Hormone Research

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Abstracts

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1

Severe Hypoglycaemia (SH) in Diabetic Children Treated with Multiple Insulin Regimen (MIR)

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The aim of our study was to assess the prevalence and characteristics of SH (altered consciousness, coma, seizures or other neurologic symptoms) in type I diabetic children and adolescents treated with MIR attending our outpatient department, in a retrospective study from 01/01/90 to 31/12/97. We obtained the information on hypoglycemic events from clinical reports and questionnaires compiled by patients' parents. 188 diabetic patients (95 females and 93 males), 16.2 ± 6.7 years old (duration of diabetes 8 ± 5.3 years), were studied. They were divided into two groups: 160 non-SH children and 28 patients that experienced 38 SH (2 had four and 4 two episodes). No difference in chronogical age, duration of diabetes, metabolic control and number of daily insulin injections was found. 45% of SH occurred in patients aged 7–14 years, 42% in patients younger than 7 years of age, and 13% in those older than 14 years of age. 24/38 episodes of SH occurred in children on a daily insulin dose ranging from 0.6 to 0.8 U/kg; 13/27 SH in patient on insulin dose >0.8 U/kg/die and SH in patients on a daily insulin dose <0.6 U/kg. SH was experienced predominantly in spring (n = 13) and summer time (n = 13). 50% of SH were nocturnal. Patients/parents were able to identify the cause of 15 SH. The predominant cause was incorrect food intake (73%), particularly in a population with a mean age of 14.3 years. SH was associated with loss of consciousness in 27/38, with seizures in 7 and transient hemiparesis in 2 patients. SH was announced by prodromes in just 39% of patients (19% trembling). 82% of SH were treated with administration i.m. glucagon and 8% with i.v. 33% glucose. Severe hypoglycemia is a recurrent problem, not related to metabolic control or to daily insulin dose, and diabetic children with a history of severe hypoglycemia are at risk to experience future episodes.

2

Nocturnal Hypoglycaemia in Danish Children with Type 1 Diabetes mellitus: A Nationwide Study

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The aim of the study was to identify predictors and evaluate the risk of nocturnal hypoglycaemia (NHG) in children and adolescents with IDDM during everyday life. All diabetics treated in paediatric departments in Denmark were invited to participate. Basic characteristics and treatment were recorded and HbA1c was determined centrally. Blood samples for analysis of blood glucose (BG) were taken in capillary tubes at home and mailed to one laboratory. BG was measured during 24 h in the fasting state, before main meals, at bedtime, at 3 a.m. and the following morning. Hpypoglycaemia (HG) was defined as BG <3.5 m*M*. Data were analysed by logistic regression using backwards stepwise exclusion. $p < 0.05$ was considered significant. Results are given as mean (SD) BG in m*M*. Of 1,009 eleglible patients 464 patients completed the blood sampling including the nocturnal sample. HbA1c was 8.46% (1.27).

Fasting	Before lunch	Before dinner	Bedtime	3 a.m.	Fasting
BG 10.7 (5.2)	12.7 (7.3)	13.3 (7.1)	12.8 (6.5)	11.4 (5.4)	11.0 (5.2)
HG 6.5%	4.4%	3.0%	4.3%	8.4	5.4%

HG was observed on at least one occasion in 23.5% of the patients. The frequency was highest at night. Significant relations were found between NHG and BG at bedtime ($p < 0.001$), male sex ($p < 0.02$), age ($p < 0.05$), small height ($p < 0.05$), ≤2 injections/day when compared to ≥3 ($p < 0.05$) and the dose of rapid-acting evening insulin ($p < 0.05$). A significant relation was found between NHG and BG the next morning ($p < 0.001$). Relations between HbA1c, pubertal stage, hypos, sport activities were not significant. The data suggest that the risk of NHG is associated to male sex, young age, high evening dose of rapid-acting insulin and low BG at bedtime. Low BG in the morning may indicate preceding NHG.

3

Central Adiposity and Insulin Sensitivity in Healthy African-American Children

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Abdominal adiposity has been implicated as a risk factor for insulin resistance and NIDDM in adults. African-Americans (AA) are at increased risk for obesity, CVD, hypertension and NIDDM. We have shown that healthy AA children are insulin resistant and have higher insulin secretion compared with their White peers [J Pediatr 129:1996; J Clin Endocrinol Metab 82:1997]. Moreover, AA children are more obese with central distributon of fat compared with their White peers. Therefore, the aim of the present investigation was to study the relationship of central obesity to insulin resistance in AA children. We studied 19 (10 male, 9 female) healthy AA prepubertal children, age (9.8 ± 0.2 years), BMI (19.6 ± 1.0 kg/m^2). Body composition was assessed with DEXA, and abdominal adiposity by CT scan at the level of L_{4-5} with measurements of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). Insulin action was

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assessed by a 3-hour hyperinsulinemic (40 mU/m^2/min)-euglycemic clamp. Insulin-stimulated glucose disposal (Rd) was calculated over the last 30 min of the clamp.

Results: Mean ± SEM.

