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Bone Age and Onset of Puberty in Normal Boys

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Abstract

Many conditions that delay skeletal maturation also delay the onset of puberty, whereas conditions that accelerate skeletal maturation often hasten the onset puberty, raising the possibility that skeletal maturation influences pubertal onset. To determine whether this concordance is also present in normal children, we analyzed data from 30 normal boys participating in a longitudinal study. Height, weight, and serum testosterone concentrations were assessed every 6 months and bone age (Fels method) every year. Pubertal onset was defined by serum testosterone ≥ 30 ng/dL. The variability in bone age at onset of puberty was not less than the variability in chronological age. In addition, there was no significant correlation between skeletal advancement and pubertal advancement ($r = 0.01$, $P = 0.9$). Similarly, there was not a significant correlation between pubertal advancement and height age advancement, weight age advancement, or BMI age advancement. Our findings do not support the hypothesis that skeletal maturation directly influences the age of pubertal onset in normal boys.

Keywords

puberty; bone age; skeletal maturation

Introduction

In many conditions, there is an association between the rate of skeletal maturation and the rate of hypothalamic-pituitary-gonadal axis maturation. Conditions that delay skeletal maturation, such as chronic disease (Kulin et al., 1982), malnutrition (Alvear et al., 1986), hypothyroidism (Pantsiouou et al., 1991), constitutional delay (Sedlmeyer et al., 2002), and growth hormone deficiency (Tanner et al., 1975), delay the onset of puberty. Conversely, conditions that accelerate skeletal maturation, such as peripheral precocious puberty (Leschek et al., 1999; Pescovitz et al., 1984; Holland et al., 1987; Merke et al., 2000), obesity (Vignolo et al., 1988) and Marfan syndrome (Erkula et al., 2002), hasten the onset of central puberty. This concordance between the rates of different maturational processes was observed by James Tanner who introduced the concept of “tempo” to refer to the overall pace of somatic maturation (Tanner 1987) which can include the rate of growth, skeletal maturation, and the timing of puberty.

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We recently studied this concordance between skeletal maturation and hypothalamic-pituitary-gonadal axis maturation quantitatively in boys with congenital adrenal hyperplasia and familial male-limited precocious puberty, two conditions that accelerate maturational tempo, and boys with idiopathic short stature in which maturational tempo is sometimes delayed. In all three conditions, the magnitude of the skeletal advancement or delay matched the magnitude of the pubertal advancement or delay. This synchrony between skeletal maturation and hypothalamic-pituitary-gonadal axis maturation was observed among patients within each condition and also between conditions (Flor-Cisneros et al., 2004).

It is possible that hypothalamic-pituitary-gonadal axis maturation and skeletal maturation are regulated in parallel but independently by multiple different conditions. However, the observed synchrony suggests that hypothalamic-pituitary-gonadal axis maturation may be regulated by somatic growth and maturation, either growth and maturation of the skeleton itself or growth and maturation of a non-skeletal tissue which parallels growth and development of the skeleton.

Previous studies suggest that this concordance between skeletal maturation and hypothalamic-pituitary-gonadal axis maturation is not present in normal children; reportedly the onset of puberty did not show a stronger correlation with bone age than with chronological age (Marshall 1974). However, in these studies the onset of puberty was determined using photographs rather than direct evaluation of the secondary sexual characteristics. Moreover, the hormonal and biochemical testing and mathematical analysis assessing the association in this study were limited.

The purpose of the present investigation was to determine whether, in normal boys, the age of pubertal onset correlates with skeletal maturation as it does in boys with abnormal tempo. We therefore, analyzed the biochemical data and bone ages of 30 normal boys at onset of puberty.

Subjects and Methods

Subjects

Subjects were part of a longitudinal study of the endocrine control of growth, maturation and body composition at the University of Virginia Clinical Research Center. Participation in the study required normal growth, including height, height velocity, and weight within 2 SD of the normal mean for chronological age. The study was reviewed and approved by the University of Virginia Human Investigation Committee. Informed consent was obtained from each parent and assent from each child. Subjects were included in the current retrospective analysis if onset of puberty occurred during this longitudinal study. One of the subjects was of Hispanic ethnicity; the others were categorized as non-Hispanic white.

Methods

The auxological measures were completed every 6 months by a single trained anthropometrist. Morning height was measured with a Harpenden stadiometer. Bone age was determined every year, based on a radiograph of the left hand and wrist by an experienced observer using the Fels method. The bone age assessment had been performed prior to the conception of the current study, thus precluding bias based on the hypothesis (Roemmich et al., 1997).

Serum total testosterone concentration was measured every 6 months by RIA using kits from Diagnostic Products Corporation (Los Angeles, CA). The sensitivity of the testosterone assay was 10.0 ng/dL with an intraassay coefficient of variation (CV) of 5% to 6% within the range of 100 to 800 ng/dL. The interassay CV ranged from 9.2% to 12.9% within the range of 70 to 840 ng/dL.

The chronological age at onset of puberty was defined as the child's age on the first visit when his serum testosterone level was ≥ 30 ng/dL. The bone age at onset of puberty was defined as the bone age at this visit, or (if a bone had not been performed at that visit) at the visit 6 months prior.

