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GROWTH OF CHILDREN AFTER LIVER TRANSPLANTATION (LT): LONGITUDINAL AND CROSS-SECTIONAL STUDY

Aims: to study the growth of children with liver disease before and after LT. *Methods*: longitudinal study (LS): 16 infants (9 M, 7 F); age 0.73 to 2.38 years ($\bar{x}$ 1.39) at LT; mean height (Ht) SDS at LT: -2.02 (SD 1.25). Post-LT medication: cyclosporine in tapering doses; prednisone, by daily regimen (DP) for the first 6-12 months, with tapering doses depending on clinical course, then on alternate day regimen (ADP). Cross-sectional study (CSS): 95 children (55 M, 40 F) aged 0.17 to 14.88 ($\bar{x}$ 3.83), observed before LT, after LT on DP, and on ADP (same medication). *Results*: LS: pre-LT height velocity (HV) SDS ($\bar{x}\pm$SD -0.60±1.31) significantly lower ($p<0.01$) than ADP-HVSDS (2.84±1.59) but not significantly different from DP-HVSDS (-1.37±1.66). CSS: DP-HtSDS ($\bar{x}\pm$SD -1.91±1.32) significantly lower ($p<0.01$) than pre-LT-HtSDS (-1.07±1.06) and ADP-HtSDS (-0.98±1.23). Similar results for sitting height (SH) SDS and subischial leg length (SLL) SDS: pre-LT and ADP-SLLSDS significantly greater than pre-LT and ADP-SHSDS ($p=0.01$); DP-SLLSDS not significantly different from DP-SHSDS. Significant improvement of head circumpherence SDS and skinfold SDS on ADP. *Conclusions*: growth in children with liver disease does not improve after LT on DP while shows catch-up growth on ADP; therefore, it mainly depends on clinical course and corticosteroid regimen.

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CONCORDANCE BETWEEN BIOLOGY AND A VISUAL MOTOR PSYCHOLOGICAL TEST IN SHORT CHILDREN. A. Fiellestad-Paulsen, A. Andronikof-Sanglade, S. Ricard-Mallvoir, D. Evain-Brion. Department of Pediatric Endocrinology, Hôpital Robert Debré, Paris, France.

We explored in 40 prepubertal short children without organic disease (age 5 to 12 y., mean height - 2,6 ± 0,6 SD), the possible expression of an abnormal GH-secretion in a neuropsychological figure drawing test analysed with an original methodology. Nocturnal GH-profile, L-Dopa test and GHRH test were performed. The children underwent the psychological assessment, including the Rey-Osterrieth test and an IQ evaluation before medical investigation. The Rey figure was scored anonymously according to the boundary type errors defined as non developmental severe distortions or disrespect of boundaries. 23 children had normal and 17 had abnormal GH-secretion. Among those,4 children had complete and 13 had partial GH deficiency but all of them had low nocturnal GH-secretion (AUC_b < 85 ng/ml/12h). 17 children had a normal Rey figure and 23 had boundary type errors. Mean IQ was normal in both groups. The biological and the psychological analysis were in agreement in 32 children ($p < 0.0005$). Night GH-secretion was lower ($p < 0.006$) in children with boundary type errors (AUC_b mean ± SEM 88.5 ± 8 ng/ml/12h) as compared to children with normal Rey figure (AUCb 140.7 ± 17.9). In conclusion, these results point to particular anomalies, independant of the IQ, at a visuomotor psychological test in short children with abnormal GH-secretion.

