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HYPODIPSIA-HYPERNATREMIA SYNDROME - A PEDIATRIC CASE REPORT. A.Balsamo, A.Cassio, S.Donati, P.Guacci, E.Cacciari. Ist Pediatric Clinic, University of Bologna, Bologna, Italy.

The cases of chronic hypodipsia and hypernatremia represent a rarity, especially for the pediatric age group, and are mostly reported as "neurogenic" or "essential" hypernatremia. This paper describes a 2 3/12 yr old girl, 3rd child of healty related parents, born from a spontaneous delivery (B.W.1200 g; G.A.36 wks) admitted to our Hospital for hyperphagia, obesity (W.E. 40.1%), absence of thirst, intensified sweating and cyanosis of the extremities all of which begun about 9 months before admission. Poliuria was absent, there was no dehydration and blood pressure was normal. She showed tendency to hyperkinetic behaviour and psicomotor development was retarded. Hypernatremia (serum Na concentration up to 167 mEq/l) and serum osmolality up to 353 mOsm/ml were the major findings. The thyroid function tests (TRH) were consistent with secondary hypothyroidism and hyperprolactinemia. Other endocrine studies, and routine tests also for collagen disease resulted normal. Several ADH measurement showed mean levels of about 4 pg/ml and did not change appropriately for serum osmolality values. Electroencephalographic recordings and cerebral NMR repeated more than once revealed normal results. A physiatric evaluation showed a chronic hypoventilation. At 3 7/12 yrs of age she was admitted in the our pediatric intensive care unit in coma and the data at that time showed a serum Na up to 170 mEq/l and an osmolality of 340 mOsm/ml. Our treatment consisted of the forced intake of 1,500 ml water/daily, hypocaloric diet and periodic oxigenation with regular respiratory exercises. Treatment with bromocriptine and L-Tiroxine was instituted. Under these regimens, the patient's situation definitely improved.

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EFFECTS OF THE hGH THERAPY ON THE HEART SIZE AND CONTRACTION.
G. Tonini, S.Marinoni, A.Benettoni, Istituto per l'Infanzia, Trieste, Italy; G.Radetti, R.Crepaz (1). G.Karolyi, M.Pinter (2), G. Soltesz, A.Molnar (3), M.Lovrencic, V.Fabecic (4): Pediatric Dept. (1) Bolzano, Italy, (2) Gyor and (3) Pecs, Hungary, (4) Zagreb, Croatia. (The Alpe-Adria Study Group for Pediatric Endocrinology and Diabetology).

Growth hormone hypersecretion, as in acromegaly, features heart hypertrophy. Despite long experience, heart changes are not regarded as adverse effects of GH therapy: however, increasing doses are being used, owing to increased availability and extension to indications other than GH deficiency. In order to ensure the safety of hGH at higher dose than in the past, we have performed echocardiography in 71 children and adolescents: 22 before treatment, 49 having received hGH (0.4-0.96 IU/kg/wk) for a period ranging 0.5 to 15.5 yrs. M-mode (left ventricle diameter, LV Posterior Wall [LVPW] and Septum [LVSW] in diastole and systole, systolic shortening [LVS] and thickening, aortic root diameter) and Doppler mode (cardiac output and index, protodiastolic to end-diastolic mitral flow ratio) have been recorded and evaluated for relationship to body size, duration of therapy, weekly and cumulated GH dose. The M-mode parameters of left heart size (LV, LVPW, LVSW) were well related to the body growth, and hence indirectly to the therapy. The cardiac index showed a negative correlation with the body size. The other dynamic parameters (LVS, LVPW and LVSW thickening) were, by contrast, not related to the body size. Univariate and multivariate linear regression analysis did not show any correlation between dynamic parameters and duration and dose of GH therapy. However, when the subjects were divided into five groups according to the duration of therapy (A, baseline; B, up to 1 year; C, 1 to 2 years; D, 2 to 4; E, over 4), analysis of variance disclosed a trend of decrease of the LVS and wall thickening during the first period of therapy (groups B and C), and subsequent return to baseline values or above. This phenomenon, which was somewhat unexpected, can hardly be explained by a direct negative inotropic effect of GH. A positive correlation between the LVS and the systolic blood pressure suggests the tentative explanation that the improvement of the lean body mass, due to the therapy, may explain the reduction of the peripheral resistance. A prospective study is in progress.

