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VERY TALL CHILDREN HAVE SIMILAR 24H-GH LEVELS AS SHORT CHILDREN BUT HIGHER CIRCULATING INSULIN AND LESS IGFBP-1

The amount of and/or the pattern of growth hormone secretion is generally considered to be the main regulator of linear growth. Spontaneous GH, insulin and IGFBP-1, and IGF-I levels were therefore investigated in very tall children and compared with those of prepubertal short children with constitutional delay of growth and adolescence. Data is given as mean (SEM).

	Tall children		Short children
	prepub	pub	prepub
	n=18	n=11	n=16
Age yr	8.4(0.5)	12.7(0.7)	9.6(0.7)
Height SD	3.7(0.3)	3.2(0.1)	-2.6(0.2)
GV cm/yr	8.0(0.5)	-	4.7(0.2)
Bone age SD	1.8(0.4)	0.8(0.5)	-2.6(0.6)
BMI kg/m²	19.2(0.5)	19.0(0.7)	15.8(0.6)
IGF-I µg/L	216(17)	434(40)	144(11)
24h/GH-mean µg/L	1.1(0.2)	4.1(0.8)	1.5(0.2)
24h/GH-basal µg/L	0.2(0.01)	0.3(0.04)	0.3(0.03)
24h/Insulin mean µU/ml	36(4)	44(5)	24(3)
Insulin fast µU/ml	17(1.4)	22(2)	14(1.2)
IGFBP-1 mean µg/L	30(2.1)	25(1.9)	52(7.5)
BP-1 high/low	4.3(0.4)	2.7(0.3)	5.3(0.6)

Conclusion: Very tall children have consistently low S-GH with a secretory pattern similar to those of short children with constitutional delay of growth. In contrast they have increased insulin levels and lower IGFBP-1 levels. Decreased S-IGFBP-1 may implicate higher free S-IGF-I promoting increased growth velocity.

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FIRST YEAR RESPONSE OF GROWTH IN SHORT CHILDREN WITH ACHONDROPLASIA OR HYPOCHONDROPLASIA TREATED WITH GROWTH HORMONE (GH)

Skeletal dysplasia often results in severe short stature. This has traditionally not been thought to respond to GH treatment. We here report the first year growth response to GH treatment of a group of children with achondro- or hypochondroplasia.
Inclusion criteria: Height < -2SD, age >4yrs and <10yrs for girls and <12yrs for boys. Only prepubertal children were included in the study and irrespective of endogenous GH levels. The GH dose was randomised to 0.1 or 0.2 IU/kgxday, 7 days a week (Norditropin, Novo Nordisk). After 12 months of treatment the following growth parameters were recorded. Data is given as mean (SEM).

GH Dose IU/kg	n	Height GV start cm/yr	Height GV 12mo cm/yr	Arm span GV 12mo cm/yr	Sitting height start % of total height	12mo
achondroplasia						
0.1	7	4.2(0.6)	6.8(0.3)	7.2(0.8)	66.1(1.0)	65.3(1.8)
0.2	5	4.8(0.6)	8.6(1.0)	9.0(0.6)	67.8(1.2)	64.7(0.9)
hypochondroplasia						
0.1	7	5.4(0.5)	9.8(1.1)	10.2(1.2)	59.7(1.0)	59.2(1.5)
0.2	7	4.7(0.4)	9.3(1.4)	10.9(1.8)	59.1(0.7)	59.3(0.8)

Conclusion: 12 months of GH treatment gives a significant increase in growth velocity without worsening body disproportions in children with achondroplasia or hypochondroplasia. No major difference was seen between the GH doses 0.1 or 0.2 U/kg

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GROWTH HORMONE TREATMENT IN PRADER-LABARTH-WILLI SYNDROME

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The P-L-W syndrome is assumed to be caused by hypothalamic dysfunction. Patients have increased appetite,severe obesity,disturbed pubertal development and growth retardation,reduced sensitivity for pain,disturbed body temperatur regulation and muscular hypotonia. This study is performed on prepubertal boys and girls above 4 years of age with retarded BA and sufficient energy intake. Diagnosis was based on clinical signs and karyotype. Growth hormone therapy was suggested to be beneficial and the objectives were to study the effects of therapy on muscular mass,fat mobilisation and the stimulation of growth. The preliminary data from 6 patients are presented in the table. hGH dosage 0.1 IU/kg/d, max.4IU/d, given 7 d/w. The result is a great effect on growth, expressed as an increase in HV and H-SDS, a reduction in fat expressend in % (Futrex - infrared refr.of s.c.fat) and fat/muscle ratio in the thigh (CT scan).

Pat.no	Sex	CA (y)	BA (y)	H-SDS	Hv before /1.y	W/H % o/u mean	% Body fat (Futrex infrared. refr. s.c. fat)	Fat/muscle (CT thigh)	IgF-1
1	M	5.1	3	-2.9	5	-6	39	1.70	7.1
		8.5	7+	0	14	14	34	1.36	26.6
2	M	10.2	9-	-2.5	3	31	31	1.66	6.7
		13.2	13+	-0.5	10	15	15	0.93	39.5
3	M	12.9	11+	-2.5	3	41	36	1.98	18.3
		13.8	-	-1.8	12	30	33	-	66.2
4	M	10.5	7+	-3.2	2.5	0	38	2.15	6.4
		11.0	-	-2.7	12	-4	31	-	29.7
5	F	8.7	5	-3.1	4	10	45	1.60	6.7
		9.7	-	-2.0	14	4	36	-	25.9
6	F	14.2	12-	-4.1	1	25	36	2.80	18.0
		14.5	-	-3.9	12	-	-	-	-

Conclusion: hGH therapy offers a great beneficial effect on growth, body weight and compisition in P-L-W patients. Families and teachers also experiences a clear improvement in scool performance and psychosocial adjustment.