Normative data were obtained from the 2000 NCHS study (Kuczmarski et al., 2002). Height age of a subject was defined as the age at which the median height of normal boys was equal to the subject's height. Weight age and BMI age were defined analogously. Bone age advancement was defined as bone age minus chronological age. Height age advancement, weight age advancement and BMI age advancement were defined analogously. Pubertal advancement was defined as the average age of pubertal onset for these boys, 11.4 yr, minus the chronological age of the individual subject at onset of puberty. For example, a boy with onset of puberty at 10.4 y would have a pubertal advancement of 1 y.

Results

In these normal boys, the chronological age at onset of puberty was 11.4 ± 0.8 y, (mean $\pm$ SD). The bone age at onset of puberty was 11.0 ± 1.5 y. Thus, the variability in the bone age at onset of puberty was greater than the variability in the chronological age at onset of puberty (Fig. 1 and 2). Similarly, the height age, weight age, and BMI age at onset of puberty showed a greater standard deviation than did the chronological age (Table 1). For each subject, we compared the skeletal advancement (assessed as the bone age minus chronological age at onset of puberty) with the pubertal advancement (assessed as the average age at onset of puberty [11.4 y] minus the subject's chronological age at onset of puberty). There was no significant correlation between skeletal advancement and pubertal advancement ($r = 0.01$, $P = 0.9$) (Fig. 3). Similarly, there was not a significant correlation between pubertal advancement and any of the other measures of growth or maturation: height age advancement, weight age advancement, or BMI age advancement and (Table 2).

Discussion

We had hypothesized that normal boys with a more advanced bone age would tend to enter puberty at an earlier age than boys with a more delayed bone age. This hypothesis predicts that the bone age at onset of puberty would be less dispersed than the chronological ages at onset of puberty. The data do not support this prediction. To the contrary, the SD and interquartile range were greater for bone age than for chronological age. Similarly, the hypothesis predicts a correlation between the degree of skeletal advancement and the degree of pubertal advancement. Again, the data do not support this prediction.

Our findings are in general agreement with those of Marshall who found that the variability in bone age at onset of puberty was similar to the variability in the chronological age at onset of puberty (Marshall 1974). Based on this finding, Dr. Marshall concluded that "the signal for the initiation of breast or genital development is independent of whatever controls the advancement or retardation of skeletal ossification." That study included a greater number of subjects than our study and included both boys and girls. However, our study employed an objective measure of pubertal onset, testosterone concentration > 30 ng/dL, whereas the previous study assessed the onset of puberty using photographs. Also, the previous study analyzed the variability in age at onset of puberty but did not use correlation analysis to detect a relationship between bone age and onset of puberty, an approach that has proven useful in a previous study.

We have previously shown a strong association between bone age and pubertal onset in boys with abnormal developmental tempo. In boys with congenital adrenal hyperplasia and in boys

with familial male precocious puberty, individuals with the greatest skeletal advancement began central puberty at the earliest age. Conversely, in boys with idiopathic short stature, boys with the greatest skeletal delay began puberty at the latest age. Furthermore, the magnitude of the skeletal advancement or delay matched the magnitude of the pubertal advancement or delay. This synchrony between skeletal maturation and hypothalamic-pituitary-gonadal axis maturation was observed among patients within each condition and also between conditions (Flor-Cisneros et al., 2004). In agonadal male monkeys treated with sex steroids, the association between skeletal advancement and pubertal advancement appears to be weaker (Fraser et al., 2005).

Why is synchrony between skeletal maturation and hypothalamic-pituitary-gonadal axis maturation maintained in boys with abnormal maturational tempo, but apparently not maintained in boys with normal maturational tempo? One possibility is simply that we are missing the correlation in normal boys. In normal boys there is less variability in the bone age advancement and the pubertal advancement and therefore it might take a larger number of subjects to detect a correlation. Furthermore, a correlation might be obscured by the measurement error in the bone age values at onset of puberty and by the fact that bone age was only obtained every 12 months. Indeed, these last two factors could account for the fact that there was actually greater dispersion in the bone age values than in the chronological age at onset of puberty.

If indeed the lack of correlation between skeletal age and pubertal onset in normal boys is correct, then it argues against the hypothesis that skeletal maturation governs the onset of puberty (Fig. 4A). The lack of correlation suggests that puberty and skeletal maturation might simply both be regulated in parallel by many nutritional, genetic, and endocrine factors (Fig. 4B), but not by all factors. However, the precise synchrony between pubertal maturation and bone age in a variety of conditions (Flor-Cisneros et al., 2004), while not inconsistent with this model, and would not necessarily be predicted by this model.

To account for the synchrony between skeletal maturation and pubertal onset in boys with abnormal maturational tempo but not in those with a normal maturational tempo, we propose a more complicated model (Fig. 4C). Many of the components of this model have been proposed previously by others (Tanner et al., 1975; Kulin et al., 1982; Wheeler 1991; De Luca et al., 1999).

