Original Article

A Retrospective Analysis of the Growth Pattern in Patients with Salt-wasting 21-Hydroxylase Deficiency

Atsuko Kawano1, Hitoshi Kohno1, and Kenichi Miyako1

1 Department of Endocrinology and Metabolism, Fukuoka Children’s Hospital, Fukuoka, Japan

Abstract. The objective of this study was to investigate the growth pattern of children with the salt-wasting form of congenital adrenal hyperplasia caused by 21-hydroxylase deficiency (21-OHD). We reviewed the medical records of 13 patients in whom salt-wasting 21-OHD was diagnosed during the first 2 mo of life at our hospital from 1980 through 2008. Six reached adult height. Growth patterns, bone age, biochemical data, and the hydrocortisone dose at each growth stage were analyzed retrospectively. The mean adult height was 155.1 ± 6.5 cm (mean ± SD) in females and 158.1 ± 7.1 cm in males. Although length at birth was normal or longer than the national mean in almost all patients, the mean height SD score of both boys and girls decreased to below 0 SD during infancy. Subsequently, both boys and girls transiently showed growth acceleration and reached their peak growth velocity at 3–10 yr of age. In conclusion, in addition to suppression of growth during infancy, there was inappropriate growth acceleration during childhood. Especially from 3 mo to 3 yr of age, decreasing the hydrocortisone dose in patients who exhibit slower growth may lead to satisfactory height outcomes. Also, strict adjustment of the hydrocortisone dose to avoid accelerated growth from childhood to adolescence might improve adult height outcomes of patients with 21-OHD.

Key words: growth, congenital adrenal hyperplasia, 21-hydroxylase deficiency, childhood

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that affects cortisol biosynthesis. Most cases are caused by a deficiency of the enzyme 21-hydroxylase. Various mutations of the 21-hydroxylase gene located on the short arm of chromosome 6 result in different degrees of CAH (1). Clinical manifestations of CAH are mainly caused by deficiencies of cortisol and aldosterone in combination with androgen excess.

Short stature is one of the most important concerns in the treatment of children with CAH (2). Androgen excess leads to rapid growth and early bone maturation. Advanced bone age due to high androgen levels is responsible for decreased adult height. In addition, androgen excess can lead to precocious puberty, which also accelerates bone maturation. Glucocorticoid replacement therapy aims at preventing adrenal crisis and suppressing excessive androgen production. However, overdoses of glucocorticoids can suppress growth and cause obesity. Thus, both
overtreatment and undertreatment can reduce adult height.

Although some studies have reported that patients with CAH can achieve an acceptable adult height (3, 4), the management of growth in this disease remains challenging. Adult height outcomes are not always satisfactory, even if patients are treated from birth (5, 6). Many attempts have been made to increase adult height, but the optimal therapeutic regimen for CAH remains a matter of debate.

The aim of this study was to delineate the characteristics of the growth pattern in patients with 21-hydroxylase deficiency (21-OHD) in our institute and to investigate problems in management.

Methods

We studied 15 patients in whom 21-OHD was diagnosed and treatment was initiated within the first 2 mo of life at Fukuoka Children’s Hospital from 1980 through 2008.

Because only 2 of these 15 patients had the simple-virilizing form of CAH, we analyzed the other 13 patients who had the salt-wasting form. None of the patients had central precocious puberty. The diagnosis of 21-OHD was confirmed on the basis of markedly elevated levels of 17-hydroxyprogesterone (17-OHP) and clinical signs of adrenal insufficiency, including pigmentation and genital ambiguity in girls. Data on biochemical variables, body weight, height, bone age, and the dose of hydrocortisone at each developmental stage were collected retrospectively from the patients’ charts. Biochemical data included the levels of 17-OHP, ACTH, and testosterone. The pattern of changes in height standard-deviation score (height SD score) and growth velocity was analyzed.

Physical and biochemical data were recorded at regular visits every 3–4 mo in infancy and childhood and every 4–6 mo in adolescence.

Bone age was evaluated according to the atlas of Greulich and Pyle (7). Adult height was defined by a growth velocity of less than 1 cm/yr or by epiphyseal closure on radiographs. Diagnosis of the salt-wasting form was based on the presence of hyponatremia that required fludrocortisone to normalize the serum sodium levels. Diagnosis of the simple virilizing form was based on the lack of clinical and biochemical evidence of salt loss. Hydrocortisone was administered to all patients 2–3 times daily. Fludrocortisone was administered to all patients with the salt-wasting form. The dosage of hydrocortisone was adjusted individually to avoid excessive elevations of 17-OHP and ACTH.

