272

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RING CHROMOSOME 5 IN A CHILD WITH SEVERE GROWTH RETARDATION.

We report the fourth case known of ring chromosome 5 with phenotype resembling that of the "ring syndrome". A female child of healthy, unrelated, Italian parents, was referred for diagnosis at 36 months of age because of growth retardation, microcephaly and clinodactyly. Her parents' and sister's height fell within normal range. The girl was born after a normal pregnancy. Delivery was posterm, at 42 weeks, spontaneous. At birth weight was 2,480 Kg (-2SD), length 47 cm (-2.5SD), head circunference 32 cm (-1.8SD), no further abnormalities were noted. The first milestones were reached in time. On admission, her length was 85 cm (-3.2SD), weight 10,900 kg (-2SD), head circumference 46 cm (-2SD). Mild psycological abnormalities and a discrepancy between verbal and nonverbal areas were noted. The mean growth hormone secretion (sampling every 30 min over 24 hours) was 2.3 ± 0.4 ng/ml. The stimulated secretion showed a partial deficiency: peak after arginine (0.5 gr/kg, iv, over 30 min) 8.4 ng/ml; peak after clonidine (150 mg/m² orally) 6.8 ng/ml. Bone age was delayed by 1 year. Chromosome analysis showed a ring chromosome 5 in 88%of the cells, a double ring in 2% and two rings in 1%, while in 9% the ring was lost. No delections were found. The sister's and parent's chromosomes were normal. This is the first case of ring chromosome 5 associated with a stimulated partial GH deficiency.

273

SHORT TERM METABOLIC CHANGES AND LONG TERM RESPONSE TO RECOMBINANT IGF-I (rhIGF-I) THERAPY IN A NORTH AMERICAN CHILD WITH GH INSENSITIVITY (GHIS; LARON SYNDROME).

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We report results of the first 9 mos of rhIGF-I Rx in a 10.6 yo Caucasian girl with apparently sporadic GHIS. She was born in the USA into a family with no significant short stature. Dx of GHIS was based on: growth failure (HT SDS=-6.2; GV=3.6cm/y over 8.5 yrs), delayed BA (-4.5 SDS), elevated GH (baseline values 27-42 ng/ml; peak to stimuli 94-192), low IGF-I and IGFBP-3, very low GHBP, and no increase in IGF-I or growth velocity during 2 courses of GH Rx. In the first 11 days of Rx, the rhIGF-I (Kabi Pharmacia, Stockholm) dose was increased from 40 to 120 ug/kg bid. Urinary Ca excretion increased >2-fold, Cr clearance rose 71%, fasting insulin declined in a dose-dependent manner, IGF-II fell from 93 to 53 ng/ml while first morning IGF-I levels remained low (<18ng/ml). During 9 mos of IGF-I Rx (120 ug/kg bid), GV rose strikingly to 10.2 cm/yr resulting in an improvement in predicted adult ht of 7.2 cm. Increased Ca excretion and Cr clearance were maintained. No significant hypoglycemia has occurred. In conclusion, rhIGF-I has been a safe and effective growth-promoting agent in a girl with sporadic GHIS. The specific gene defect in this child is unknown.

274

GROWTH HORMONE THERAPY IN TRACHEOMALACIA.

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Growth hormone may be involved in normal cartilage production. Two patients with GH deficient states were treated with GH. Both patients, one with panhypopituitarism (patient 1) and another with pseudohypoparathyroidism (patient 2) presented with severe tracheomalacia. Both patients required tracheostomy. Patient 1 had his tracheostomy at age 3 years and 9 years later, despite numerous ENT procedures to reduce granulation tissue, could not be extubated due to collapse of the tracheal cartilage. Patient 1 was treated for hypothyroidism and hypoadrenalism. An insulin-glucagon test showed no GH values greater than 2 ng/ml (Hybritech IRMA). At one month of life, patient 2 had a tracheostomy and was diagnosed with pseudohypoparathyroidism with no significant rise in phosphate excretion, cyclic-AMP, or calcium (urinary or serum ionized) after PTH administration. This patient had a low IGF-1 and IBP-3. Patient 1 was treated with GH at a dose of 0.05 mg/kg/dose SC 6X per week; patient 2 at a dose of 0.1 mg/kg/day SC (the higher dose due to resistance to peptide hormones), each for six months. After treatment, the tracheal cartilage had become more firm, allowing extubation in both patients. This experience suggests a role for GH in the development of tracheal cartilage.

