Endocrinology and Diabetes

G32 SCREENING FOR CONGENITAL HYPOTHYROIDISM (CH) IN A DEVELOPING COUNTRY—PROBLEMS AND SUCCESSES AS SEEN BY A TREATING PAEDIATRICIAN

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Introduction: Our National Screening Programme for Thyroid Stimulating Hormone (TSH) started in January 1998. (Phenylketonuria from 1995)

Aims: To screen all newborns and to scan and start treatment on all cases of CH before two weeks. To assess the problems and successes in progressing towards this ideal.

Method: DELPHI heel prick samples are taken on day 4 or 5. There follows at least seven stages involved in the sampling, delivery, lab testing, notification of positive cases and treatment. TSH cut off level for recall is >20mU/l.

Problems include: Failure to give parents the card; wrong labelling; non compliance; unsatisfactory samples; hold-ups at various stages; laboratory problems; doctors not abiding by the protocol and communication problems.

Results: Numbers screened:1998–22,600; 1999–29,700; and 2000 to 31/10–22,000.

Percentage screened: This district 90%; nationally 60–90%.

Positive cases—60. Incidence: Approximately 1 in 1240.


Adrenalin response—1 scan post treatment—2—uninterpretable.

Transient hypothyroidism—1 (maternal antibodies)

Thyroxine (app 10mcg/kg) started <2 weeks 11 cases; <1 month 29; later 4.


Conclusions: The incidence of CH, with dysmorphogenesis in particular, in this country, relatively high. For success, early detection and early treatment in a disciplined, committed approach is needed at all stages of the chain of events.

G33 HYPERTHYROTROPINAEMIA: TRANSIENT, PERSISTENT AND DECOMPENSATED

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Background and aims: Since screening for congenital hypothyroidism was introduced in the late seventies other disorders of thyroid function including hyperthyrotropinaemia, where normal levels of serum thyroxine occur in association with increased TSH, have been detected. Our aim was to assess the course of this condition and whether follow-up of these patients was necessary.

Methods: The medical records of patients attending Alder Hey hospital with thyroid disorders over the last 20 years were examined. Those with hyperthyrotropinaemia were ascertained and their case-notes and clinical outcome were reviewed.

Results: 8 patients were diagnosed with this condition over this period. 4 patients had a transient form of the disorder lasting between 3—16 months. They had normal growth and development. Three patients ( now aged 4, 9 and 18 years) still have hyperthyrotropinaemia. The younger two had both normal growth and thyroid scans while the older patient had delayed puberty and a solitary thyroid nodule on scanning. One other patient had evidence of persistently raised TSH from birth before decompensating at 11 months of age and necessitating treatment with thyroxine. Thyroid scanning showed normal left-sided uptake with a small right lobe.

Conclusion: Although growth and development are mostly normal in children with hyperthyrotropinaemia we believe that this disease may represent a form of compensated hypothyroidism. The risk of decompensation, as occurred with one child, necessitates long-term follow-up until the thyroid function tests have normalised.

G34 CAN A RANDOM ACTH LEVEL REPLACE THE SYNACTHEN TEST IN THE DIAGNOSIS OF PRIMARY ADRENAL INSUFFICIENCY?


Aims: To compare measurement of a random ACTH level with the short Synacthen test in the diagnosis of primary adrenal cortical deficiency. To describe the causes and presentations of this condition.

Methods: The notes of all patients seen between April 1983 and April 1998 with a diagnosis of primary adrenal insufficiency were reviewed. Those with congenital adrenal hyperplasia were excluded.

Results: Twenty nine patients were identified, 16 were male. Addison’s disease was found in 16 (55%), AAA syndrome (alacrima, acha- lasia, adrenal deficiency) in 4 (14%), congenital adrenal hypoplasia in a (21%), and adrenocorticotrihrohydrosis in 3 (10%). The findings on presentation of 27 of the 29 children are described, 16 presenting acutely and 2 suffering neurological sequelae. Fourteen patients had both a Synacthen test and random ACTH level. The ACTH level was abnormally high in all patients with a suboptimal response to Synacthen. One patient with a raised ACTH level had a normal cortisol response to Synacthen and his clinical adrenal insufficiency improved with the introduction of hydrocortisone. Where the plasma renin activity was available this was also abnormally high.

