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Determinants of Growth during Gonadotropin-Releasing Hormone Analog Therapy for Precocious Puberty

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In children with precocious puberty (PP), treatment with GnRH analogs (GnRHa) often decreases height velocity below normal. Based on previous animal studies, we hypothesized that this impaired growth is due to excessive advancement in growth plate senescence induced by the prior estrogen exposure. This hypothesis predicts that the height velocity during treatment will be inversely related to the severity of prior estrogen exposure.

We analyzed data from 100 girls (age, 5.8 ± 2.1 yr; mean ± SD) with central PP who were treated with GnRHa. During GnRHa therapy, height velocity was low for age (−1.6 ± 1.7 SD score; mean ± SD). The absolute height velocity correlated most strongly with the bone age (BA), which we used as a surrogate marker for growth plate senescence ($r = -0.727$, $P < 0.001$). The severity of the growth abnormality (height velocity SD score for age) correlated inversely with markers of the severity of prior estrogen exposure, including duration of PP ($r = -0.375$, $P < 0.001$), Tanner breast stage ($r = -0.220$, $P < 0.05$), and BA advancement ($r = -0.283$, $P < 0.01$). Stepwise regression confirmed that BA was the best independent predictor of growth during GnRHa therapy.

The findings are consistent with our hypothesis that impaired growth during GnRHa therapy is due, at least in part, to premature growth plate senescence induced by the prior estrogen exposure. (*J Clin Endocrinol Metab* 89: 103–107, 2004)

IN GIRLS WITH precocious puberty (PP), elevated estrogen levels accelerate both linear growth and bone maturation and impair final height (1). Treatment with GnRH analogs (GnRHa) effectively halts pubertal development and improves adult height (2, 3). However, in some patients, treatment with GnRHa does not just normalize height velocity but decreases it below the age-appropriate normal range (2–5). Previous studies have not revealed a clear hormonal cause for this phenomenon (6–8), raising the possibility that the poor growth is due, at least in part, to a mechanism intrinsic to the growth plate.

We hypothesized that the decreased height velocity observed during GnRHa therapy is due to excessive growth plate senescence induced by the prior estrogen exposure. Growth plate senescence refers to the normal structural and functional changes that occur with age in the growth plate cartilage, including a decline in the chondrocyte proliferation rate, the longitudinal growth rate, the height of the growth plate, and the number of chondrocytes in each zone of the growth plate (9, 10). Although this process has been studied most extensively in rats and rabbits, similar structural and functional senescent changes occur gradually in the human growth plate throughout childhood (11, 12), culminating in epiphyseal fusion.

We have recently demonstrated in an animal model that estrogen treatment accelerates all aspects of this senescence program (9). These findings suggest that the high levels of estrogen present in girls with PP might accelerate growth plate senescence. Although subsequent GnRHa therapy may normalize hormonal concentrations, the growth rate during therapy might be subnormal because of this excessive growth plate senescence.

Our hypothesis predicts that the height velocity observed during GnRHa therapy, *i.e.* in the absence of ongoing estrogen effects, will be most closely correlated with bone age (BA), which we have used as a surrogate marker for growth plate senescence. This hypothesis also predicts that the severity of the growth abnormality, expressed as height velocity SD score (SDS) for chronological age (CA), during GnRHa therapy will be inversely related to the severity of prior estrogen exposure and, thus, to 1) duration of puberty, 2) pubertal stage, 3) BA advancement (BA − CA), and 4) serum estradiol (E2) concentrations before treatment.

To test these predictions, we analyzed growth data and BA assessments from 100 girls treated with GnRHa for central PP as part of a clinical trial at the National Institutes of Health (2).

Subjects and Methods

Subjects

All 100 girls were diagnosed with central PP (83 girls with idiopathic PP and 17 with hypothalamic hamartoma) and treated with daily sc injections of deslorelin (D-trp6-pro9-des-gly10-LHRH-ethylamide, 4 μg/kg·d; n = 90) or histrelin (D-His[bzl]6-pro9-des-gly10-LHRH-ethylamide, 4–10 μg/kg·d; n = 10). The diagnosis of central PP was based on a pubertal response to GnRH according to the criteria of Oerter *et al.* (13). The diagnosis of idiopathic PP was based on absent central nervous system pathology by imaging studies. None of the 100 girls had growth-affecting medical problems other than PP at the time of the study. The

Abbreviations: BA, Bone age; CA, chronological age; E2, estradiol; GnRHa, GnRH analogs; PP, precocious puberty; SDS, SD score.

treatment protocol was approved by the National Institute of Child Health and Human Development Institutional Review Board, and informed consent was obtained from the parents, and assent was obtained from the older children.

