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24-HOURS PLASMA GROWTH HORMONE (GH) PROFILES, URINARY GH-EXCRETION AND PLASMA IGF-I AND -II LEVELS IN PREPUBERTAL CHILDREN WITH SHORT STATURE AFTER INTRAUTERINE GROWTH RETARDATION (IUGR).

We studied plasma GH levels during 24-h GH profiles and after arginine stimulation (ATT) and measured day and night urinary GH secretion (U-GH) and IGF-I and -II levels in 40 prepubertal children (25 boys/15 girls) with short stature after IUGR (defined as a birthlength < P3). Mean (range) age was 7.5 (3-11) years. Mean (SD) height SDS (H-SDS) and height velocity SDS (HV-SDS) was -2.95 (0.62) and -1.06 (0.97), respectively. GH profiles were analysed with PULSAR. RESULTS (expressed as mean(SD) values):

Classification of profile	Mean GH ≥ 6 mU/l	At least 1 GH-peak ≥ 20 mU/l	No. (%) of Patients	Peak GH during ATT	U-GH µU/day	IGF-I SDS_{CA}
"Normal"	+	+	6 (15)	34.2 (12.0)	15.8 (7.0)	0.29 (0.46)
"Subnormal"	-	+	23 (57.5)	20.9 (3.6)*	9.1 (3.6)*	-0.90 (1.44)
"Low"	-	-	11 (27.5)	18.5 (9.7)*	9.3 (3.3)*	-0.69 (1.84)

CA= Calendar Age; * P<0.05 vs "normal" GH profile

ATT: Max. GH response during ATT (peak ATT) was 22.3 mU/l (12.1) with a range from 4.5 to 56 mU/l; 18/40 (45%) children had a max. GH-response less than 20 mU/l. IGF-I and -II: Plasma IGF-I SDS_{CA} was -0.88 (1.39) and IGF-II SDS_{CA} was -0.64 (1.48). U-GH: U-GH excretion was 10.42 (4.91) µU/24h, divided in 5.90 (3.16) µU/daytime and 4.38 (2.62) µU/nighttime. Correlations: The 24-h GH profile characteristics such as mean GH, number of peaks > 20 mU/l, AUC_b, and the sum of the amplitudes correlated significantly with the peak ATT (r-values:0.31-0.35; P<0.05) and the U-GH excretion (r-values: 0.33-0.67,P between <0.001 and <0.05). No correlations were found with the growth parameters (H-SDS, HV and HV-SDS) or the IGF-I and -II levels. However peak ATT correlated significantly with IGF-I SDS_{CA} (r=0.43;P<0.01). The growth parameters were not correlated with either IGF-levels, U-GH excretion or peak ATT. CONCLUSIONS: GH secretion in children with short stature after IUGR is heterogeneous, but many children show low or subnormal spontaneous GH secretion, while IGF-I as well as IGF-II levels tend to be in the low-normal range.

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EFFECTS OF DIIFFERENT GH DOSES ON THYROID METABOLISM, ENERGY EXPENDITURE AND BODY COMPOSITION IN THYROXINE SUBSTITUTED GH DEFICIENT PATIENTS

OBJECTIVE: To examine the effects of different doses of GH on thyroid metabolism, body composition and energy expenditure in GH deficient patients.

DESIGN: Eight GH deficient patients treated with thyroxine (age 21-39) were studied after 4 weeks without GH followed by 3 consecutive 4 weeks periods, where the patients received GH in a fixed order 1, 2, and 4 IU m^{-2} sc. per day. At the end of each period the patients were hospitalized for a 24 h examination.

RESULTS: Mean 24-hour levels of GH (µg/l) were 0.9 ±0.1 (0 GH), 2.4 ±0.3 (1IUm^{-2}), 3.6 ± 0.5 (2IUm^{-2}) and 6.30 ±0.9 (4IUm^{-2}) (p<0.01). Serum IGF-I (µg/l) levels increased dose-dependently from 61 ±21 to 206 ±65, 260 ±70 and 468 ±171 respectively (p<0.05). Serum TT_3 (mmol/l) levels increased from 1.13 ±0.18 to 1.66 ±0.21, 1.85 ±0.20 and 1.86 ±0.21 (p=0.03) respectively. A corresponding significant decrease in serum rT_3 (ng/ml) was observed. Serum TT_4 (mmol/l) decreased from 103 ±8 to 102 ±8, 86 ±7 and 77 ±6 (p=0.04). Similar changes in serum FT_3 and FT_4 were observed. Serum TSH decreased during the study: 0.407 ±0.193 (0 GH), 0.078 ±0.030 (1IUm^{-2}), 0.067 ± 0.027 (2IUm^{-2}) and 0.036 ±0.013 (4IUm^{-2}) (p<0.01). Likewise mean diurnal serum TSH levels were lower during GH (0.065 ±0.033 4IU m^{-2}) (0.546 ±0.246 0 GH) (p<0.01). GH caused a significant increase in resting energy expenditure (EE): 1595 ±148 (94% of predicted value) (0 GH), 1673 ±168 (99%) (1IUm^{-2}), 1917 ±127 (113%) (2IUm^{-2}) and 1889 ±157 (112%) (4IUm^{-2}) (p<0.05). Fat mass was increased without GH therapy and decreased dosedependently during the study.