	Males	Females	p
BMI, kg/m^2	19.4 ± 1.4	19.9 ± 1.5	n.s.
%BF	20.4 ± 3.8	24.7 ± 3.5	n.s.
VAT/SAT ratio	0.3 ± 0.1	0.2 ± 0.02	n.s.
Rd, mg/kg/min	13.4 ± 1.4	10.0 ± 1.3	n.s.

Rd correlated with %BF (r = –0.76, p = 0.0005), SAT (r = 0.80, p = 0.005) and VAT (r = –0.71, p = 0.001). However, in a multiple regression analysis SAT was the only significant determinant of RD explaining 64% of its variability independent of %BF.

We conclude that the risk of abdominal obesity to insulin resistance is already established in the first decade of life in AA children. It remains to be determined if this risk is of greater magnitude than that in American-White children.

4

Childhood Diabetes in Iceland: Genotyping of the DRB Gene

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The incidence of childhood diabetes is low in Iceland compared to the other Nordic countries. Of special interest is the difference in incidence between Norway and Iceland in light of the alleged Norwegian origin of the Icelandic population. The incidence of IDDM in Iceland is close to 10/100,000/year, or less than half of the reported incidence in Norway. A major part of the genetic predisposition is believed to be encoded in the HLA complex residing on chromosome 6. A strong association has been found with certain alleles of the HLA-DR and DQ genes in the MHC class II region. Some studies suggest that there may be other loci in the HLA gene complex that play a role. The genetic background of the diabetic population in Iceland and in Norway has not previously been compared with respect to HLA allelic distribution and frequency. We genotyped the DRB locus of unrelated Icelandic IDDM patients diagnosed before 15 years of age and of unrelated control samples from the Icelandic population. PCR amplification and dot blot hybridisation method was performed with oligoprobes distinguishing between 18 different alleles of the DRB gene. The results from genotyping of 60 patients and 183 controls show no major differences in DRB allelic distribution between Icelandic and Norwegian patients and between control groups of both countries. Specifically the frequency of DR301 (48 vs. 54%), DR401 (60 vs. 59%) and DR404 (20 vs. 25%) Iceland vs. Norway, respectively. More patients are being genotyped at the DRB genes and genotyping of the DQ genes is in progress. These first results indicate that the difference in incidence of childhood diabetes seen between Iceland and Norway can not be explained by a major difference in the DRB allelic distribution. An explanation must be sought elsewhere.

5

Treatment of the Dawn Phenomenon in IDDM Adolescents with Amorphous Zinc Insulin (Semilente®) at Bedtime

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Early morning hyperglycaemia without nocturnal hypoglycaemia (dawn phenomenon) is a common finding in adolescents with IDDM and contributes to the deterioration of metabolic control during puberty. The aim of this study was to examine whether Semilente®, an amorphous zinc insulin with kinetics different from NPH insulin, is better suited to alleviate the dawn phenomenon in adolescent patients. This prospective study included 26 IDDM adolescents (age: 14.9 ± 2.0 years; diabetes duration: 7.8 ± 3.6 years) treated with multiple insulin therapy. All patients suffered from dawn phenomenon which could not be satisfactorily suppressed by a bedtime injection of NPH insulin. Bedtime insulin was switched to Semilente insulin and patients were followed up for 15.9 ± 10.1 months. Change in metabolic control (fasting and mean daily blood glucose of 1 month and 3-monthly measured HbA_{1c} of 1 year before and after switch, respectively), insulin requirement, BMI, and rate of hypoglycaemia was assessed to estimate the effect of therapeutic modification. As a result of change in therapy, fasting [median (95% CI): 13.05 (12.35–14.50) vs. 9.20 (8.07–9.92) mmol/l; $p < 0.0001$] and mean daily blood glucose [10.70 (10.23–11.45) vs. 9.20 (8.50–9.56) mmol/l; $p < 0.0001$] values and HbA_{1c} levels [10.30 (9.06–10.79) vs. 8.80 (8.11–9.20)%; $p = 0.0024$] decreased significantly, meanwhile a diminution in bedtime [0.32 (0.28–0.41) vs. 0.25 (0.20–0.34) U/kg/day; $p = 0.0078$] and total daily insulin requirement [1.14 (1.00–1.32) vs. 1.02 (0.98–1.11) U/kg/day; $p = 0.0117$] was observed. Neither the rate of hypoglycaemia nor the BMI changed significantly. It is concluded that Semilente insulin given at bedtime is effective to suppress dawn phenomenon and to improve long-term metabolic control in adolescents with IDDM.

6

Validation of a Multidimensional Quality-of-Life Measure for Children and Adolescents with Insulin-Dependent Diabetes mellitus (IDDM)

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The aim of this multicenter study was to develop and assess the psychometric properties of a quality-of-life measure for children and adolescents with IDDM. Quality of life was defined as perceived satisfaction/difficulty in three different key domains of life: (1) diabetes-related social differences (6 items); (2) diabetes-related barriers (7 items); (3) diabetes-related future worries (6 items). Item scores ranged from 1 (low quality of life) to 4 (high quality of life).