Conclusion: Primary adrenal cortical insufficiency may be extremely serious and cause significant long term morbidity. Features at presentation can mimic more common illnesses. In children with a pre-existing associated condition a single random ACTH level at presentation is a more sensitive diagnostic tool than the short Synacthen test and avoids the need for serial sampling.

G35 THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS RESPONSE TO HEAD INJURY

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Background: Traumatic brain injury (TBI) is a major cause of childhood mortality and morbidity. Glucocorticoids are widely prescribed for TBI patients despite lack of clear evidence of benefit. Recent evidence, however, does suggest that endogenous alterations in the HPA axis may play a role in the pathogenesis of secondary neuronal loss following TBI.

Aim: To define in detail the HPA response to experimental TBI.

Methods: Male Wistar rats were sacrificed at 2 or 4 hours after sham surgery or fluid percussion injury (FPI) (n = 6 in each group). In-situ hybridization was used to determine the expression of mRNAs of corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) in the hypothalamus and pro-opiomelanocortin (POMC) in the pituitary. Animals undergoing no surgery were used as a further control. (n = 6) An indwelling intravenous catheter was used for repeated blood sampling to determine plasma cortisol (CORT) levels by radioimmunoassay in subjects undergoing sham or FPI surgery.

Results: Plasma CORT levels peaked 30 minutes following surgery in sham and FPI animals, but there was no significant difference in CORT concentration between these 2 groups at any time point.

Conclusion: These data indicate that the anaesthesia and surgery associated with FPI or sham FPI induces a stress response with generalised activation of the HPA axis. FPI also results in selective increase in CRH mRNA which appears to be a specific response to TBI and may suggest an additional neurotransmitter role for CRH after head injury. The absence of an AVP response suggests that the effects of FPI may be mediated through the CRH-alone-containing sub-population of neurons.
CAN GROWTH HORMONE IMPROVE THE GROWTH OF SHORT NORMAL CHILDREN? A SYSTEMATIC REVIEW


Aim: Does treatment with growth hormone lead to an improvement in the growth of short normal children in terms of predicted adult height, growth velocity, or height standard deviation scores?

Methods: We searched the literature for randomised-controlled trials of growth hormone treatment in short normal children. We appraised the primary studies for their quality, in terms of randomisation procedure, intention to treat, adequacy of follow-up, and conducted a systematic review of the studies selected.

Results: In total 9 studies were selected for review. It was not possible to conduct a meta-analysis due to the heterogeneity of the primary studies. The studies showed improvements in growth parameters of treated groups compared to control groups in the short term. Height improved by between 0.4 and 1.3 Standard deviation scores (SDS) after 1 year, and between 0.62 and 1.3 SDS after 2 to 5 years of treatment.

Height velocity improved by between 4.4 and 5.9 SDS after 1 year of treatment, but fell back towards baseline in subsequent years. Predicted adult height improved by between 2.2 and 3.0 cm after 1 year, and by as much as 5.8 cm after 3 years of treatment.

We found no studies looking at growth hormone treatment over longer time periods.

Conclusion: Although growth hormone appears to improve the growth of short normal children in the short-term, as yet there is no evidence to support its effects in the long-term.

REDUCED IODINE INTAKE DURING PREGNANCY

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Introduction: The incidence of congenital hypothyroidism is 1 in 4000 births. Subclinical maternal hypothyroidism has been identified as a cause of poor neurodevelopment outcome (Haddow et al 1999). Iodine deficiency in mothers living in iodine deficient areas leads to severe mental outcomes. Thus nutritional iodine deficiency may be a contributing factor to maternal subclinical hypothyroidism. Screening for maternal thyroid deficiency has been suggested.

Aim: To determine the prevalence of reduced iodine intake during pregnancy.

