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MR IMAGING AND HORMONAL FINDINGS IN PATIENTS WITH IDIOPATHIC GROWTH HORMONE DEFICIENCY

W. Schönberger, A.Blettgen, W.Grimm, W.Müller-Forell
Department of Pediatrics, Univ. of Mainz, 65-Mainz, Germany

Until the introduction of MR imaging in neuroradiological diagnostic, diagnosis of the ecotopic posterior pituitary lobe, first described by the pathologist Priesel in 1920, was rare. Recently it has increasingly been diagnosed by MR in patients whose anamnesis showed birth trauma. We performed MR of the hypothalamic-pituitary region in 17 patients with idiopathic growth hormone deficiency. 8 patients had additional deficiencies of the anterior pituitary lobe whereas the function of the posterior lobe of the hypophysis was normal in all patients. Indications of birth trauma were present in only 2 patients. The cause of anterior lobe insufficiency was determined by MR in 8 patients with panhypopituitarism to be the result of the absence of the pituitary stalk. In 5 patients with isolated HGH deficiency the stalk was extremely hypoplastic. The posterior lobe was imaged in 11 patients as an ectopic bright spot of a small nodule at the median eminence and in 2 patients in the proximal infundibulum whereas in 3 patients other cerebral malformations were evident. Only in 1 patient there was no pathological finding in the hypothalamic-pituitary region. As the anamnesis showed indications of birth trauma in only 2 patients, we conclude that the absence or hypoplasia of the stalk and ectopia of the posterior lobe may frequently be of developmental origin and date from early intrauterine life.

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COMPARATIVE EFFECT OF GROWTH HORMONE (GH)-RELEASING HORMONE(GHRH) AND THE NEUROPEPTIDE GALANIN ON GH SECRETION IN SLOWLY GROWING LIVER TRANSPLANTED CHILDREN UNDER CHRONIC GLUCOCORTOCOID THERAPY.

A.Giustina, A. Girelli, D. Alberti*, F. Buzi$, M. Licini, M. Schettino. Clinica Medica, *Chirurgia Pediatrica, $Clinica Pediatrica, University of Brescia, 25125 Brescia, Italy.

The precise mechanisms of glucocorticoid-induced inhibition of growth are not known; children receiving long-term steroid treatment show growth retardation and a blunted GH secretion. Galanin is a novel neuropeptide which is reported to increase GH secretion via an unknown hypothalamic mechanism. Aim of our study was to evaluate the effects of GHRH and galanin on GH secretion in children on daily glucocorticoid treatment after liver transplantation. Five male patients (age 2.6±1.8 yrs) within the first year (6.9±0.8 mths) after orthotopic liver transplantation slowly growing (HV< 3rd centile) under daily glucocorticoid treatment (0.47±0.06 mg/kg/day) and 5 prepubertal normally growing controls, underwent: a) GHRH (1-29)NH, 1μg/kg, i.v. bolus at time 0; b) synthetic porcine galanin, 15 μg/kg i.v. infusion, from 0 to 60 min. Steroid-treated children showed a blunted GH peak after GHRH (9.6±1.3 μg/L) with respect to normal children (20.4±2.5 μg/L). The GH peak after galanin was also blunted ($p<0.05$) in steroid-treated children (4.5±2.3 μg/L) with respect to controls (5.9±1.6 μg/L). We conclude that chronic glucocorticoid therapy impaires the GH response to galanin as well as to GHRH in liver-transplanted slowly growing children.

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ESTRADIOL AFFECTS THE METABOLIC CLEARANCE RATE OF HUMAN GROWTH HORMONE (GH) AS DETERMINED BY DECONVOLUTION ANALYSIS.

R.W. Holl, U. Schwarz, P. Schauwecker, J.D. Veldhuis and E. Heinze. Department of Pediatrics I, University of Ulm, D-7900, Germany, and Division of Endocrinology, University of Virginia, Charlottesville, VA 22908, USA.

Fluctuations in peripheral GH concentrations are traditionally attributed to variation of pituitary hormone secretion. However, metabolic clearance of GH represents an equally important mechanism determining GH levels in serum. In order to dissociate pituitary responsiveness and peripheral clearance, GHRH (1 μg/kg) was injected at 8 pm in 20 healthy normal-weight volunteers (10 female, 10 male) and GH was followed for 3 hours by IRMA (q 5 min; Medgenix, Belgium). $T_{1/2}$ of GH was determined by deconvolution analysis (2-compartment model, fixed first component: 3.5 min, ratio of second component to total: 0.65). GH half-life was not significantly different between men (26.2±2.0 min; mean±SE) and women (21.9±1.3 min). DHEA-S correlated negatively with $t_{1/2}$ of GH ($r=-0.54$, $p<0.02$, Spearman). In addition, in males, serum estradiol was negatively related to the half-life of GH ($r=-0.68$, $p<0.03$), while no relation to androstendione or testosterone was present. Surprisingly, in women, the $t_{1/2}$ of GH correlated positively with estradiol concentrations ($r=+0.67$, $p<0.05$). Sex hormone binding globulin correlated marginally with $t_{1/2}$ in males ($r=+0.57$; $p=0.08$), but not in females ($r=+0.29$). In contrast to previous reports, there was no significant effect of body mass index on GH half-life in either group of normal-weight subjects. Conclusion: Sex steroids not only affect pituitary GH release, but also the elimination of human growth hormone from the circulation. Serum estradiol is more relevant than androgens and presumably affects the half-life of GH in a biphasic manner. As both secretion and clearance subserve the pulsatility of peripheral GH concentrations, effects of gonadal steroids on either process have to be considered.