Study protocol

Details of the study design are reported elsewhere (2). Briefly, the children underwent inpatient evaluations at the Clinical Center of the National Institutes of Health at 2, 6, and 12 months during the first year of treatment and then yearly until treatment was discontinued. At each visit, morning height (average of 10 measurements) was obtained using a Harpenden stadiometer, pubertal stage for breast development was assessed according to the criteria of Tanner (14), based on the averaged Tanner stage of both breasts, and BA was determined by the method of Greulich and Pyle by a single investigator who was blinded to the growth data and the age of the children. In addition, a GnRH test with measurements of gonadotropins and E2 was performed approximately 12 h after the last GnRHa administration to evaluate adequacy of suppression of the pituitary-gonadal axis.

Assays

Serum gonadotropin and E2 levels were determined by RIA (Covance Laboratories, Vienna, VA).

Statistics

Some patients showed suboptimal pubertal suppression during the first 6–12 months of GnRHa therapy and required dose adjustments. Therefore, we chose the second year of treatment for analyses because we wished to study height velocity in the absence of ongoing estrogen effects. The height velocity was calculated as the height 2 yr after onset of therapy minus the height 1 yr after onset of therapy divided by the intervening time interval. For determination of BA advancement as a consequence of PP, we chose to use the BA and CA at initiation of GnRHa therapy because this time point would best reflect the severity of estrogen exposure before treatment. For correlations with the height velocity in the absence of ongoing estrogen effects, *i.e.* during the second year of treatment, we chose to use the BA and CA at the beginning of the second year of treatment because this time point would best reflect the skeletal state during the period in which height velocity was measured. Height velocity SDS was determined using anthropometric reference data for U.S. children (15). The significance of the growth impairment (height SDS of subjects *vs.* height SDS = 0) was assessed by one-sample *t* test. The correlations between growth parameters and BA, CA, and the various markers of prior estrogen exposure as well as the correlations among the markers of prior estrogen exposure were assessed using linear regression analysis and Pearson's correlation coefficients. Stepwise multiple regression analysis was used to determine the best predictors of growth during GnRHa therapy. Significance was accepted at $P < 0.05$.

Results

Pretreatment group characteristics are listed in Table 1. Estrogen exposure before GnRHa therapy ranged from mild to severe as indicated by the wide ranges for duration of PP, pubertal stage, BA advancement, and serum E2 levels. Of the 100 girls, 40 were postmenarchal, with most experiencing irregular menses or spotting at the time therapy was initiated; 56 were premenarchal; and for four girls, no information on their menarchal status was available.

During the second year of GnRHa therapy, the pituitary-gonadal axis was adequately suppressed in all girls. Mean height velocity was low for age in girls younger than 10 yr of age and more pronounced in girls 10 yr of age or older ($P < 0.0001$ for both, Table 1). Mean height velocity was also low for BA in girls with a BA 10 yr or more ($P < 0.0001$, Table 1) but was not low and even slightly high in girls with a BA less than 10 yr ($P < 0.05$, Table 1). Forty-five percent of the girls had a subnormal height velocity for CA (< -2 SD), and 39% of the girls had a height velocity less than 4 cm/yr.

TABLE 1. Clinical characteristics of patients before and during the second year of GnRHa therapy

	Mean ± SD	Range
Pretreatment		
Age (yr)	5.8 ± 2.1	1.0–9.4
Duration of PP (yr)	2.6 ± 1.6	0.5–7.1
Tanner stage (breast)	3.5 ± 0.7	1.3–5.0
BA (yr)	9.7 ± 2.5	2.5–14.0
BA advancement (yr)	3.8 ± 1.6	0.3–7.8
Serum E2 (pmol/liter)	230 ± 188	26–837
Second year of GnRHa therapy		
Age (yr)	7.0 ± 2.1	2.5–10.4
Bone age (yr)	10.4 ± 2.2	3.3–14.0
Height velocity (cm/yr)	4.8 ± 1.9	0.7–10.5
Height velocity SD-score for CA	−1.6 ± 1.7	−5.7–2.0
CA < 10 yr (n = 95)	−1.5 ± 1.6	−4.5–2.0
CA ≥ 10 yr (n = 5)	−3.8 ± 1.6	−5.7–−2.1
Height velocity SD-score for BA	−1.2 ± 2.0	−4.7–4.3
BA < 10 yr (n = 29)	0.8 ± 0.2	−3.2–4.3
BA ≥ 10 yr (n = 71)	−1.9 ± 1.5	−4.7–2.0