Methods: Urine for urine iodide excretion (UIE) rate and blood for FT4 and TSH were collected from 250 pregnant mothers at 15 weeks gestation. Urine was obtained from non-pregnant healthy women of childbearing age. Pregnant women with known thyroid disease were excluded from the study. UIE rate was estimated by calorimetric method using autoanalyser. TSH and FT4 were measured using Elecsys TSH and Elecsys FT4 (Roche-Elecsys).

Results: UIE rate median was 147 and 158 micrograms/litre, with a mean (sd) of 148(114) and 181(68) micrograms/l for patients and controls respectively. 9% had UIE of <50micrograms/l which indicates inadequate dietary iodine intake.

Summary: 9% of pregnant women in our study population had inadequate iodine intake.

Conclusion: Nutritional iodine intake is inadequate in a large proportion of pregnant women. This study has implications for subclinical maternal hypothyroidism and neurodevelopmental outcomes of babies born to these mothers. Screening or return to iodised salt is indicated.

FINAL HEIGHT OUTCOME AND VALUE OF HEIGHT PREDICTION IN BOYS WITH CONSTITUTIONAL DELAY IN GROWTH AND ADOLESCENCE TREATED WITH INTRAMUSCULAR TESTOSTERONE 125 mg MONTHLY THREE MONTHS

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Although essentially a normal, physiological variant of growth, constitutional delay in growth and adolescence (CDGA) in boys may cause considerable psychological distress. Management includes appropriate counselling with prediction of final height based on skeletal maturity (bone age) and, if desired by the family, growth promoting therapy. Oxandrolone and low dose oral or intramuscular testosterone are commonly used, and accepted as having no adverse influence on final height but their effects on growth and pubertal development are modest. Higher doses of testosterone are associated with dramatic improvement in height velocity and pubertal development but are still viewed with concern over possible impairment of final height due to premature closure of the epiphyses.

We have compared final height (FH) outcome in 41 subjects receiving testosterone oenanthate 125 mg monthly for three months, and 24 untreated subjects. We have also assessed the accuracy of initial height prediction in these patients using the RUS (TW2) method with a single observer. All boys were >19 years at the most recent measurement. The treated boys showed a good linear response to testosterone therapy with mean (SE) height velocity 9.2 (0.4) cm/year at 6 months post-treatment, compared with 4.4 (0.3) cm/year pre-treatment.

There were no significant differences between the groups (treated mean/SD vs untreated mean/SD) in pre-treatment/Comparable age (14.3/3.0 vs 14.0/1.1) and height 144.7/6.2 vs 144.2/6.3), mid parental heights (170.4/5.6 vs 171.1/4.5/5.0), and bone age (12.0/1.2 vs 12.3/1.2). FH in both groups (168.9/6.0 vs 168.2/5.3; p=0.6) were closely related to predicted FH (169.8/5.1 vs 168.1/4.1; p=0.22) and only slightly less than the mid-parental heights. Only three subjects had FH below the initial height prediction range.

Our data indicate that this treatment regime does not adversely effect FH in boys with CDGA and that height prediction using the RUS (TW2) method is a useful and accurate tool.

A COMMON MTDNA VARIANT MAY BE A SUSCEPTIBILITY FACTOR IN 2 MULTIFACTORIAL DISEASES

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Introduction: Type 2 diabetes and dilated cardiomyopathy (DCM) are both multifactorial conditions, DCM being the leading cause of heart transplant-tation in young people. Diabetes and cardiomyopathy are both features of mitochondrial disease. We previously demonstrated that a common mtDNA polymorphism, the 16189 variant, is associated with both raised fasting insulin (Diabetologia 1998;41:54) & thinness at birth (Lancet 1999 353 1499).

Methods: The presence of the 16189 variant in blood DNA from patients and controls was investigated by PCR and sequencing.

Results: Diabetes study—Case control study of the 16189 variant in 417 UK diabetics recruited from general practice along with controls matched for age and sex. The odds ratio is 1.63 (p=0.037, 95% confidence intervals 1.00–2.65).