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GROWTH HORMONE RESPONSES TO GROWTH HORMONE RELEASING PEPTIDE (GRP) AND TO GROWTH HORMONE RELEASING HORMONE (GRF) IN GROWTH HORMONE DEFICIENT CHILDREN (GHD). V. Mericq, F. Cassorla, H. García, A. Avila, C. Bowers and G. Merriam. Institute of Maternal and Child Research, University of Chile, Santiago, Chile; DEB, NICHD, Bethesda, MD; University of Washington, Seattle, WA; and Tulane University, New Orleans, LA, USA

GRP is a potent and specific stimulator of growth hormone (GH) secretion. It is a 6 aminoacid peptide with lower molecular weight and longer half life than GRF. To clarify how this peptide acts, we administered separately and together 1 ug/kg bolus doses of GRP and GRF iv to 22 children (13 M, 9 F), ages 3-16 years, with previously documented GHD. Tests were separated by at least 1 week. Bone ages ranged from 1-10 years and growth velocities were less than 3 cm/year. GH was measured by RIA with an intraassay cv of 5 %. A positive response was defined as a GH increase greater than 4 cv's. We observed 12 (≤6 %) positive responses to GRP, and 15 positive responses to GRF (68 %). Nineteen (86 %) patients responded to both peptides administered together. Out of the 12 GRP responders only 9 patients had a positive response to GRF, and out of the 15 GRF responders only 9 had a positive response to GRP. GH peak levels were observed between 5 and 60 min (mean 30 min) after GRF, and between 10-45 min (mean 24 min) after GRP. We conclude that GRP is a potent secretagogue of growth hormone in a substantial proportion of GH deficient children. The dissociated response to GRP and GRF suggests that they stimulate GH release through different mechanisms.

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EFFECT OF GROWTH HORMONE (GH) ADMINISTRATION ON TOTAL AND SEGMENTAL BODY COMPOSITION IN CHILDREN WITH GH DEFICIENCY. Osorio, MGF; Mendonca, BB; Segura, TC; Estefan, V; Arnhold, IJP; Nicolau, W; Bianco, AC. Division of Endocrinology, Hospital das Clinicas, University of Sao Paulo, and Unidade de Densitometria Ossea, Sao Paulo, S.P., Brazil.

To investigate the GH-induced changes in body composition we studied the lean and fat tissues, bone mineral content (BMC) and density (BMD) of GH-deficient children by DEXA (Lunar, WI), before and after they were 174±14 days on hGH (0.075 U/Kg/day). Eight pre-pubertal children (4 boys), aging 6.2-14.1 yr (bone ages: 2-9 yr), were enrolled. All had peak GH responses to clonidine and insulin <5 ng/ml. **BEFORE** GH was given, body fat (4.2±2.5 kg) was distributed as 31±15 % in arms, 25±10 % in legs and 20±10 % in abdomen (abdm), while body lean tissue (13.7±3.1 kg) was 47±3 % in abdm, 24±2 % in legs and 10±4 % in arms. Total BMC was 0.64±0.16 kg, of which 47±7 % was in the head, 25±4 % in legs and 9±1 % in arms. Total BMD (g/cm2) was 0.8±0.04; it was higher in the head (1.4±0.1), followed by legs (0.6±0.074), pelvis (0.6±0.05), spine (0.6±0.01) and arms (0.5±0.03). GH treatment resulted in (i) height increase (4.6±1 cm; $p>0.05$) and no change in body weight (+0.9±1.4 Kg; $p>0.05$); (ii) decreased body fat (-32±16 %; $p<0.05$: -42±32 % in arms, -30±10 in abdm and -29±20 % in legs); (iii) increased lean body mass (+11±12 %; $p<0.05$: +26±9 % in legs); (iv) increased BMC (7±6 %; $p<0.05$: -5±4 % in the head; +21±21 % in arms; +18±9 % in legs); (v) decreased BMD (-2.3±2.9 %; $p<0.05$: -6.4±4.3 % in the head, +6.9±6.6 % in pelvis, +4.3±3.1 % in arms, +3.7±2.2 % in legs). In conclusion, GH treatment caused body fat to decrease and lean mass to increase; because BMC increased significantly, the lower BMD is probably related to increased bone surface.