Growth, Growth Factors, GH Therapy

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ADVANTAGES OF THE COMPUTER-AIDED IMAGE ANALYSIS SYSTEM FOR ESTIMATING TW SKELETAL MATURITY: INCREASED RELIABILITY AND A CONTINUOUS SCALE. J.M. Tanner, R.D. Gibbons, and R.D. Bock, University of London, University of Illinois at Chicago, University of Chicago.

The two major problems besetting the Tanner-Whitehouse estimation of skeletal maturity (as also the Greulich-Pyle) are (1) low inter-observer reliability and (2) a discontinuous scale, so that a change of rating results in a jump in bone age. To solve these problems we designed an image analysis system producing bone-age estimates automatically. The radiograph is placed under an imaging camera and an operator brings each bone to overlay a template displayed on the screen. The bone is digitized and a degree 64 two-dimensional Fourier transformation is obtained, giving a coefficient matrix characterizing that bone. This matrix is compared with the average matrix for each stage of the bones of the "Golden Series", the radiographs rated by the originators of the TW method. Distances between these matrices comprise a quantitative scale of measurement so *stage scores* are generated which run continuously from 0.0 to 9.0. Longitudinal analysis of radiographs of the Harpenden Growth Study shows the smooth increase of score in the computer-aided system compared with the stepped increase obtained manually. Between operator reliability much exceeds that of the manual system; in 300 comparisons whole-stage differences occurred twice compared to the 30 times expected of human operators. The average inter-observer difference was one-third of a stage. Validity is high; the average difference from the Golden Series standards was 0.3 stage. We conclude that the computer-aided method renders manual methods of assigning bone age obsolete. We thank Ares-Serono for support.

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GROWTH IMPAIRMENT AND DELAYED PUBERTY IN THALASSEMIA. M. Caruso-Nicoletti, M. Mancuso, G. Spadaro, D. Lo Presti, V. Panebianco, G. Reitano, Department of Pediatrics, University of Catania, Catania, Italy.

Children affected by thalassemia major frequently present growth disturbances. To investigate the role of delayed sexual development in the growth impairment associated with thalassemia, we studied 29 patients (age range 10.7-19.5 years) with short stature (< 3rd centile), reduced growth velocity (< 10th centile) and delayed bone age. All patients were under regular transfusion and chelation therapy according to standard protocols. Growth hormone (GH) secretion was evaluated by peak GH response to arginine-insulin. Results are shown in the Table . Patients were divided in subgroups based on bone age, pubertal status and whether they had been submitted to sex steroid priming. Patients in group 4) where tested both before and after priming. Patients in group 5) were already on sex steroid treatment. Responders are patients who exhibited a peak GH level > 10 ng/ml at least to 1 stimulus.

PATIENTS	N°	NON RESPONDERS	RESPONDERS
B.A. < 10 yrs	2	-	2
B.A. > 10 yrs	27		
1) puberal	3	-	3
2) priming	7	-	7
3) no priming	3	3	-
4) no priming/priming*	2	2	2*
5) sex steroid therapy	12	1	11

We have treated twelve patients belonging to groups 2) and 5) for 6-21 months (mean 11±4) with sex steroid in the attempt to increase growth velocity and induce puberty. Treatment consisted of monthly injection of 50-100 mg of testosterone enanthate for boys and transdermic estrogens (0.025-0.05 mg/die) for girls. We observed a significant increase of growth velocity during treatment (2.6±0.8 cm /yr vs. 6.1±1.3 cm/yr; P <0.01); bone age advanced from -2.6 to -1.7 SDS. These data suggest that GH deficiency is not frequent among short thalassemic patients and when present is mainly due to delayed puberty; in addition sex steroids therapy is effective in inducing a significant growth acceleration in these patients.