The height SD score was calculated using Japanese population data provided by the Japanese Ministry of Health, Labor and Welfare and Ministry of Education, Culture, Sports, Science and Technology. Growth velocity curves were constructed at 6-mo intervals. Body mass index was calculated by dividing the weight (in kilograms) by the height (in meters squared). Obesity was defined as a body mass index of >25 or a body weight equivalent to >120% of standard body weight. The growth stages were defined as follows: infancy, 0–23 mo; early childhood, 2–4 yr; middle childhood, 5–10 yr; late childhood and adolescence, 11–21 yr. Because only 6 patients had reached adult height and the others were still growing, the numbers of subjects differed according to age group. The numbers of subjects were 13 for infancy, 12 for early childhood, 10 for middle childhood, 8 for late childhood, and 6 for adolescence.

In order to study the relationship between growth and the dose of hydrocortisone, we compared the change in length during the first year of treatment in patients who received relatively lower dose of hydrocortisone (<40 mg/m²/d) with higher dose of hydrocortisone (>40 mg/m²/d).

This study was approved by Ethics Committee of Fukuoka Children’s Hospital.
**Results**

**Patient characteristics**

The study group comprised 13 patients (4 females, 9 males) with salt-wasting 21-OHD. No patient had other illnesses potentially altering the growth pattern (e.g., renal failure) or was receiving other drugs known to affect growth, including those used to manage precocious puberty. All patients were given a diagnosis of 21-OHD within the first 2 mo of life. The mean age at diagnosis was 15 d (range, 3–49 d). Four patients were born before the initiation of neonatal mass-screening for CAH.

At the beginning of treatment, oral hydrocortisone was divided into 3 times daily. But 4 patients changed from three times to twice daily dosing during childhood. Poor adherence to medication was suspected in 6 patients.

Six of the 13 patients developed acute adrenal crisis during treatment. All episodes were secondary to acute respiratory infection or gastroenteritis. The frequency of crisis was once or twice, and the severity was mild.

**Adult height**

Adult height was achieved by 6 patients (3 men and 3 women). The mean adult height was 155.1 ± 6.5 cm (mean ± SD) in females and 158.1 ± 7.1 cm in males. The median adult height was 153.0 cm (range: 149.2–163 cm) in females and 161.8 cm (range: 151.2–163.5 cm) in males. The height SD score of the mean adult height in our patients was –0.56 in females and –2.21 in males. Because their parental heights were not available, a comparison between their target height and adult height could not be made. However, with the exception of 1 woman who reached 163.5 cm, all adult heights were shorter than the mean adult height for the Japanese general population (158.1 cm for females; 170.8 cm for males).

**Growth**

In all patients, body length at birth was normal or longer than the national mean, except for 2 patients who had perinatal problems (premature membrane rupture and gestosis). The mean lengths of the boys and girls subsequently decreased to below the respective national means by 6 mo of age (Fig. 1). Although Fig. 1 shows that there was great variability in height SD score at each age, a decrease in height SD score was found in all patients during infancy. The decrease in height SD score was greater in boys than in girls. On the other hand, both boys and girls transiently showed growth acceleration between 3 and 10 yr (Fig. 2). Excessive growth was more apparent in boys than in girls. Both boys and girls tended to reach their peak growth velocity at 3–10 yr of age. The mean pubertal growth velocity in the patients with CAH was lower than that of the standard population.
Biochemical data and bone age

The mean levels of ACTH, 17-OHP, and testosterone are shown according to age in Fig. 3. All 3 variables showed similar patterns. The levels of ACTH, 17-OHP and testosterone were suppressed in infancy. Even though the hydrocortisone dose per square meter body surface was decreased according to growth, the decrease in hydrocortisone dose was not enough to normalize the levels of ACTH and 17-OHP. Suppression of the levels of ACTH and 17-OHP was continued during the first 2 yr of life. Conversely, these parameters began to rise in early childhood, consistent with growth acceleration. Changes in these variables were more dynamic in boys than in girls. The bone age was delayed during infancy in both boys and girls, but subsequently advanced in parallel to the elevation of hormonal variables (Fig. 4).

Hydrocortisone dose

Figure 5 shows the mean dose of hydrocortisone according to age. Similar to the height SD score and biochemical data, changes in the dose of hydrocortisone were more prominent in boys than in girls. The hydrocortisone dose was
An analysis of the growth pattern in 21-OHD

largely unchanged during childhood, which led to a growth-related decrease in the hydrocortisone dose per square meter of body surface area.

Although 6 of the 13 patients received relatively low doses of hydrocortisone (<40 mg/m²/d), all showed poor growth in infancy, and their height at 1 yr was below the mean of the general population. The mean doses of hydrocortisone during the first year of treatment in lower dose group and higher dose group were 24.8 and 41.8 mg/m²/d. Growth suppression in infancy was more remarkable in patients who received higher doses of hydrocortisone (>40 mg/m²/d). The mean change between the height SD score at birth and that at 1 yr was −2.3 in males and −2.2 in females who received >40 mg/m²/d of hydrocortisone, as compared with −0.65 in males and −0.4 in females who received <40 mg/m²/d of hydrocortisone.