Absolute height velocity correlated strongly with BA and CA (Fig. 1). The height velocity SDS for CA during GnRHa therapy correlated inversely with markers of prior estrogen exposure, including duration of PP, BA advancement, and pubertal stage (Fig. 2). Stepwise regression analysis including all investigated parameters revealed that BA was the single best predictor of absolute height velocity as well as of the severity of growth abnormality during GnRHa therapy. BA, duration of PP, BA advancement, and pubertal stage explained 33, 14, 8, and 5%, respectively, of the variance in height velocity SDS for age.

Relationships among the investigated markers of prior estrogen exposure are shown in Table 2. Duration of puberty correlated significantly with breast Tanner stage and BA advancement.

Discussion

Our data demonstrate that, in girls with central PP, GnRHa treatment does not just return the linear growth rate to normal but actually often results in an abnormally low height velocity. Although this impairment in linear growth has been observed previously in smaller studies (2–5), the size of our study population allows a more conclusive estimate of its extent and frequency.

The cause for this linear growth impairment was unknown. Previous studies had sought hormonal explanations. For example, it has been hypothesized that the growth impairment might be due to inadequate GH secretion (3). Although estrogen-induced stimulation of the GH-IGF-I axis does probably contribute to the growth acceleration that occurs in normal puberty (16) and untreated PP (17–22), lack of GH does not appear to be responsible for growth impairment during GnRHa treatment. Although some studies have suggested a subnormal GH secretion during treatment with GnRHa (7, 23), others have not (6, 8, 18). Evaluation of subpopulations of children with poor growth during GnRHa therapy has also not clearly demonstrated GH deficiency (4, 7, 23–26). Modest declines in GH concentrations may simply

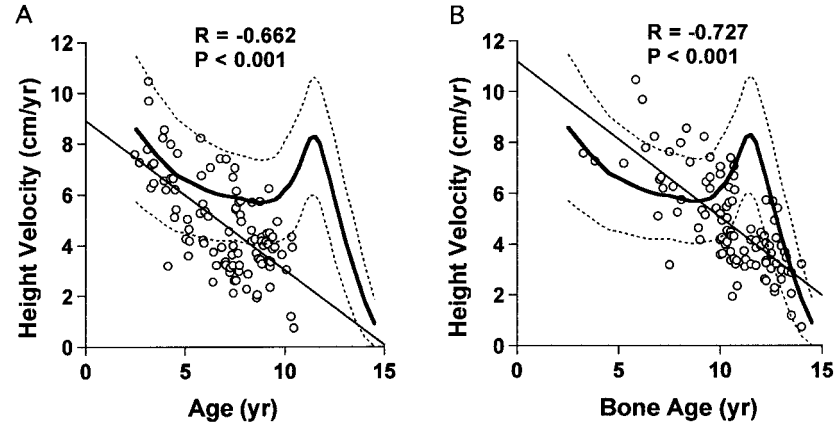

FIG. 1. Height velocity during GnRHa therapy in relation to age (A) and BA (B). *Open circle*, Individual patients; *solid line*, regression line; *dotted line*, reference range (3rd–97th percentile) for height velocity as a function of CA (Tanner); *bold line*, 50th percentile of the reference range.