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S.Miller-Davis[1], J Cogan[1],J.A. Phillips III[1], R.D.G. Milner[2], A. Al-Ashwal[2] and N.A.Sakati[2]. [1]Vanderbilt University School of Medicine, Nashville, Tennessee and [2]King Faisal Specialist Hospital, Riyadh, Saudi Arabia.

DETECTION OF HETEROGENEOUS GROWTH HORMONE (GH) GENE SPLICING BY DNA ANALYSIS OF DRIED BLOOD SPOTS FROM GH DEFICIENT SUBJECTS.

The molecular basis of familial isolated GH deficiency (IGHD) is heterogeneous. We have previously found a G --> A transition in codon 20 of the GH gene that produces a stop codon and two donor splice site mutations (a T--> C transition in the sixth base of IVSIII and G--> C transversion in the first base of IVS IV). The G--> C transversion, which destroys an *HphI* (GGTGA) restriction site at the exon IV/intron IV boundary (G/GTGA --> G/CTGA), was found in a Saudi family with IGHD. To determine the frequency of this mutation among Saudi IGHD subjects, dried blood spots were analyzed from 12 additional Saudi cases from different families. The methodology involved a one-step PCR amplification of DNA obtained from 2 mm^2 portions of dried blood spots which were collected on filter paper. These amplification products were then digested with *HphI* and analyzed on agarose gels. One subject was homozygous and the single, parental sample obtained was heterozygous for loss of this *HphI* site. Interestingly a simple repeat polymorphism adjacent to the GH gene differed between the two non-related Saudi subjects, who lacked the *HphI* site, suggesting that the GH mutations were independent. To determine if the GH mutations causing loss of the *HphI* site differed between the two Saudi IGHD cases, direct sequencing of the PCR products obtained from the filter paper samples was performed. In contrast to the first Saudi case which had a G-->C transversion in the first base of IVS IV (G/CTGA) the second had a G-->T transversion (G/TTGA). Analysis of the transcription products of the G-->C mutation documented aberrant splicing and transcript analysis of the G-->T mutation is being done for comparison. Our findings demonstrate 1) detection of GH splicing defects by restriction analysis and sequencing of DNA from dried blood spots and 2) 2/13 (15%) of Saudi IGHD subjects have IVS IV donor splice site defects. These findings suggest that heterogeneous mutations which lead to transcript splicing errors may constitute a significant proportion of IGHD cases.

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PJ Pringle, JS Barton, PC Hindmarsh, *DR Matthews, CGD Brook, Endocrine Unit, Middlesex Hospital and *Diabetes Research Laboratories, Oxford, UK.

THYROTROPHIN STIMULATING HORMONE (TSH) PULSATILITY IN CHILDHOOD: EFFECTS OF A SOMATOSTATIN ANALOGUE ON PULSATILITY AND THYROXINE (T4) GENERATION

TSH has been shown to be secreted in a pulsatile manner in adults. We have analysed 24 hr serum TSH concentration profiles in 29 short normal prepubertal subjects and in 9 tall children before and during one year of treatment with a nocturnal infusion of a somatostatin analogue (50-100 mg infused subcutaneously for 12 hrs). In short and tall children a circadian variation in serum TSH concentrations was observed with nocturnal values greater than diurnal. Nocturnal values were often greater than the upper limit of normal for a random sample (5 mU/l). Two pulse periodicities were observed: a fast frequency of 120 minutes and a slower one of 280 minutes. No change in mean serum 24hr TSH concentrations with age was observed (0.7-5.10 mU/l, median 2.1 mU/l). Treatment with the somatostatin analogue led to a suppression of the nocturnal rise in serum TSH concentration, to a disruption of the dominant periodicities so that no clearly defined pulse frequency could be discerned and to a 30%-50% reduction in 24 hr mean serum TSH concentration (0.7-1.2 mU/l, median 1.0 mU/l). Despite these changes serum T4 concentrations remained unchanged during treatment. These data demonstrate pulsatility of serum TSH concentrations in children and confirm previous observations that somatostatin inhibits TSH secretion. The precise role of pulsatile TSH secretion in the generation of T4 levels is unclear as disruption of the pulsatile pattern did not affect serum T4 concentration.

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A.P.Winrow,H.Spoudeas,P.J.Pringle,P.C.Hindmarsh,C.G.D.Brook.
Endocrine Unit, The Middlesex Hospital, London.

THE LOW-DOSE GROWTH HORMONE RELEASING HORMONE (GHRH) STIMULATION TEST.

Since the discovery,isolation and purification of GHRH in 1982, its potential role in the diagnosis of growth hormone (GH) insufficiency has been unclear.The doses of GHRH administered have varied greatly. Supramaximal somatotroph stimulation and release of various GH pools may account for variation in results within and between individuals.We have investigated the GH response to low-dose GHRH (1-29)NH_2, doses 0.5-10mcg,in 5 adult male volunteers (mean weight 84kg) with subsequent GH sampling at 5 minute intervals for 1 hour post-administration.The ED_{50} calculated from the dose-response curve was 7.8mcg GHRH corresponding to a dose of 0.09mcg/kg.Adequate GH peaks above our unit's "cut-off" value of 13mU/l were obtained with a GHRH dose of 8.5mcg (0.1mcg/kg).Whilst all GH peaks were identified within 30 minutes of GHRH administration, none were detected before 10 minutes and the mode of the distribution was 15 minutes.Maximal somatotroph stimulation occurred at a dose of 10mcg (0.12mcg/kg).Higher GHRH dosage altered the timing of the initial GH peak and the subsequent clearance time of circulating GH.**We conclude that** a dose of 0.1mcg/kg GHRH(1-29)NH_2 is sufficient to produce "normal" GH values.This dose is a ten-fold decrease in comparison with current recommended protocols.The low-dose GHRH stimulation test probably represents a more physiological test of the readily releasable GH store than other tests which incorporate larger GHRH doses.