

Long-Term Follow-Up of Antibody-Positive Siblings of Diabetic Children

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Risk of IDDM was estimated in 234 siblings of recent-onset diabetic children, aged 2–29 years. Twelve subjects developed diabetes during a median follow-up of 11 years (range 1.7–14 years). Islet-cell antibodies (ICA) and antibodies to insulin (IAA), glutamic acid decarboxylase (GADA) and the IA-2 protein (IA-2A) were tested in sequential serum samples. ICA had the highest sensitivity (83%) and IA-2A the highest predictive value (70%). IAA and GADA had poor sensitivity and predictive value. Combinations of antibodies achieved better predictive value with lower sensitivity. The predictive values were 83% for the combination of GADA and IA-2A, 70% for any combination of two or more antibodies other than ICA. The actuarial risk progressed from around 50% after 5 years to 100% after 13 years. Taking into account HLA-DR3/4 and age ≤ 10 years increased the predictive value of each antibody combination, whatever the number of antibodies. Younger age was also associated with a more rapid progression to IDDM. Sequential antibody screening resulted in higher sensitivity because of seroconversion during follow-up. In conclusion, the combination of several antibodies in sequential serum samples is satisfactory for the identification of subjects at risk to develop IDDM. Age and HLA-DR3/4 as risk markers may contribute to a more efficient prediction in antibody-positive subjects.

Effects of the Duration and Control of Insulin-Dependent Diabetes mellitus on the Dental Caries Status of Diabetic Children and Adolescents

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The aim of this study was to investigate the dental caries status in children and adolescents with insulin-dependent diabetes mellitus (IDDM). Sixty-seven patients aged 3–17 years were divided into three age groups (3–5, 6–11 and 12–17 years). The dental caries status of diabetic children and adolescents was examined in relation to diabetic control and duration of IDDM. Diabetic control was assessed for each patient by determining the level of HbA_{1c} (well-controlled HbA_{1c} $\leq 7\%$ and poorly controlled HbA_{1c} $> 7.8\%$). The dental caries status of children and adolescents with IDDM of the 3–17 years of age group was similar to that of non-diabetics of similar age groups (UK official epidemiological reports). Poor diabetic control seemed to affect the caries levels in the diabetic children on a long-term basis ($r = 0.418$). The duration of IDDM did not appear to influence the caries levels of well-controlled diabetic children and adolescents ($r = -0.63$). In conclusion, dental caries may be an additional complication of poor diabetic control. Therefore, oral hygiene instructions should be reinforced in young diabetic patients.

Concentrations of Copper and Zinc in Blood Cells in Children and Adolescents with Diabetes mellitus Type 1

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Renal losses of zinc, a special diet and an increased need in growing up could lead to a lack in zinc (Zn) and copper (Cu) in children with diabetes. Zn and Cu were analysed in plasma, whole blood, erythrocytes, platelets, and leucocytes (PL, WB, ERY, PTL, LEUCO) by electrothermal atomic absorption spectrometry. The investigated groups included 94 diabetic children (IDDM, age: 14.0 ± 4.0 years), and 41 healthy children (N, age: 12.5 ± 3.1 years). There was no difference in Zn and Cu in the compounds of whole blood between N and IDDM. Zn in IDDM with HbA_{1c} $> 9\%$ were higher in WB and ERY and lower in PL than in N (each $p < 0.05$). Both groups showed age-dependent changes in Zn (increases in WB and ERY, decreases in LEUCO), and Cu (decreases in WB, each $p < 0.05$). Further increasing age went with increasing HbA_{1c} in IDDM. Not considering the influence of age on Zn, Cu and HbA_{1c}, an insufficient metabolic balance led to higher Zn in WB and ERY ($p < 0.05$, $r = 0.43$ and $p < 0.05$, $r = 0.39$, respectively) and lower Zn in PL ($p < 0.05$, $r = -0.25$). The changes are thus caused on metabolic control. Hyperglycemia may lead to reduced Zn in PL by renal losses. A high activity of superoxide dismutase containing both elements explains the increase of Zn and Cu in ERY. This accumulation in ERY leads to an insufficient amount of Zn in PL, where Zn is responsible for storing and activating insulin. Decreasing Zn in LEUCO is found during the development of preschool children to adolescents. A long-term deficit of Zn is possibly associated with disturbances in wound healing and the susceptibility for infections observed in older diabetics.

