Growth Impairment in a Boy with Late-Onset Congenital Adrenal Hyperplasia and Anorexia Nervosa

Abstract

Treatment of congenital adrenal hyperplasia (CAH) in its salt-wasting form with appropriate doses of glucocorticoids and mineralocorticoids should promote growth, puberty and final height in a similar to normal pattern. However, the individual requirements for these drugs to normalize the hormonal profile and to achieve a physiologic growth pattern may differ. Moreover, the time of onset of puberty is also unpredictable since the course of the disease may predispose for precocity. The aim of this study was to explain the unexpected arrest of growth during puberty in a boy with late-onset CAH, who had been treated with glucocorticoid from early childhood. A short course of GnRH agonist treatment was also introduced in later years. The growth chart reflects two periods of impaired growth velocity preceded by weight loss. The reason for the first decline is difficult to prove retrospectively, but during the second episode the boy became both clinically and hormonally hypogonadal. At that time the anorexia nervosa (AN) was diagnosed according to APA DSM-IV criteria. We conclude that there were several reasons for the discontinued growth spurt and reduced final height in this boy with CAH: (a) early variant of puberty and subsequent late treatment with GnRH agonist, (b) AN possibly occurring during mid-childhood and clearly during puberty and (c) the repeated use of high doses of glucocorticoids. AN, a relatively rare disorder in boys, appears to have had a significant negative effect on this patient’s growth and should be considered in the differential diagnosis in CAH children with impaired growth.

Introduction

Optimal treatment of congenital adrenal hyperplasia, particularly in its most severe salt-wasting form (CAH-SW), with appropriate doses of glucocorticoids and mineralocorticoids should promote growth, puberty and final height in a close to normal pattern. The disease may predispose for early puberty because children with the diagnosis of CAH and late initiation of corticosteroid treatment and/or poor compliance are at risk of developing secondary central (GnRHa-dependent) precocious puberty (CPP) with early maturation of the hypothalamic-pituitary-gonadal axis (Soliman et al., 1997, Parths and Sippell, 2001). The precocious initiation of puberty causes acceleration of growth, bone age advancement and secondary sexual characteristics, isosexual in boys and initially heterosexual (virilization) in girls followed by breast development. Gonadotropin-releasing hormone agonist (GnRHa) therapy can improve the final adult height, bringing it closer to that expected from the genetic potential (Soliman et al., 1997). The problem of decreased appetite is uncommon in CAH children, in whom rather weight gain is a problem during long-term treatment. However, there are a few reports on CAH patients, all girls, who developed anorexia nervosa (AN) (Brand et al., 2000). The aim of the study was to explain the unexpected arrest of growth during puberty associated with a rapid decline in body weight in a boy with late-onset CAH who had undergone GnRHa treatment, and to analyse his final height.
Patient Report

A male patient with late-onset CAH was studied in whom the 21-hydroxylase deficiency was detected by serum hormone analysis and urine steroid profile during early childhood. After diagnosis at 4 years (growth acceleration, precocious pubarche and penile enlargement), the patient was treated with hydrocortisone (later with prednisone) and fludrocortisone (Cortineff). He also received short-term treatment with GnRHa (between years 11.5 and 12.8) and with 0.25 mg dexamethasone (at bedtime) combined with morning doses of hydrocortisone and fludrocortisone between years 13.0 and 14.8. The auxological data plotted on a growth chart (Krawczynski et al., 2000) were combined with the available hormonal data and bone age (Fig. 1). At 12.5 years bone age, originally advanced, was fortunately the same as chronological age at which was a very promising finding in view of his predicted adult height (PAH) close to 178 cm compared to his target height (TH) of 177 cm. PAH was calculated according to Bayley and Pinneau 1952, based on height and corresponding bone age (BA). At the age of 5.3 years, PAH was calculated to be 166 cm, at 9 to be 178 cm, at 11 years to be 176 cm and at 15.3 years it was still 170 cm. Long-term analysis of his growth chart revealed 2 periods of impaired growth velocity, the first between 9 and 11 years and the second, with an arrest of growth, between 15.3 yrs (BA 14.75) and 17.8 years of age, when his height was 162 cm (Fig. 1, Table 1). A concomitant weight loss was observed in both periods. The reason for the first decline in growth, possibly due to AN, is difficult to prove retrospectively but it appears not to be as relevant for his PAH as the second drop. During the second episode, the clinical and hormonal features of hypogonadism were observed with a dramatic decline in testosterone levels (from 20.6 nmol/L...
to 4.0 nmol/L) and an accompanying decrease of LH from 7.0 (evaluated after withdrawal of GnRHa) to 1.8 mIU/mL and of FSH from 33.3 (evaluated after withdrawal of GnRHa) to 8.7 mIU/mL. Serum GH levels were normal in two tests (spontaneous nocturnal secretion and after clonidine-stimulation test). IGF-1 level at the time of arrested growth was below the mean for age and sex, and this significant reduction and low IGFBP-3 level are in line with partial GH resistance, as suggested by reduced GHBP concentrations, and these values do not normalize even after recuperation of more than 10% of body weight (Barrios et al., 2001). Patients with AN may present with partial GH resistance, as suggested by reduced GHBP concentrations (Argente et al., 1997). The anorectic male patient with late-onset CAH described here had reduced IGF-1 concentration at the time of diagnosis as well as normal or even elevated GH levels, thus supporting the above. Moreover, this happened during a critical period for growth spurt which results from the synergistic action of GH (via IGF-1) and testosterone. Both critical compounds, IGF-1 and testosterone, were decreased, therefore very probably causing arrested growth. It should be noted that treatment with GnRHa was not indicated retrospectively, at least in the period between 11 and 13 years, which is the physiological time for pubertal onset in boys and in view of the fact that his age of 15 is very probably causing arrested growth. It should be noted that treatment with GnRHa was not indicated retrospectively, at least in the period between 11 and 13 years, which is the physiological time for pubertal onset in boys and in view of the fact that his bone age was not significantly advanced (12 years at a chronological age of 11.2 years). Based on findings in studies in rats (Caldefie-Chezet et al., 2001) we should also consider the role of dexamethasone in the induction of AN in this patient. Moreover, Tronche et al 2004 demonstrated that low glucocorticoid levels previous value during a clinical course with testosterone (100 mg/4 weeks for 8 months) followed by a height gain of 2 cm. The testosterone treatment was stopped when his gonadotropin values reached pubertal levels (LH 2.5 mIU/mL and FSH 6.7 mIU/mL) and his serum testosterone level was pubertal (14.0 nmol/L) before the next testosterone injection, showing recovery of the hypothalamic-pituitary-gonadal axis. He completed growth at a final height of 164 cm (height SDS for BA = – 1.9, height percentile for BA: – 3, height SDS – target height SDS = – 1.7). In retrospect it seems very likely that the first episode of weight loss was also a manifestation of early-onset AN in a prepubertal boy.

