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LONG-TERM EFFECTS OF GROWTH HORMONE, ESTROGEN, OR PLACEBO ON SELF-IMAGE AND BEHAVIOR IN TURNER SYNDROME. J.L.Ross, E. McCauley,L. Freund, and G.B. Cutler,Jr.,Dept. of Ped, The Medical College of PA, Phila, PA and DEB/NICHD/NIH, Bethesda, MD, USA.

Girls with Turner syndrome (TS) are short and lack endogenous estrogen. Our aim in this study was to evaluate the behavioral effects of continuous growth hormone (GH), ethinyl estradiol (E), or placebo (P) treatment in TS girls. Subjects were recruited from an ongoing randomized trial, consisting of 4 TS treatment groups: 1.E (25-50 ng/kg/day until age 12,100 ng/kg, ages 12-14, 200-800 ng/kg/day above 14), 2. GH (0.1 mg/kg, SQ, tiw), 3. E, as above, plus GH, and 4. P until age 12, followed by E, as above. The psychological assessment (at baseline and yearly intervals) included 2 tests: The Child Behavior Checklist (CBCL), a parental report of social and behavior problems, and the Piers-Harris Self-Concept Scale (child reported), a test of overall self-concept. Results were analyzed from 106 girls with TS, ages 5-16 years, with treatment durations of 0-5 years. Baseline karyotype, age, SES level,and growth rate were similar in all 4 groups. Multiple regressions explored the association between treatment group, duration, and the psychological measures for TS girls treated early (prior to age 11.5) or late (after age 11.5). In the early-treated girls,no associations between type or duration of treatment and the psychological measures were revealed. In the late-treated girls,longer E treatment was associated with improved ratings on the Piers Total self-concept scale (p=.0001). Longer GH treatment was associated with more positive ratings on the intellectual and physical subscales (p=.0001). On the CBCL,longer GH treatment was associated with decreased, negative Internalizing and Externalizing (p=.004) behaviors and improved school functioning (p=.0001). We conclude: (1) for early-treated TS girls,treatment with E,GH,or P had no significant effects on the behavioral variables and (2) for late-treated TS girls,both E and GH treatment was associated with improved behavioral outcomes.

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THE AGE DETERMINANT IN THE PREDICTED HEIGHT (HP) GAINED DURING GH THERAPY.

GH therapy has been reported to accelerate growth, but also to expedite bone maturation and pubertal development. The present study was undertaken to evaluate the effect of these changes on HP, and it's relationship with the child's age. Sixty-five male patients with GH-deficiency, age range of 3.1-17.7 yr (11.3±3.2[SD]), were treated with hGH (0.3 mg/kg/wk), and completed 3 years of therapy. Of these, 33 were diagnosed by subnormal pharmacological tests, and 32 by low 24-hr profiles. HP were calculated annually by the TW-II, Roche, and Bailey-Pinneau methods. The advancement of bone maturation, calculated as [δ-bone age / δ-chronological age], as well as the pace of pubertal development, calculated as δ-Tanner stage over 3 years of therapy, correlated positively with age ($p<0.001$). Best-fit correlations and plots of age at outset of therapy [O-age] against the gained (or lost) HP for the 1st, 2nd or 3rd years of therapy, revealed insignificant correlations for the first 9.6-9.8 years of life, with mean gained HP of 4.5, 3 and 2.1 cm resp. With further increase in O-age δ-HP declined, with x-intercepts (δ-HP=0) at 12.6, 12.1 and 11.8 years of O-age, resp. (13.6, 14.1 and 14.8 actual [A] age, resp). The mean over-all 3 years gained HP was 7.9 cm for O-age 3.1-10.1 years, declining in older children to 0 cm at 13.1 years O-age (mean 16.1 years A-age), and to lost HP in older children. It is concluded that hGH therapy of GH-deficient children with this dose results in effective HP gain over the first decade of life, with decreasing efficacy thereafter, due to advancement of puberty and bone age and HP loss after the O-age of 13.1 years (A-age 16.1 yr).