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GONADAL STEROIDS ARE CAPABLE OF ACTING WITHIN THE HYPOTHALAMUS TO MODULATE SOMATOSTATIN (SS) GENE EXPRESSION IN PUBERTAL AGED RATS. P.M. Martha, Jr., J.A. Brewer and E.O. Reiter, Department of Pediatrics, Baystate Medical Center, Springfield, MA 01199, USA.

Due to the highly complex nature of neuroendocrine-target organ "feedback" relationships, the primary site(s) at which gonadal steroids exert effects on the GH axis remain largely unknown. Therefore, we sought to test the hypotheses that testosterone (T) and estradiol (E2) can exert direct cell-specific regulatory effects in vivo on hypothalamic neurons which control GH secretion. 7 male rats were castrated at 25d (prepubertally). On day 40, T or E2 was stereotaxically placed into the hypothalamus lateral to the periventricular nucleus (PeN) at the level of the paraventricular n. (PvN). Vehicle (cholesterol) was placed at the identical contralateral location. Preliminary studies using peroxidase-conjugated E2 demonstrated no crossover of test steroid to the control side. This model allowed exposure of only one side of the hypothalamus to a change in gonadal steroid milieu during a developmental period within which the systemic rise in gonadal steroids occurs naturally in vivo. Using in situ hybridization, we then compared the level of SS gene expression in PeN neurons of the treatment (TX) vs control (CON) sides. In all 7 brains, the level of SS gene expression was lower ($p<.05$) in neurons of the TX vs. CON side (86.7+0.3% of CON for T and 80.4 ± 3.6% for E2). Furthermore, the TX effect was anatomically discrete with the dominant effect in the mid PeN region (level of the PvN) and either absent or minor toward the rostral-caudal extremes. These data demonstrate direct in vivo intrahypothalamic regulatory effects of T and E2 on one neuronal subpopulation critical for control of pituitary GH secretion. This finding strongly indicates that at least one important site for the modulatory effects of T and E2 on the GH axis is within the hypothalamus. This technical approach of highly localized delivery of putative regulatory substances followed by subsequent assessment of gene expression within discrete neuronal subpopulations carries great potential to provide insight toward answering numerous remaining questions regarding neuroendocrine control of GH and other hypothalamic pituitary hormone systems.

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A LONGITUDINAL ASSESSMENT OF IGFBP-3 CONCENTRATION IN NORMAL BOYS. P.M. Martha, Jr., R. M. Blizzard and A. D. Rogol, Departments of Pediatrics, Baystate Medical Center, Springfield, MA and University of Virginia, Charlottesville, VA, USA.

Recent data indicate the serum concentration of IGFBP-3 (the major post-natal IGF binding protein) may be clinically important in some pathophysiologic states. Existing cross-sectional data suggest an ontogeny exists for IGFBP-3, with levels increasing with age and peaking during puberty. To investigate the pattern of change in IGFBP-3 within individuals, and expand understanding of this potentially important component of the human GH axis, the IGFBP-3 level was determined in 309 serum samples obtained from 23 boys over 4.1-6.4 yrs as they progressed through puberty (assayed at Endocrine Sciences). IGFBP-3 conc. ranged from 1.7 to 7.0 mg/L. Though there was a general trend of rising IGFBP-3 conc. with age (intrasubject $r=0.33$, $p<.001$), values within individuals often fluctuated unpredictably. However, intrasubject variability was signif. less than that present in the larger population (CV=19.8±1%vs26%, $p<.001$). Within individuals, IGFBP-3 level correlated with growth velocity ($r=0.38$, $p<.001$). For all data, IGFBP-3 conc. correlated with BA ($r=0.43$), testosterone conc. ($r=0.31$) and height SDS ($r=0.26$; all $p<.001$). We conclude that the serum concentration of IGFBP-3 follows the general trend of an increase with age and pubertal stage suggested by previous cross-sectional studies. There is significant fluctuation over time within individuals suggesting some caution when using this as a diagnostic tool though the range of this intra-individual variation is tighter than that of the larger "normal" range.