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DOES THE HIGH PREVALENCE OF CYTOPLASMIC ISLET CELL ANTIBODIES IN A GENERAL FINNISH CHILD POPULATION REFLECT AN INCREASED PREDISPOSITION FOR INSULIN-DEPENDENT DIABETES (IDDM)?

Islet cell antibodies(ICA)have been detected previously in 0.0-0.8% of normal populations.The highest incidence of IDDM reported is in Finland. To find out,whether this is reflected in the prevalence of ICA in the general Finnish population, we studied 1206 normal 3-18 year-old children (558 boys,46.3%)for conventional(IF-ICA) and complement-fixing(CF-ICA)ICA.The samples for ICA determination were obtained from a study on atherosclerosis precursors started in 1980. Subjects,who turned out to be ICA positive in 1980, were restudied 1983.A cohort of 300 subjects originally negative for ICA in 1980 was restudied in the year 1983 in order to evaluate the annual incidence of ICA.

In 1980 the mean age of subjects was 11.1±5.1 years. Fifty subjects (4.1%) had IF-ICA and 12 of those CF-ICA in their sera(24.0%). 4.5% of boys and 3.9% of girls had IF-ICA while 1.3% of boys and 0.8% of girls were positive for CF-ICA. The age distribution was similar in the ICA positive and negative groups. At the beginning there was no significant difference in the mean IRI levels between IF-ICA positive and negative subjects[9.8 (6.0)mU/l vs.10.1 (5.9)mU/l]or those with or without CF-ICA [7.7 (4.7)mU/l vs.10.1 (6.0)mU/l]. Four (12.9%) of the 31 initially IF-ICA positive children so far re-evaluated had turned negative in 1983, whereas 3 (25.0%) of 12 subjects originally positive for both ICA were CF-ICA negative and 1 (8.3%) had turned negative for both ICA. Among those 300 children negative in 1980 six (2.0%) had turned positive for IF-ICA and 3 (1.0%) for CF-ICA 1983.

The high prevalence of ICA in normal Finnish children indicates an increased exposure to B-cell damage predisposing to IDDM.This may contribute to high incidence of IDDM in Finland. However,the conversion from negative to positive observed over a period of 3 years and follow-up results in the positive children give support to the suggestion that ICA,in some cases,may be transient in nature and possibly reflect minor beta cell damage not necessarily progressing to clinical diabetes.

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INCREASED CYTOCHROME P-450 (P450j) LEVELS IN LYMPHOCYTES OF CHILDREN WITH POORLY CONTROLLED INSULIN DEPENDENT DIABETES MELLITUS (IDDM).

We have previously shown that P450 dependent hepatic metabolism is increased in poorly controlled insulin dependent diabetes mellitus (IDDM) affecting all three isozymes involved in antipyrine metabolism (Ped. Res. 21:346A, 1987). We now describe elevated P50j in lymphocytes of poorly controlled IDDM patients. P450j plays a major role in the metabolism of nitrosamine, a carcinogen, and in metabolic conversion of acetoacetate and acetone to acetol. Levels of P450j are increased in diabetic animals by specific mRNA stablization (Molec. Endocr. 1:542, 1987). In this study, P450j was measured in peripheral lymphocytes (5ml of blood), of 8 patients with IDDM (age 6-14, mean 10.2 yr) in poor control. Their Hgb A_1 was 13.2±2.1% (nl<7.8%). P450 was measured using a polyclonal antibody (AB) against P450j. Lymphocytes were obtained from nl volunteers and IDDM patients, grown in tissue culture at 37°C for 4 days, in the presence of mitogen. Lymphocytes were homogenized and analyzed by SDS polyacrylamide gel electrophoresis followed by Western blot analysis using polyclonal AB's against P450j. Levels of P450j in IDDM patients were 3-6 times higher than those of nl controls. The highest P450j levels (5 and 6 fold increases) were seen in the 2 patients with the highest Hgb A_1 levels (12,14.3%). This is the first direct demonstration of a potentially reversible elevation of a member of the cytochrome P450 gene family in IDDM using a readily available tissue source.

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MATURATION OF THE HORMONAL ENTEROINSULAR AXIS IN NEWBORN INFANTS OF INSULIN-TREATED DIABETIC MOTHERS

To study whether the increased glucose levels in the amniotic fluid during diabetic pregnancies induce an early maturation of the hormonal enteroinsular axis we measured blood glucose (BG) levels and plasma concentrations of C-peptide (CP), pancreatic glucagon, enteroglucagon (EG) and gastric inhibitory polypeptide (GIP) before and after the first feed in 20 newborn infants of diabetic mothers (IDM) and 12 infants of nondiabetic mothers. All infants were given their first feed comprising human milk (5 ml/kg) by a nasogastric tube at the age of 2 hours. Blood samples were taken before and at 5, 30, 60 and 120 minutes after feeding. At the beginning the IDM had significantly lower BG levels, higher CP and lower EG concentrations. There was a significant increase in BG levels in both groups after the feed and 2 hours after feeding the BG concentrations were of the same magnitude in both groups. No significant CP response could be observed in either of the groups but the IDM had significantly higher C-peptide concentrations at all time points studied. A significant EG and GIP response could be seen in the IDM but not in the controls. However, we did not find any significant differences between the two groups in the absolute plasma concentrations of these two hormones. Our results show that enteral feeding with human milk corrects the early postnatal hypoglycemia within 2 hours in most IDM without causing any exacerbation of their hyperinsulinemia. The absence of any differences in the absolute concentrations of GIP and EG in the peripheral circulation after the first feed suggests that the enteroinsular axis matures postnatally in IDM as well as in normal infants.

