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Growth Pattern of Untreated Boys with Simple Virilizing Congenital Adrenal Hyperplasia Indicates Relative Androgen Insensitivity during the First Six Months of Life

W. Bonfig^{a, b} H.P. Schwarz^b^aDivision of Pediatric Endocrinology, Department of Pediatrics, Technische Universität München, and^bDivision of Pediatric Endocrinology, Dr. von Haunersches Kinderspital, Ludwig-Maximilians Universität München, Munich, Germany

Key Words

Congenital adrenal hyperplasia · Glucocorticoids · Androgen sensitivity

Abstract

Context: Mild forms of simple virilizing congenital adrenal hyperplasia (CAH) may be missed in newborn screening. In the pre-newborn-screening era, missed diagnosis of simple virilizing CAH was not infrequent in boys. Elevated adrenal androgens lead to accelerated growth and bone maturation. Traditional treatment of CAH consists of the suppression of ACTH through glucocorticoid replacement, in an attempt to reduce excessive androgen production. **Objective:** To retrospectively analyze early growth pattern and bone maturation in untreated boys with simple virilizing CAH. **Patients:** In the pre-newborn screening era, 13 boys had a late diagnosis of simple virilizing classical CAH. Diagnosis of 21-hydroxylase deficiency was confirmed by mutation analysis of the *CYP21A2* gene in all patients. Growth data were retrospectively collected from standardized preventive medical checkups at the regular pediatrician until the time of diagnosis of CAH. **Results:** Length was 0.1 ± 0.8 SDS (mean \pm SD) at birth, 0.2 ± 1 SDS at 3 months, 0.2 ± 0.9 SDS at 6 months,

0.7 ± 1 SDS at 1 year, $+1.1 \pm 0.9$ SDS at 2 years and $+1.8 \pm 1.2$ SDS at 4 years. At diagnosis, mean chronological age was 4.4 ± 1.6 years and height SDS was 2 ± 1.7 . Bone age was accelerated (9.4 ± 4 years) at diagnosis. Signs that had led to diagnosis were pubic hair ($n = 11$), accelerated growth rate ($n = 6$) and birth of an affected sister ($n = 3$). Despite late start of hydrocortisone treatment, mean final height was -1 ± 0.9 SDS. Seven of 18 patients had a final height within 1 SD of target height. **Conclusion:** Height velocity is not markedly increased in untreated boys with simple virilizing CAH in the first 6 months of life, indicating that infants are relatively androgen insensitive during that period. After the first 6 months of life, growth velocity increases significantly and elevated androgens lead to advanced skeletal maturation. This observation has implications for lower hydrocortisone doses to be used in CAH children during the first 6 months of life. In addition, staying alert for clinical symptoms and signs of simple virilizing CAH is still warranted, since mild forms may be missed in newborn screening.

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Fax +41 61 306 12 34
E-Mail karger@karger.ch
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www.karger.com/hrpWalter Bonfig
Klinik und Poliklinik für Kinder- und Jugendmedizin
Klinikum Rechts der Isar, TU München
Kölner Platz 1, DE–80804 München (Deutschland)
Tel. +49 89 3068 2350, Fax +49 89 3068 3950, E-Mail Walter.Bonfig@lrz.tum.de

Introduction

Congenital adrenal hyperplasia (CAH) is caused by the loss or severe decrease in activity in 1 of the 5 steroidogenic enzymes involved in cortisol biosynthesis. 21-Hydroxylase deficiency is found in over 90% of all cases [1]. It is caused by mutations in the 21-hydroxylase gene *CYP21A2*, which is located in the human leukocyte antigen (HLA) gene cluster region on the short arm of chromosome 6 (6p21.3) [2]. The disease is divided on clinical criteria into the classical and the nonclassical forms. The worldwide incidence of classical 21-hydroxylase deficiency is approximately 1 in 14,000 births [3]. Therefore, carrier frequency of this autosomal-recessive disease is about 1 in 60. The deficiency of 21-hydroxylase leads to accumulation of 17-hydroxyprogesterone and results in increased production of adrenal androgens, and decreased production of cortisol. In addition to impaired cortisol biosynthesis, aldosterone production may be decreased as well (salt-wasting CAH).

In simple virilizing CAH there is virilization of external genitalia in newborn females, and pseudoprecocious puberty due to overproduction of androgens in both sexes. In salt-wasting CAH, additional severe renal salt loss occurs as a consequence of aldosterone deficiency.