**Discussion**

Although AN is usually considered a disorder of girls and young women, 5–10% of cases occur in boys (Sreenivasan, 1978, Romeo, 1994) and adult men (Andersen and Holman, 1997). Time of onset of AN can range from the prepubertal years to adulthood (Fosson et al., 1987, Barry and Lippmann, 1990). The AN patients in the study by Nussbaum et al. 1985 were significantly shorter than their parents, and comparisons suggest impairment of growth rather than familial etiology. In those subjects who developed AN after menarche, malnutrition did not appear to be responsible for height deficits. AN is therefore not causative in ending the growth phase. Nutritional status must be regarded as a major determinant in the regulation of the somatotropin-somatotropin- somatotropin-somatotropin axis in animals and humans. Chronic undernutrition induces an increase in spontaneous GH secretion with a decrease in insulin-like growth factor-1 plasma levels (Scacchi et al., 2003). CAH is not a disorder with an increased risk of developing AN (Robb and Dadson, 2002). To date no data are available describing this problem in boys with CAH and there is only one paper describing AN in girls with this condition (Brand et al., 2000). AN is improbable in a boy with CAH since in this disease the problem of androgen excess rather than deficiency occurs, the latter a known important secondary parameter in AN boys. There is no adequate data supporting the association of CAH and AN in terms of the primary reason, e.g. whether long-term treatment of chronic disease with hydrocortisone had any relevant effect on psychological behaviour resulting in AN crisis. Anorectic patients have significantly reduced IGF-1 and IGFBP-3 and increased IGFBP-1 concentrations, and these values do not normalize even after recuperation of more than 10% of body weight (Barrios et al., 2001). Patients with AN may present with partial GH resistance, as suggested by reduced GHBP concentration (Argente et al., 1997). The anorectic male patient with late-onset CAH described here had reduced IGF-1 concentration at the time of diagnosis as well as normal or even elevated GH levels, thus supporting the above. Moreover, this happened during a critical period for growth spurt which results from the synergistic action of GH (via IGF-1) and testosterone. Both critical compounds, IGF-1 and testosterone, were decreased, therefore very probably causing arrested growth. It should be noted that treatment with GnRHa was not indicated retrospectively, at least in the period between 11 and 13 years, which is the physiological time for pubertal onset in boys and in view of the fact that his bone age was not significantly advanced (12 years at a chronological age of 11.2 years). Based on findings in studies in rats (Caldefie-Chezet et al., 2001) we should also consider the role of dexamethasone in the induction of AN in this patient. Moreover, Tronche et al 2004 demonstrated that low glucocorticoid levels
may result in decreased STAT5 activation and thus in reduced growth. This could provide a very convincing and novel explanation for growth disorders in later life due to an extended period of very low glucocorticoid levels, below the age of 4 in this boy when this boy was not treated.

In conclusion, the main reason for arrested growth in the boy with late-onset CAH described here was the suppression of puberty, shown by a sharp decline in gonadotropins and testosterone secretion with a concomitant decrease of IGF-1 concentration into the prepubertal range. The reasons for the discontinued growth spurt and reduced final height in this boy were multifactorial: (a) secondary early central puberty and subsequent treatment with GnRH agonist, (b) AN during puberty with a severe decline in sex hormone levels and (c) long-term treatment with periodically high doses of glucocorticoids. The diagnosis of AN, which is quite a rare disorder in boys, seems to be an important influencing factor and should be considered in children suffering from CAH with impaired growth.

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Conflict of Interest: None.

References

7 Boys IGF-I normal range. IGF-I normogram developed by Diagnostic Systems Laboratories, Inc., Texas, USA http://www.dslabs.com/ 2005