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Growth and Timing of Puberty: Reciprocal Effects

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Abstract. Based on the analysis of the pubertal growth spurt and final height in different pathological conditions, this paper provides evidence that variations in age at onset of puberty have a major influence on the subsequent acceleration of the growth rate but a minor impact on final height. A reciprocal effect of the growth rate on the timing of onset of puberty is also suggested by a number of clinical observations.

Introduction

Puberty and growth are two processes linked by mutual interactions mediated through different endocrine or paracrine factors at different anatomic levels. The purpose of this paper is to analyze the relationship between growth and timing of puberty. We will describe some physiological and pathological conditions providing evidence that age at onset of puberty affects growth and, also, that growth can influence the timing of onset of puberty.

Modulation of Growth by the Timing of Onset of Puberty

The pubertal growth spurt and final height are two distinct growth issues to be considered separately. The pubertal spurt results from an acceleration of the growth rate followed by a reduction. The capacity to accelerate growth during puberty can be reflected by the peak height velocity or maximal growth rate attained. However, the total pubertal height gain is a better index of the impact of puberty on growth since it takes into account not only the rate of growth but also the possible variations in duration of puberty [1].

Influence of Age at Onset of Puberty on the Pubertal Growth Spurt

During exposure to sex steroids, there is an acceleration of the rate of growth resulting from their synergistic action with growth hormone (GH) [1]. As shown in table 1, this acceleration is negatively correlated with age at exposure to sex steroids in several conditions: the physiological variants of the tempo of growth and puberty [2, 3]; central precocious puberty beginning at different ages; girls with Turner syndrome starting estrogen

Table 1. Conditions showing the reduction of growth capacity with age

Under the combined effects of sex steroids and GH
Pubertal spurt in subjects with different 'tempos' of growth
Pubertal spurt in central precocious puberty beginning at different ages
Sex steroid therapy in Turner syndrome
Puberty or sex steroid therapy in GH-treated hypopituitary patients
Under GH effect, in the absence of sex steroids
GnRH agonist therapy in central precocious puberty
Untreated Turner syndrome
GH therapy in Turner syndrome
GH therapy in prepubertal hypopituitary patients

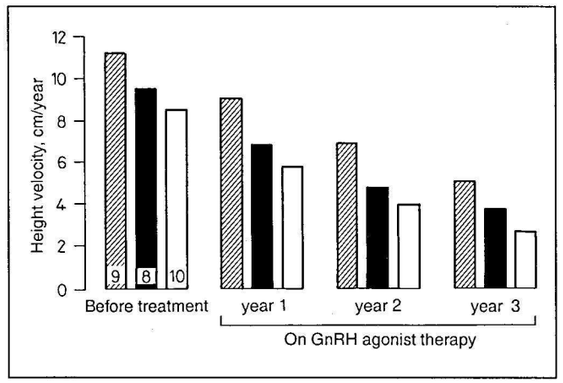

Fig. 1. Annual growth rate before therapy and during 3 years of treatment using an agonist of GnRH (buserelin) intranasally in 27 girls with central precocious puberty. The patients were separated into 3 groups according to bone age at onset of therapy: ▨ = < 10 years; ■ = 10–12 years; □ = > 12 years.

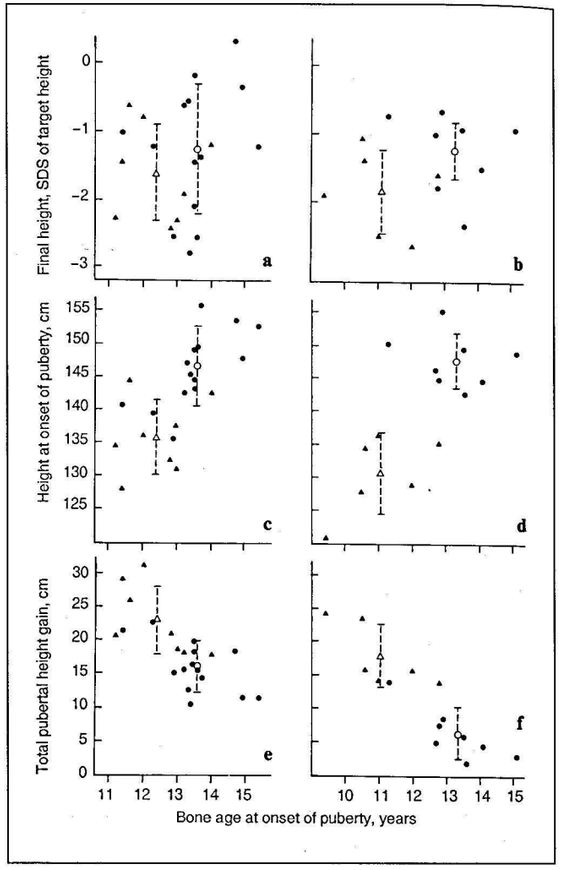

Fig. 2. Final height (corrected for midparental height; **a, b**) height at onset of puberty (**c, d**) and total pubertal height gain (**e, f**) plotted against bone age at onset of puberty in boys (**a, c, e**) and girls (**b, d, f**) with idiopathic hypopituitarism treated using GH. The open symbols denote mean ± SD values in the patients with spontaneous puberty and those treated using sex steroids. ▲ = Spontaneous puberty; ● = induced puberty. [Adapted from ref. 4 and 5].

