

Long-Term Growth in Juvenile-Acquired Hypothyroidism: The Failure to Achieve Normal Adult Stature

Hypothyroidism was diagnosed and treated in 18 girls and six boys with a mean age of approximately 10.5 years and a mean bone age of 6.1 years. At diagnosis, heights were 4.05 ± 0.5 standard deviations (SD) and 3.15 ± 0.5 SD below the 50th percentile in girls and boys, respectively. Prior to deceleration of growth the mean height of all patients was less than ± 0.3 SD from the 50th percentile. The bone age at diagnosis closely matched the age at which deceleration of growth began, which suggests that the bone age at diagnosis corresponds well with the onset of severe hypothyroidism. L-thyroxine was given at 3.4 ± 0.3 $\mu\text{g}/\text{kg}/\text{day}$ for treatment. Serial bone age determinations were available in most cases.

Mature heights were 2.1 ± 0.2 SD below the 50th percentile. Differences between the predicted mature heights and the actual mature heights were 7.7 ± 6.0 cm and 6.7 ± 5.5 cm for females and males, respectively. The loss occurred primarily in the first 18 months of treatment and correlated significantly with the duration of hypothyroidism and the height SD at diagnosis. There was no correlation between the loss in mature height and the

chronologic, height, or bone ages at diagnosis.

The authors demonstrated that catch-up growth is incomplete after treatment of long-standing juvenile hypothyroidism. In brief, these patients rarely achieve their full genetic growth potential. The authors conclude that the possible etiologies for this deficit include: (1) overtreatment; (2) prolonged hypothyroidism, which diminishes the potential for catch-up growth; and (3) puberty coinciding with initiation of therapy, which results in completion of skeletal maturation prior to the completion of catch-up growth.

The thyroid function tests did not indicate overtreatment. Loss in predicted height during the first 18 months of treatment occurred in children who did not exhibit pubertal changes. The authors suggest that multiple factors may be involved but a delay in therapy is a critical factor in limiting catch-up growth that underscores the need for early recognition of hypothyroidism.

Rivkees SA, Bode HA, Crawford JD. *N Engl J Med* 1988;318:599-602.

Editor's comment—Failure to

reach expected adult heights in patients with prolonged juvenile hypothyroidism has been apparent to most pediatric endocrinologists but data documenting its occurrence and extent have been lacking. Rivkees et al have provided us with those data, thereby permitting postulations that can be tested to be made. They are to be congratulated for their contribution.

The decision to be made now is what to do for the next patient with prolonged hypothyroidism so that he or she can achieve the height inherent in his or her genetic potential. I would use a lower dose of thyroxine than that used by the authors, as 3 $\mu\text{g}/\text{kg}/\text{day}$ in older children may be more than is necessary to attain a euthyroid state. Alternative approaches might include the use of an analogue of leutinizing-hormone-releasing hormone(a) to block puberty and/or the addition of growth hormone. These latter approaches, if chosen, should be used within rigid protocol guidelines and, therefore, should not be considered by most of us unless we are willing and able to establish and follow such a protocol.

Robert M. Blizzard, M.D.

Mechanism of the Adolescent Growth Spurt Induced by Low-Dose Pulsatile GnRH Treatment

Stanhope et al studied growth velocity and growth hormone (GH) secretion in 14 females and 12 males with pubertal delay during treatment with gonadotropin-releasing hormone (GnRH). The findings were then related to stages of sexual development. All 26 patients in this study had puberty delayed by two standard deviations or had puberty arrested for at least 18 months. The mean ages were 16.4 years for girls and 16.8 years for boys.

GnRH was administered subcutaneously in a pulsatile fashion via pump. Initially, GnRH was administered only at night to mimic the normal nocturnal pattern of gonadotropin secretion in early puberty. However, when girls attained breast stage 3 and boys attained a testicular volume of 8 mL, pulsatile GnRH was administered over the 24 hours of each day. The duration of treatment averaged 1.05 years in both boys and girls.

Serum GH levels were sampled every 15 minutes between 8 P.M. and 6 A.M. prior to the initiation of the study, at 1- to 3-month intervals throughout the study, and 1 month

after the cessation of treatment. GH profiles were analyzed using the PULSAR computer program. GH pulse frequency, the sum of the GH peaks, and the area under the GH pulses were calculated for each overnight GH profile, and then correlated with breast stage in girls and mean testicular volume in boys.

