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CLINICAL UTILITY OF SERUM RIA IGFBP-3 IN THE DIAGNOSIS OF GH INSUFFICIENCY

We analysed whether serum IGFBP-3 was a useful parameter of GH secretion status. The subjects were complete GHD patients(cGHD, n=40 ; stimulated GH peaks < 5 ng/ml), partial GHD patients(pGHD, n=55 ; <10 ng/ml) with normal IGF-I levels and with low IGF-I, and normal short children(NS, n=111, >10 ng/ml). (1)The sensitivity of IGFBP-3 for cGHD(true positive) and the specificity of IGFBP-3 for NS (true negative) were almost 90%. The sensitivity of pGHD with low IGF-I was 67%, whereas that of pGHD with normal IGF-I was 20%. Thus, IGFBP-3 may reflect GH secretion status and it is one of the screening parameters in the diagnosis of GHD. (2)Among the prepubtal subjects, their height and height gain after the GH treatment (tx) were analysed. There was a significant correlation between their height SDS and IGFBP-3 SDS. Furthermore, there was a correlation between IGFBP-3 SDS before GH tx and delta height SDS after 1 year GH tx, suggesting IGFBP-3 may reflect GH secretion status. In conclusion, IGFBP-3 is one of the screening parameters in the diagnosis of GHD and may reflect GH secretion status.

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HUMAN GROWTH HORMONE (GH) TREATMENT OF IMMATURE MALE MONKEYS FOR SIX MONTHS. M.J. Cronin, K. Elias, A. Celniker, D. Giltinan, J. Tanner* and M. Wilson**, Genentech, S.S.F., CA 94080, USA; *Inst. Child Health, Univ. London, England WC1N1EH, U.K.; **Yerkes Primate Res. Ctr., Lawrenceville, Georgia, 30243, USA.

Little is known about the effect of exogenous GH to accelerate or disrupt statural development in normally growing primates. Prepubertal male rhesus monkeys were injected for 2 months with placebo (sc daily) and then randomized to treatment groups by body weight (BW). They were then treated daily with placebo or recombinant human GH (rhGH) at 0.05 or 0.35 mg/kg for 6 months. The placebo monkeys grew as expected, with significant increases in BW gain, tibial length, skeletal maturation score (SMS) and crown-rump length (CRL); these also had a stable IGF-1 baseline. Both groups treated with rhGH had significant increases in BW, while only the high dose group had an increase in CRL (+31%) greater than placebo controls. The IGF-1 areas under the treatment curves were also elevated above placebo in the rhGH groups (+46% & +51%). There were no anti-rhGH antibodies measured in the high rhGH dose monkeys. No group differences were observed in fasting insulin, glucose, cortisol, testosterone, triglycerides, urea nitrogen, cholesterol, albumin, calcium, alkaline phosphatase or alanine transaminase. We conclude that this rhGH treatment regimen over 6 mo did not disrupt the normal growth pattern of prepubertal monkeys. Daily exposure to rhGH enhanced BW gain, CRL and IGF-1 levels. Changes in tibial length and SMS were not different from placebo controls.

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CHARACTERIZATION AND REGULATION OF IGFBP-4 IN CULTURED MOUSE LEYDIG CELLS (TM-3)

The characterization and regulation of IGFBPs in TM-3 cells was performed. Western Ligand blots of conditioned media(CM) demonstrated the presence of 24 and 28 kDa bands as major IGFBPs, and 40 and 44 kDa as minor ones. The 24 and 28 kDa bands were immunoprecipitated with an antibody to rat IGFBP-4. The 28 kDa band was deglycosylated with endoglycosidase-F to 24 kDa. Treatment of TM-3 cells with IGF-I increased the levels of IGFBP-4. Both IGF-II and [Leu27] IGF-II treatment resulted in a significant decrease in IGFBP-4. Neither IGF-I nor -II affected the expression of mRNA for IGFBP-4. Affinity cross-linking of IGF-I and -II to crude membranes prepared from TM-3 cells revealed type 1 and 2 receptors and a 31 kDa band. Immunoprecipitation of solubilized crude membranes indicated that the 31 kDa protein was membrane bound IGFBP-4. In conclusion, TM-3 cells can produce IGFBP-4 and glycosylated IGFBP-4 as major IGFBPs. A unique divergent effect of IGF-I and -II on the levels of IGFBP-4 in CM must be post-transcriptional and occur through different mechanism. The significance of the presence of IGFBP-4 in CM and membrane bound IGFBP-4 should be elucidated.

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THE EFFECT OF GH (SAIZEN) THERAPY (28 IU/M²/WEEK) ON LINEAR GROWTH AND CARDIAC MORPHOLOGY IN SHORT CHILDREN WITH NOONAN SYNDROME.