treatment at bone ages ranging from 8 to 14 years [1], and hypopituitary patients beginning spontaneous or sex-steroid-induced puberty at bone ages ranging from 10 to 15 years [4, 5]. The age-related reduction of growth response to sex steroids can be seen in patients with central precocious puberty (fig. 1) as well as in hypopituitary boys and girls (fig. 2e, f). Interestingly, the pubertal height gain is markedly reduced in girls entering puberty at 13 years of bone age or later while a greater pubertal height gain is observed in boys at similar bone ages. This discrepancy can be related to the physiologically earlier occurrence of pubertal growth in girls than in boys.

In the absence of sex steroids, the rate of growth also shows a reduction with age which can be observed in several conditions (table 1): central precocious puberty during suppression of sex steroids by a gonadotropin-releasing hormone (GnRH) agonist therapy (fig. 1) [6]; girls with Turner syndrome either untreated [7] or treated using GH [8] and prepubertal hypopituitary patients treated using GH [9]. Thus, the capacity to respond to different growth-promoting agents such as GH and sex steroids decreases steadily with age.

Using mathematical models of growth, it has been shown that the age-related reduction of the childhood component of the pubertal spurt is a major reason why pubertal growth decreases in amplitude with age [10]. A second reason why the pubertal growth spurt declines with age is a reduced duration of pubertal growth. We observed a shortened duration of pubertal growth in GH-treated hypopituitary patients of both sexes beginning puberty at late bone ages [4, 5]. Others reported similar findings [11–13]. This phenomenon may have biased a study where GH-treated patients treated with cyproterone were compared to untreated patients [12]. Since bone age at onset of puberty was 2 years less in the treated group than in the untreated patients, this age difference may have contributed to the longer duration of pubertal growth which could not result from cyproterone therapy . In girls, a reduction of the mean growth rate was also observed following onset of puberty at late bone ages [5].

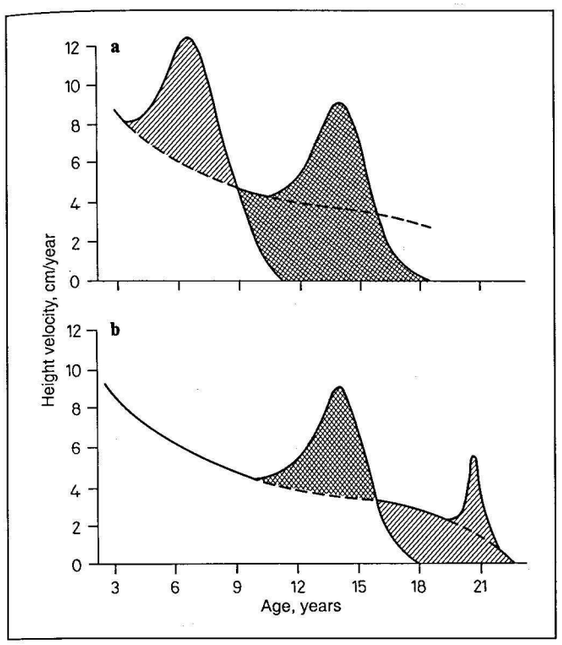

Fig. 3. Schematic representation of height velocity in relation to age in precocious puberty (**a**) and delayed puberty (**b**) compared with the normal growth spurt. The dashed line indicated the prolongation of prepubertal growth rate during the spurt, separating the pubertal and childhood components of the spurt. The hatched area represents the relative height gain due to early or late onset of puberty while the shaded area represents the relative height loss.

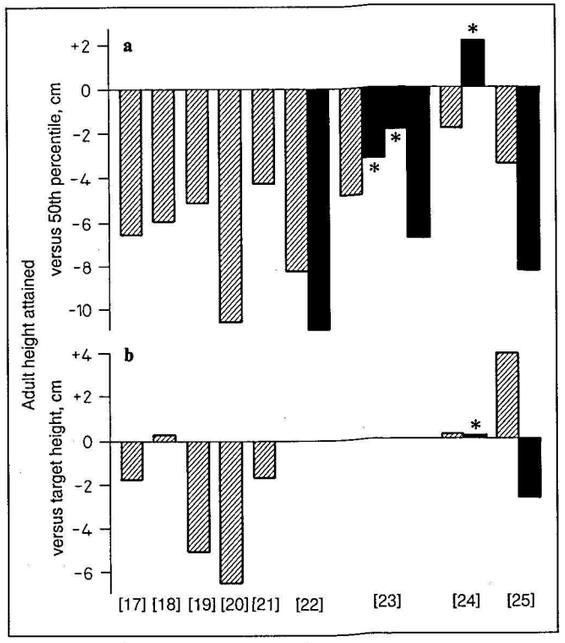

Fig. 4. Mean adult height of boys with constitutional delay of growth and puberty either untreated (▨) or treated with long-acting esters of androgens (■). Data are compiled from 9 different studies [17–25] and presented as the difference between adult height of patients and the 50th centile (**a**) or target (sex-corrected midparental) height (**b**). * < 200 mg/month.