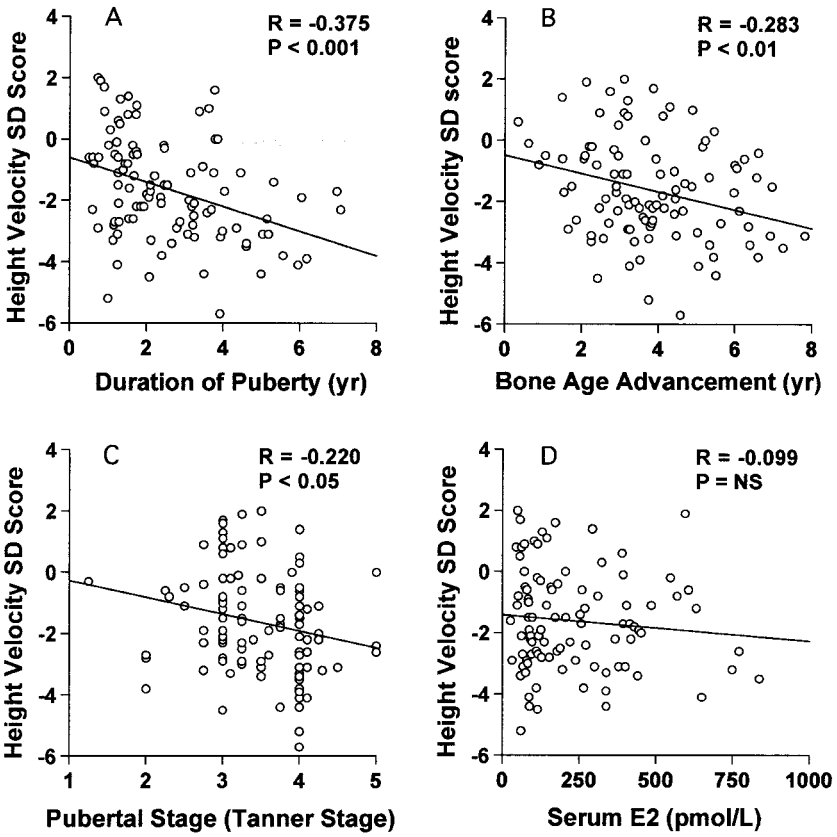

FIG. 2. Relationship between height velocity SDS for CA during GnRHa treatment and the duration of PP (A), BA advancement (B), stage of pubertal development (C), and serum E2 levels (D) in 100 girls with central PP. These latter four variables were assessed before the start of treatment and were considered to be markers of the severity of estrogen exposure. *Open circle*, Individual patients; *solid line*, regression line.

reflect the increased body fat that often develops during GnRHa treatment (7, 27). Furthermore, during GnRHa treatment, circulating IGF-I levels often do decrease from pretreatment values but remain above normal for age (8, 17–19, 21, 22, 28, 29). Because IGF-I concentration is dependent on GH secretion, this finding of increased IGF-I provides further evidence that GH deficiency is not the culprit responsible for poor growth during GnRHa therapy.

It has also been hypothesized that GnRHa treatment might inhibit growth by suppression of estrogen concentrations to levels below those of prepubertal children (30). However, estrogen measurements using an ultrasensitive recombinant cell bioassay are not consistent with that explanation (31).

Because there is no clear evidence for a hormonal abnormality causing the growth impairment during GnRHa therapy, we considered the possibility that the defect might be intrinsic to the growth plate. Under normal circumstances, the linear growth rate declines with age because the growth plate undergoes programed senescence (9, 10). We have previously demonstrated in an animal model that estrogen accelerates this senescent decline in growth plate function (9). We hypothesized that this same phenomenon might occur in humans and that the estrogen exposure in PP would cause excessive growth plate senescence. During GnRHa therapy, when hormonal concentrations are normalized, this excessive senescence would be expected to result in decreased linear growth.

Our findings support, but do not prove, this hypothesis.

TABLE 2. Correlations among markers of prior estrogen exposure

Variable 1	Variable 2	r^2	*P*
Duration of puberty	Breast Tanner stage	0.08	0.004
Duration of puberty	BA advancement	0.06	0.01
Duration of puberty	E2 concentration	0.01	0.3
Breast Tanner stage	BA advancement	0.003	0.6
Breast Tanner stage	E2 concentration	0.02	0.2
BA advancement	E2 concentration	0.008	0.4

During GnRHa treatment, height velocity showed a strong inverse correlation with BA. In fact, despite the relative inaccuracy of BA compared with CA determination (32), which was expected to adversely affect any correlation, height velocity was more closely correlated with BA than with CA or any other investigated variable. Before puberty, height velocity also decreases with age in normal girls. In addition, the height velocity SDS for CA during GnRHa therapy correlated inversely with markers of prior estrogen exposure, including the duration of PP, BA advancement, and pubertal stage. If BA serves as a valid radiological marker for growth plate senescence, this finding supports our hypothesis that the decreased height velocity of these children is largely determined by the degree of growth plate senescence.

