Growth in Patients with Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

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Key Words

Congenital adrenal hyperplasia • CYP 21 • Growth

Abstract

Background: One important goal in the management of children with classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is to achieve normal growth. Reviewing available data published over the last few years on growth and height outcomes in CAH patients, it becomes evident that an acceptable height can be achieved by many CAH patients. However, linear growth and final adult height may be stunted in some patients due to factors related to the timing of diagnosis, the age at therapy onset, the start of therapy, the adequacy of metabolic control, the quality of therapy, patient compliance and the experience of the treating physician. In children with CAH who have a poor height prognosis, additional treatment options should be considered. **Conclusions:** Treatment of children with CAH requires individualized approaches to prevent long-term growth failure.

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Introduction

Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (CYP21) is the most frequent inherited disorder of adrenal cortisol biosynthesis and includes salt-wasting (SW) or simple virilizing (SV) forms. The treatment of patients with CAH must be balanced, avoiding undertreatment (Addisonian crisis and androgen excess) or overtreatment (glucocorticoid [GC] excess). A main goal in the management of patients with classic CAH is to achieve normal growth. The answer to the question 'Is growth in CAH children normal or not?' can be approached in different ways. First, one can analyze final height (FH) data of CAH patients and compare them with published reference data, or compare FH with parental height or calculate FH data in standard deviation score (SDS) values and correct them with midparental height SDS values. Second, one can analyze different stages during the growth of a child with CAH to identify periods when optimization of therapy is especially important.

When comparing published reports on FH data of children with CAH, one must take into account that different growth data have been used as references and that FH data have not always been corrected for parental target height, particularly in older studies. The FH of adult male CAH patient is 170 cm; according to British refer-

ences [1], this is -0.71 the height SDS calculated, but -1.16 according to Swiss references [2] and -1.55 according to German references [3]. All calculated SDS values in this example are normal, but with regard to growth, the German CAH patient is more normal in the United Kingdom than in Germany. Moreover, a mean FH-SDS value of -1.0 (± 1.3 SD) for the cohort of CAH patients reveals that the mean value lies within the low-normal range of the reference group. These data also indicate that some patients with CAH have short stature with a height SDS below -2 SDS.

Goals of Therapy

In the consensus statement on 21-hydroxylase deficiency from the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society, the goals of CAH therapy were defined as adequate replacement of deficient steroids while minimizing adrenal sex hormone and glucocorticoid excess, preventing virilization, improving growth and protecting potential fertility [4].

Adult Height Data

Untreated, children with CAH are extremely short as adults [5, 6]. It is also commonly believed that most treated CAH patients achieve a final adult height that is shorter than that predicted based on mean parental height [7]. There are numerous publications showing that final adult height of CAH patients is less than the general population and that of the midparental height [8–21]. Comparison of different studies is limited, since different reference standards were used in different studies.

Eugster et al. recently published a retrospective chart review of 65 patients and a meta-analysis of height outcome from 18 studies reported in the medical literature over the past 22 years [22]. All height data were recalculated in SDS value, using the reference of Tanner et al. [1]. The final height SDS – target height SDS for the patients at the authors' institution was -1.03 . The meta-analysis of 561 patients revealed a mean final height SDS of -1.37 , and a mean final height SDS of -1.21 corrected for target height (204 patients). Thus, most patients with CAH lose final height.

Slightly better results were recently reported by Bonfig et al., who analyzed the height data of 125 adults with CAH [23]. Height SDS data were calculated using the Zu-

rich references [2]. Final height SDS corrected for target height SDS was -0.6 for females (no difference between SW- and SV-CAH), -0.9 for males with SW-CAH and -1.1 SDS for males with SV-CAH. These results differ from publications in which differences in final height between the different forms of CAH were found [24, 25].

Growth in CAH Children from Birth to Puberty

It has been shown that the birth length of Finnish patients with CAH is significantly greater than the national mean [13]. This observation was confirmed by Balsamo et al., who studied 101 children with different clinical forms of CAH and compared the data with standards for birth length and weight in an Italian control population [26]. In both sexes, the average birth length of patients with classic CAH was greater than the mean birth length of the patients in the control population, and both length and weight were greater in children with classic CAH than in those with the nonclassic form. Among the patients with classic CAH, those with the SW form were longer but also weighed less than those with the SV form. The authors speculated that genotype affects the birth length, as greater enzymatic activity impairment is associated with the longer birth length in CAH.

A retrospective analysis of untreated patients showed a normal growth pattern until 18 months of age, indicating that growth is insensitive to androgens during this period [27]. In a Finnish study, the mean length decreased from $+0.8$ SDS at birth to -1.0 SDS at 1 year of age [13]. The hydrocortisone dose of the first year correlated negatively with the growth velocity of the first year ($p < 0.001$), indicating that growth during infancy is sensitive to GCs. A negative correlation between GC dose and height at 2 years of age was also reported [16].