Influence of Age at Onset of Puberty on Final Height

From the early observations of untreated patients with precocious puberty, it was shown that final height was reduced by 10–15% as a result of a 40% reduction of the total period of postnatal growth [1]. As shown in figure 3a, the pubertal component (part above the childhood component) of the growth spurt seen in precocious puberty is similar to that seen normally. The height lost by those patients is represented by the childhood component of the pubertal growth spurt which is determined by the prepubertal growth rate. The relatively greater importance of this prepubertal growth rate in younger subjects contributes to the height loss in sexual precocity. In contrast, delayed onset of puberty results in a minor height gain because the pubertal component of the spurt shows a reduced duration while the childhood component of the spurt is reduced as well due to the progressive decline in prepubertal growth rate with age (fig. 3b). Therefore, the height gain resulting from late onset of puberty is not significantly greater than the pubertal component of the spurt which would have occurred at normal ages. This accounts for the absence of increase in final height following a delayed onset of puberty.

Recent studies of final height in different conditions have confirmed that a possible increase in adult height resulting from late onset of puberty was a misconception. Final height is not significantly affected by physiological differences in tempo of sexual maturation [3]. While Tanaka et al. [14] reported a significant positive correlation between adult height and age at peak height velocity, this correlation would only account for a 5-cm difference in height resulting from a 5-year difference in age at onset of puberty. In patients with hypogonadotropic hypogonadism, adult height is also very close to the 50th percentile [15, 16]. The classic impression of tall stature in those patients may result from the changes in body proportion with a relative increase of the lower segment and a reduced spinal growth due to the absence of

Table 2. Conditions with altered growth rate preceding altered timing of onset of puberty

Increased growth rate preceding early onset of puberty
Untreated congenital adrenal hyperplasia
Gonadotropin-independent sexual precocity
Recovery after nutritional or psychosocial deprivation
Recovery after debilitating diseases
Late initiation of replacement therapy in hypothyroidism
Reduced growth rate preceding late onset of puberty
Isolated GH deficiency
Constitutional delay of growth and puberty
Chronic diseases
Undernutrition
Highly trained gymnasts

sex steroids. In GH-treated hypopituitary patients, we showed that final height was not correlated to bone age at onset of puberty [4, 5]. This was explained by the fact that the increase in height at onset of puberty with age was counterbalanced by the reduction in pubertal height gain seen subsequently (fig. 2).

Constitutional delay of growth and puberty is a most frequent condition were a possible reduction of adult height following adjuvant sex steroid therapy has been discussed for many years. In figure 4, data are compiled from 9 studies reporting on final height of boys with constitutional delay of growth and puberty [17–25]. In all 9 studies, mean adult height of untreated patients was below the 50th percentile while adult height was consistent with target (sex-corrected midparental) height in 5 out of 7 studies [17, 18, 21, 24, 25]. This suggests that the genetic factors account for a reduced adult stature in many of those patients. In 3 studies, the administration of long-acting esters of testosterone using dosages of 200 mg/month or more was shown to result in some possible reduction (mean: 2–5 cm) of adult height when compared to untreated patients [22, 23, 25]. In contrast, lower dosages of testosterone given for up to 1 year did not affect final height which was slightly above that of untreated patients [23, 24]. A normal adult height was recently reported in children with anorchia or hypogonadotropic hypogonadism treated using similar dosages for a longer period of time [26].

Summary and Practical Implications

Sex steroids are potent stimulators of the rate of growth, this effect being inversely related to age. In contrast, when given at replacement dosages, sex steroids have a small impact, if any, on adult stature, irrespective of age. This is particularly obvious in delayed puberty while some reduction of adult height may be seen in sexual precocity. Based on those observations, there is no auxological reason for delaying onset of puberty beyond the normal age in short children entering puberty at a physiological time. Similarly, there is no auxological reason for delaying onset of replacement (low-dose) sex steroid therapy in hypogonadal subjects. Finally, adjuvant (low-dose) sex steroid therapy might be proposed to patients with constitutional delay of growth and puberty without altering final height.

Possible Modulation of the Timing of Onset of Puberty by Growth

While the growth rate is evidently affected by the timing of onset of puberty, the reverse relation should be considered as well. A number of conditions (table 2) are consistent with a possible role of growth in modulating the timing of onset of puberty since increased growth rate can precede early onset of puberty [27–31] while a reduced growth rate can precede late onset of puberty as well. This concept warrants further studies based on clinical conditions and animal models to establish whether and how the growth rate can impinge upon the biological clock driving onset of puberty.

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