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REGULATION OF THE GH-RECEPTOR (R) / BINDING PROTEIN (BP) BY GH PULSATILITY

GH secretion is pulsatile in man and in every mamalian species that has been so far studied. The magnitude of pulses, their frequency and their regularity vary. The R on it's part, undergoes cycles of internalization and recycling, which are in synchrony with the frequency of GH pulses. The present study correlated GH profiles with GH-R and GH-BP human and animal in the course of ontogenesis, effects of short stature, fasting, anorexia nervosa, obesity, diabetes, GH-therapy, acromegaly and cirrhosis. In short, slowly growing children GH-BP correlated negatively with mean GH-pulse amplitude and integrated concentration. GH pulsatility is high in newborns, fasting, anorexia nervosa, diabetes, acromegaly and cirrhosis. GH-BP is low in all these conditions. GH pulsatility is low, and GH-BP is high, in GH-therapy and obesity. Negative correlation of GH pulsatility with GH-BP exists across the mammalian class, with increasing pulsatility in rabbit < man < female rat < male rat < guinea pig, whereas GH-BP levels and liver membrane's GH-R decrease in the same order. Newborn rats have high GH pulsatility and low GH-R and GH-BP, whereas obese rats have low GH levels and high GH-receptors. It is concluded that the pattern of GH profiles is the major determinant of the GH-R / GH-BP, that the various physiological and pathological conditions regulate primarily the pattern of GH pulsatility, which, in turn, regulates the GH-R / GH-BP, and thereby exert the specific effects on target cells to promote or to suppress growth, or to express distinct metabolic actions.

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SEASONAL VARIATION IN GROWTH RATE OF CHILDREN TREATED WITH BIOSYNTHETIC GROWTH HORMONE. C.M. Tiwary, E.S. Lightner, K.M. Connelly, K. M. Attie and the National Cooperative Growth Study (NCGS), Brooke Army Medical Center, San Antonio, TX, University of Arizona, Tucson, AZ, and Genentech, Inc., So. San Francisco, CA.

Seasonal variation in growth rate is documented in normal children, however conflicting reports have been published regarding children treated with growth hormone (GH). We analyzed the growth rate of children who were treated with GH and enrolled in the NCGS for GH deficiency or idiopathic short stature. Only pre-pubertal children (males ≤11 y.o., females ≤10 y.o.) were included. Two-thirds of the data points were for male patients. A growth rate was assigned to a season based on the month in which the midpoint of the interval fell. Winter was defined as the 3 months of December, January, and February, and so on for the other 3 seasons. The table below shows seasonal growth rate by latitude [mean±SD, (n)]:

		Winter	Spring	Summer	Fall
Northern	Yr 1	8.6±3.8 (26)	8.9±3.7 (32)	10.3±4.0 (29)	9.3±4.6 (27)
Latitudes	Yr 2	6.0±3.3 (29)	8.1±3.1 (30)*	8.8±3.7 (28)*	7.7±3.3 (36)*
Southern	Yr 1	9.2±3.7 (52)	9.9±3.8 (55)	9.2±3.3 (49)	8.8±3.3 (50)
Latitudes	Yr 2	7.3±3.2 (39)	8.7±2.5 (44)**	7.7±3.2 (40)	6.9±2.8 (39)

*$p<0.05$ vs winter **$p<0.05$ vs fall

An analysis of variance for year 2 showed no interaction between seasonal growth and either dosing schedule or sex, although each of these factors had a significant effect on the growth rate individually. CONCLUSIONS: As noted for normal children, those treated with growth hormone also show seasonal variation in growth rate, suggesting that factors other than circulating growth hormone concentrations are related to variations in growth rate.