Dilated cardiomyopathy study—The 16189 variant is associated with an increased risk of DCM in Caucasian and African populations. Of the Caucasian DCM patients, 17.2% (16/93) had the 16189 variant compared with 8.8% (48/545) of controls (p=0.01; OR= 2.15 [95% CI 1.16–3.98]). The 16189 variant with associated length variation was present in 46% (11/24) of Black South African DCM patients compared with only 16% (2/19) of controls 4.51 (95% CI 103–193; p=0.036).

Conclusions: The 16189 variant is significantly associated with 3 phenotypes in a total of 7 independent populations (Europeans, Africans and Polynesians), easily fulfilling the minimal criteria for informative association studies in multifactorial diseases. The 16189 variant may subtly affect mitochondrial function, as none of these associations is explained by a mitochondrial founder effect.

This is the first evidence that a common mtDNA variant (frequency 9–95%) may play a role in significant multifactorial diseases, and its interaction with birth weight has implications for prevention of type 2 diabetes.

INFANTILE TYPE 1 DIABETES MELLITUS AND ACUTE LIVER FAILURE. A NEW MITOCHONDRIAL DEPLETION SYNDROME?

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ARCH DIS CHILD first published as 10.1136/adc.84.suppl_1.A18 on 1 April 2001. Downloaded from http://adc.bmj.com/
Insulin-requiring diabetes presenting in the first few months of life is rare, with an incidence in the first 3 months of life below 1 in 45,000. At least 50% of these children have only transient insulin requirements. Of those with permanent diabetes, only three sets of siblings have been described in the literature.

We report a consanguineous pedigree with four children; two identical twins in one family and a sib pair in the second. All developed insulin-requiring diabetes within the first four months of life. Three of the four affected individuals developed acute liver failure during intercurrent viral illnesses and death. Post-mortem histology revealed acute fatty degeneration of the liver in all three children, as well as a reduction in the size of the islet cells within the pancreas. The fourth child, now aged 10, is still insulin dependent, has growth failure, chronic renal impairment, and liver disease which has been shown to be exacerbated by intercurrent infections. We found no reports of type I diabetes with presenting liver disease in the literature.

Extensive investigation of the affected sib pair has shown a Mitochondrial Depletion Syndrome. Mitochondrial DNA levels were reduced to 16% of normal values, in muscle tissue, obtained from the sib of the surviving child.

This is the first report of permanent early onset type 1 diabetes and liver dysfunction in association with a Mitochondrial Depletion Syndrome.

**Results:**

- Mean QTc ranged from 350 to 440 msec. Minimum BG occurred in 9 (31%) and hypoglycaemic children demonstrated prolonged QTc (>440 msec) compared to 3/20 without hypoglycaemia (Fishers exact test, p=0.01).

**Conclusions:**

- We found the incidence of CD to be 8% in our population of diabetic children compared with average national incidence of 0.02—0.06% in general population.
- We recommend routine screening as part of general care of diabetic children.

**Background:**

Little is known about microvascular complications in diabetic children.

**Aims:**

- To determine the prevalence of hypertension and microalbuminuria and study 24 blood pressure (BP) profiles of diabetic children.

**Methods:**

- Children with diabetes (duration more than 5 years) were included in the study. BP was measured using an automated BP device and 24-hr BP monitor in 34 diabetic children and 30 matched healthy controls. Patients and controls gave 3 consecutive morning samples for urinary albumin/creatinine (UAC) ratio estimation. Mean BP (systolic + diastolic) were compared to local controls and to published normal data (Task Force). Raised UAC ratio was compared between diabetic patients and controls.

**Results:**

- Diabetic children had a significantly raised normal standard deviate (nsd) for systolic BP when compared to published data (p<0.006). Nocturnal ‘dip’ in either systolic or diastolic BP or both was not observed in 40%. 7 diabetic children had raised UAC ratio compared to 2 controls but confidence intervals for difference in proportion did not reach statistical significance. There was no association between loss of nocturnal dipping and raised UAC ratio.

