine children were WB. 21.1 % of males and 28.5% of females were overweight. There was no significant difference in mean BMI SDS (SD) for boys (minus 0.2 plus or minus 2.0) and mean BMI SDS (SD) for girls (0.03 plus or minus 1.6).

BMI SDS (SD) for WB (minus 1.35 plus or minus 2.62) was significantly less than BMI SDS for IM (0.1428 plus or minus 1.46) $p = 0.007$.

Conclusion:

1. The prevalence of overweight in this group of disabled children is higher than in the general population.
2. Independently mobile disabled children are significantly more overweight than their wheelchair bound counterparts.

P39 (36)**Braking The Accelerator Hypothesis?**

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The accelerator hypothesis suggests diabetes is due to three accelerators; insulin resistance, autoimmunity and genetic susceptibility (Wilkin T (2001) The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetologia* 44:914-922). The theory predicts that type 1 diabetes will present earlier if body mass index, and thus insulin resistance is higher. Our aim was to test this hypothesis in our diabetes population. Our secondary aim was to test whether the relationship was more evident in South Asian children, who are more insulin resistant than white UK children. In our population we compared age of onset of diabetes with standardised body mass index standard deviation score (BMI SDS) at first clinic after diagnosis, and one year later. Inclusion criteria were type 1 diabetes; age < 16 years; ethnic origin White UK or South Asian. We analysed the data with Spearman's rank correlation.

131 children fulfilled our criteria. We had data on 24 South Asian (10 female) and 71 White UK children (40 female). The mean ages at diagnosis were 9.3 yrs (range 1.4-15.5) South Asian, 7.3 years (range 1.28-14) White UK, a significant difference ($p=0.04$). Mean BMI SDS were 0.4 (95% confidence interval 0.17-0.63) white UK and 0.36 (95% confidence interval minus 0.32-1.04) South Asian.

There was no significant correlation between age at onset of diabetes and BMI SDS in 24 South Asian ($r = 0.3$ $p>0.1$), and 71 White UK children ($r = -0.038$ $p>0.5$) at diagnosis or one year after diagnosis Asian ($r = 0.235$, $p>0.1$), White UK children ($r = -0.2$, $p>0.1$).

We found no link between age at presentation and body mass index in our population of children with type 1 diabetes. It is possible that other factors have a larger influence on age of onset of type 1 diabetes in our cohort than obesity.

P40 (33)**Has the time come to start treating dyslipidaemia in children with obesity?**

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INTRODUCTION; Childhood obesity has well established links with the development of insulin resistance, Type II diabetes and cardiovascular disease. This has become known as the metabolic syndrome although debate continues as to which individuals meet the desired criteria for diagnosis. Despite this, there is clear evidence that children with obesity have specific cardiovascular risk factors that may need early treatment if long-term morbidity and mortality is to be avoided. **AIM;** We aimed to investigate the prevalence of dyslipidaemia in a cohort of obese children who attend our specialist paediatric obesity clinic. **METHODS;** 45 obese children (8 prepubertal girls, 19 prepubertal boys, 10 adolescent girls and 8 adolescent boys; mean age(range) 10.3 years (3.3 to 16 years); mean BMI SDS(range) plus 3.7 (2.7 to 6.7)) who have attended the clinic had fasting bloods taken for lipid analysis. In accordance with published guidelines, abnormal results were considered to be a cholesterol >5.2 mmol/l, an LDL >3.4 mmol/l, an HDL <0.9 mmol/l in boys and <1 mmol/l in girls, and/or a triglyceride level >1.2 mmol/l in children aged <14 years or >1.7 mmol/l in children aged >14 years. **RESULTS;** In the whole group, 56% had evidence of dyslipidaemia with 27% having 1 abnormal parameter, 27% having 2 abnormal parameters and 2% having 3 abnormal parameters. Subgroup analysis revealed a dyslipidaemic profile in 75% of the prepubertal girls, 42% of prepubertal boys, 70% of adolescent girls and 40% of adolescent boys. **CONCLUSION;** These data demonstrate that dyslipidaemia is present in a substantial proportion of obese children, with girls having the highest rates. Whilst dyslipidaemia is a well established cardiovascular risk factor, it is unclear as to whether these children with obesity-related dyslipidaemia warrant long term treatment with lipid-lowering agents. Urgent consideration of this area is now required if a future explosion in obesity-related cardiovascular disease is to be avoided.