Helicobacter pylori in Diabetic Children and Adolescents

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Helicobacter pylori is a recognised gastroduodenal pathogen and *H. pylori* infection is one of the most common bacterial infections, usually acquired during childhood. However, diabetes mellitus is characterized by an increased susceptibility to infections. We compared the prevalence of *H. pylori* infection as well as CagA and VacA positivity in 103 children and adolescents with type 1 diabetes mellitus and in 236 nondiabetic children. We used a novel Recombinant ImmunoBlot Assay-Strip (RIBATM SIA) with individual band for whole *H. pylori* lysate and recombinant CagA and VacA.

Results: *H. pylori*-positive subjects, both diabetics and controls, were significantly older than negative subjects. In the whole group of diabetic patients the prevalence of each of the three reactivities was higher than in control subjects, reaching significance only for lysate.

Only diabetic patients over 12 years of age, with a longer disease duration, had a higher prevalence of positive cases, although not significantly so, than control subjects of the same age (27 vs. 17%).

Conclusions: In the first few years of disease diabetic children do not differ from the nondiabetic population. Subsequently, they show an *H. pylori* seroprevalence tendentially higher than that of controls of the same age. Therefore, *H. pylori* infection acquired in childhood and lasting several years could be one of the causes of chronic atrophic gastritis, which is more frequent in longstanding diabetes mellitus.

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IDDM in a Boy with 10p Trisomy: Is GAD2 Gene Involved?

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In the last 20 years trisomy 10 was reported, isolated or associated with other chromosomal rearrangements, in about 40 patients with mental retardation, craniofacial anomalies including dolichocephaly and hypertelorism, congenital heart disease, renal anomalies and flexion deformity of the limbs. This is a report of a 13-year-old boy with severe mental retardation due to a de novo total 10p trisomy. The karyotype was 46,XY,-22,+der(22)t(10;22)(p11.1;p11.1). We used high-resolution QFQ and GTG banding for cytogenetic definition of the rearranged chromosome. For FISH analysis, we used Cytocell multiprobe multipainting, cosmid pretelomeric 10p probe, and the following YAC probes: 940-F-9; 754-D-10; 837-B-5 and 895-D-3, respectively, mapped to 10p12.33 (48 cM), 10p11.21 (63 cM), 10p11.21(68 cM), 10q11.1 (69 cM from 10p telomere). The phenotype of the patient matches the clinical features reported in the literature for 10p trisomy. Moreover, this boy shows agenesis of the corpus callosum, conjugated bilirubin jaundice (Rotor type) and type 1 diabetes mellitus. HLA typing of locus D resulted in a DR4/DR11 heterozygosis. ICA, GAD65 and ICA512 antibodies resulted all positive. Anticerebellum antibodies were negative. Significantly higher hexokinase 1 (HK1) activity in red blood cells was reported in patients with chromosome 10p trisomy as a consequence of gene dosage effect and this observation leads to a conflicting assignment of HK1 gene to 10q22 and 10p11.23, could also be overexpressed leading to enhancement of the immune response of a susceptible immune system. We raise the question whether GAD2 gene overexpression is involved in IDDM pathogenesis in this particular subject.