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A NEW TYPE OF INHERITED GROWTH HORMONE DEFICIENCY: A COMPOUND HETEROZYGOTE OF A 6.7 KB DELETION, INCLUDING THE GH-1 GENE, AND TWO BASE DELETION IN THE THIRD EXON OF THE GH-1 GENE. Y. Igarashi[1)], T. Kamijo[2)], M. Ogawa[3)], Y. Nishi[4)], N. Iwatani[5)], H. Kono[6)], T. Masumura[7)] and J. Koga[7)], 1)Department of Pediatrics, Tohoku University, Sendai 980, Japan, 2)Nagoya National Hospital, 3)Department of Pediatrics, Nagoya University, 4)Hirosima Red Cross Hospital, 5)Department of Child Development, Kumamoto University, 6)Fukuoka Children's Hospital, 7)JCR Pharmaceuticals Co., Ltd. Kobe, Japan

The genomic DNA in a patient with severe growth retardation was analysed and a new type of mutation, a compound heterozygous mutaion, was found in her GH-1 gene. The patient was a 13 years old girl, a first child of unrelated parents and born by normal delivery. She had been diagnosed as growth hormone deficiency at the age of 8 years 11 months. Her height and weight were 86.1 cm (-7.8SD) and 10.2 kg (-3.4SD), respectively. She has been treated with exogenous hGH successfully over years without producing antibody against hGH by now. The genomic DNA of this patient and her parents were analyzed by polymerase chain reaction followed by restriction enzyme digestion as reported by Vnencak-jones et al. and the existence of 6.7 kb deletion including whole GH-1 gene was found in one allele of the patient and her father but not in her mother. The sequence analysis of this family revealed the 2 bp deletion in exon 3 of GH-1 gene in the patient and her mother but not in her father. A termination codon at the position of amino acid residue 132 in exon 4 was assumed to be introduced through this mutation. These results might suggest the new type of inherited GH-1 gene deficiency caused by heterozygous mutation in GH-1 gene.

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CAN BIOCHEMICAL MARKERS PREDICT RESPONSE TO GROWTH-PROMOTING TREATMENTS IN SHORT NORMAL CHILDREN?
P.M. Crofton[1], E. Schönau[2], H.F. Stirling[1] and C.J.H. Kelnar[1], [1]Royal Hospital for Sick Children, Edinburgh EH9 1LF, U.K. and [2]Children's Hospital, University of Cologne, D-5000 Köln 41, Germany.

Early prediction of response to growth-promoting treatments in children is needed so that ineffective treatment may be discontinued at an early stage. We have evaluated a number of biochemical markers for their ability to predict growth response in 33 short, healthy, prepubertal children. Treatments (for which ethical approval was given) were as follows: placebo growth hormone (4 children), growth hormone alone (18), oxandralone alone (4), growth hormone and oxandralone combined (7). We measured total alkaline phosphatase (ALP), bone ALP (by lectin affinity electrophoresis), procollagen type I propeptide (PICP) and procollagen type III propeptide (PIIIP, both by radioimmunoassay) at entry to the study, and after 3 months of treatment. Height velocity was recorded at entry to the study and after one year. In the placebo group, there was little change in any of the markers after 3 months, nor in height velocity after one year ($p > 0.1$, paired t-test). In each of the other treatment groups, significant increases in all four markers occurred at 3 months, and in height velocity at one year ($p < 0.05$, paired t-test). For all treatment groups combined, the increment in each biochemical marker at 3 months was significantly correlated ($p < 0.01$) with the increment in height velocity found after one year; the best overall predictor of response was bone ALP ($r = 0.70$). Within the group treated with growth hormone alone, PIIIP was the best predictor of growth response ($r = 0.52$, $p < 0.05$); pre-treatment height velocity was of little value ($r = -0.29$, $p > 0.05$). We conclude that biochemical markers of growth can successfully predict response to growth-promoting treatments in children.