**Summary:**

- Children with diabetes do not have ‘hypertension’ but have a raised nsd systolic BP. Some diabetic children do not show nocturnal dipping of BP.

**Conclusions:**

- The results indicate changes in BP profiles at an early stage in diabetic children. More patients are required to clarify these early changes in blood pressure.

**Aims:**

- Prolongation of the QT interval occurs during hypoglycaemia in adults and is a risk factor for the development of cardiac arrhythmias. We have examined variations in QTc in relation to blood glucose (BG) and potassium in prepubertal children with Type 1 diabetes.

**Methods:**

- Children (n=13, 5–10 years, aged 7–12 yrs) were studied over 18:00–07:00hrs on 2 occasions. BG was measured every 15 min and potassium every 60 minutes. During sleep, ECGs were recorded for 3 minutes every 30 minutes on a single channel high-resolution computer system. These were signal averaged over 100–200 beats and QT interval measured on the computer.

**Results:**

- Mean QTc ranged from 350 to 440 msecs. Minimum BG correlated with minimum serum potassium (r=0.40 p=0.013). Maximum QTc (412–480 msecs) was inversely related to minimum blood glucose (r=-0.39 p=0.037) and potassium (r=-0.49 p=0.007).

**Hypoglycaemia** (blood glucose <3.5mmol/l on two measurements) occurred in 9 (31%). 6/9 hypoglycaemic children demonstrated prolonged QTc (>440 msecs) compared to 3/20 without hypoglycaemia (Fishers exact test, p=0.01).

**Conclusions:**

- We recommend routine screening as part of general care of diabetic children.
Conclusions: These data suggest a relationship between prolonged QTc and hypoglycemia in children, mediated by hypokalemia both of which are risk factors for arrhythmias. More studies are needed to examine the role of hormonal counter-regulation in this response.

G45 RETINOPATHY SCREENING IN CHILDREN AND ADOLESCENTS WITH DIABETES

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Background: Current recommendations regarding optimal timing of retinopathy screening in IDDM, reflect consensus views rather than evidence. Recent guidelines suggest screening pre and post pubertal children.

Aim: To determine the optimal timing of screening for retinopathy.

Method: All children with IDDM currently attending our clinics, who had undergone formal retinal screening, either by slit lamp or non mydriatic retinal camera, were included in our analysis. During this time, screening was done annually, after 5 years duration of diabetes, irrespective of age. Other information collected included duration of diabetes, blood pressure, pubertal status, smoking and lipid profile.

Results: 73 patients with an age range between 10 and 21 years and a median duration of diabetes of 7 years had been screened. 70 (95.9%) had no retinopathy. 3 (4.1%) had retinopathy of varying degrees; 2 with background retinopathy and 1 with maculopathy. All 3 were pubertal and smokers, aged 17, 18, and 19 with poor diabetic control (median HbA1C 11.7) and a duration of diabetes ranging from 6–15 years.

All had normal blood pressure and lipid profile. No child had retinal changes with diabetic duration of less than 6 years

Conclusion: As retinopathy was not seen in patients under 15 years of age, screening of all pre pubertal children is probably not justified. Following our study, screening in our local diabetic population, will be performed on all teenagers, irrespective of duration of diabetes and selectively on pre pubertal children, with risk factors known to contribute to micro vascular disease.

G46 INFLUENCE OF POSTNATAL AGE ON PLASMA LEPTIN AND ADIPOSE TISSUE DEPOSITION

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Aims: Leptin is the 16kDa protein encoded by the ob gene. The primary source of plasma leptin is white adipose tissue. Leptin levels are influenced by the rate of adipose tissue deposition. The extent to which the biological function of leptin may change over this period remains to be established.

Methods: Jugular venous plasma samples and perirenal adipose tissue (the primary source in the lamb) were taken within two hour of birth. The time course of postnatal changes after birth and the role of adipose tissue deposition in the development of leptin levels was assessed.