CONCLUSION: T_3 and EE are subnormal in GH untreated GH deficient patients. GH increased peripheral conversion of T_4 to T_3 in T_4 substituted GH deficient patients in a dosedependent way. GH lowered TSH levels. GH increased energy expenditure and decreased fat mass also in a dosedependent way.

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EFFECTS OF BIOSYNTHETIC GROWTH HORMONE (GH) TREATMENT (Rx) ON GROWTH IN TURNER'S SYNDROME (TS).

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The effects of biosynthetic GH (0.375/kg/week) on anthropometric measurements and IGF-1 level were assessed in 13 patients (pts) with TS treated for 4 yrs. Three pts received Synthroid for hypothyroidism; one pt had spontaneous puberty in her 2nd yr of Rx. Before Rx, the mean (±SD) age and bone age (yrs), height and weight (SDS), height velocity (cm/yr) and IGF-1 (ng/ml) were 11.3 + 1.8, 9.5 ± 1.9, -3.5 ± 0.9, -0.9 ± 0.6, 4.6 ± 1.4 and 182 ± 91.7 respectively. Mean IGF-1 which was lower than normal for age at start of Rx (182 ± 91 vs 295) increased significantly (p<.0005) during Rx to levels greater than normal for age; 468 ± 200 vs 260 after 1/2 and 1 yr, 670 ± 205 vs 484 after 2 yrs and 744 ± 104 vs 484 after 3 and 4 yrs of Rx. Height velocity increased significantly to 6.7 ± 1.3 cm/yr in the first 6 months (p<.0005)(n=13), to 6.9 ± 1.2 in the first yr (p<.0005)(n=13) and to 5.8 ± 0.9 in the 2nd yr (<.05)(n=7). During the 3rd yr of Rx, height velocity was 4.8 ± 1.4 cm/yr and similar to baseline while in the 4th yr it was only 3.4 ± 1.4 and significantly less (p<.05) than before Rx. A significant improvement in height SDS was noted only after 2 yrs (p<.05) and persisted throughout the 4th yr of Rx. A disproportionate increase in hands and feet and mild coarsening of facial features were noted in pts treated for more than 3 yrs. This data suggests that GH is effective in increasing height velocity and decreasing the height SDS deficit mostly in the first 2 yrs of Rx. It is possible that the apparent weaning effect of GH noted in this study was due to increased bone maturation and that initiation of Rx at an earlier age may produce better results. The fact that the abnormally elevated IGF-1 levels did not result in a greater height velocity suggests that the long bones of pts with TS may be resistant to the effects of IGF-1.

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RAPID CHANGES IN BODY COMPOSITION AFTER GH TREATMENT IN PATIENTS WITH GH DEFICIENCY.

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This study was designed to assess the changes in the body composition in patients with GH deficiency after 3 months of human growth hormone (hGH) treatment. Nine prepubertal patients (1 female and 8 males, aged 8 - 14 yr old) with GH deficiency were studied. The changes were measured on a monthly basis. The body composition measurements were made by the bioelectrical impedance analysis (BIA) method (BIA 101, RJL Systems, USA). The mean percentage (% FAT) and kilograms (kg FAT) of body fat significantly decreased at 2 months of hGH therapy from 15.3 +/-3.7 to 13.0 +/- 3.8% (P<0.005) and from 4.1 +/- 1.5 to 3.7 +/- 1.6 kg (P<0.05), respectively. The mean percentage (% LBM) and kg (kg LBM) of lean body mass increased from 84.7 +/- 3.7 to 86.6 +/- 3.9% (P<0.05) and from 22.7 +/- 5.5 to 24.1 +/- 5.9 kg (P<0.01), respectively. Subsequently, the mean LBM/FAT ratio (L/F) increased from 6.03 +/- 1.82 to 7.42 +/- 2.23 (P<0.05) in terms of the percentage of FAT and LBM, and from 5.82 +/- 1.38 to 7.30 +/- 2.25 (P<0.05) in terms of the kilograms of FAT and LBM. There were no significant changes in FAT and L/F between 2 and 3 months of hGH therapy. These results indicate that the body composition changes rapidly by 2 months of hGH treatment, and then settles into a stabilized state.

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16 YEARS OF NORMAL GROWTH WITHOUT GROWTH HORMONE(GH),WITHOUT IGF-I AND IGFBP-3 AND WITHOUT OBESITY.