Overproduction of androgens causes virilization, accelerated growth, advanced skeletal maturation, and early epiphyseal fusion. Whereas the various forms of CAH differ in their degree of enzymatic deficiency, they all represent a therapeutic challenge to pediatric endocrinologists attempting to optimize growth.

Nowadays diagnosis of classical CAH is no longer delayed in industrialized countries, since newborn screening is available, but mild forms of simple virilizing CAH may be missed in newborn screening [4].

Traditional treatment of CAH consists of the suppression of ACTH through glucocorticoid replacement in an attempt to reduce excessive androgen production and its consequences. Parsimonious treatment with glucocorticoids may result in androgen excess with advancement of bone age, and a reduced final height. In overtreatment, growth is suppressed by the growth-inhibiting effects of glucocorticoids. Further side effects of overtreatment are truncal obesity and osteoporosis. According to the consensus statement of the Lawson Wilkins Pediatric Endocrine Society and the European Society of Pediatric Endocrinology, typical hydrocortisone doses range from 10 to 15 mg hydrocortisone per m² per day, but higher doses up to 25 mg per m² per day are believed to be necessary initially [5]. Alternate approaches to the treatment of

CAH have been investigated recently, including the use of antiandrogens, aromatase inhibitors, and adrenalectomy [6]. However, the mainstay of therapy remains judicious glucocorticoid treatment along with careful monitoring of growth velocity, skeletal maturation and monitoring of urine, serum and salivary steroid hormone levels [7].

In this paper, we report on the growth pattern of 13 male patients with delayed diagnosis of simple virilizing CAH.

Patients and Methods

In the pre-newborn screening era 13 boys were belatedly diagnosed with simple virilizing CAH. Growth data were collected retrospectively from standardized medical check-ups at their regular pediatrician at 3, 6, 12, 24, 48 and 60 months of age. Patients were diagnosed clinically by symptoms and signs of pseudoprecocious puberty, accelerated growth, or birth of an affected sister. Diagnosis of CAH was reconfirmed by comprehensive genotyping [8] later in all patients (deletion of one gene and mutation of a second gene $n = 4$, compound heterozygous mutations $n = 9$). Two patients had the P30L mutation, which usually presents with a non-classic CAH phenotype. However, these 2 patients presented with the clinical picture of simple virilizing CAH. After the diagnosis of CAH was established, all patients were treated with hydrocortisone three times daily with doses between 12 and 20 mg/m² body surface area per day. All patients were followed until they reached adult height. Height standard deviation scores (H-SDS) were calculated with a growth calculator, using reference data from Prader et al. [9], which is used in the 'Alpine' region (Switzerland, Austria, southern Germany). Body mass index (BMI) was calculated as weight [kg]/height [m]² and BMI-SDS was derived from data published by Cole et al. [10].

Bone age was assessed by X-ray of the left hand using the Greulich and Pyle method [11]. Bone age was read by both an experienced pediatric endocrinologist and a radiologist.

Statistical analyses were performed with the nonparametric Wilcoxon test and correlation was assessed by the nonparametric Spearman-Rho method. Statistical analyses were done with the SPSS 15.0 software, SPSS Inc., Chicago, Ill., USA 2002. $p < 0.05$ was considered statistically significant.

Results

Birth length corrected for gestational age was average in all boys with delayed diagnosis of CAH (mean birth length 0.1 ± 0.8 SDS, median 0.1 SDS). Table 1 shows data on mutation analysis, clinical presentation, height SDS and bone age at the time of diagnosis. Signs that had led to diagnosis of CAH were pubic hair ($n = 11$), acceler-

Table 1. Mutation analysis, clinical presentation, height and bone age at diagnosis