P41 (7)**All cranial tumours are at risk of increased weight gain following treatment**

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Background

As survival from childhood brain tumours improves, the management of late effects becomes more important. One of the most severe and resistant forms of obesity occurs in craniopharyngioma patients, particularly if the hypothalamus is involved. It is not known whether other cranial tumours, suprasellar or otherwise, are at risk of weight gain.

Methods

Case note review of children who had survived at least 5 years from diagnosis. Data was available on 39 children. Pre and post treatment auxological data was extracted at yearly intervals.

Results

Of the 39 patients, the majority were medulloblastomas (11) and astrocytomas (15); only 7 had tumours in or near the suprasellar region. 30 patients had received crani-spinal radiotherapy.

There was a gradual increase in both mean BMI (Body Mass Index) SDS and Weight SDS, with the BMI SDS first becoming statistically significant ($p < 0.05$) at 2 years from diagnosis, an increase from a mean BMI SDS of 0.11 to 0.92, and at 5 years reaching a mean SDS 1.20 ($p < 0.01$).

Mean weight SDS increased from 0.04 at diagnosis to 0.37 at 4 years, but did not achieve statistical significance.

Mean height SDS decreased from minus 0.30 to minus 1.43 over 5 years ($p < 0.05$).

Conclusion

The exact nature of how weight increases in these children remains unclear. Radiotherapy will damage the hypothalamus, with some having demonstrable endocrinopathies. The damage to the hypothalamus will also affect appetite and energy metabolism, and hence result in increases in weight and BMI. Although our study numbers are small, they demonstrate that all survivors of childhood brain tumours are at risk of increases in weight and BMI.

P42 (35)**Comparison of the rates of obesity/overweight between South Asian and white Caucasian children with type 1 Diabetes Mellitus**

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Background: The increasing rate of obesity and type 2 diabetes mellitus in children is well recognised. However, there is little information on differences in obesity between South Asian and white Caucasian children with type 1 diabetes mellitus.

Aim: To compare overweight/obesity rates between South Asian and white Caucasian children with type I diabetes mellitus in Leicester and to correlate these to age, duration of diagnosis, daily insulin requirements and metabolic control (HbA1c).

Method: Retrospective analysis of case notes of children with type 1 diabetes mellitus, between the ages of 2 -18 years and diagnosed for more than one year. The following parameters were examined: age, sex, duration of diagnosis, weight, height, body mass index (BMI), insulin dosage and HbA1c. BMI was calculated and plotted on Cole charts (overweight above 91st centile and obesity above 98th centile).

Results: Data were collected on 150 children. The median BMI of the whole population was 20 (17 to 24) and median HbA1c 8.6 % (8.0% to 9.9%).

25% (38/150) of the children were South Asians.

Obesity/overweight was present in 35% (53/150) of the whole group, with obesity in 18% (27/150). There was no significant difference in rates of overweight/obesity between South Asians and white Caucasians.

In the overweight/obese subgroup ($n=53$), median BMI was 24 (20-27) in South Asians (13/53) compared to 26 (24-30) in the white Caucasians (40/53). There was no significant difference between the two subgroups in relation to age, sex and duration of diagnosis and daily insulin requirement. Median HbA1c among obese/overweight South Asians was 8.8 % (8%-10.4%) against 8.4% (7.8% -9.8%) among white Caucasians ($p=0.30$).

Conclusion: 35% of children with type I diabetes mellitus in Leicester were overweight/obese. There was no difference in these rates between South Asians and white Caucasians. Larger studies are required to confirm these findings.

