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COMPARISON OF DYNAMIC TESTS FOR GROWTH HORMONE SECRETION IN CHILDREN OF NORMAL STATURE AND NORMAL INTEGRATED CONCENTRATION OF GROWTH HORMONE

Subnormal integrated concentration of growth hormone (IC-GH) is an established criterion for GH-deficiency. Since IC-GH of normal children is higher than in adults and short stature may be associated with subnormal IC-GH, we previously established the normal range for children of normal stature. Arginine, insulin-induced hypoglycemia (ITT), and clonidine are commonly-used stimulants. The range of normal response to each of these drugs was established through testing volunteers who were mostly either young adults or children with "constitutional delay". Since it is now recognized that the GH response of adults may be different from that of children, and that many children who were formerly diagnosed as having a constitutional delay, actually have a partial GH-deficiency or low IC-GH, it may be necessary to reexamine the normative data by testing a cohort of children of normal stature and normal IC-GH. The IC-GH of 66 children (7-18 yrs) of normal stature (>5%) and the responses to stimulation tests were as follows (ng/ml):

	No.	Mean	SD	Range
IC-GH	66	6.4	2.2	3.2-11.8
Stimulant:				
Insulin	9	19.4	4.3	14.8-27
Arginine	7	18.8	4.3	15.0-27
Clonidine	21	26.9	6.4	16.5-42

The normal range of the IC-GH was slightly wider than we previously reported. The new mean and SD of the normal IC-GH is not significantly different from our previous study. The mean and SD of maximal response of our normal children is similar to that reported on "short normal children". However the range of response was lower in the short children, overlapping the range seen in GH deficiency.

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GROWTH-HORMONE (GH) AND OSTEOCALCIN (GLA-P) RELATIONSHIPS IN CHILDREN.

Serum bone Gla-P was measured (ORIS-CIS) in 65 children with normal stature for age and in 116 children with growth retardation (<-2 DS), excluding endocrine disorders, in matched groups according to age:1-6 years (n=33);7-10 years (n=49);11-14 years (n=72);15-18 years (n=27). 30 of these patients have been retested at 2 weeks interval.In addition, Gla-P and growth hormone (GH) were assayed in blood samples obtained every 20 minutes during sleep in 12 children with growth retardation.

In younger children, Gla-P levels are significantly lower in patients with growth retardation,when compared with normals: 8.5 +/-4.4 versus 17.2 +/-6.3 ng/ml; $p < .001$ in the group 1-6 and 12.7 +/-6.0 versus 18.2 +/-5.9 ng/ml; $p < .02$ in the group 7-10 .In contrast,this difference is no more significative in children above 11, either with normal or delayed puberty: 14.6 +/-6.0 versus 16.0 +/-4.7 ng/ml; N.S. in the group 11-14 and 10.0 +/-4.3 versus 7.9 +/-4.6 ng/ml ; N.S. in the group 15-18. However, important intra-individual variations of Gla-P levels are observed on blood samples obtained at 2 weeks interval.

Nocturnal rhythmicity of Gla-P was found; Gla-P rose slightly during night in the patients studied,maximum concentration being reached between 4 and 6 A.M (14.7+/-7.3 versus 6.7+/-4.8 ng/ml at 20 P.M.). No correlation between integrated concentrations of GH and Gla-P was found.

We conclude that : 1/Gla-P determination may be of interest in the evaluation of young children with short stature. 2/ nocturnal rhythmicity of Gla-P is documented and nocturnal Gla-P concentration is not related to nocturnal GH secretion. 3/standardized conditions of blood sampling for Gla-P utilization in children remain to be determined.

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RESTRICTION FRAGMENT LENGTH POLYMORPHISM (RFLP) STUDIES IN THYROGLOBULIN SYNTHESIS DEFECTS.

Data obtained from the screening on congenital hypothyroidism show that hereditary thyroid disorders in the Netherlands occur with an incidence of about 1:20,000. The etiologic classes we found in this population are thyroglobulin (Tg) synthesis defects and (partial) organification defects. Patients with Tg synthesis defects have been detected by an increased amount of urinary low molecular weight iodinated material (LOMWIOM) and a low to normal plasma Tg concentration.

The structure of the human Tg gene has been elucidated (Baas et al, Nucleic Acids Res. 1986; 14: 5171-5186). The gene is found to be well conserved even in the intervening sequences. Looking for RFLPs with 15 restriction enzymes and about 100 control persons only one HindIII RFLP was found in the 3' part with a minor allele frequency of 2.2%. Three RFLPs were found in the 5' (flanking) region with BaeIII, TagI and EcoRV (minor allele frequency: 15-20%). With the available TgcDNA and Tg cosmid clones we studies six families in which Tg synthesis defects occur. In only two of the six families the results were informative. In one family we found that the defect inherited in an autosomal dominant way. In another family in which the defect was inherited recessively, we found besides the affected child a homozygous normal one. These results show that despite the low RFLP frequency, in the Tg gene, this method can be of value for heredity studies.