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MOLECULAR ANALYSIS OF A LARGE BEDOUIN KINDRED WITH IGHD, TYPE IB. E. Leiberman, R. Carmi, Y. Limoni, H. Abdul Latif, M.R. Brown and J.S. Parks, Department of Pediatrics, Soroka Medical Center, Beer-Sheba, Israel, and Emory University, Atlanta, GA 30322, USA

We present a highly inbred Bedouin kindred of 4 families containing 7 males and 6 females with isolated growth hormone deficiency (IGHD). Patients have normal height parents, exhibit extreme short stature (Hts - 4 to -5 SDS), absent to low responses to GH stimulation tests, no response to GHRH stimulation and low levels of IGF-binding proteins. They responded well to GH therapy and did not develop antibodies to GH. We used a two stage PCR strategy to study GH-1 genes in two of the families. Amplification of a 2.2 kb GH-1 gene fragment from each specimen excluded IGHD IA (GH-1 gene deletion). The second round of PCR amplified 500 bp of GH-1 promoter sequence for SSCP analysis, a technique which detects single base differences. Polymorphisms disclosed by Hin cII digestion of the 2.2 kb product and by SSCP analysis of the 500 bp product were informative. Affected individuals displayed three different GH-1 haplotypes. This eliminated the possibility that their IGHD is caused by inheritance of a mutation in or near the GH-1 gene. This kindred provides an excellent example of IGHD IB with homozygosity by descent and illustrates the need to identify and examine other candidate genes that contribute to GH synthesis and/or secretion.

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THE RELATIONSHIP BETWEEN OVERNIGHT PLASMA GROWTH HORMONE PROFILES AND NOCTURNAL URINARY GROWTH HORMONE EXCRETION

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Simultaneous overnight 12 hour plasma growth hormone profiles and timed urine collections were obtained in 100 patients (mean age 11.0yrs, range 3.4-33.9yrs) undergoing investigation of growth hormone (GH) secretion. All have normal renal function. Plasma samples obtained at 20 minute intervals from 20.00-08.00hrs were assayed by an in-house IRMA employing an MAb as label (between-batch CV <8.5% from 2.2-49 mU/l). GH profiles obtained were analysed using the Munro modification of PULSAR. Urine GH was assayed using the Novo Nordisk Novoclone amplified enzyme immunoassay (between-batch CV <12% from 9-28ng/l).

Mean plasma GH concentration was 7.7 mU/l (SD 4.0, range 0.6-25.3). Mean plasma pulse amplitude was 15.6 mU/l (SD 8.6, range 1.9-48.0). Mean 12 hr urine GH concentration was 6.65 ng/l (SD 4.23, range 0.6-19.7). There were highly significant correlations (p=0.001) between urine GH concentration and mean pulse amplitude (r=0.54), mean overnight plasma GH levels (r= 0.53), sum of pulse amplitude (r=0.49) and sum of pulse area (r=0.49). Children with severe GH insufficiency were readily identified by low urine GH levels. This large series shows that timed overnight urine GH concentration reflects nocturnal plasma GH profiles.

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INTERRELATIONSHIP OF IGFBP-1 AND INSULIN IN PEDIATRIC CHRONIC RENAL FAILURE (CRF). P.D.K. Lee, D.R. Powell, E.D. Brewer, Dept Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA, and the Southwest Pediatric Nephrology Study Group and associated study centers.

The pathogenesis of growth failure in pediatric CRF may involve abnormalities of the IGF system. We have previously shown that serum IGF levels are normal in CRF, while levels of intact IGFBP-1, an IGF-inhibitory binding protein, are elevated. In normals, IGFBP-1 production is suppressed by insulin; fasting IGFBP-1 and insulin levels show a curvilinear inverse relationship. We studied this relationship in 20 patients [age = 7.1± 3.5SD yr, 3F/17M, GFR (iothalamate) = 28± 7SD mL/min/1.73m²] involved in a study of GH treatment of CRF. Fasting serum was collected at 0, 3 and 12 months (n = 60). Insulin and IGFBP-1 levels were measured using immunoassay kits (Diagnostic Systems Labs) with mean levels of insulin = 52± 7(SE) pmol/L (nl 15-100) and IGFBP-1 = 719± 72(SE) ng/mL (nl < 150). The relationship between IGFBP-1 and insulin is described by an inverse curvilinear plot with a >20-fold increase in IGFBP-1 levels at the inflection point as compared to normal and obese subjects. The "critical" suppressive insulin level may be slightly less than the level we have previously described for non-CRF patients (70-90 pmol/L). Since GFR was low and homogenous in this group, an independent relationship with IGFBP-1 could not be defined. Compared to baseline, IGFBP-1 levels were reduced 29% and 57% after 3 and 12 months of GH therapy (n = 14 pts), while levels were 92% and 94% of baseline for untreated patients (n = 6). GH treatment had no effect on the inverse relationship of IGFBP-1 and insulin. Our results provide evidence that IGFBP-1 production is insulin-dependent in CRF as it is in normals, and that increased levels of this IGF-regulatory protein are probably determined primarily by impaired clearance. Furthermore, while exogenous GH lowers IGFBP-1 levels in CRF, this effect may be mediated by changes in insulin concentrations.

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