Results: Plasma leptin concentrations remained unchanged over the first 2 days of postnatal life (e.g. 2 days — 2.3 ± 0.4 ng/ml), before increasing to peak at 7 days of age (5.4 ± 0.9 ng/ml (P<0.05; Mann Whitney)) as perirenal adipose tissue weight doubled (0 days 20.8 ± 2.4 g; 7 days — 69.0 ± 9.6 g/day (P<0.01)). This was followed by a decline in plasma leptin up to 30 days of age (2.4 ± 0.3 ng/ml), despite a further two-fold increase in adipose tissue deposition during this period (156.5 ± 13.4 g/day (P<0.01)).

Conclusion: Changes in plasma leptin concentration over the first month of life are not associated with concomitant changes in adipose tissue deposition. The extent to which the biological function of leptin may change over this period remains to be determined.

G47 PROSPECTIVE NATIONAL DATA ON INFLAMMATORY BOWEL DISEASE IN CHILDREN AGED LESS THAN FIVE YEARS

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Introduction: There are few published series of IBD in children aged less than five years, and there are no data on incidence, ethnicity, or whether these children represent a distinct clinical sub-group.

Methods: From June 1998 to June 1999 the British Paediatric Surveillance Unit and the British Society of Gastroenterology Research Unit (BSGRU) prospectively surveyed paediatricians and gastroenterologists respectively, to identify newly diagnosed cases of IBD.

Results: 28 newly diagnosed cases of IBD were identified aged < 5.0 years, giving an incidence of 0.2 cases per 100,000 children per year, and representing 4% of all cases aged 0 to 16.0. The youngest child was aged 6 months and 5 others were < 2.0 years at diagnosis. 2/28 cases were identified by the BSGRU survey, indicating that the initial management of such young children was provided by adult services. There were 9 cases of Crohn’s Disease (CD), 2 of Orofacial Granulomatosis (OGF), 10 of Ulcerative Colitis (UC) and 7 of Indeterminate Colitis (IC). Only a minority (39%) of children aged < 5.0 were diagnosed as CD/OGF compared to a majority of older children aged 5.0–16.0 (61%), p = 0.03. The proportion of children from an ethnic background and the number with a family history of IBD in the CD/OGF group was the same as in older children but there was a trend for more IC/UC children aged < 5.0 to come from an Asian Background (18% v 11%, p = 0.08). Pain, lethargy and weight loss were reported less often, and rectal bleeding more often in younger children with CD/OGF. Investigation and disease distribution of CD/OGF was the same as in older children, except for a trend to less involvement of the ileum (36% v 61%, p = 0.10) Presenting symptoms, investigation, disease extent and management in the UC/IC group aged < 5.0 were not significantly different to that of older children.

Conclusion: 4% of children with IBD present aged < 5.0 yrs. In this age group children ( Ulcerative or Indeterminate) is more common than Crohn’s disease and is positively associated with an Asian ethnic background. At presentation the group does not have any other definitive clinical features.

G48 SEVERE LIVER DISEASE IN CYSTIC FIBROSIS IS ASSOCIATED WITH HETEROZYGOSITY FOR MUTATIONS IN THE α-ANTITRYPSIN PROTEASE INHIBITOR GENE

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Background: Liver disease (LD) in cystic fibrosis (CF) has not been associated with any specific mutations within the cystic fibrosis transmembrane conductance regulator (CFTR) gene, or other gene mutations known to cause LD. Accurate prediction of patients who will develop severe CF LD is not possible.

Aims: We aimed to test the hypothesis that mutations in the α-1 antitrypsin (protease inhibitor, PI) or hereditary haemochromatosis (HFE) genes are associated with severe CF LD.

Methods: 61 CF patients with severe LD with portal hypertension and 119 control CF patients without known LD were identified. We tested for CFTR mutations, for the Z and S mutations in the PI gene and for the C282Y and H63D mutations of the HFE gene.

Results: 97% of the CF LD patients had CFTR genotypes associated with severe CF, with an excess of ∆F508 and other CFTR folding or processing defects. There were 6 heterozygotes for PI Z, 7