Cushing’s syndrome did not develop in any patient, but 2 patients became obese during the study. Both obese patients had risk factors for obesity, such as bad eating habits and a family history of obesity.

Discussion

In addition to avoidance of a life-threatening crisis of adrenal insufficiency, maintaining normal height velocity and achieving normal adult height are important treatment goals in children with 21-OHD. In our study, the adult heights of the patients with CAH did not reach the mean adult height for the Japanese general population. These results indicate that short stature remains an important problem in patients with 21-OHD in our institute, despite early diagnosis and initiation of treatment.

Height velocity in our patients changed dramatically during two different periods and was characterized by growth suppression in infancy and inappropriate growth acceleration in childhood. Many studies have documented growth restriction during infancy in patients with CAH who receive hydrocortisone (8–10). Delayed bone age and growth restriction during infancy are attributed to overtreatment with hydrocortisone. Consistent with previous reports, patients who received a relatively high dose of hydrocortisone had more severe growth

Fig. 4. Bone age at each age in boys (black circle) and girls (gray circle).

Fig. 5. Mean dose of hydrocortisone according to age in boys (black bars) and girls (gray bars) with salt-wasting CAH.
retardation during infancy than those who received a lower dose in our study. In addition, the mean dose of hydrocortisone during the first 6 mo of life was higher in boys than in girls, which probably resulted in more prominent growth suppression in boys. However, there is no clear explanation for the difference between boys and girls in the hydrocortisone dose during the first 6 mo of life.

A recent study showed that growth during the first year of life is not very sensitive to androgens because increased height velocity does not occur during the first year of life in untreated patients with simple-virilizing CAH (11). Given that hydrocortisone levels exceeding the physiological levels of cortisol secretion are not required to adequately suppress adrenal androgen production and to prevent growth acceleration during infancy, the higher prevalence of growth suppression during infancy associated with hydrocortisone treatment can be explained. Treatment with lower doses of hydrocortisone could hypothetically improve growth during infancy. However, the optimal dose of hydrocortisone required to prevent adrenal insufficiency and to maintain normal growth in infants with CAH remains unclear.

Growth suppression during the first year of life is thought to be responsible for reduced adult height. Manoli et al. also reported that adult height positively correlates with the height at 2 yr of age in patients with salt-wasting CAH (12). A negative correlation between the glucocorticoid dose and growth during infancy has been reported (13–15). However, there was no correlation between adult height and height during infancy in our study (data not shown); this is probably because growth patterns changed after infancy. Most patients transiently showed growth acceleration during childhood.

Although normal growth up to puberty has been reported by many authors in patients with an early diagnosis of CAH (12, 16), our patients showed inappropriate growth acceleration during childhood. The growth acceleration during childhood in our study may be attributed to three reasons. First, the growth-related decrease in the hydrocortisone dose per square meter of body surface area resulted in an insufficient hydrocortisone dose. Second, oral hydrocortisone was often divided into 2 daily doses, rather than 3, in children after they entered kindergarten or grade school. Third, poor compliance with prescribed medication often occurred from childhood to adolescence. Although the precise cause remains unclear, the combined effects of these factors might have resulted in inappropriate growth acceleration after infancy.

Giving hydrocortisone three times rather than twice daily and adjusting the hydrocortisone dose according to regular monitoring of bone age and growth may be helpful in preventing acceleration of growth and bone maturation during childhood.

There are conflicting reports as to whether peak growth velocity during puberty is impaired in CAH. Decreased pubertal peak growth velocity has been reported (8, 9, 16, 17). The advanced bone age at the onset of puberty is assumed to explain the reduced pubertal growth in patients with a late diagnosis of CAH. Moreover, overtreatment at the onset of puberty can also reduce pubertal growth by excessively suppressing androgen production. Nike et al. found a negative correlation between the glucocorticoid dose and pubertal growth (18). Conversely, some previous studies reported that growth height velocity during puberty is normal in some patients with CAH (4, 10). A longitudinal analysis performed by Harigitai et al. showed that peak growth velocity is normal, but occurs approximately 2 yr earlier (16). In the present study, the mean pubertal height gain was reduced. Moreover, bone age was advanced during early childhood. Advanced bone age might be responsible for the reduced pubertal growth. Growth acceleration in childhood remains to be fully explored in patients with an early diagnosis of CAH.

To our knowledge, this is the first report to clearly document the distinctive pattern of
growth acceleration during childhood in patients with CAH. However, our study had several limitations. First, this study is a single institution review with small sample size, resulting in limited statistical power. Second, because national longitudinal data on growth velocity were not available, we used cross-sectional data for reference. Comprehensive data on the onset of pubertal development and parental height were also lacking.

