224

CATCH-UP GROWTH IS INTRINSIC TO THE EPIPHYSEAL GROWTH PLATE. J. Baron, K.E. Oerter, J.A. Yanovski, J.A. Novosad, J.D. Bacher, G.B. Cutler, Jr., Developmental Endocrinology Branch, NICHD, NIH, Bethesda, MD 20892, USA.

Catch-up growth is believed to result from a central nervous system mechanism that compares actual growth to a set point and adjusts growth velocity accordingly. Alternatively, we hypothesized that catch-up growth is intrinsic to the growth plate. To test this hypothesis, we infused dexamethasone phosphate for 4 weeks directly into one proximal tibial growth plate of 5-week old rabbits and infused vehicle into the contralateral growth plate. Growth velocity at each tibial growth plate was determined radiographically. Dexamethasone decreased the growth velocity of the treated growth plate by 37 ± 8 % (mean ± SEM, $p < 0.01$) compared to the control, causing a growth deficit of 4.8 ± 1.2 mm ($p<0.01$). After the end of the infusion, the growth velocity of the dexamethasone-treated growth plate rebounded above that of the control and ultimately corrected 52 ± 10 % of the deficit ($p<0.01$). Because the catch-up growth occurred solely within the dexamethasone-treated growth plate, we conclude that catch-up growth is intrinsic to the epiphyseal growth plate and cannot be explained by a systemic mechanism.

225

THYROID FUNCTION IN NON-GH-DEFICIENT SHORT CHILDREN DURING A PLACEBO-CONTROLLED DOUBLE-BLIND TRIAL OF GH THERAPY.

G.M.Leong, S.R.Rose[1], K.M.Barnes, G.B.Cutler Jr. & the DEB GH Study Group, NICHD, NIH, Bethesda, MD, 20892, [1]U. Tennessee. Memphis, TN, 38103, U.S.A.

Growth hormone (GH) therapy has been reported to cause changes in thyroid function in GH deficiency including decreases in T4 and TSH and an increase in T3. We sought to determine if GH therapy alters thyroid function in non-GH-deficient short children. Twenty-two children (19 boys) were followed for 12 months while receiving either GH (Humatrope, Eli Lilly) 0.074mg/kg t.i.w. s.c. (n=10) or placebo (n=12). Total T4, free T4, T3 and TSH were measured every 3 months and in 13 children also at 1 and 2 months. A TRH test and nocturnal TSH surge were performed at baseline and 6 months in 19. There were no significant clinical differences at baseline between the placebo and GH groups. The results below are mean (SD).

	Months	0	1	2	3	6	12
T4	Placebo	8.3 (1.3)	8.0 (1.1)	8.3 (1.1)	7.6 (1.2)	8.1 (1.4)	7.4 (1.6)
(ng/dL)	GH	7.4 (1.2)	8.4 (1.3)	8.1 (1.6)	8.0 (1.5)	7.4 (1.5)	7.2 (1.3)
Free T4	Placebo	1.3 (0.2)	1.4 (0.2)	1.4 (0.2)	1.2 (0.2)	1.4 (0.2)	1.2 (0.1)
(pg/mL)	GH	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)	1.2 (0.1)	1.3 (0.2)	1.3 (0.1)
T3	Placebo	181 (31)	170 (20)	177 (24)	171 (12)	162 (22)	175 (42)
(ng/dL)	GH	157 (21)	179 (12)	183 (22)	184 (24)	165 (22)	179 (31)
TSH	Placebo	2.8 (0.8)	2.2 (0.8)	2.2 (0.7)	2.6 (0.9)	1.8 (0.6)	3.1 (0.9)
(uIU/mL)	GH	2.5 (1.5)	1.8 (1.5)	1.9 (0.8)	1.8 (1.1)	2.8 (1.7)	2.2 (1.3)

There were no significant differences between the two groups in any of the above measurements or in TSH response to TRH or in nocturnal TSH surge. We conclude that GH therapy over 12 months does not alter thyroid function significantly in non-GH-deficient children.

226

LINEAR GROWTH IN THE RABBIT IS CONTINUOUS, NOT SALTATORY. K.E. Oerter, J.D. Bacher, G.B. Cutler, Jr., J. Baron, Developmental Endocrinology Branch, NICHD, NIH, Bethesda, MD 20892

A recent report (Science 258:801) suggests that human growth occurs in brief bursts separated by extended periods of stasis. We tested this hypothesis in an animal model in which growth rate could be measured with greater accuracy than that achieved in the human. Metal pins were inserted into the bone immediately adjacent to the proximal tibial and distal femoral growth plates of 6-week old rabbits. Growth rates were determined by measuring the change in distance between pins on serial radiographs taken daily for 10 days. All measurements were made in quadruplicate by an observer blinded as to the day and animal number. The error of measurement was small (0.05 mm/d) compared to the mean growth rate (0.27 mm/d). The individual growth curves revealed continuous growth. To analyze statistically the pattern of growth, we examined the frequency distribution of daily growth velocities. The model of saltation and stasis predicts a majority of daily growth velocities clustered around zero, and a minority of high daily growth velocities. The pattern we observed was significantly different ($p<0.001$), showing instead a single Gaussian distribution about an intermediate growth velocity, indicating continuous growth. We conclude that linear growth in the rabbit is continuous, not saltatory.

227

TREATMENT OF A BOY WITH GROWTH HORMONE INSENSITIVITY SYNDROME WITH rhIGF-I AND LHRH ANALOG. D.R. Counts, M.D., and G.B. Cutler, Jr., M.D., Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA.