Many studies have proven that growth during puberty is diminished in CAH patients [16, 21, 28]. Peak height velocity occurs approximately 2 years earlier than normal in both male and female children with CAH and velocity peaks are reduced [11]. Total pubertal growth of CAH patients was significantly decreased (mean values; females SV-CAH: 11.9 cm, females SW-CAH: 13.8 cm; males SV-CAH 15.4 cm, males SW-CAH: 18.5 cm) in comparison with the reference population (females: 20.3 cm, males: 28.2 cm) [23]. One study confirmed the data of a multicenter analysis of a large database of 598 patients, which showed that pubertal growth is more impaired in patients with SV-CAH compared to SW-CAH patients [11].

Fig. 1. Growth chart of a boy with SW-CAH. Diagnosis was made at the age of 3 weeks due to a salt-wasting crisis. The main graph shows the height, the smaller graph shows the height velocity. Final height of 177 cm (-0.45 SDS) was within the target height (Z). Auxological reference data for height and height velocity: German references [3].

Published data reveal that GC dosing is critical for height gain in puberty. Patients treated with less than 20 mg of hydrocortisone/m² at the start of puberty were significantly taller than patients treated with more than 20 mg of hydrocortisone/m², irrespective of treatment with hydrocortisone or prednisone [23]. According to Stikkelbroeck et al., the critical period where overtreatment should be avoided is from 8 years of age until puberty [28].

Children with CAH who also have advanced skeletal maturation (indicating poor compliance with therapy or the late diagnosis of boys with the non-salt-losing form) may develop central precocious puberty due to androgen activation of the hypothalamic-pituitary-gonadal axis, exacerbating premature epiphyseal fusion. This condition can be managed with long-acting gonadotrophin-releasing hormone (GnRH) agonists similar to children with idiopathic central precocious puberty, but reports on the efficacy of GnRH agonist therapy in children with CAH are rare [29, 30].

Growth Curves of Selected CAH Patients

Figures 1 and 2 show the growth curves of two children with CAH. The boy with SW-CAH was diagnosed at the age of 3 weeks because of a salt-wasting crisis (fig. 1). He was treated with 10 to 15 mg/m²/d of hydrocortisone and 0.05 to 0.1 mg/d of fludrocortisone. Compliance and metabolic control were good. His final height (177 cm) was -0.45 SDS as compared to the reference population and -0.5 SDS corrected for target height.

Figure 2 shows the growth chart of a boy with SV-CAH. Diagnosis was made at the age of 2.6 years, and treatment with hydrocortisone was initiated with a dose of 14 mg/m²/d. At the age of 6 years, the boy was presented for a second opinion. His height was 136 cm, and his bone age (per Greulich and Pyle skeletal age standards) was 13 years. He was at Tanner stage 2 with testicular sizes of 5 ml. Metabolic control was poor, and in a 30-min GnRH test, a pubertal increase of luteinizing hormone and follicle-stimulating hormone was found. Despite

Fig. 2. Growth chart of a boy with SV-CAH. Diagnosis was made at the age of 2.6 years and treatment with hydrocortisone was started then. The main graph shows the height; the smaller graph shows the height velocity. The final height of 168 cm (−1.86 SDS) was significantly below the target height (Z). Auxological reference data for height and height velocity: German references [3].

long-standing therapy with a GnRH agonist and optimization of CAH therapy, his final height of 168 cm was −1.86 SDS below the reference and −2.89 SDS below target height.

Factors with Negative Impact on Growth

Many different factors influence growth and final height in children with CAH, and impaired growth is not caused by one factor alone. It has been shown that the mean final height SDS was better for CAH patients who were treated from early infancy [5], and significantly better if treatment was started before 1 year of age [13, 31]. These results were confirmed by a meta-analysis of 561 CAH patients [22]. Thus, one important factor in poor height outcome is late diagnosis and/or late initiation of therapy. It has also been shown that patients with good compliance had a better outcome than those with poor compliance. Noncompliant pa-

tients have periods of androgen excess, which causes premature fusion of the epiphyseal growth plate. However, the effect of poor compliance has not been clearly demonstrated [32].