Although the height velocity was low for CA, it was normal (or even slightly high) for BA in girls with BA less than 10 yr, suggesting that the growth rate was essentially appropriate for the degree of growth plate senescence. The slightly increased height velocity for BA in these girls might reflect the fact that GnRHa treatment results in E2 levels that are slightly above the normal prepubertal range (31). For subjects with BA 10 yr or more, the height velocity was low not only for CA but also for BA. This decreased height velocity for BA in these girls presumably reflects the fact that normal girls with BA 10 yr or more are usually in puberty and thus have higher estrogen levels and more rapid growth than the subjects on GnRHa. Therefore, in all subjects, the height velocity appears to be determined by the following two factors: 1) the degree of growth plate senescence, which is determined by the prior estrogen exposure (a negative effect), and 2) the current estrogen levels (a positive effect).

In contrast to the strong inverse relationship between absolute growth rate and BA, the inverse correlations between height velocity SDS for CA during GnRHa therapy and the markers of prior estrogen exposure, although statistically significant, were not very strong. This may be attributable to the inaccuracy of short-term growth rate measurements (33) and BA assessments. Particularly, the size of the measurement error inherent in the discontinuous atlas matching method of Greulich and Pyle (32) might have a greater impact on the calculation of BA advancement than on absolute BA. In addition, pubertal stage and duration of PP may imperfectly reflect the severity of estrogen exposure to the growth plate. Even though puberty clearly advances BA progression, the association between pubertal stage and BA is remarkably loose (34). Indeed, in our own data set, the correlations among the various markers of estrogen exposure (duration of puberty, breast Tanner stage, BA advancement, and E2 concentration) were not particularly strong (all $r^2 \leq 0.08$), indicating that these are imperfect markers of estrogen exposure. The very fact that statistically significant correlations with height velocity SDS exist (and are in the predicted direction), even though these markers are far from perfect, provides evidence for the hypothesis. However, the unexplained variance could also reflect a second fundamental mechanism that also contributes to the impairment in linear growth.

Height velocity SDS for CA was not significantly correlated with pretreatment E2 levels, but E2 was also not correlated with any other marker of pubertal severity. Possible explanations for this lack of correlation may be the relative insensitivity of the E2 assay (used at the time of the study); the wide fluctuation of E2 levels with time, particularly in the 40% of girls who were experiencing menstrual cycles; and/or the observation that, once full sexual maturation is achieved, E2 levels may not further increase but growth plate senescence may continue to advance.

In this study, we used BA as a surrogate marker for growth plate senescence. In animal studies, senescence can be assessed more directly by measuring the chondrocyte proliferation rate and histological changes that occur with age (9, 10). The justification for using the BA as a marker for human growth plate senescence is based on several lines of evidence. First, the determination of BA is based partly on the thickness of the radiolucent bands between the epiphyses and metaphyses, and thus, BA depends in part on growth plate height, a structural marker of senescence (9). Second, BA is inversely associated with the remaining linear growth potential. This association is the basis for most height prediction methods (35). Thus, BA is associated with a functional marker of senescence, the decline in growth potential of the growth plates. Third, conditions that delay growth plate senescence, thus conserving growth potential and delaying epiphyseal fusion, also delay BA advancement. These parallel effects on senescence and BA are observed with glucocorticoid excess, GH deficiency, hypothyroidism, malnutrition, chronic disease, and constitutional delay of growth (36–38).

The diminished linear growth during GnRHa treatment can be considered catch-down growth, a term used to describe a diminished growth rate that follows a period of growth acceleration. The converse condition, catch-up growth, in which rapid growth follows a period of growth inhibition, is due, at least in part, to a delay in growth plate senescence (36–38). Thus, catch-up growth and catch-down growth appear to be mirror-image conditions not only phenomenologically but also mechanistically.

In humans, estrogen accelerates longitudinal bone growth at the growth plate in the short term, but it also accelerates growth plate senescence, which leads to a decline in longitudinal bone growth in the long term. As a result, girls with untreated PP are tall for their age initially, but their linear growth slows and stops early, producing short stature in adulthood (1). Treatment with GnRHa removes the stimulatory effect of estrogen on growth, thus unmasking the growth impairment which, our data suggest, is due to excessive senescence.

We conclude that impaired linear growth occurs frequently in girls with PP treated with GnRHa. Our findings are consistent with the hypothesis that the impaired growth

is due, at least in part, to a local abnormality in the growth plate, premature senescence, induced by the prior estrogen exposure.

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