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Seasonal Variation of the Duration of Exclusive Breastfeeding Corresponds to the Seasonal Variation of IDDM

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There is a seasonal variation of diagnosis of IDDM in children. Recent studies have shown that there is also an association between month of birth and the risk of developing type 1 diabetes. As breastfeeding has been considered to protect against diabetes in children, we decided to investigate if the seasonal variation of type 1 diabetes can be explained by seasonal variation of exclusive breastfeeding. Retrospectively, we studied a population-based group of 297 children with diabetes and 792 individually matched referent children. Reliable data were collected from well-baby clinics. Children (both with diabetes and controls) born during summer were breastfed exclusively for a period of 2.2 months (mean). Corresponding figures for children born during winter were 2.8 months ($p < 0.2$), spring 2.5 months (n.s.) and autumn 2.7 months ($p < 0.04$). Children born in June had the shortest period of exclusive breastfeeding (2.0 months) while children born in February had the longest (3.2 months). Children who got diabetes before 10 years of age had no significant seasonal variation while children diagnosed between 10 and 15 years of age showed a seasonality with a very short duration of breastfeeding if they were born during summer. The same age group had also the most pronounced seasonal variation of onset of diabetes with nadir during summer.

We conclude that there is a seasonal variation in duration of exclusive breastfeeding, which corresponds to the risk of getting type 1 diabetes during childhood.

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High Frequency of Microangiopathic Manifestations in Insulin-Dependent Children and Adolescents

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Considering microangiopathy as a major predictive factor for the evolution of IDDM patients, we aimed at estimating the frequency and severity of diabetic retinopathy (DR) and diabetic nephropathy (DN) in children and adolescents. We performed a cross-sectional study on 245 patients, whose average age was 15.74 ± 5.37 years, hospitalised in our medical center. The method of study consisted of ophthalmoscopy and a semiquantitative determination of the microalbuminuria by the Micral test. The results were correlated with the patients' age and sex, the average duration of the disease, the HbA1 concentration, and the performing of self-control. We thus found DR in 14.28% of patients aged 18.87 ± 5.32 , with 10.86 ± 5.30 years of IDDM evolution; 68.57% among them had a background DR, and 31.42% a proliferative DR, 4 of them being treated

by laser. The patients without DR have had a similar duration of disease (10.91 ± 5.30) but their age (12.61 ± 5.39 years) was lower ($p < 0.0001$). This frequency, although considerably higher ($p < 0.01$) in patients not subjected to self-control, did not significantly correlate with the HbA1 concentrations. DN was assessed in 24% of the patients (93.23% in incipient and 6.77% in the clinical stage). Age, duration and HbA1 concentration were similar in patients with and without DN.

Conclusion: The frequency of microangiopathy in our patients is alarmingly high. The presence of DR and DN independent of the recent glycemic self-control proves the role of a long-term bad glycemic control in the pathogenesis of these complications.

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Epidemiological Peculiarities of Children with IDDM in Romania

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Accurate epidemiological investigation performed in children (0–16 years) in the last 6 years pointed out for the first time an annual incidence of IDDM between 3.57 and 3.76/100,000 and a cumulated incidence of 0.28‰, a fact that placed Romania among the countries with the lowest frequency of that disease. This finding justified the undertaking of a descriptive epidemiological study in order to correlate the incidence with some parameters: ethnic group, territorial distribution, feeding customs (breast-feeding period), multi-annual epidemic dynamics of various viral infections (mumps, rubella, hepatitis, rubeola). The multivariate analysis only rendered a significant support for the differential frequency of IDDM in different ethnic groups in Romania. Thus, the most endangered ethnic group was that of the Hungarian, characterized by an annual incidence of 7.8/100,000 and a cumulated incidence of 0.55‰, similar to the parameters reported in Hungary. We further specified that the annual incidence for the other ethnic groups ranked at 3.29/100,000 for Romanians, 3.4/100,000 for Gypsies and 4.1/100,000 for Germans, the cumulated incidence being 0.24‰ for Romanians, 0.28‰ for Gypsies and 0.26‰ for Germans. The significant statistical difference ($p < 0.001$) motivated the second part of this study, the correlative analysis of the groups constituted on ethnic criteria with the above-mentioned parameters. The epidemiological peculiarities could not be attributed to the feeding customs, geographic factors or the infectious diseases. In conclusion, the factor pertaining to diabetes heredity remained to be discussed further, as it seemed to confer an epidemiological individuality to the people belonging to the same ethnic group, not depending on geographic territory or country of abode. The difference regarding the frequency of IDDM in German children living in Romania versus those in Germany could be explained by the fact that all of the children belonging to the German minority in Romania come from mixed marriages.

