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SERUM PITUITARY AUTOANTIBODIES IN CHILDREN WITH INSULIN-DEPENDANT DIABETES MELLITUS (IDDM), AND CORRELATION WITH GH SECRETION AFTER TRH ADMINISTRATION.

The frequency of GH elevation observed in subjects with IDDM prompted us to look for pituitary autoantibodies. An indirect immunofluorescence technique utilizing human and guinea pig hypophysis was used to detect their presence in GH, TSH, and prolactin pituitary cells. Studies are now in progress to discriminate these specific endocrine cells autoantibodies. 26 subjects (12 boys, 14 girls, ages 7-20, mean age 12 ½ yr) were tested after TRH administration (7 µg/kg i.v., max. 200 µg). In controls, none had a significant response of plasma GH as defined by an increase to at least twice the baseline levels and greater than 5 ng/ml. In IDDM children, a significant GH elevation was observed in 17 of 26 cases (9 girls, 8 boys) with a mean ± SE level of 17.1 ± 2.9 ng/ml (range 7.2 - 39 ng/ml) ($p<0.02$ with normal). Among the responders to TRH, 14/17 had positive serum pituitary autoantibodies, while in the 9 children with no GH response to TRH, 7/9 had a negative determination. However, it is of interest to note that all patients except one had positive islet-cell antibodies in their serum. In conclusion, these results are in agreement with the known paradoxical response of GH after TRH in IDDM patients, but not with the lower incidence reported in adult females. In addition, the study of pituitary autoimmunity could partly explain the changes in GH secretion observed in IDDM patients.

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FASTING BLOOD GLUCOSE (BG) LEVELS IN THE LATENT PERIOD (LP) OF IDDM IN CHILDREN.

We retrospectively analyzed the occasional fasting BG concentration of 21 children and OGTT of 7 subjects who developed IDDM 60-8 months later. Approaching symptomatic diabetes the fasting BG levels (72-115 mg/dl) progressively increased with a r-value of 0.68($p<0.005$) and the peak insulin release at OGTT (40-26 uU/ml) declined in a similar linear manner ($r=0.97$; $p<0.01$). Abnormal BG elevations in response to OGTT have been noticed in all subjects at 60 min. (> 180 mg/dl)and in 3 of them also at 180 min (> 140 mg/dl);glycosuria appeared in 2 subjects.In spite of these abnormalities BG levels were not further controlled before the overt onset of IDDM. These retrospective data (rarely available in the PL of IDDM in children) confirm that the abrupt clinical onset of diabetes may be preceeded by a long period of abnormal BG levels and insulin secretory capacity. We suggest that monitoring of these parameters may constitute an effective and non-expensive measure to identify children at risk for IDDM and to admit them to immunological and genetic investigations.

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DIRECT ROLE OF GH IN THE METABOLIC DERANGEMENT OF INSULIN DEPRIVATION: STUDY IN A CHILD WITH INSULIN DEPENDENT DIABETES MELLITUS (IDDM) AND GH DEFICIENCY.

In a child with IDDM and growth retardation (2cm/yr) GH deficiency was documented on the basis of 3 GH stimulation tests and low SmC. Under GH therapy growth rate was 5.5 cm/yr and SmC 3220 mUI/ml. Metabolic consequences of insulin deprivation were studied in situations I, II and III: I without GH, II and III 36 and 12 hrs respectively after GH injection. Normalisation of blood glucose (BG) was obtained by overnight IV insulin. At 8 am insulin was stopped and GH, glucagon, BG, FFA, OH-Butyrate were measured every hr for 6 hrs. At 8 am plasma SmC (mUI/ml) was 201 (I), 3220 (II) and 2953 (III), GH was undetectable in I and II and 7.1 ng/ml in III. At 8 am and + 6hrs glucagon (pg/ml) was 213 and 107 in I, 160 and 155 in II, 176 and 266 in III. BG (mmol/l) rose from 5.6 to 7.4 (I), 8.3 (II) and 15.6 (III), OH-Butyrate (umol/l) from 33 to 225 (I), 45 to 203 (II), and 172 to 1850 (III), FFA (umol/l) from 210 to 680 (I), 110 to 430 (II) and 670 to 1750 (III).