P43 (11)**Extreme hypervascularity and bruit in a treated hypothyroid goitre**

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An 11-year-old girl of South-Asian non-consanguineous parentage presented with a hypothyroid goitre. Biochemical euthyroidism was achieved within four weeks of starting oral thyroxine. Fifteen months later, a loud bruit was noted in the neck associated with a diffusely and markedly enlarged goitre. There were no clinical features of hyperthyroidism or high output cardiac failure.

Investigations confirmed euthyroid state. Colour Doppler imaging showed bilaterally dilated superior thyroid arteries with greatly increased blood flow to the goitre. She underwent near total thyroidectomy with embolisation of thyroid arteries 48 hours prior to the surgery to reduce the vascularity of the thyroid. Histopathology of the thyroidectomy specimen showed features of dysmorphogenesis, greatly increased vascularity and widespread diffuse staining for vascular endothelial growth factor (VEGF). Currently she remains euthyroid on thyroxine replacement with no recurrence of goitre.

In the hypothyroid state, the stimulus for the release of VEGF is thyroid stimulating factor (TSH). Following thyroxine treatment, a decrease in the serum levels of TSH is most likely to be associated with reduction in the serum levels of VEGF levels, intrathyroid vascular area and thyroid volume.

In this unique case, a high level of VEGF in the thyroid gland seems to have occurred during adequate thyroxine replacement with a normal TSH level. The loud bruit and extreme degree of hypervascularity in a dysmorphogenetic hypothyroid gland were due to enlarged thyroid arteries, which has not previously been reported in literature.

P44 (38)**Multiple Contacts with Healthcare Professionals in Newly Diagnosed Patients Presenting with Diabetic Ketoacidosis**

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Background: New patients with type 1 diabetes who present with Ketoacidosis (DKA) have a three fold risk of developing cerebral oedema as compared with DKA in patients known to have diabetes. Reducing the number of children presenting with DKA at diagnosis would be an important factor in reducing the incidence of cerebral oedema in patients with DKA.

Aims: To look at the frequency of contacts with healthcare professionals (HCPs) in patients with DKA when newly diagnosed.

Methods: Information was obtained prospectively from all patients admitted with a new diagnosis of diabetes over six months. The frequency of contacts with HCPs, investigations done to rule out diabetes and the symptoms of the patients and their duration was determined.

Results: Twenty five patients were newly diagnosed with diabetes. Three patients were excluded (acute leukaemia). Ten (45%) were male and 12 (55%) female.

A total of eight patients (36.4%) had DKA, and included all three children who were under five years of age. One of the eight patients (12.5%) was referred at the first primary care contact. Four patients (50%) had two HCP contacts, one (12.5%) had three and two (25%) had more than three contacts. Seven out of eight (87%) had multiple contacts before referral. Six of these seven (86%) presented with polydipsia with or without polyuria of 4 to 21 days duration.

No patient with ketoacidosis had blood glucose tested outside hospital and only four out of eight (50%) had urine tested with dipsticks. Four out of seven (57%) with multiple contacts had symptoms suggestive of diabetes but had no investigations to exclude the diagnosis until they developed DKA.

Conclusions: The awareness of polydipsia and polyuria as a presentation of diabetes mellitus in childhood needs to be increased in primary care to try and reduce newly diagnosed patients presenting with DKA.

P45 (34)**Follow up data of type 2 diabetes in children & adolescents in Birmingham**

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Background:

Type 2 diabetes has recently been reported in UK children. Their clinical characteristics are relatively well known but very little data is available on long term follow up.

Method:

We undertook retrospective case note study of children with type 2 diabetes across 4 hospitals of Birmingham. Type 2 diabetes was defined by presence of predominant features of Insulin resistance, absence of autoimmune markers for type 1 diabetes or management with oral hypoglycemic for > 1 year. Response to management was assessed by change in HbA1c (delta HbA1c) and change in BMI SDS (delta BMI SDS). Presence of complications and type of treatment was also noted.

Results:

There were 20 patients diagnosed with type 2 diabetes between 1995 to 2002. Median age of presentation was 15 years. Median duration of follow up was 36 months .80% was obese. 45% needed Metformin whereas 40% had Metformin and Insulin in addition to advice on life style changes.