Patient No.	Mutation analysis		Clinical presentation	Age at Dx years	Height at Dx (SDS)	Bone age at Dx years	Final height (adult height) (SDS)	FH-TH (SDS)
	allele 1	allele 2						
1	complete deletion	P30L	pubic hair, genital status	6.8	1.4	11	-1	-0.8
2	Intron 2	I172N	pubic hair, genital status, growth spurt	1.3	2.8	2	0.8	-0.5
3	complete deletion	P30L	pubic hair, genital status	6.3	1.5	10	-0.7	0.4
4	Intron 2	I172N	birth of sister with CAH, growth spurt	4.1	2.2	7	-0.2	-0.6
5	I172N	I172N	pubic hair, genital status, growth spurt	2.6	1.6	5.5	-2.2	-0.8
6	I172N	I172N	pubic hair, genital status, growth spurt	3.6	3	11.5	-0.9	-1.6
7	Intron 2	Intron 2	pubic hair, genital status	2.8	0.3	6	-1.2	-0.8
8	complete deletion	I172N	pubic hair, genital status, birth of sister with CAH	4	3	9	-1.5	-1.3
9	I172N	I172N	pubic hair, genital status, growth spurt	5	3.7	12	-1.1	-2.4
10	Intron 2	I172N	pubic hair, genital status, birth of sister with CAH	5.7	3.5	10	-0.7	-1.2
11	Intron 2	I172N	pubic hair, genital status	5.1	2.5	8	-1.5	-1.7
12	I172N	I172N	completed growth	16	-2.6	18	-2.9	-1.9
13	complete deletion	I172N	pubic hair, genital status, growth spurt	5	3.4	12.5	0.2	0.2

Dx = Diagnosis; FH-TH = Final height-target height = corrected final height.

ated growth rate ($n = 6$) and birth of an affected sister ($n = 3$). At diagnosis, mean chronological age of the 13 boys was 4.4 ± 1.6 years (median 4.6 years) and H-SDS was $+2 \pm 1.7$ SDS (median 2.5 SDS) and bone age was significantly accelerated [9.4 ± 4 years (median 10 years)]. A positive linear correlation between age at diagnosis and bone age acceleration was found ($r = 0.7$, $p < 0.05$) (fig. 1). The growth pattern of these boys with delayed diagnosis of simple virilizing CAH is shown in figure 2: at birth ($n = 13$) length was 0.1 ± 0.8 SDS (mean \pm SD), at 3 months ($n = 13$) 0.2 ± 1 SDS, at 6 months ($n = 13$) 0.2 ± 0.9 SDS, at 1 year ($n = 13$) 0.7 ± 1 SDS, at 2 years ($n = 9$) $+1.1 \pm 0.9$ SDS and at 4 years ($n = 8$) $+1.8 \pm 1.2$ SDS. Accordingly, mean height SDS increased by 0.1 SDS during the first 6 months ($p > 0.05$), by 0.5 SDS between 6 and 12 months ($p < 0.05$), by 0.4 SDS in the second year ($p < 0.05$), and by 0.7 SDS between the ages of 2 and 4 years ($p < 0.05$).

BMI-SDS did not change significantly during the first 4 years of life (BMI-SDS at 1 year -0.7 ± 1 [median -0.6], at 2 years -0.4 ± 0.9 [median -0.7] and at 4 years -0.4 ± 1 [median -0.2]).

Despite late start of conventional hydrocortisone treatment with doses between 12 and 20 mg/m² body surface area, mean final height (adult height) was -1 ± 0.9 SDS. Mean corrected final height (final height-target height) was -1 ± 0.8 SDS (median -0.8 SDS) and 7 of 13 patients reached a final height within 1 SD of parental target height.

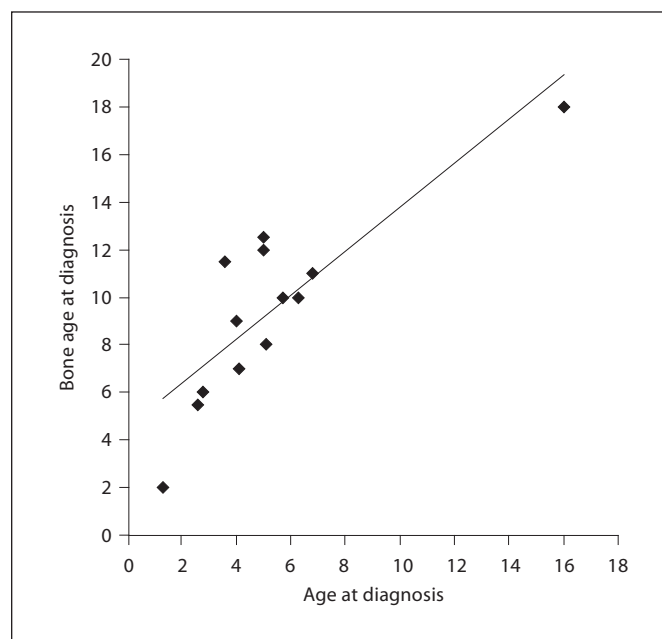
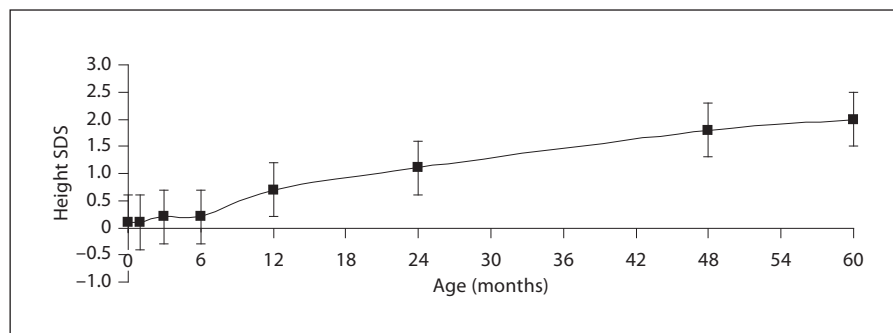