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Growth without GH has been well described: in utero;with obesity and hyperinsulinism following surgery for craniopharyngeoma or hypothalamic tumors(Frasier;Kenny,1968);temporarily,with hyperprolactinemia in optic nerve hypoplasia(Costin,1985);in acromegaloidism(Ashcraft,1983);with obesity,low RIA-IGF-I but normal IGF-bioassay(Geffner,1986);in a single child before removal of a craniopharyngeoma (Wit,1988);the "invisible" GH:normal receptor binding and bioactivity but absent detectability by RIA(Bistritzer,1988).

The patient: a boy with optic nerve hypoplasia has now been followed for 16.5 yrs.,growing along the 3rd to 10th percentile of Zürich standards with only little bone age delay.GH-deficiency was proven at 13 mos.and 9 yrs. of age.Insulin and prolactin were normal.Obesity never existed: BMI 21.2;puberty occurred spontaneously at 13 yrs. of age.ACTH-and ADH-insufficiencies appear to develop gradually recently.

Results:(ng/ml) IGF-I-RIA:19(71-431);IGF-I-RRA:36(52-325);IGF-II-RIA: 522(441-1003);IGF-II-RRA:468(407-1227);IGFBP-3:1457(2119-4262).IGF-bioassay:0.41 U/ml(0.90±0.26).

There was no "burst promoting activity",when the patient's serum was incubated with erythroid progenitor cells(in contrast to Geffner's patient).

Conclusion: this patient has grown for 16 yrs.without GH and IGF-I with low-normal IGF-II.The low IGFBP-3 supports GH-deficiency,while low IGF-I by bioassay excludes enough free IGF.He differs from all similar patients and demonstrates our ignorance of some growth types.

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GROWTH HORMONE TREATMENT OF SHORT CHILDREN BORN SMALL FOR GESTATIONAL AGE : A MULTICENTRE STUDY.

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The effect of growth hormone (GH) treatment was studied in children born small for gestational age, who were not deficient in GH. A total of 131 patients was studied after 12, 18 and 24 months of therapy. Inclusion criteria for the study were : chronological age (CA) between 3 and 8 years and prepubertal, gestational age (GA) not less than 35 weeks, birth length for GA below -2 SD (MacLean), height/ca below -2 SD (Sempé), height velocity (HV) for CA not above 0 SD (Sempé), and peak GH greater than 10 ng/ml after one provocation test. Children in the control group (group A) were untreated ; those in the treatment groups were given GH at either 0.7 IU/kg/week (group B) or 1.4 IU/kg/week (group C).

TABLE 1 : CHARACTERISTICS OF PATIENTS BEFORE TREATMENT

	GROUP A	GROUP B	GROUP C
n	27	55	49
GA (weeks	38.9 ± 1.4	39.2 ± 1.7	38.7 ± 1.4
Birth length/GA (SD)	-2.7 ± 0.8	-3.2 ± 0.9	-3.0 ± 0.8
CA (years)	5.3 ± 1.4	5.3 ± 1.4	6.2 ± 1.2
Bone age (BA;years)	3.8 ± 1.4	4.1 ± 1.3	4.8 ± 1.4
HV (cm/year)	5.2 ± 1.0	5.2 ± 1.5	4.7 ± 0.8
HV/CA (SD)	-1.3 ± 1.0	-1.6 ± 1.3	-1.5 ± 1.3
Height/CA	-2.7 ± 0.9	-2.8 ± 0.7	-2.7 ± 0.7

TABLE 2 : EFFECT OF GH AFTER 12 AN 24 MONTHS OF TREATMENT

	GROUP A	GROUP B		GROUP C	
	12 months	12 months	24 months	12 months	24 months
n	27	55	7	46	7
HV (cm/year)	5.8 ± 1.3	8.5 ± 1.9*	6.5 ± 0.9	9.5 ± 1.6*	6.7 ± 1.3
HV/CA (SD)	-0.5 ± 1.4	+2.7 ± 1.6*	+1.0 ± 1.0	+4.0 ± 2.2*	+1.3 ± 1.6
Height/ca (SD	-2.6 ± 0.6	-2.1 ± 0.8*	-1.9 ± 0.8	-1.8 ± 0.8*	-1.5 ± 0.8
ΔBA (years)	+1.2	+1.2	-	+1.1	-

*p < 0.001 compared with pretreatment value or between groups C and B.

Treatment was well accepted and tolerated. One child in group C developped osteochondritis after 9 months of treatment ; GH treatment was not interrupted. HV was accelerated in both treated groups, with a significant difference between groups B and C (p<0.001). BA was not accelerated in any group. In conclusion, GH treatment would appear to be useful in the treatment of short children born short for gestational age. There appears to be a dose-dependent effect of GH, although further, longterm studies are required to determine the optimum dose and duration of treatment.