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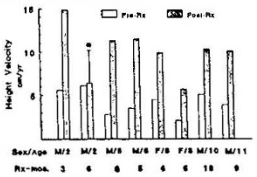
EFFECTS OF PROLONGED IGF-I TREATMENT IN CHILDREN WITH GROWTH HORMONE INSENSITIVITY SYNDROME (GHIS). Philippe F. Backeljauw, Louis E. Underwood, University of North Carolina at Chapel Hill, NC 27599. (with M Miras, MC Arriazu & J Heinrich (Argentina), L Ghizzoni (Italy), S Blethen, D Donaldson, W Cleveland & N Gesundheit (USA))



We administered recombinant IGF-I to 8 children with GHIS, due either to GH receptor deficiency (Laron syndrome, n=5) or growth-attenuating antibodies to GH (3 pts. with GH gene deletion). Their ages range from 3 to 11 years and they have been treated for 3 to 18 months (fig.). The dose of IGF-I (Genentech, Inc.) ranged between 80 and 120 mcg/kg sc, twice daily. Two hours post-injection the patients consumed a snack or meal. Height velocity improved significantly in all but one patient (*). He had poor growth (2.6cm/yr) during the first 3 months, when he had intercurrent illnesses and poor nutrient intake. His growth velocity increased to 10.2cm/yr (error bar) during the second three months of treatment. Hypoglycemia has occured infrequently and only in the two youngest patients early in treatment. No adverse changes in biochemical profile have been observed. Increased height velocity has been accompanied by increased caloric intake and weight gain, a reduction in subcutaneous adipose tissue and catch-up growth of kidneys and spleen (by ultrasound). These data show that IGF-I stimulates linear growth by endocrine mechanisms and suggest that chronic treatment with IGF-I is likely to be a successful form of therapy for patients with GHIS.

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LONG-TERM hGH TREATMENT OF SHORT PREPUBERTAL CHILDREN IMPROVES THEIR HEIGHT. Z. Laron, P. Lilos*, A. Pertzelan, S. Anin and B. Klinger, Inst. Pediat. & Adolesc. Endocrinology, Children's Medical Center & Dept. of Statistics*, Tel Aviv University, Israel

Forty-six short children classified as familial short stature (FSS) or intrauterine growth retardation (IUGR) and normal GH reserve ($\geq$10 ng/ml) were treated with rhGH (Norditropin - Novo/Nordisk, 0.1 U/kg/d) for periods between 24-30 months. Their age ranged from 2.6 to 10 yrs (7 F, 39 M). The body measurements and bone age (BA) estimations were made by the same persons. The changes in SDS height registered were as follows:

hGH	Total			FSS			IUGR		
(mos)	n	m	(±SD)	n	m	(±SD)	n	m	(±SD)
0	46	-2.7	(0.6)	32	-2.0	(0.4)	14	-3.1	(0.6)
12	41	-2.2	(0.6)	27	-1.9	(0.4)	14	-2.6	(0.6)
24	34	-1.8	(0.6)	22	-1.6	(0.5)	12	-2.2	(0.6)
30	23	-1.6	(0.6)	15	-1.5	(0.6)	8	-1.9	(0.7)

In 17 children treatment was stopped mainly after 24 months treatment because of relative advancement of BA, and in 5 because of non-compliance. The remaining children advanced their BA parallel to the chronological age. The mean overall SDS height gain in all children over 30 months was 1 SDS, but IUGR children gained more height than the FSS. It is concluded that many young FSS and IUGR children can benefit from long-term hGH treatment without seemingly precluding their further height potential.

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SERUM HALF-LIFE OF GROWTH HORMONE-BINDING PROTEIN (GH-BP) ASSESSED IN THE HUMAN NEWBORN. G. Massa, F. de Zegher and M. Vanderschueren-Lodeweyckx, Department of Pediatrics, University of Leuven, Leuven, B 3000, Belgium.

The serum half-life of the glycosylated GH-BP in the human is currently unknown. Circulating levels of the high affinity GH-BP are low in the neonatal period compared to adult life (Massa et al, Pediatr Res 1992). During an exchange transfusion (ET) for neonatal hyperbilirubinemia, the blood of the newborn is nearly completely replaced by adult donor blood. To evaluate the elimination rate of GH-BP we measured serum levels of GH-BP by HPLC gel filtration before and at different time intervals after an ET in 4 term neonates. Before the ET the mean±SE serum binding of ^{125}I-hGH (GH-BP) was 6.7±1.2%. At the end of the ET, serum GH-BP was increased to 25.3±2.6% (P<0.005). Thereafter serum GH-BP decreased slowly and was 84 to 96 hours later still higher than before the ET. Analysis of the elimination curve by exponential stripping suggested an elimination according to a bi-exponential model : GH-BP(%) = 40 x $e^{(-5.1E-03 \times time)}$ + 64 x $e^{(-2.5E-04 \times time)}$. The serum half-life of the GH-BP complex was estimated to be 1.9 days. These data demonstrate : 1) that the GH-BP can be transfused, and 2) that the serum half-life of the GH-BP complex in neonates is in the order of magnitude of days. (This work was supported by a grant from the Belgian Study Group of Pediatric Endocrinology).

