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CHRONIC BETA-ADRENERGIC BLOCKADE ENHANCES GROWTH VELOCITY TO GROWTH HORMONE RELEASING HORMONE IN GROWTH HORMONE DEFICIENT CHILDREN (GHD). V. Mericq, F. Cassorla, H. Garcia, A. Avila, A. Boric and G. Merriam. IDIMI. University of Chile DEB, NICHD, Bethesda, Maryland, U.S.A.

GHRH is effective in improving the growth velocity in GHD children. Atenolol is a beta adrenergic antagonist which acutely inhibits somatostatin secretion. To determine whether the combined therapy of GHRH+Atenolol improves the growth response to GHRH in GHD children we studied in a double blind, randomized trial 11 prepubertal GHD children (5F,6M) divided in 2 groups:Group A n=5 (3F,2M),chronologic age (CA) X 8±2.7 years, bone age (BA) X 4.9 ± 2.8 years received daily GHRH 20 ug/kg sc + daily oral Atenolol (1mg/kg). Group B n=6 (2F, 4M) CA X 10.6±3.7 years, BA X 5.5±2.9 years received baily GHRH 20 ug/kg sc + placebo.The children were admitted to the hospital before and after 1 year of treatment to meassure GH every 20 minutes for 24 hours and height was determined every 6 months. Growth velocity increased in group A from 3.3 ± 0.6 cm/year to 6.7 ± 1.2 cm/year (p<0.0005) and in group B from 3.2 ± 0.8 cm/year to 5.4 ± 1.4 cm/year (p<0.025). Growth velocity was significantly different in group A compared to group B (p< 0.05). Mean 24 hour GH secretion increased in group A from 1.8 ± 1.1 to 2.2±1.2 ng/ml (NS) and in group B from 1.2 ± 0.14 to 1.6 ± 0.4 ng/ml (NS).This study demonstrate that the beta-adrenergic blockade with Atenolol enhances the growth velocity to GHRH in GHD children.

This suggests that the growth velocity in GHD children treated with GHRH can be potentiated with an agent that blocks Somatostatin secretion.

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THE CIRCULATING LEVELS IGF-2 ARE INCREASED IN SMALL FOR GESTATIONAL AGE (SGA) INFANTS WHO SHOW EVIDENCE OF CATCH-UP-GROWTH (CUG) DURING THE FIRST YEAR OF LIFE.H.Garcia,C.Henriquez,F.Ugarte,G.Iñiguez,F. Beas,E.Fernandez,A.Avila. IDIM, Fac. de Med., Universidad de Chile.

To study the influence of IGF-1 and IGF-2 levels in the catch-up-growth(CUG) of small for gestational age (SGA) infants, we followed 32 newborns (18 boys and 14 girls) with birth weight of 2344±195 g and birth length of 45.7 ± 2 cm. during the first year of life.We measured weight, lenght, IGF-1 and IGF-2 at 0, 3,6,9 and 12 months of age. CUG was defined as an increase in lenght 2 score greater than 1 SD at 6 months of age, based upon the fact that accelerated growth, when observed in CUG (+) infants, occurs during this period. We compared the concentrations of IGF-1 and 2 between the infants who demostrated evidence of CUG and those who did not.

Results: IGF-2 (pg/ml)

N ♂/♀	0	3	6	9	
CUG+	1610/6	31.0±25.2	189.5±110.1	123.7±32.5	130.7±34.9	108.0±32.6
cug-	16 8/8	16.1±14.4	120.9±28.9	93.9±24.3	126.3±28.6	117.5±39.4
		P=NS	P<0.05	P<0.02	P=NS	P=NS

Height Z score was lower in CUG(+)infants at birth and increased during the first 6 months of life.IGF -2 levels were significantly greater at 3 and 6 months in CUG (+) infants. These were no differences in IGF-2 levels at 0, 9, 12 months, nor in IGF-1 levels at any time. We conclude that circulating IGF-2 levels at 3 and 6 months correlate with height velocity. This growth factor may be involved in the mechanism of CUG in SGA age infants. This suggests that IGF-2 may be useful as a potential therapeutic agent for the treatment of SGA infants who do not demostrate evidence of CUG.