Another important factor in the treatment of patients with CAH is the adequacy of replacement therapy. Treatment includes lifelong substitution with GC and with mineralocorticoids as well in patients with the salt-losing form of CAH. Many studies show that adequate sodium balance is essential for normal growth, and that adequate mineralocorticoid therapy may allow for lower GC dosing [33]. According to the consensus statement from the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society, hydrocortisone is the medication of choice until completion of growth [4]. Typical hydrocortisone dosing is 10 to 15 mg/m²/d, three times daily. Undertreatment with GC leads to androgen excess comparable to the status of noncompliance. However, inadequate final height in CAH patients is often attributed to overtreatment with

GC. Patients treated with high doses of GC (27 to 55 mg/m²/24 h) did not grow as well as patients receiving lower doses (15 to 36 mg/m²/24 h) [34]. In a prospective randomized crossover trial, significant negative correlations were found between height velocity and GC doses. Height velocity was significantly decreased during treatment with 25 mg/m² hydrocortisone compared with 15 mg/m² in 26 children ranging in age from 4 months to 15 years [35].

GCs interfere with the growth hormone (GH)-insulin-like growth factor I (IGF-I) axis at different levels [36]. High-dose, long-term treatment with GC may lead to growth disturbance, and this effect is mediated by several different mechanisms. These factors include impaired spontaneous GH secretion, impaired stimulated GH secretion and impaired responsiveness of target tissues to growth factors [37]. On the other hand, children with CAH show a more regular pattern of spontaneous GH secretion and a more synchronous joint GH-cortisol secretory dynamic if exogenous hydrocortisone is administered at fixed doses and at fixed time intervals [38].

The risk of overtreatment is increased when potent longer-acting GCs, such as prednisone, prednisolone or dexamethasone, are given at excessive doses. Treatment with prednisone leads to decreased growth in children and adolescents with CAH [23]. Hydrocortisone-equivalent doses were significantly higher in the prednisone-treated group at the age of 2 years and at the start of puberty. Different GC formulations have to be transformed into an equivalent dose of hydrocortisone using dosage equivalents if they are to be compared. Bonfig et al. considered one for hydrocortisone and four for prednisone [23], whereas the consensus statement recommends one for hydrocortisone and five for prednisone [4]. However, important studies by Punthakee et al. suggest that prednisolone is 15-times more potent than hydrocortisone per results of a small cohort of children with adrenal insufficiency [39].

There is one study showing normal growth and normal skeletal maturation in a small cohort of 26 children with CAH treated with dexamethasone, during a mean observation period of approximately 7 years; final height data have not been published [40]. The dosage equivalents were calculated as one for hydrocortisone and 70 for dexamethasone; whereas, according to pharmaceutical manufacturers' claims, dexamethasone is 30-fold more potent than hydrocortisone. Thus, conventional hydrocortisone equivalencies for dexamethasone will result in overtreatment and growth failure in children. When

used in the treatment of CAH, prednisone should be considered 15-times and dexamethasone at least 70-times more potent than hydrocortisone.

Experimental Therapies for Growth Improvement

The discussion about the significance of bilateral adrenalectomy for selected CAH patients is ongoing, but there have been no controlled trials to date. This treatment procedure was chosen because children with Addison disease receive lower GC replacement doses than children with CAH and do not suffer from short stature, overweight or androgen excess [20].

Other efforts to improve outcome include the use of drugs to decrease androgen levels or actions. There is an ongoing study comparing conventional treatment with reduced hydrocortisone dose (8 mg/m²/d) versus a regimen that includes fludrocortisone, an androgen-blocking substance (flutamide) and an aromatase inhibitor (testolactone) to avoid bone age acceleration [41]. The published 2-year data showed that the children in the experimental group had increased androgen levels, but normal linear growth and bone maturation. The authors concluded that this regimen allows effective control without the use of excessive doses of GCs. No FH data are yet available.

A small group of short CAH patients have been treated with GH either alone or in combination with a GnRH agonist. This regimen significantly improved the growth rate and predicted FH during an observation period of 2 years [42]. Recently, adult height data were published in a small group of 14 patients with CAH (8 males, 6 females) who received human growth hormone 0.3 mg/kg/week and the GnRH analogue leuprolide acetate 300 µg/kg intramuscularly every 28 days. The mean duration was 4.4 years for GH therapy and 4.2 years for GnRH analogue therapy. In the treatment group, the final height SDS of -0.4 ± 0.8 was significantly greater than both the initial prediction of -1.5 ± 0.9 and the final height SDS of the untreated group of -1.4 ± 1.1 [43]. This result suggests that some CAH patients with a poor height prediction were able to benefit from GH therapy.

Conclusions

Many patients with CAH can achieve an acceptable adult height; however, linear growth and FH may be compromised. The timing of diagnosis and start of therapy,

adequacy of metabolic control, quality of therapy, patient compliance and the treating doctor's experience are important factors in optimization of growth and in attainment of normal FH. When children with CAH have a poor height prognosis, additional treatment options should be considered. Treatment of children with CAH also requires an individual approach to maximize long-term growth.

Disclosure Statement

There is no conflict of interest declared.

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