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PERSISTENT HYPERINSULINENIC HYPOGLYCEMIA OF INFANCY -- LONG-TERM EXPERIENCE WITH 28 PATIENTS.

We studied 28 patients with Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI). Twenty-two developed symptomatic hypoglycemia within 2 days of life (15 of these required surgery) while 5 developed first symptoms at age 2-7 months (1 required surgery). Twelve patients belonged to 5 families indicating a genetic basis for the disease (autosomal recessive). Non-pancreatectomized patients received frequent high carbohydrate feedings, raw cornstarch, diazoxide and/or somatostatin analogue (Sandostatin™, Sandoz, Switzerland, n=5). All 85-90% pancreatectomized patients (n=15) required some medical treatment for hypoglycemia post-operatively. Three patients died (2 of sepsis and 1 of acute gastric perforation). Diabetes developed only in the 1 patient who had a total pancreatecomy. Of 25 living patients, 16 entered remission between 0.3 & 8 years of age (follow-up 0.3-12 years, mean 5.5 years). Of the 22 living patients who were not retarded at diagnosis, 21 developed normally while 1 is retarded (IQ 65). Pathologic examination of 16 pancreata showed focal findings in 3, the rest being histologically normal for age. Beta-cells from 3 histologicaly normal pancreata were cultured on extra-cellular matrix and showed significant & unchanged insulin secretion at all levels of glucose tested (0-16.7 mmol), which suppressed with epinephrine or somatostatin and stimulated with IBMX or forskolin. **In conclusion:** PHHI appears to be caused by a functional ß-cell defect, presumably genetic in origin, manifested by a lack of suppression of insulin secretion by low glucose, and which may resolve spontaneously with time. Intensive conservative treatment, with 85-90% pancreatectomy only when absolutely necessary, resulted in a good long-term prognosis in 95% of our patients in whom the diagnosis was made before the onset of neurologic damage.

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ADRENAL AND STEROIDAL CELL MEMBRANE PROTEINS OF 54 K AND 50 K ARE AUTOANTIGENS IN AUTOIMMUNE POLYENDOCRINOPATHY - CANDIDOSIS - ECTODERMAL DYSTROPHY.

Adrenal antibodies (AA, binding to adrenal cortex) and steroidal cell antibodies (SCA, binding to gonadal and placental steroid-producing cells) demonstrated by immunofluorescence (IFL) staining have a high predictive value for the development of adrenal and ovarian failure in patients with APECED (JCEM 1987;64:494).

To characterize the adrenal autoantigens membrane fractions of isolated bovine adrenocortical or rat ovarian cells, or mouse Leydig cell tumor were run in SDS-PAGE (8-12% slab gels) under reducing conditions. The proteins transferred to nitrocellulose strips were used for immunoblotting (IB) experiments. 90 sera from 37 patients with APECED, 17 sera from persons with various cytoplasmic ab and 8 normal human sera were tested at dilution 1/50 by IB using peroxidase-labeled anti-human IgG as the second ab. Of the patients' serum samples, 69 (77%) contained ab against adrenal membrane proteins (IB). Of these, 34 contained IgG binding only to 54 K, 16 binding only to 50 K, and 19 binding to both antigens. All AA+ or SCA+ sera and 8/29 AA-SCA- sera were IB+. The 21 IB- sera were also IFL-. The 7 AA+ sera bound only to the 54 K antigen(s). Of AA-SCA+ sera, 9/10 bound only to the 50 K antigen(s). Of SCA+ sera, 8/9 tested on ovarian and 6/8 tested on Leydig cell membranes had IgG binding to 50 K antigen(s). Five of the control sera had ab binding to 54 K, but not to 50 K adrenal antigen(s).

Conclusions: The 54 K and 50 K membrane proteins are major adrenal autoantigens. The 54 K antigen(s) appears specific for adrenal cortex while the 50 K antigen(s) is shared by all steroid producing cells.

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CUSHING'S SYNDROME DUE TO PIGMENTED MICRONODULAR ADRENOCORTICAL DYSPLASIA: FAMILIAL PRESENCE OF ADRENAL STIMULATING IMMUNOGLOBULINES.

Immunoglobulins (Ig's) stimulating the thyroid (TSI) have been described in Graves' disease. By analogy, we earlier reported on the presence of Ig's stimulating adrenal DNA synthesis and/or steroidogenesis in patients with pituitary non dependent Cushing's syndrome due to Pigmented Adrenocortical Micronodular Dysplasia (PAMD)[(1)]

In some of the patients with this syndrome, cardiac myxomas and spotty skin pigmentation are also present and a familial occurrence of this complex of symptoms has been described. We now report on a familial occurrence of Ig's stimulating the adrenal in this syndrome.Sera were obtained from 2 sisters with PAMD, their parents and 2 remaining sibs (all clinically unaffected by PAMD).Guinea-pig adrenal segments were kept in organ culture (37°C, 95% O_2 and 5% CO_2, for 5 h) with protein A sepharose purified IgG added in concentrations of 15-125 µg IgG per ml culture fluid. At the end of the culture period the cortisol present in the culture fluid was determined by RIA. The culture segments were snap frozen and sectioned. Feulgen densitometry was performed on 50 randomly chosen nuclei residing in the zona fasciculata to calculate the percentage of cells in S-phase.

IgG's of both patients with PAMD stimulated in vitro adrenal DNA synthesis and cortisol production. IgG's from their mother who is clinically unaffected also stimulated adrenal DNA synthesis and cortisol production in vitro. IgG's from the remaining family members were negative for these effects.

The positive findings of Ig's stimulating the adrenal in the clinically unaffected mother suggest that separate mechanisms (immune? metabolic? are necessary to bring about overt Cushing's syndrome.

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