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TREATMENT OF CHRONIC RENAL FAILURE WITH GROWTH-HORMONE-RELEASING HORMONE. T. Pasqualini, S. Moyano, P. Fainsteins-Day, R. Gutman, A. Eymann, J. Ferraris. Hospital Italiano, Departamento de Pediatria, Buenos Aires, Argentina.

Growth retardation is common in children with chronic renal failure (CRF) and after renal transplantation (Tx). For this reason we treated 9 children (3 on conservative treatment, CT; 3 on dialysis, D; and 3 Tx), aged 1.6 to 14.0 (x±sd; 8.1 ± 4.3) years, with twice daily subcutaneous injections of growth - hormone-releasing analogue, GHRH (1-29)NH2 Serono at a mean dose of 26±7 ug/kg/day, during 2 to 6 months. Mean serum urea and creatinine remained stable, although in CT patients serum creatinine increased moderately. Before treatment, mean bone age was 5.2 ± 3.1 years, height SDS -2.2±0.6 and growth velocity 4.5±2.9 cm/year (-2.3±2.0 DS for chronological age). Mean nocturnal spontaneous growth hormone (xGH) was 3.3±1.6 ng/ml, smooth line 1.6±0.9 ng/ml, amplitude 5.4±2.6 ng/ml, number of peaks 3.8±1.3 and growth hormone (GH) response to GHRH test (1 ug/kg IV) 61.7±52.5 ng/ml. Five patients, all 3 on CT included, increased the height velocity from 3.8±1.6 to 8.0±2.6 cm/year. The peak GH response to GHRH was significantly higher in the group of growth non-responders than the responders (p<0.05). Conclusion: GHRH treatment increased growth velocity in 55% of our patients. All CT patients had a worthwhile response to therapy: height velocity increased by more than 2 cm/year. Growth response to GHRH was lower when GH response to GHRH test was high, suggesting peripheral resistance to the biological action of GH.

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EVALUATION OF EFFICACY AND SAFETY OF RECOMBINANT HUMAN GROWTH HORMONE (rhGH) IN PRE-PUBERTAL SHORT CHILDREN WITH CHRONIC RENAL FAILURE (CRF). MCS. Boguszewski, R. Sandrini, I. Cat and L. de Lacerda. Division of Endocrine Dept of Pediatrics, UFPR, Curitiba, Paraná, Brazil.

Growth retardation is a common problem in children with CRF more pronounced the earlier the renal failure occurs. This study was designed to evaluate the efficacy and safety of rhGH treatment in pre-pubertal childrem with CRF and short stature. 10 patients(5 girls aged 5.9-11.5,mean 8.1 and 5 boys aged 3.8-12.2,mean 8.0)were enrolled in the study according to the following criteria: CRF diagnosed at least 12 months prior to entry into the study;glomerular filtration rate (GRF) 50 ml/min/1.73m2 body surface area (Schwartz's formula) and normal thyroid function. rhGH (Genotropon (R), 1 IU/kg/week was given in daily sc injections for 12 months. Clinical and biochemical assessment was carried out every 3 months. Mean height velocity (HV)increased from 4.5 to 8.6cm/year (p<0.01); mean HV -SDS increased from -1.58 to 2.92 (p<0.01); mean height SDS improved from -3.3 to -2.8(p<0.01).Mean weight gain was 3.2kg and mean bone age advanced 1 year. Two girls started puberty after 6 months of therapy. GRF increased significantly (p<0.05) at 6 months and returned to pre-treatment values at 1 year of therapy. Serum phosphate and insulin increased (p<0.01)at 12 months. Other biochemical paremeters (calcium, alkaline phosphatase, creatinine,T3, T4, TSH, hematocrit, cholesterol, tryglycerides, Na, K, BUN, glucose and frutosamine)did not change.No side effects were observed. Thesè results confirm previous reports on the effectiveness of rhGH in increasing height velocity of short slowly growing patients with CRF.