Twenty-four patients responded to pulsatile GnRH treatment with the normal sequence of sexual maturation. Peak growth velocity occurred between breast stages 2 and 3 in girls; GH secretion was increased at stage 2 but was significantly increased with its peak value at stage 3. GH secretion de-

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creased at the attainment of stage 4, after which it was altered cyclically depending on the stage of the menstrual cycle. There were no significant changes in GH pulse frequency.

In boys who responded to pulsatile GnRH treatment, there was an initial significant fall in the sum of GH peaks and in the area under the GH pulses with the onset of treatment, although testicular volume increased to 5-6 mL and virilization was initiated. A rapid increase in growth rate occurred at a testicular volume of 9-10 mL and reached a peak value between 11 and 15 mL. Peak height velocity (between 11 and 12 cm per year) coincided with peak GH secretion. The mean change in GH secretion demonstrated a pattern similar to the change in growth velocity. Se-

rum testosterone concentrations rose progressively throughout puberty, with no dramatic rise at the onset of the growth spurt.

Based on their study findings, the authors suggest that the mechanism of increased GH secretion is not due solely to sex steroid secretion, since testosterone secretion and virilization in boys occurs during early puberty while the growth rate and GH secretion continues to decelerate. They suggest that the level of testosterone achieved at a testicular volume of 10 mL may be important in the etiology of the increase and amplitude of the GH pulses. They also suggest that there may be an interaction between GnRH and somatotroph function.

Stanhope R, Pringle P, Brook C. *Clin Endocrinol* 1988;28:83-91.

Editor's comment—This study adds important information to the understanding of the mechanism

and timing of growth acceleration in puberty and the relationship to testicular volume and serum testosterone. Unfortunately, serum testosterone values are not reported in this paper. Others have demonstrated the relationship between testosterone and the increase in GH secretion and have demonstrated that testosterone increases mean GH secretion and the amplitude of GH pulses in prepubertal boys. The authors of this article have presented longitudinal data on a small group of patients, half of whom were later determined to have hypogonadotropic hypogonadism and half to have constitutional delay of puberty. They correctly point out that there are no longitudinal data available on physiologic GH secretion during normal puberty with which to compare their findings. Such studies should shed further light upon the mechanism of growth acceleration during puberty.

William L. Clarke, M.D.

Diagnosis of GH Deficiency and GH Treatment

The availability of recombinant growth hormone (GH) has directed much attention to the diagnosis and treatment of GH deficiency (GHD). Rose et al of the NIH recently published in the *New England Journal of Medicine* an extensive analysis comparing the use of pharmacologically stimulated GH levels with spontaneous GH secretion—as determined by the GH levels over 24 hours—to diagnose GHD.

Three pharmacologic stimuli were used in 54 children with severe short stature. In 23, all GH values were ≤ 7 ng/mL, and these children were classified as GH-deficient on this basis. These results were compared with the mean integrated GH concentrations (ICGH). All 31 children who responded to pharmacologic tests with values >7 ng/mL had ICGH

values in the range found in 46 normal-statured prepubertal children. Therefore, the authors conclude that no additional patients with GHD were detected and that the timely and costly measurement of ICGH in short children is of little diagnostic value.

The correlation between the results of the pharmacologic tests and ICGH levels in the GHD patients was poor, as only 57% of the 23 patients had ICGH levels below the range found in the 46 controls. Therefore, the authors recommend that the use of pharmacologic stimuli is sufficient to diagnose GHD.

The authors explain that the inclusion of more appropriate control subjects accounts for the discrepancy between their studies of ICGH with those of others. They postulate that the 43% of children with GHD, who had ICGH levels in the lower 20% of normal range, were children who require a higher GH level than most to grow nor-

mally; some defect reduced the spontaneous secretion of GH until it was in the lower normal range, and the defect was revealed after pharmacologic testing. Rose et al readily point out that further studies are indicated to determine how to best diagnose GHD.

They also report that the ICGH levels in the 46 controls did not correlate significantly with age, sex, height, weight, insulin-like growth factor (IGF-I) level, or growth velocity for age, although the IGF-I levels in the 31 short children without GHD were between the values seen in controls and GHD children.

In an editorial in the same journal, Grumbach addressed the use of GH therapy in GHD and short stature. He states that the criteria of Rose et al for the selection of short children for treatment with GH was rigidly defined and straightforward.

In the past, treatment was restricted to children with growth