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Elevated Serum Insulin Levels in a Case of Congenital Hypertrichosis, Gum Hyperplasia and Macromastia

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A 13-year-old girl presented with congenital hypertrichosis, gum hyperplasia and macromastia. She had normal glucose tolerance with elevated serum insulin levels. The patient was born at full term by normal vaginal delivery. At birth, she was reported to have short dark hair all over her body and her gums were enlarged. Developmental milestones were normal. Her scholastic performance had been average. She had onset of breast enlargement at the age of 12 years, which rapidly progressed to large pendulous breasts reaching the inguinal region. There was no galactorrhea. Menarche occurred at the age of 13 years. Her father and brother were reported to have hypertrichosis. The patient was 150 centimeters tall (75th percentile by Indian standards for her age). Body mass index was 22.2 kg/m². There was no acanthosis nigricans. There was dark terminal hair all over her body. Axillary and pubic hair were normal. Both her breasts were large and pendulous, reaching the inguinal region, and the overlying skin was ulcerated. External genitalia were normal. No visceromegaly was present. After 75 g oral glucose tolerance test, fasting blood glucose value was 150 mg/dl, after 1 h 150 mg/dl and after 2 h 110 mg/dl. The corresponding serum insulin levels were 2,450, 6,000 and 710 pmol/l, respectively. Intravenous glucose tolerance test revealed normal K value for glucose utilisation ($K = 2$). Serum estradiol, luteinizing hormone, follicle-stimulating hormone and prolactin were normal. Basal and post-ACTH-stimulated serum cortisol, testosterone, dihydrotestosterone, androstenedione and 17-hydroxyprogesterone were also normal. Reduction mammoplasty was performed. In summary, we describe an association of insulin resistance and hyperinsulinemia in this rare syndrome.

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Screening for Thyroid Dysfunction in Children with Type 1 Diabetes mellitus

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Adult patients with type 1 diabetes mellitus (IDDM) have a higher prevalence of thyroid disease than the general population, and the detection rate by annual screening may be as high as 13.4%.

The aim of this study was to determine the prevalence of thyroid disease in children attending the Slovak diabetic center because of IDDM. 210 randomly selected children (98 boys and 112 girls, age 5–18 years) attending a diabetic outpatient clinic received an annual screening for thyroid disease by estimating serum free thyroxine and TSH concentrations. The overall prevalence of thyroid disease was found in 17 (8.9%) children with IDDM, mean age 14.4 (9–17) and

was highest in girls with IDDM (14 of 17). As a direct result of screening, new thyroid disease was diagnosed in 14 (8.1%) of the children screened. The commonest diagnoses were subclinical hypothyroidism (2.3%) and hypothyroidism (2.3%), followed by hyperthyroidism (1.4%) and subclinical hyperthyroidism (0.5%).

This study suggests that thyroid function should be screened annually in children with IDDM to detect asymptomatic thyroid dysfunction which is increased in frequency even in the youngest age groups of patients with diabetes mellitus.

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Variable and Ethnic Differences in Carbohydrate Intake Predisposing to Nocturnal Hypoglycaemia

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Modern dietetic recommendations emphasise healthy eating (high carbohydrate (CHO) and low fat) without measurement of grams/exchanges. To study the hypothesis that children from Indo-Asian (IA) culture have fewer nocturnal hypoglycaemic (NH) episodes because of later evening meals of different nutritional quality, we chose two age- and sex-matched groups, each of 11 children (age range 10–17) from white Caucasian (WC) and IA families. They completed 3-day diet intake diaries with timed recordings of BG (including 3 a.m.) and insulin doses.