Fig. 1. Correlation between age at diagnosis and bone age at diagnosis.

Discussion

In this small but well-documented cohort of belatedly diagnosed boys with simple virilizing CAH, growth during the first 6 months of life was not accelerated in the

Fig. 2. Growth pattern of 13 boys with delayed diagnosis of simple virilizing CAH. Course of height SDS in untreated simple virilizing CAH boys.



absence of glucocorticoid treatment. So far, similar observations have been published in 32 patients only [12, 13]. At first sight one might ask if this is a noteworthy finding, but we believe that this is an important observation, because it points out that infants with early diagnosed CAH might not need high doses of hydrocortisone during the first 6–12 months of age and that suboptimal hormonal control could be tolerated at that age. Initial treatment with higher doses of up to 25 mg hydrocortisone per m^2 per day, as suggested by the consensus statement of the LWPES and the ESPE [5], might have long-term deleterious effects on growth and metabolism and may not be necessary. Our experience is that hydrocortisone doses at the lower end of the consensus statement recommendation are sufficient for normal linear growth and avoidance of adrenal crisis, if hydrocortisone doses are duplicated during illness and acute stress.

Thilén et al. [12] report that early growth is not increased in 14 untreated Swedish children with moderately severe 21-hydroxylase deficiency during the first 18 months of age. They also report on one British 4-month-old female infant that was diagnosed with simple virilizing CAH, whose parents refused glucocorticoid treatment until the age of 4 years. That girl was prospectively followed, and until the age of 18 months, growth was linear and bone age was not accelerated despite high concentrations of plasma androgens.

In a Dutch study of 17 untreated patients with late diagnosis of simple virilizing CAH, a similar growth pattern was observed [13]. Until the age of 12 months, growth velocity was not accelerated. But after 1 year of age, growth velocity increased significantly.

This observation suggests that the androgen excess is either relatively moderate during the first year of life or that the androgen sensitivity changes after the first year of life.

The thesis of relative androgen insensitivity of infants can also be supported by the observation of linear growth of infants during the minipuberty of infancy. During the first 6 months of age in boys and during the first 12 months of age in girls, sex hormones may reach pubertal concentrations. Nevertheless, infants show normal linear growth and regular advancement of bone age [14].

In our cohort, birth length was average in boys with classical CAH. In contrast, significantly increased birth length was observed in an Italian and in a Finnish population with classical CAH [15, 16]. Worldwide, healthy males are known to be heavier than healthy females at term birth. This difference is at least partially explained by androgen action in utero [17].

In the majority of our patients, the I172N mutation was found on the mildest disease-causing allele. This genotype correlates clearly with the simple virilizing CAH phenotype [8]. The P30L mutation, which usually presents with a non-classic CAH phenotype, was present in 2 patients. However, these 2 patients presented with the clinical picture of simple virilizing CAH. Today, it is still important to stay alert for clinical symptoms and signs of simple virilizing CAH and not to rely on newborn screening alone, because mild forms (e.g. I172N genotype) may be missed by newborn screening [4]. In our cohort, the most frequent symptoms and signs were pubic hair, enlargement of genitalia and increased height velocity after the age of 6 months.

In summary, infants with simple virilizing CAH seem to be relatively androgen insensitive during the first 6 months of life. This observation has implications for glucocorticoid therapy of children with moderate forms of CAH during the first 6 months of life, especially when diagnosed early by newborn screening. In these children, treatment with conventional doses of hydrocortisone might result in growth suppression during the first year of life when growth velocity is fastest.

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