275

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MEASUREMENT OF BODY COMPOSITION IN CHILDREN WITH PRADER-LABHART-WILLI SYNDROME (PWS)

We are currently investigating the effect of biosynthetic growth hormone (rhGH one year duration) on body composition, resting energy expenditure (REE) and total daily energy expenditure in 12 PWS children. We report here the measurements made before and after 6 weeks of rhGH therapy on 7 children (4F; age range 5.1-16.7 yr.; BMI 13.8-43.4). Total body water (TBW) was measured by $H_2{}^{18}O$ dilution, and calculated from measurements of skin fold thickness (SKF) and bioelectrical impedance analysis (BIA). These results were compared to those made in children with short stature. The different techniques were compared statistically by comparing the difference between the methods against their means.[1]. There was a significant correlation between total body water (TBW) measured by $H_2{}^{18}O$ dilution and the methods of BIA and SKF. However, the limits of agreement were greater than those seen in children with short stature (SS):

	BIA			SKF		
	'r'	bias	limits of agreement	' r'	bias	limits of agreement
PWS	0.98	1.16	-7.3 to 9.6	0.95	-5.64	-14.1 to 2.8
SS	0.98	0.10	-1.7 to 2.0	0.98	-0.30	-1.90 t 1.3

Body composition calculated from BIA and SKF measurements are likely to be erroneous in very obese children. This should be taken into consideration if longitudinal changes of body composition are being monitored.

[1] Bland JM Altman DG Statistical methods for assessing agreement between two methods of clinical measurement Lancet 1986:i:307-310

276

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THE EFFECT OF SIX WEEKS GROWTH HORMONE TREATMENT ON BODY COMPOSITION AND RESTING ENERGY EXPENDITURE IN PRADER-LABHART-WILLI SYNDROME (PWS).

Growth hormone deficiency (GHD) is suggested as part of the hypothalamic disorder considered to be the basis for PWS - short stature, gross obesity, hypotonia . We are measuring the effect of treatment with biosynthetic growth hormone (rhGH one year duration) on body composition, resting energy expenditure (REE) and total daily energy expenditure in 12 PWS children. We report here the changes observed at 6 weeks on 7 children (4F; age range 5.1-16.7 yr.; BMI 13.8-43.4) compared with children treated with rhGH for GHD. Fat free mass (FFM, kg) and fat mass (FM, kg) were obtained from $H_2{}^{18}O$ dilution, REE (kj/24hr) was measured by indirect calorimetry. All results are expressed as mean(SE) and variance analysed by Wilcoxon rank test. All subjects gained weight. However, all 7 subjects significantly increased their FFM and in 6 there was a decrease in FM.: (* $p<0.05$)

	Wt (kg) *	FFM (kg) *	FM (kg)	REE (kj) *	REE/FFM (kj/kg/d)
Before	45.2(12.8)	24.8(6.5)	24.3(8.0)	4494(1004)	184(16)
After	47.4(13.3)	28.9(8.2)	22.5(7.0)	5027(1050)	179(12)

The mean change in FFM in PWS was significantly greater than in GHD subjects (14.4 v. 6.9%., $p<0.01$) One subject (14.2 yr., weight 78.2kg, BMI 33.9) developed diabetes mellitus after 3 wks of therapy (pre-treatment glycosylated haemoglobin 7.2%). Following 6 weeks of rhGH treatment, PWS children show a greater change in FFM than children with short stature. Growth hormone therapy may be appropriate for long term use in PWS as a means of increasing FFM with possible beneficial sequelae. However, it should be recognised that there is some risk of diabetes occurring.

277

ARGININE INFUSION FOLLOWED BY ARGININE PLUS GROWTH HORMONE(GH) RELEASING HORMONE ADMINISTRATION: A TEST TO ASSESS GH SECRETION.

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To combine a classical test for GH secretion with the assessment of GH pituitary reserve, we evaluated GH secretion in short children by two sequential Arginine(Arg) tests: a first Arg test(Arginine HCL,0.5 g/kg,infused in 30 min),immediately followed by a combined Arg+GHRH test (1 µg/kg iv bolus of GHRH-(1-24). Peak GH responses were considered normal when ≥7 ng/ml after Arg test and ≥20 ng/ml after Arg+GHRH test. Subjects were 103 children (aged 6-16 years;63 males;77 prepubertal; height <5th centile); 41 with normal growth rate (height velocity SD score >-0.80); 26 with borderline growth rate (HVSDS -0.80 to-2); 35 with slow growth rate (HVSDS <-2). Results. a) Normal responses to both tests were found in 79 (76.7%) subjects (33,22,24, in normal, borderline and slow growth groups, respectively); low responses to Arg but normal to Arg+GHRH were found in 22 (21.4%) children (8,3,11 in normal, borderline and slow growth groups,respectively); low responses to both test were found in 2 subjects, with borderline and slow growth. b) In 72 children, a Clonidine test(0.15 mg/m²;normal peak >7 ng/ml) showed a 73.3% concordance with the Arg test. c) In 20 children, mean overnight GH secretion was evaluated (MGHC) and a score was assigned to both GH peaks after Arg+GHRH test: a combined score > 10 predicted 91% of MGHC greater than 3 ng/ml. In conclusion, the sequential Arginine-Arginine plus GHRH test is a safe and convenient procedure for an initial characterization of GH secretion and GH pituitary reserve in short children.