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ANDROGEN PATTERN IN PREPUBERTAL HYPERTRICHOSIS. M. Gryngarten, ME. Escobar, S. Campo, S. Ayuso, P. Bedecarrás, C. Bergadá. CEDIE. División de Endocrinología. Hospital de Niños R. Gutierrez. Buenos Aires. Argentina.

The cause of prepubertal hypertrichosis (H) is unknown. Plasmatic androgen levels were determined in 17 girls with H, (ca: X±SD: 5.5±1.41 years), 11 girls with precocious pubarche (PP) and 9 normal prepubertal girls (CP).

All of them were assesed according to their distribution score of vellus hair. Group H. was characterized by excessive growth of vellus hair (score>7),CP showed normal distribution and PP group had pubic hair II-III without excessive growth of vellus hair (score<5)17OH Progesterone,Androstenedione (A),DHEA-S,Testosterone(T),SHBG and 3 Androstanediol glucoronide(3 AG)were measured by RIA.

	# DHEA-S ng/ml	# A ng/dl	# AG ng/dl
CP	210.66 ± 42.58	46.33 ± 8.91	62.11 ± 8.32
H	203.05 ± 44.77	54.76 ± 6.14	111.41 ± 13.73
PP	782.54 ± 151.84*	81.81 ± 15.93	130.72 ± 33.19

X±SE * p < 0.02

Normal levels of A and DHEA-S and elevated 3 AG levels suggest an increase in the peripheral activity of 5 reductase in most prepubertal girls with hypertrichosis.

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MOLECULAR ANALYSES OF STEROID 5αREDUCTASE 2 GENE IN MALE PSEUDOHERMAPHRODITES. **Mendonça BB;Arnhold IJP;Bloise W;Nicolau W;Wajchenberg BL;Wilson JD; Russell DW.** Dept.of Molecular Genetics and Internal Medicine, UT Southewestern Medical Center, Dallas, USA., Gonads and Intersex Unit,Division of Endocrinology, University of São Paulo,Brasil.

We analyzed the molecular genetics and biochemistry of 5α-reductase 2 (5α-RD 2) deficiency in 7 patients with male pseudohermaphroditism. The diagnosis of 5α-RD 2 was established by clinical data (all patients were born with ambiguous genitalia-microphallus, perineal hypospadias and bifid scrotum and were raised as females until 6-15 y when they change to male gender) and by T/DHT ratio over normal in basal condition in pospubertal cases or after hCG in prepubertal cases. (Normal basal T/DHT ratio=14±5.2; after hCG=13.8±3.5). The 5 exons of the 5α-RD 2 gene were amplified by polymerase chain reaction (PCR) using exons-specific pairs of oligonucleotides, with a termocycler program of 35 cycles of 1 min./94°C, 3 min./68°C. The mutations and the presence of homozygosity or compound heterozygosity were detected by SSCP analyses and the DNA sequences of the putative mutations were determined by PCR sequencing.

			Molecular Defects			
CASE	CA(ys)	T/DHT	Type	Exon	Mutation	Class
1#	6	44	nonsense	4	C→T, R227*	True Homozygote
2#	9	36				
3	14	30	missense	3	G→A, G183S	True Homozygote
4√	13	37		2	A→G, Q126R	Compound
5√	14	40	missense	4	A→G, N193S	Heterozygote
6√	19	46				
7	15	83	missense	5	C→T, R246W	True Homozygote

#: Siblings √: Siblings

We found four different mutations in our patients. These results confirm the genetic heterogeneity of the 5α-RD 2. We conclude that in all patients studied mutations in type 2 gene account for 5α-reductase 2 deficiency.