In conclusion, a sufficient adult height was not achieved in some patients with CAH, despite the early initiation of treatment. Our findings indicate that adult height in CAH is influenced not only by growth suppression in infancy, but also by inappropriate growth acceleration during childhood. Thus, treatment with lower doses of hydrocortisone in infancy to maintain normal growth, followed by strict adjustment of the hydrocortisone dose during childhood, could be one of the keys to achieving favorable height outcomes in patients with CAH.

Disclosures: Atsuko Kawano wrote the first draft of this manuscript. No persons received an honorarium, grant, or other form of payment to produce this manuscript.

References

1. Trakakis E, Loghis C, Kassanos D. Congenital adrenal hyperplasia because of 21-hydroxylase deficiency. Obstet Gynecol Surv 2009;64:177–89. [Medline] [CrossRef]

2. Young MC, Ribeiro J, Hughes IA. Growth and body proportions in congenital adrenal hyperplasia. Arch Dis Child 1989;64:1554–8. [Medline] [CrossRef]

3. Hoepffner W, Kaufhold A, Willgerodt H, Keller E. Patients with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency can achieve their target height: the Leipzig experience. Horm Res 2008;70:42–50. [Medline] [CrossRef]

4. Dürr HG. Growth in patients with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Horm Res 2007;68(Suppl 5):93–9. [Medline] [CrossRef]

5. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet 2005;365:2125–36. [Medline] [CrossRef]

6. Joint LWPES/ESPE CAH Working Group. Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. J Clin Endocrinol Metab 2002;87:4048–53. [Medline] [CrossRef]

7. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist, 2nd ed. Stanford University Press;1959.p.18–60.

8. Van der Kamp HJ, Otten BJ, Buitenweg N, De Muinck Keizer-Schrama SM, Oostdijk W, Jansen M, et al. Longitudinal analysis of growth and puberty in 21-hydroxylase deficiency patients. Arch Dis Child 2002;87:139–44. [Medline] [CrossRef]

9. Muirhead S, Sellers EA, Guyda H, Canadian Pediatric Endocrine Group Indicators of adult height outcome in classical 21-hydroxylase deficiency congenital adrenal hyperplasia. J Pediatr 2002;141:247–52. [Medline] [CrossRef]

10. Frisch H, Waldhauser F, Lebl J, Solyom J, Hargitai G, Kovacs J, et al. MEWPE-CAH Study Group Congenital adrenal hyperplasia: lessons from a multinational study. Horm Res 2002;57(Suppl 2):95–101. [Medline] [CrossRef]

11. Claahsen-van der Grinten HL, Noordam K, Borm GF, Otten BJ. Absence of increased height velocity in the first year of life in untreated children with simple virilizing congenital adrenal hyperplasia. J Clin Endocrinol Metab 2006;91:1205–9. [Medline] [CrossRef]

12. Manoli I, Kanaka-Gantenbein C, Voutetakis A, Maniati-Christidi M, Dacou-Voutetakis C. Early growth, pubertal development, body mass index and final height of patients with congenital adrenal hyperplasia: factors influencing the outcome. Clin Endocrinol (Oxf) 2002;57:669–76. [Medline] [CrossRef]

13. Silva IN, Kater CE, Cunha CF, Viana MB. Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia. Arch Dis Child 1997;77:214–8. [Medline] [CrossRef]

14. Young MC, Hughes IA. Response to treatment of
congenital adrenal hyperplasia in infancy. Arch Dis Child 1990;65:441–4. [Medline] [CrossRef]  
15. Jääskeläinen J, Voutilainen R. Growth of patients with 21-hydroxylase deficiency. Pediatr Res 1997;41:30–3. [Medline] [CrossRef]  
16. Hargitai G, Sólyom J, Battelino T, Lebl J, Pribilincová Z, Hauspie R, et al. MEWPE-CAH Study Group Growth patterns and final height in congenital adrenal hyperplasia due to classical 21-hydroxylase deficiency. Results of a multicenter study. Horm Res 2001;55:161–71. [Medline] [CrossRef]  
17. Bonfig W, Bechtold S, Schmidt H, Knorr D, Schwarz HP. Reduced final height outcome in congenital adrenal hyperplasia under prednisone treatment: deceleration of growth velocity during puberty. J Clin Endocrinol Metab 2007;92:1635–9. [Medline] [CrossRef]  
18. Stikkelbroeck NM, Van’t Hof-Grootenboer BA, Hermus AR, Otten BJ, Van’t Hof MA. Growth inhibition by glucocorticoid treatment in salt wasting 21-hydroxylase deficiency: in early infancy and (pre)puberty. J Clin Endocrinol Metab 2003;88:3525–30. [Medline] [CrossRef]