In conclusion : During insulin deprivation BG, FFA and OH-Butyrate rose dramatically in protocole III. This observation demonstrates the crucial role of GH in the metabolic anomalies observed in IDDM. The fact that these anomalies were seen only when GH was recently injected speaks in favor of a direct role of GH not mediated by somatomedin.

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ABNORMALITIES OF BLOOD-RETINAL BARRIER (BRB) IN IDDM CHILDREN AND ADOLESCENTS.

Breakdown of BRB is reported as one of the earliest retinal changes in adult diabetic patients (Cunha-Vaz,1975). In this study we investigated whether vitreous fluorophotometry (VFPT) may permit the detection similar changes in young patients. The permeability of BRB was examined by VFPM in 32 young diabetic patients. (8.4-20 yrs old) and in 10 non-diabetic subjects of same age. All patients had normal fundi and were treated with insulin injection twice a day. VFPM was performed at 2 p.m. before and 60,120.240 min.after 1 gr of p.o. fluorescein, given on empty stomach.The Penetration Vitreous Coefficient (expressed as the ratio of posterior vitreous fluorescence/total blood fluorescence) was higher ($p < 0.001$) in 48% of the patients (0.38±0.07)than in controls (0.23±0.04), indicating an abnormal permeability of BRB.The values were not related to chronological age,duration of diabetes,age at onset of diabetes,HbA1c values, insulin requirement, glucose levels at the time of examination.microalbuminuria. In conclusion, VFPM technique is able to detect defects of BRB permeability in IDDM young patients also with adeguate metabolic control and recent diagnosis. Prospective studies are needed to establish whether these changes lead to irreversible retinopathy.

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NOCTURNAL SUBCUTANEOUS INSULIN INFUSION IN CHILDREN - EFFICACY AND ACCEPTABILITY

Many younger children consider 24 hour Continuous Subcutaneous Insulin Infusion (CSII) unacceptably intrusive. We have attempted to test an alternative infusion system using a Nocturnal Subcutaneous Insulin Infusion (NSII) which is removed before breakfast at which time an intermediate-acting insulin is injected to cover daytime requirements.

Ten children took part in a cross-over trial of 8 weeks on either conventional insulin treatment (CIT) or NSII. Six previously well-controlled children (average age 13 years) completed the study. BG profiles showed a significant improvement in the post-breakfast BG level (10.4 mmol/l on CIT vs. 8.1 on NSII) but a higher BG before the evening meal (7.5 on CIT vs. 10.3 on NSII). This deterioration in the afternoon profile improved as the trial progressed. Overnight control was good both on CIT and NSII.

Acceptance of NSII was less favourable - only three children elected to stay on an insulin infusion and 12 months after the trial only one child remains on NSII, and another uses it intermittently.

NSII in young children would appear to be effective but more impractical than CIT.

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INSULIN INTERNALIZATION STUDY IN CORD BLOOD ERYTHROCYTES.(E)

Insulin internalization has been extensively studied in target cells,this process has not been characterized in human (E). Cord blood (E) were incubated with ^{125}I-insulin at 4ºC.or at 37º C. in the presence and absence of Methylamine (M) which induces intracellular accumulation of insulin or Phenylarsine oxide (P) a well known inhibitor of endocytosis.At various time points,insulin binding (I.B.),haemolysis and degradation were determined,and insulin internalization was quantified using an acid extraction technique. Our results show that (M) and (P) failed to alter (I.B.) in (E).Insulin bound at 4ºC. was 90-95% extractable and TCA precipitable while at 37ºC. with increasing time of incubation the extractability of cell bound insulin and the proportion of intact,undegraded,extractable insulin decrease. In adition (I.B.) degradation and non-extractable acid insulin were increased by haemolysis even at 4ºC.

In conclusion our (I.B.) values in cord blood (E) from preterm and term were 13.2±4.7 and 7.9±2.2 % x3.3x10^9(E) or 370 and 257 sites/(E) respectively and the differences were accounted for by a membrane interaction with minimal internalization.

Incubation at low temperature to prevent haemolysis and degradation must be taken into consideration in (I.B.) studies in (E) for clinical application.