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EFFECTS OF THYROXINE ON THE DEVELOPMENT OF THE STRESS RESPONSE IN THE NEONATAL RAT.

Neonatal rats exhibit a diminished pituitary and adrenal stress response during the first two weeks of life but the physiological bases for this phenomenon are still unclear as the pituitary and adrenals are functional at birth and CRF can be released at early ages. Enhanced sensitivity to glucocorticoid feedback during this period appears to critically mediate the activation of the hypothalamus-pituitary adrenal axis following stress. Since thyroid hormones (TH) are known to impinge on brain maturation and to influence corticosterone availability to target cells, we investigated the effect of TH on development of the stress response. Daily T4 injections (100 ug/kg bw,sc) in normal rats from day 1 to 20 resulted in premature appearance of ACTH response to ether stress: 5 day-old rats exhibited a small increase ($p < 0.05$) in ACTH secretion following stress while no response was observed in vehicle-treated rats. On days 10, 14 and 20, stress-induced ACTH levels were significantly higher than unstressed controls in both T4 and vehicle treated groups but no differences in ACTH response to stress were observed between the two groups. Additionally, T4 treatment produced marked signs of hyperthyroidism, namely increased locomotor activity, premature eye opening (3 days) and decreased pituitary (33%) and body (12%) weight. Other modifications of neonatal maturation like hypothyroidism are currently under study. In conclusion, T4 treatment is able to alter the developmental pattern of endocrine response to stress possibly through accelerated maturation of central afferents to hypothalamic CRF neurons (increased myelinization).

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ANTIBODY DEPENDENT CELL MEDIATED CYTOTOXICITY (ADCC) IS A FREQUENT FINDING IN CHILDREN WITH ACQUIRED AND NEONATAL HYPOTHYROIDISM (NH).

In children with autoimmune thyroiditis and hypothyroidism thyreoglobulin (Tab) and microsomal antibodies (Mab) are present,but not in children with NH. In contrast, thyroid growth blocking antibodies have been detected frequently in newborns with connatal hypothyroidism by our and other groups. This study presents data on cytotoxic thyroid autoantibodies in children with hypothyroidism. ADCC was measured using a ^{51}Cr- release assay in human thyroid cells (JCEM 59: 734, 1984). 12 of 37 (32%) NH newborns were positive for this antibody, 6 of 12 (50%) older children with NH T4-treated for more than 4 years, and 4 of 4 children (100%) with autoimmune thyroiditis were positive, too. ADCC studies in 29 mothers of 37 NH newborns revealed positive titers in 7 (28%), and these had delivered 6 of 12 positive newborns. In addition, 2 of 7 mothers of older NH children with positive titers were positive for ADCC. 2 mothers and their NH newborns were also positive for Mab and Tab. We conclude that ADCC is a frequent finding not only in acquired but also in NH which might be of pathogenetic significance. The persistence of ADCC in older children suggests independent antibody production in the fetus and newborn. Since ADCC in inflammatory autoimmune thyroiditis leads to destruction of thyroid tissue accompanied by hypothyroidism, similar etiological factors (e.g. viral, HLA, environmental) may be responsible for the destruction of the fetal organ.

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IODIDE OVERLOAD IN MOTHERS AT DELIVERY INCREASES SERUM TSH AND THE RECALL RATE AT SCREENING FOR CONGENITAL HYPOTHYROIDISM (CH) IN THEIR BREASTFED INFANTS.

Skin disinfection with povidone iodine (PVP-I) is widely used in obstetrics in case of epidural anesthesia (Epi) or cesarian section (C.S.). It causes iodine overload of the mothers. We recently showed that this procedure also resulted in a marked increase of the iodine content of breastmilk and in an iodine overload of the breastfed infants. Therefore, we evaluated the influence of one cutaneous application of PVP-I in mothers at delivery on the TSH values of their infants at the time of screening for CH. The 1578 breastfed and the 557 bottlefed infants born during a 2-year period in our maternity section were divided into 3 groups : infants born to mothers with no iodine overload (gr 1) or to mothers with one cutaneous application of PVP-I for Epi (gr 2) or C.S. (gr 3). Results : 1) Breastfed infants : neonatal TSH were shifted towards high values in groups 2 and 3 and the recall rates (% TSH >50 µU/ml) increased from 0.2 % in gr.1 to 4.6 % in gr.2 and to 3.7 % in gr.3 The control examinations were normal in all recalled infants. 2) Bottlefed infants : there was a slight shift towards moderately elevated TSH values; however, the recall rate was unchanged. In conclusion, the use of PVP-I in mothers at delivery induces a transient impairment of thyroid function in their infants. This situation is much more severe in breastfed infants where maternal milk induces a prolonged state of iodine overload, with a 25 fold increase in the recall rate at screening for CH. Therefore, PVP-I is not recommended in obstetrics.