Majority improved HbA1c at 3 months (Median delta HbA1c= minus 0.6). But this was not sustained at 6 months and 12 months (median HbA1c= minus 0.1 and 0). The corresponding data for delta BMI SDS at 3 months, 6 months and 1 year were 0.09, 0.09 and 0.9 respectively. Two patients who showed sustained improvement in BMI SDS and HbA1c reverted to non-diabetic state as judged by oral glucose tolerance test. 45% had abnormal LFT during treatment.

Conclusion:

We report short term improvement in diabetic control after diagnosis followed by progressive deterioration in HbA1c and BMI. Research is needed into the factors which influence these changes in diabetic control.

P46 (12)**The Influence of Aetiology of Congenital Hypothyroidism on Growth in the First 3 Years of Treatment**

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Aim: To study the growth of children with Congenital Hypothyroidism (CH) over the first 3 years of life in relation to aetiology.

Methods: The growth of patients with CH was studied retrospectively by determining the length standard deviations scores (SDS) and body mass index (BMI) SDS over the first 3 years of life. Plasma TSH and total T4 at diagnosis and the time required for suppression of plasma TSH to less than 6 milli-units per litre (normalisation) were determined. Patients were categorised into athyreosis, dysgenesis and dyshormonogenesis. Length SDS, BMI SDS and time for normalisation of plasma TSH were compared between the groups.

Results: There were 125 children: athyreosis (34), dysgenesis (73) and dyshormonogenesis (18). Starting dose of L-T4 was 25 microgram in all patients. Linear growth did not differ between the 3 groups. Children with athyreosis and dysgenesis showed significantly higher BMI SDS at 1, 2 and 3 years of age compared with dyshormonogenesis ($p < 0.02$). Median time for normalisation of TSH for dyshormonogenesis, 1.5 months was significantly lower than for in athyreosis and dysgenesis at 24 months ($p < 0.0001$). BMI SDS at 3 years is positively correlated with TSH at diagnosis ($r = 0.33$, $p = 0.002$) and age at normalisation of TSH ($r = 0.26$, $p = 0.01$)

Conclusion

1. Linear growth in CH does not vary with aetiology but children with athyreosis and dysgenesis have significantly higher BMI SDS in the first 3 years compared with dyshormonogenesis and this is associated with significantly later TSH normalization.
2. BMI may be a more sensitive index of thyroid function than length in the first 3 years of life in CH.

P47 (41)**What services do families want in a Diabetic Clinic?**

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Introduction: The Aim of the National Service Framework for Diabetes is to ensure that: 1) The special needs of children and young people with diabetes are recognised.

2) Parents of young children with diabetes need active involvement with day to day care of children. 3) Educational, physical, psychological, intellectual and social development needs are met. Aim: To evaluate whether existing services are fulfilling the standards set by involving parents and patients to suggest ways of improving the care delivered. Method: The survey was undertaken in the form of a patient directed questionnaire. Parents completed the forms for those under eight. Existing services were evaluated in a scoring system 1 to 5. Subjects: 86 patients attending the Diabetic Clinic at RAEI, Wigan. Results: 49 questionnaires were returned. Parents responded in 34 cases and patients responded in 15 cases. There was overall satisfaction with the existing services provided in the Diabetic clinic. The majority of families scored car parking facilities as poor (26/49). 12 teenagers who answered the questionnaire felt that the clinics lacked privacy and opted for a Young Person's or Transitional Clinic. Some also suggested need for more age appropriate information within the clinic about puberty, pregnancy and sex education relating to diabetes. 26/49 patients felt that recreational facilities in clinic to be satisfactory and suggestions for improvement included installing a computer within the clinic with latest information on Diabetes and research. It was interesting to note that while parents preferred evening clinics, the majority of patients above eight years opted for day time clinics. Conclusion: 1. Age appropriate educational material needs to be provided for teenagers within clinic. 2. Young Persons / Transitional clinic for adolescents is the way forward for smooth transition to adult clinics. 3. Timing of clinics should be acceptable to patients, parents and medical staff providing their care.

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