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A MATHEMATICAL MODEL DESCRIBING CATCH-UP GROWTH IN CELIAC DISEASE. B.Boersma and J.M. Wit, Department of Pediatrics, Division of Endocrinology, Wilhelmina Children's Hospital, Utrecht University, The Netherlands

The phenomenon of catch-up growth (CUG) is well known, but still poorly understood. One of the best examples of CUG is the growth pattern after the institution of a glutenfree diet in children with celiac disease (CD). Treatment leads in almost all cases to complete catch-up growth within 2 years. Therefore, the pattern of CUG during adequate treatment of CD may be considered as a model for optimal catch-up growth in children treated with any form of therapy for any growth disturbance. In order to describe this pattern mathematically, we analysed growth data of 17 CD patients who showed growth retardation before therapy and completed CUG before the start of puberty. Two subgroups were formed on the basis of the initial height standard deviation score (HSDS). Nonlinear regression analysis of the individual growth data expressed as HSDS (corrected for parental height SDS) was carried out using a monomolecular growth function. For each subgroup an equation was found from which the expected HSDS at any given moment($HSDS_t$) can be calculated:

Group 1 ($HSDS_i \leq -1.5$) (n=9) $HSDS_t = 4.5 * (1 - 0.42 * e^{-1.05 * t}) - 5$

Group 2 ($-1.5 < HSDS_i \leq 0$) (n=8) $HSDS_t = 5.4 * (1 - 0.28 * e^{-0.66 * t}) - 5$

Graphical representation of these equations shows that group 1 undergoes a relatively quick CUG which stabilizes at -0.5 SDS after two years of therapy. Group 2 catches up at a lower rate and stabilizes one year later, but reaches a higher endpoint at +0.4 SDS. These equations provide the clinician with a reference instrument for assessing the efficacy of a growth promoting therapy.

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LONG-TERM GROWTH RESPONSE TO GROWTH HORMONE (GH) TREATMENT IN GH DEFICIENT MEDULLOBLASTOMA (PNET) SURVIVORS. T Moshang, Jr., D. Gruccio, Anna Carmargo and J. Goldwein. The Children's Hosp of Phila, The Univ of Pa Dept of Ped, Phila, Pa.

The present therapeutic modality of combining radiation and chemotherapy to treat PNET patients cause significantly worse growth than radiation alone in PNET survivors. Unlike previous reports focused upon growth response to GH treatment following cranio-spinal irradiation, we evaluated the growth response to GH treatment (Rx) in 16 GH deficient PNET pts treated with radiation and chemotherapy and compared their response to 29 pts with idiopathic GH deficiency (IGHD). The GH treatment was identical, using recombinant GH at a dose of 0.04 mg/kg/daily subcutaneously. The mean duration of time from diagnosis of PNET to GH Rx was 4.2 (+/- 1.6) yrs. Growth response to GH is presented as a velocity standard deviation score (Z) with SD in brackets.

Group	PreRx Vel Z	Yr1 Vel Z	YYr2 VelZ	Yr3 Vel Z
PNET	-3.6 (1.9)	1.7 (2.2)	1.4 (2.7)	2.2 (0.7)
IGHD	-1.5 (2.1)	5.0 (2.9)	2.15 (3.1)	1.9 (1.4)

The pre-Rx height (Ht) Z score was greater in the PNET pts than IGHD pts, but the pre-treatment growth velocity was significantly worse. The PNET pts demonstrated a significantly poorer response to GH in the first year as compared to IGHD, unlike previous reports. Although PNET pts, as a group, continued to show positive growth velocity Z scores, Ht Z scores (as shown by others) did not increase significantly. Growth response was not correlated to age at diagnosis of PNET, nor to age at GH Rx, nor to duration between diagnosis and initiation of GH Rx. Crown-rump measurements would indicate that impaired spinal growth does not account for the modest response to GH during the first year. A possible explanation is that chemotherapeutic agents can, in certain circumstances, cause relative insensitivity to growth factors.