Noonan Syndrome (NS) is a dysmorphic condition associated with short stature and cardiac defects (pulmonary stenosis and ventricular hypertrophy [VH]). Early studies reported linear growth increases with GH. Anecdotal reports, however, suggested an association between GH and VH progression. We therefore undertook a multi-centre open trial of GH (28IU/m2/wk Saizen daily sc) in children with NS. Entry criteria were: NS confirmed by single observer(ME) in Genetics dept(MAP), HtSDS < -2, HtVelSDS < 0, normal maximal LV wall thickness(LVWT) by 2D echocardiography (single observer WJM), breast stage 1 or testicular volume <6ml and age 5-14y. 14 subjects are now receiving GH [9 male, 5 female; 9.5±0.7y (range 12.6-5.1), HtSDS -2.81±0.12 (-3.79 - -2.17), HtVel 4.1±0.3 cm/y (2.6-6.0), maximal LVWT 7±1mm. Linear growth and QRS voltage on ECG were monitored 3mthly, and maximal LVWT at 1y. To date (1/12/92) 7 subjects have completed 6mth and 4 subjects 1y of therapy. There has been a clinically significant increase in HtSDS and HtVel without change in maximal LVWT or ECG voltages.

	Ht SDS	HtVel (cm/y)
Pretreatment	-2.88 ± 0.07	3.8 ± 0.5
6 months	-2.55 ± 0.10	8.8 ± 0.8
12 months	-2.13 ± 0.17	10.5 ± 0.5

In conclusion GH appears effective and not associated with significant change in cardiac morphology in Noonan Syndrome.

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CHANGES IN BONE MINERAL CONTENT (BMC) IN PREPUBERTAL CHILDREN WITH MARKED SHORT STATURE SECONDARY TO CHRONIC RENAL FAILURE (CRF): EFFECTS OF rhGH THERAPY. P. Gunczler R. Lanes, N. Orta, M. Bosquez, R. Scovino, L. Dominguez, S. Esaa, V. Paz-Martinez and J.K. Weisinger. Hospital de Clinicas Caracas, Hospital Central Valencia, Hospital de Niños and Hospital Universitario de Caracas, Venezuela.

Children with CRF are characterized by markedly short stature and low bone mass. Thirteen prepubertal children with severe CRF(GFR<20.8 ml/min/1.73 m²)and short stature (HSDS<3.6 below the mean)with a mean chronological age 6.7 ± 3.5yr. were studied using Dual X-ray Absorpsiometry before and after 6 months of treatment with rhGH (1 I.U./Kg/Week) bone mass was measured in total body, lumbar spine (trabecular bone) and femoral neck (cortical bone). Total BMC was significantly lower in our patients compared to age matched healthy controls(443.2 ± 155.2 vs. 903.1 ± 369 g;p<0.003). After 6 months of rhGH treatment total BMC increased to 516.7 ± 147 g;p<0.05, in the group of CRF patients. Trabecular BMC increased from 0.496 ± 0.04 to 0.585 ± 0.1g/cm² and cortical BMC increased from 0.605 ± 0.1 to 0.651 ± 0.08g/cm² after 6 months of rhGH. Our findings indicate that children with CRF present with a low bone mass, and short term treatment with rhGH seems to increase their bone mineral content. Long term studies will be necessary to asses the real effect exerted by rhGH therapy on the skeleton of children with CRF as they increase their growth velocity.

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J.Leonard, M.Samuels*, J.Murphy, C.E.Brain, A.M.Cotterill, M.O.Savage. Div. Paediatric Endocrinology and *Dept. of Clinical Photography, St Bartholomew's Hosp, London, U.K. ANTHROPOMETRIC ASSESSMENT OF ANABOLIC AND LIPOLYTIC EFFECTS OF RECOMBINANT IGF-I THERAPY IN 3 CHILDREN WITH GROWTH HORMONE INSENSITIVITY SYNDROME(GHIS).

GHIS (Laron Syndrome) is characterised by normal or elevated GH secretion, impaired IGF-I production, characteristic facial phenotype and extreme growth failure. 3 patients with GHIS [basal GH(mU/L) 102, 34.5, 99.5 respectively; IGF-I (μg/L) generation test (GH 0.1U/kg/day for 4 days s.c.) 24 (before) -27 (after), 26 - 26, 24 - 20] received therapy with recombinant IGF-I (IGEF, Kabi Pharmacia) at 120 μg/kg b.d. s.c. Anthropometry gave the following results:

Pt	age	sex	pub.	dur. IGF-I (mnth)	Ht SDS	Ht Vel (cm/y) pre	Ht Vel (cm/y) on	skinfold(mm) Tric. pre	Tric. on	Subs. pre	Subs. on	Bone age RUS pre	Bone age RUS on
1	16.1	f	3	9	-8.1	5.7	6.6	9.9	8.0	15.5	12.4	12.3	12.7
2	13.9	m	2	9	-4.7	5.3	9.6	24.4	14.6	27.4	15.1	11.8	13.38
3	7.9	m	1	4	-7.9	1.9	10.1	8.2	7.4	7.8	7.1	4.13	

Craniofacial measurements during 4 months therapy (patient 3) showed the following changes (cm): head length (-4 SD)+0.9, head circumference (-3.5SDS)+0.5, skull height(-3.5SD)+0.8, facial height(-8.0SD)+0.3. Standardised photography in all 3 patients showed a change in facial phenotype.

IGF-I stimulates linear growth in all patients, the greatest changes being in the youngest. Skinfold thicknesses fell during treatment indicating a lipolytic effect of IGF-I.Anthropometric and photographic assessment suggest a change in facial morphology.