Results showed a weak correlation between mean bedtime and 3 a.m. BG but on individual nights there was wide variability. 21% of 63 BG at 3 a.m. were less than 4 mmol/l, occurring in 7/11 WC and 3/11 IA. BG less than 7 at bedtime preceded BG less than 4 at 3 a.m. in 24% (5/21) measurements.

Diet analysis revealed extreme variability in evening CHO intake: mean variation 97% in WC and 85% in IA. CHO eaten during the evening by children having 3 a.m. BG less than 4 was significantly less on hypo (96 g) than non-hypo nights (119 g) and in several cases clearly explained the low night-time BG. IA children ate more CHO, had later meals, had fewer low BG recordings and had higher fat intake (WC 35%, IA 42%).

Conclusions: Modern dietary recommendations for diabetes are associated with wide variations in CHO intake, continuing high fat intake and, despite regular advice, occasions occur when insufficient evening CHO is consumed predisposing children and adolescents to nocturnal hypoglycaemia.

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Intensive Insulin Therapy for Treatment of Diabetes mellitus Type 1 in Preschool and Early-School Children

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The method of multiple insulin injection regimen is rarely used in the therapy of diabetes mellitus type 1 in young children. The aim of this study was to estimate effectiveness and safety of intensive insulin therapy (IIT) in preschool and early-school children. 14 diabetic

children (8 male, 6 female) aged 1.5–9 years (6.4 ± 2) with duration of diabetes mellitus 0.5–7.5 years (2.7 ± 2) were recruited. The patients' current diabetic regimen consisted of mixtures of soluble and isophane insulin. We estimated the metabolic control (HbA_{1c}), total insulin dose and frequency of severe hypoglycaemia. As a result of IIT, we achieved an improvement of metabolic control. There were significant decreases in HbA_{1c} values: 9.17% before, 8.53% after 6 months, 7.5% after 12 months, 6.97% after 18 months, 7.66% after 24 months and 7.42% after 36 months ($p < 0.01$; Wilcoxon test). There were no significant differences in insulin dose. The yearly incidence rate of severe hypoglycaemia was 0/patient/year in the first year, 0.14 in the second, and 0.14 in the third year. This method of IIT was accepted by the patients and their parents. During these 3 years nobody resigned from this method of treatment. In conclusion, this study showed that insulin intensive therapy can be effectively and safely used in young children.

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Longitudinal Analysis of ICA, GAD Antibody (Ab), GAD65Ab and IA-2Ab in Children with IDDM during the Course of Diabetes

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We examined the longitudinal changes of ICA, GAD antibody (Ab), GAD65Ab and IA-1Ab in 103 patients with juvenile-onset (40 males and 63 females, age 13.9 ± 6.5 years, duration 4.3 ± 5.3 years) during the course of the disease.

In newly diagnosed patients, the prevalence of ICA, GADAb, GAD65Ab and IA-2Ab was 90.2, 60.8, 69.7 and 69.7%, respectively. The incidence of ICA was higher than those in GADAb ($p < 0.01$), GAD65Ab and IA-2Ab ($p < 0.05$) at onset. The prevalence of positivity for all the autoantibodies decreased yearly. However, the decline in frequencies of both GADAb and GAD65Ab seemed less marked than that in ICA and IA-2Ab after a duration of ≥ 5 years. The prevalence of ICA as well as IA-2Ab tends to rapidly decrease with increasing duration of diabetes (table). These results suggest that ICA and IA-2Ab are different from GADAb and GAD65Ab with respect to the positivity for autoantibodies. Humoral autoimmunity could be heterogenous in IDDM and various autoantibodies may potentially be found in different subsets of patients.

Duration, years	0	1–3	3–5	5–10	≥ 10
ICA	90.2**	90.9	72.7	27.8	29.4
GADAb	60.8*	60.4	72.7	42.1	53.3**
GAD65Ab	69.7**	62.5	66.7	38.5	58.3**
IA-2Ab	69.7**	71.4	50.0	23.1	8.3**

% values.

* $p < 0.01$, ** $p < 0.05$.