To determine the effect of rhIGF-I treatment plus LHRH analog on growth velocity and bone maturation in a pubertal patient with growth hormone insensitivity syndrome (GHIS), we treated an 18.5-year old mid-pubertal boy with GHIS with rhIGF-I 100 ug/kg twice daily plus LHRH analog (deslorelin) 4 ug/kg/day. Pretreatment height was 111.2 cm (-10 S.D.), growth rate was 4.1 cm/year, bone age 14.5 years, peak plasma LH 32.1 IU/L, peak FSH 7.2 IU/L and testosterone (T) 342 ng/dL. Serum IGF-I increased from an undetectable level at baseline to 108 ng/mL at 1 h post administration. GH secretion, measured q 30 min for 24 h, was suppressed from 1 h to 12 h post IGF-I administration. IGFBP-3 was unchanged. After three months of therapy, growth rate had increased from 4.1 to 8.7 cm/year, bone age was unchanged, gonadotropins were suppressed by the deslorelin, and T had fallen from 342 to 53 ng/dL. We conclude that rhIGF-I therapy in combination with LHRH analog can increase growth rate in pubertal patients with GHIS. Longer follow-up is needed to assess the long-term outcome of rhIGF-I plus LHRH analog treatment on growth velocity, and bone age advancement, and adult height.

228

THE RELIABILITY OF TWO METHODS TO PREDICT ADULT HEIGHT IN 132 TALL GIRLS. N.M.Drayer and L.Cox. Dept.of Paediatrics,Univ.of Groningen,9713 EZ Groningen,the Netherlands and Institute of Child Health, Univ.of London,London WC1N 1EH, England.

How reliable is the ultimate height prediction (UHP) for tall girls? 78 Girls who were pre-menarcheal (pre-m) and 54 who were post-menarcheal(post-m) when initially measured during childhood, had their adult heights measured. All girls were then aged more than 17 years. They had all chosen not to receive treatment on the basis of the UHP.Height was measured according to the same standardised techniques using Harpenden stadiometers. X-rays of the left hand were assessed according to Greulich-Pyle (G-P) and Tanner-Whitehouse TWII RUS (RUS). For the UHP the Bailey-Pinneau (B-P) and the Tanner-Whitehouse method for tall girls (TW) were used.

		pre-m (mean ±SD)	post-m (mean ±SD)
initial age	(yrs)	12.6 ±1.1	13.7 ±1.4
initial height	(cm)	174.1 ±5.0	177.4 ±5.2
skeletal age G-P	(yrs)	12.6 ±0.6	13.7 ±0.9
RUS	(yrs)	13.1 ±0.5	14.0 ±0.9
UHP B-P	(cm)	184.8 ±4.1	183.1 ±4.4
TW	(cm)	183.6 ±3.9	182.0 ±4.7
Adult age	(yrs)	20.4 ±2.4	21.7 ±2.7
Adult height	(cm)	184.5 ±3.6	182.4 ±4.2

B-P overpredicted more than 5.08 cm (2") for 4 pre-m and 2 post-m girls, TW for 2 pre-m girls. B-P underpredicted more than 5.08 cm for 6 pre-m girls, TW for 11 pre-m and 1 post-m girl. The adult height for tall Dutch girls as a group can be predicted using methods developed more than 30 years ago for the USA and UK populations.

229

INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 3 (IGFBP-3) CONCENTRATION IN CEREBROSPINAL FLUID (CSF) OF CHILDREN WITH BRAIN TUMORS OR LEUKEMIA. H.L.Müller, Y.Oh, S.E.Gargosky, R.L.Hintz, R.G.Rosenfeld, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA 94305, USA

The major IGFBPs in CSF are IGFBP-2 and IGFBP-4, whereas IGFBP-3 is a minor component in CSF of healthy subjects. We investigated IGFBP-3 levels in CSF from patients with brain tumors, leukemia or meningitis. IGFBP-3 was measured by radioimmuno-assay with αIGFBP-3g1, a rabbit polyclonal antibody. Further, as proteolysis of IGFBP-3 is part of the modulation of IGF activity IGFBP-3 fragmentation was quantified by densitometric analysis of [^{125}I]IGFBP-3 protease assays. We examined CSFs of 24 children with malignant brain tumors, 18 children with leukemia and 13 children with meningitis. CSFs of 38 children, who received a lumbal puncture in order to exclude meningitis, were used to define a normalative range for IGFBP-3 concentration and IGFBP-3 protease activity in normal CSF. Elevated IGFBP-3 concentrations were found in CSF of 17 of all 24 (71%) brain tumor patients and 7 of 8 (87%) brain tumor patients who had microscopically detectable malignant cells in CSF. 13 of 14 (93%) patients with medulloblastoma or ependymoma and all 7 medulloblastoma/ependymoma patients with malignant cells in CSF had elevated IGFBP-3 concentrations in CSF. IGFBP-3 protease activity in CSF was elevated in 15 of 17 (88%) patients with histological high grade (WHO III°/IV°) brain tumors. 5 of 6 (83%) patients with acute leukemia and microscopically detectable malignant cells in CSF at the time of diagnosis showed elevated IGFBP-3 concentrations in CSF that normalized under chemotherapy. Leukemia patients without any detectable malignant cells in the CSF had normal IGFBP-3 concentrations in CSF. We conclude that in CSF of children with high grade malignant brain tumors or CNS leukemia, IGFBP-3 is elevated. We hypothesize that this phenomenon could be caused by local production of IGFBP-3 by the brain tumor tissue and secretion into CSF or by local secretion of IGFBP-3 by malignant cells that spread into CSF. This hypothesis is supported by the observation that only 2 of 13 (15%) meningitis patients had slightly elevated IGFBP-3 concentrations in CSF while high numbers of non malignant inflammatory cells were present in all cases. Further studies will analyse the origin of elevated IGFBP-3 levels in CSF of tumor patients and will show whether these findings are of diagnostic or prognostic value.