A total of 78 patients (36% boys) from 6 German pediatric centers (Bonn, Frankfurt, Giessen, Hannover, Leipzig, Stuttgart) com-

pleted the first measure (values are means ± SD): age 15.3 ± 1.8 years, diabetes duration 6.5 ± 3.9 years, HbA_{1c} 8.3 ± 1.7%. Retest measure after 2 months involved 42 patients with similar characteristics. All scales and the total questionnaire had high degrees of internal consistency (Cronbach's $\alpha = 0.67–0.79$) and stable test-retest reliability ($r = 0.54–0.69$). All scales appeared sensitive to external criteria of diabetes management. Higher levels of HbA_{1c} correlated with worries about diabetes ($p < 0.01$, $r = 0.33$) and diabetes related barriers ($p < 0.01$, $r = 0.38$). Diabetes-related barriers were associated with severe hypoglycemia in the past ($p < 0.05$, $r = 0.26$). Mean scores of the scales show that adolescents do not feel very different from peers (3.5 ± 0.6) and that they perceive diabetes as a modest barrier in their life (3.0 ± 0.6). In contrast, worries about diabetes seem to have the major negative effect on quality of life (2.5 ± 0.5).

Quality-of-life data reflect psychsocial problems in different life areas. This can be used for treatment decisions and educational interventions, e.g. to inform carefully adolescents about long-term complications and its prevention. The questionnaire will be revised and extended to a fourth scale to measure diabetes related coping resources.

7

T-Cell Responses to Proinsulin and IA2 Mark High-Risk First-Degree Relatives of IDDM Patients

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The identification of predictors of imminent development of IDDM in subjects at risk for the development of the disease is a major goal that must precede the initiation of preventive therapies. In order to assess whether T cell responses to autoantigens could fulfill this role, we compared responses to 11 test antigens or peptides in 132 new onset IDDM children (10.1 ± 4.2 years) with those in 50 high-risk first-degree relatives (ICA+ plus DQ markers) and 218 relatives without all these markers (FDR). In this assay system responses to the ICA69/BSA derived antigens, GAD65 and HSP 60 were all IL2-dependent. In contrast, responses to IA2 and proinsulin (PI) were IL2-independent. T-cell responses did not correlate with ICA or antibodies to GAD or IA2, nor to the presence of high risk HLA DQ heterodimers. As can be seen in the table, the frequency of T-cell responses to PI and/or IA2 in high-risk relatives and new-onset cases is similar. In the former, the frequency is significantly greater than the responses in other relatives or to other antigens. The aquisition of IL2-dependent responses may occur at the time of progression of the disease. In new-onset cases, T-cell responses to all antigens persist with the same frequency for at least 1 year implying that these T-cell clones are sustained. Prospective studies are needed to assess the predictive value of IL2-dependent and/or -independent T-cell responses for the rapid development of IDDM, in relationship to the presence of autoantibodies, particularly in subjects without high risk HLA genes.

	% Positives			
	HSP	GAD	p69/BSA	PI/IA2
FDR	9	28	37	37
High risk	8	36	50	86
IDD onset	12	55	73	82
0.5 years	10	58	76	75
1 year	11	54	75	75

8

An Audit of Paediatric Diabetes Care in Russia and England: An Experience in International Collaboration

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On behalf of the Paediatric Teams in Moscow, Moscow Region, Tula, Tambov and Southampton

A joint Anglo/Russian team audited diabetic care in children < 16 years over 4 weeks in 3 Russian centers (R) and Southampton (S). A questionnaire was completed for 265 children in R and 82 in S. Control and complications were assessed by HbA1c and ACR determinations (Bayer DCA 2000), BP, growth and retinal examination. The prevalence of diabetes was greatest in S (1:833 vs. 1:2,136). At diagnosis, R children had a higher incidence of ketoacidosis (69 vs. 29%) and stayed in hospital longer (30 vs. 3 days). In management R children received more injections/day (5 vs. 2) but insulin dose was less and did not increase with age (R $r = 0.09$, $p = 0.14$ vs. S $r = 0.5$, $p = < 0.001$). 29% of R children reported that they had insufficient insulin and 14% had to buy extra. HbA1c was 2% higher in R children (10.4 vs. 8.5%), increasing significantly with age ($r = 0.4$, $p < 0.001$) and their height deficit correlated with HbA1c and duration. HbA1c did not rise similarly in S. Severe hypoglycaemia was more common in S children (31 vs. 12%), who were heavier with a > BMI. Retinopathy was reported in 13% of R children (S = 0%) and Systolic BP > 95th in 23% (S = 6%) but ACR was similar in the two countries. This study demonstrates the advantages of an ambulatory philosophy of care in S compared with hospital-based education and prolonged stay in R where, last year, 81% of children missed a median of 24 days from school/nursery education (S = 38%, median 3 days). Higher insulin dosage and lower HbA1c results in S were associated with more severe hypoglycaemia and weight gain but in R the high HbA1c results indicate a greater risk of long term complications. Comparative International studies are encouraged to share experience and can be of benefit in planning the introduction of new policies in health care.