The first component of the model is that the onset of puberty in humans might be governed by a signal coming from a growing tissue or tissues (Plant et al., 1989; Fraser et al., 2005) which we can refer to as tissue(s) X. Tissue(s) X might elaborate a signal that inhibits puberty, presumably acting on the central nervous system through neural circuitry that regulates the GnRH pulse generator. As the individual approaches adult size, the growth capacity of tissue(s) X begins to be depleted and consequently, the puberty-inhibiting signal diminishes, thus triggering puberty. Alternatively, as growth subsides, tissue(s) X might increase production of a signal that stimulates the onset of puberty. Therefore, an inhibitory signal might be produced by rapidly growing cells or a stimulatory signal might be produced by mature, quiescent cells.

The second component of the model is that the growth of tissue(s) X might be regulated by endocrine signals such that optimal growth occurs only in a healthy, well-nourished individual. If the individual is ill or malnourished, the levels of circulating IGF-I decrease, thyroid hormone levels decrease, cortisol levels increase and growth of tissue(s) X is down-regulated. Growth inhibiting conditions would conserve the growth capacity of tissue(s) X. This component of the model would account for the fact that the onset of puberty is regulated by the same nutritional and endocrine factors that regulate somatic growth. Similarly, premature exposure

to sex steroids might cause growth acceleration in tissue(s) X, earlier depletion of the growth capacity, and therefore earlier central puberty.

The third component of the model is that growth of tissue(s) X and growth of the skeleton are synchronized. Indeed growth of many tissues is synchronized temporally, conditionally, and evolutionarily. Temporal synchrony is evidenced by the fact that many tissues grow rapidly in early life, but decelerate with age as the individual approaches adult size. For the growth plate, this decline in growth rate appears to be due to a local mechanism (van der Eerden et al., 2003). Conditional synchrony is demonstrated by the fact that many conditions, such as growth hormone deficiency or malnutrition slow growth of multiple tissues. Evolutionary synchrony is demonstrated by the fact that, in large mammals, such as the elephant, the size of multiple organs is proportionally increased compared to small mammals, such as the mouse. The temporal, conditional, and evolutionary synchrony between growth of different tissues may reflect common underlying biological mechanisms. This component of the model would explain why multiple conditions that delay skeletal growth (such as malnutrition, systemic diseases, constitutional delay, and growth hormone deficiency) also delay puberty whereas conditions that accelerate skeletal growth (such as exposure to sex steroids) hasten the onset of central puberty.

The fourth component of the model is that the growth of the skeleton correlates with bone age advancement. This correlation is the fundamental reason why bone age is useful for height prediction; the bone age reflects the approximate fraction of growth in the growth plates that has been expended. This component of the model would explain the concordance between bone age and skeletal growth and therefore with growth of tissue X (model component 3) and therefore pubertal onset (model component 1).

The fifth component of the model is that the normal variability in bone age and the normal variability in pubertal onset involve steps in this causal sequence after the two paths (skeletal growth and growth of tissue(s) X) diverge. This component of the model would explain why, in normal children, the bone age does not correlate with pubertal onset.

This model, which resembles ideas suggested by James Tanner, (Tanner 1987) is highly speculative. However, it does account for the concordance of growth, bone age, and puberty in many conditions but not in normal children. Additional studies are needed to test this model.

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Figure 2.

Comparison of the interquartile range of bone age (BA) and chronological age (CA) at onset of central puberty in normal boys. Pubertal onset was defined by a serum testosterone concentration (measured every 6 months) ≥ 30 ng/dl. The box indicates the 25th and 75th percentile and the error bars indicate the 10th and 90th percentile.

FIGURE 3.

Lack of correlation between bone age advancement and pubertal advancement in normal boys. For each subject, we compared the bone age advancement (assessed as the bone age minus chronological age at onset of puberty) with the pubertal advancement (assessed as the average age at onset of puberty [11.4 y] minus the subject's chronological age at onset of puberty). There was no significant correlation.

FIGURE 4.

Diagram of possible relationships between skeletal maturation and onset of puberty. (A) Nutrition and endocrine signals regulate skeletal maturation which might govern the onset of puberty. (B) Puberty and skeletal maturation might be regulated in parallel but independently. (C) Nutritional and endocrine signals might regulate growth of the skeleton and growth of specific non-skeletal tissue(s) in parallel. Bone age is regulated by skeletal growth whereas pubertal onset might be governed by growth of the non-skeletal tissue(s) (designated tissues X).

TABLE 1 Characteristics of subjects at the onset of central puberty (mean $\pm$ SD)

Maturational markers	
CA (yr)	11.4 $\pm$ 0.8
BA (yr)	11.0 $\pm$ 1.5
Ht age (yr)	11.6 $\pm$ 1.3
Wt age (yr)	11.6 $\pm$ 2.0
BMI age (yr)	12.2 $\pm$ 3.2

TABLE 2

Correlation between pubertal advancement [11.4-CA] and other maturational markers at onset of central puberty. BA, bone age; CA, chronological age; WA, weight age; HA, height age; BMI, body mass index age.

BA-CA		WA-CA		HA-CA		BMI age-CA	
r	P	r	P	r	P	r	P
0.01	0.9	0.08	0.7	0.001	1	0.01	0.9