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EFFECT OF GROWTH HORMONE TREATMENT ON HEIGHT IN CHILDREN WITH NORMAL VARIANT SHORT STATURE (NVSS): 3 YEAR RESULTS. G. Massa, M. Maes, M. Du Caju, M. Craen, C. Heinrichs and M. Vanderschueren, Department of Pediatrics, Universities of Leuven, Louvain, Antwerp, Ghent and Brussels, Belgium.

In 1988 a multicenter trial to evaluate the effect of treatment with rhGH (Humatrope, Lilly, Indianapolis) on height was started in 40 children (aged 3.8 - 14.6 yr) with NVSS. During the 1st year of treatment rhGH dose was 3 IU/m^2/day 6 days/week. After the 1st year treatment was interrupted for a mean±SD period of 258±47 days. Thereafter treatment was restarted in 31 patients at a dose of 4.5 IU/m^2/day 6 days/week. 30 patients have now received rhGH treatment for 3 years: 15 remained prepubertal and 15 entered puberty. Height expressed as SDS for chronological age at the start and after 3 yrs of treatment was resp. -2.6±0.6 and -1.9±0.5 SDS (P<0.005) in the prepubertal subjects, and -2.5±0.5 SDS and -1.9±0.6 SDS (P<0.005) in the pubertal subjects. Expressed as SDS for bone age height SDS did not change: -0.6±1.5 SDS at the start and -0.6±0.9 SDS after 3 yrs of treatment in the prepubertal subjects, and -1.6±1.3 SDS and -1.3±1.5 SDS in the pubertal subjects. The ratio delta bone age to delta chronological age was 1.1±0.2 in the prepubertal subjects and 1.2±0.4 in the pubertal subjects. These data suggest that rhGH treatment in NVSS children accelerates bone maturation and that the beneficial effect on final height remains dubious.

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GROWTH PROMOTING EFFECT OF GROWTH HORMONE AND LOW DOSE ETHINYL ESTRADIOL IN GIRLS WITH TURNER SYNDROME: FINAL HEIGHT RESULTS. G. Massa, M. Maes, P. Malvaux, M. Craen, C. Ernould, C. Heinrichs and M. Vandeweghe, Department of Pediatrics, Universities of Leuven, Louvain, Ghent, Liège and Brussels, Belgium.

In 1987 a multicenter trial was started to evaluate the effect of daily s.c. rhGH treatment (0.15 IU/kg/day Genotonorm, Kabi Pharmacia, Sweden) in 40 girls with Turner syndrome (TS) (mean±SD age: 11.3±2.6 yrs). Twenty randomly selected girls received in addition 25 ng/kg/day ethinylestradiol (EE2) orally. From the 3rd year of treatment puberty was induced with 100 ng/kg/day EE2 in the girls with a bone age older than 11 years. Thirty-six patients have been followed for 5 years. Except early breast budding in 9 out of 20 girls treated with rhGH and 25 ng/kg/day EE2, no differences were found between the patients treated with rhGH alone and those also treated with low dose EE2. In 28 patients with a bone age above 13 yrs, height attained 5 years after the start of rhGH treatment is 150.5±4.4 cm. This is higher (P<0.001) than the adult height of 144.8±5.8 cm of 43 untreated TS girls. In these 28 girls, the difference in height attained after 5 years of treatment and corrected mid parental height is 10.8±4.8 cm, which is less (P<0.001) than in untreated adult TS patients (16.2±4.8 cm). These results provide further evidence that treatment with rhGH increases final height in TS girls.

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METABOLIC CONSEQUENCES OF HIGH DOSE GH TREATMENT E.S.McCaughey, L.D.Voss, J.Mulligan, P.R.Betts. Dept Child Health, Southampton University Hospitals, Southampton, SO94XY, UK

Unwanted metabolic effects of growth hormone (GH) in the early phase of treatment have been reported but are thought to be transient. Persisting changes after 12 months are less well documented. 15 short normal children, identified in the community, mean age 7.8 years (T group), were monitored for 3 years on high dose GH treatment (30IU/m2/week) together with a control group of untreated short children (C group). At the onset no significant differences were observed between groups for any parameter. At 3 years mean fasting serum insulin was significantly higher in the T group, (T 9.3, C 6.2mU/L, p=.011). Neither group showed significant changes in mean fasting glucose or HbA1, therefore insulin/glucose ratio was significantly different (T 2.03, C 1.34, p=.017). Cholesterol and triglyceride levels increased very slightly in both groups. We have already reported early changes in body composition and these appear to persist. The treated children are still leaner (lean body mass T 26.1, C 20.9Kg, p<.001) with less body fat (T 13.5, C 18%, p=.015). This pattern is observed in both sexes. Treated children have grown well with a significant improvement in height SDS from -2.4 to -1.17. Bone age matured appropriately resulting in an improved predicted adult height. Although a satisfactory growth response has been obtained, it is of concern that some metabolic and body composition changes persist. Continued close monitoring is indicated.