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Growth Patterns in the First Three Years of Life in Children with Classical Congenital Adrenal Hyperplasia Diagnosed by Newborn Screening and Treated with Low Doses of Hydrocortisone

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Key Words
Congenital adrenal hyperplasia · Newborn screening · Growth · Glucocorticoids

Abstract
Background: Linear growth is the best clinical parameter for monitoring metabolic control in classical congenital adrenal hyperplasia (CAH). ***Objective:*** To analyze growth patterns in children with CAH diagnosed by newborn screening and treated with relatively low doses of hydrocortisone during the first year of life. ***Patients and Methods:*** 51 patients (27 females) were diagnosed with classical CAH by newborn screening. All patients were treated with relatively low doses of hydrocortisone (9–15 mg/m^2 body surface area). 47 patients were additionally treated with fludrocortisone. ***Results:*** At birth, height SDS (H-SDS) was 1.1 ± 1 in girls and 0.9 ± 1.5 in boys. After 3 months, H-SDS decreased to 0.4 ± 0.9 in girls and to 0.1 ± 1.3 in boys. Over the 3-year period, H-SDS further decreased to –0.4 ± 1.8 in girls and to –0.8 ± 1 in boys and approached the genetic height potential (target H-SDS of girls –0.5 ± 0.3 and target H-SDS of boys –0.9 ± 0.7). During the first 9 months of age, growth velocity was slightly decreased in girls (18.2 ± 1.9 cm) and boys (17.3 ± 1.6 cm) when compared to a healthy reference population (girls 19.0 ± 3.9 cm and boys 18.7 ± 4.7 cm). At the age of 3 years, bone age was appropriate for chronological age in both girls (2.7 ± 0.5 years) and boys (2.9 ± 0.5 years). ***Conclusion:*** Birth length is above average in children with classical CAH, which might be the result of untreated hyperandrogenism in utero. With relatively low doses of hydrocortisone treatment, growth velocity decreases slightly during the first 9 months and H-SDS then approaches the genetic height potential.

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. In over 90% of all cases, 21-hydroxylase deficiency is found [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 grounds into the classical and the nonclassical forms.

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There are different degrees of severity of the same enzymatic deficiency in these two forms of the disease. 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. 21-hydroxylase deficiency 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. While 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.

Traditional treatment consists of the suppression of ACTH through glucocorticoid replacement, in attempt to reduce excessive androgen production and its consequences. Low-dose 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. Alternate approaches to the treatment of CAH have been investigated recently, including the use of antiandrogens, aromatase inhibitors and adrenalectomy [4]. However, the mainstay of therapy remains judicious glucocorticoid treatment along with careful monitoring of growth velocity and skeletal maturation, along with urine, serum and salivary steroid hormone levels [5].

Since newborn screening is available nowadays, diagnosis of CAH is no longer delayed. There is some evidence that infants with CAH are relatively androgen-insensitive during the first year of life [6]. Thus, it seems reasonable and ethical to treat infants with CAH with lower doses of hydrocortisone during that period.

Patients and Methods

In Bavaria, newborn screening for CAH started on January 1, 1999. Since then, 51 patients (27 females, 24 males) diagnosed with classical CAH due to 21-hydroxylase deficiency were referred to our institution. The diagnosis of 21-hydroxylase deficiency was confirmed by genotyping in all patients (5 patients with homozygous deletion of the whole gene, 15 patients with deletion of one gene and mutation of second gene, 7 patients with conversion of one gene and mutation of second gene, 24 patients with compound heterozygous mutations; table 1). The diagnosis was also reconfirmed by hormonal analysis (low cortisol and elevated 17-hydroxyprogesterone concentration). During the first 6 months of life, all patients were treated with 1 mg of hydrocortisone 3 times daily and 0.05 mg of fludrocortisone 2 or 3 times daily. Thereafter, hydrocortisone doses were individually increased and the fludrocortisone dose was reduced. When plasma renin activity rose >18 ng/ml/h after reduction of fludrocortisone during the first 6 months of life or >8 ng/ml/h after 6 months of life, fludrocortisone was increased and patients were assumed to have the salt-wasting form of CAH. All patients were continuously cared for in our clinic, with follow-up appointments every 3 months during the first 2 years of life, and every 6 months thereafter.

Adjustment of the glucocorticoid dose was made using auxological data (goal: linear growth as best clinical parameter of metabolic control) and hormonal data (treatment goals: morning serum 17-hydroxyprogesterone <18 nmol/l and plasma renin activity <18 ng/ml/h until 6 months of age, <5.5 ng/ml/h above the age of 6 months). These cutoffs were determined using age and sex-specific normative data for assays at the own endocrine laboratory. When enough serum was available, androstenedione and testosterone were measured as well, but these parameters were not available for all patients at all times and were therefore excluded from the analysis. Until the age of 2 years, height was measured in a lying position using a pediatric measuring device (infantometer); after 2 years of age, height was measured in a standing position using a digital telescopic wall-mounted stadiometer (Ulmer Stadiometer). Height standard deviation scores (H-SDS) were calculated with a growth calculator, using reference data from Prader et al. [7] which are used in the 'Alpine' region of Europe (Switzerland, Austria, Southern Germany). Height was compared with matched controls among healthy children with the same birth years. Controls were recruited from an outpatient pediatrician. In Germany, children have regular check-ups at their pediatrician and height, weight and head circumference are documented in a little yellow booklet.

Weight was determined to the nearest of 0.1 kg using an electronic scale (Seca 753 E). Body mass index (BMI) was calculated as weight (kg)/height (m^2) and BMI-SDS was derived from data published by Cole et al. [8].

Bone age was assessed at the age of 3 years by X-ray of the left hand using the Greulich and Pyle method [9]. Bone age was read by both an experienced pediatric endocrinologist and a radiologist, who both agreed on the result of each other's reading after discussing the X-ray.

Most parental heights were asked and available on all patients. Parental heights could not be measured in all parents because both parents were not present in most cases. When asked for, parental heights mostly result in overestimation, especially among fathers, which has to be taken into account. The genetic target height was calculated as midparental height (the mean of the two parents' heights) plus 6.5 cm for boys and minus 6.5 cm for girls.

Statistical analyses were performed with the nonparametric Wilcoxon test and for group comparisons with the nonparametric Mann-Whitney U test.

Table 1. Genotype/phenotype of the study group

Patient	Sex	Genotype	Phenotype
1	M	del del	SW
2	M	del del	SW
3	M	del del	SW
4	M	I2G del	SW
5	M	I2G R356W	SW
6	M	I172N I172N	SW
7	M	I2G I172N	SV
8	M	I2G I160N	SW
9	M	I2G I2G	SW
10	M	Q318X Q318X	SW
11	M	I2G I2G	SW
12	M	del I2G	SW
13	M	del Q318X	SW
14	M	I2G I2G	SV
15	M	del I2G	SW
16	M	I2G del	SW
17	M	I2G ?	SW
18	M	I172N conv	SW
19	M	I2G I172N	SW
20	M	I2G del	SW
21	M	I2G del	SW
22	M	I2G I2G	SW
23	M	I2G I2G	SW
24	M	del I2G	SW
25	F	I172N I2G	SW
26	F	I2G I2G	SW
27	F	I2G I2G	SW
28	F	I172N conv	SW
29	F	I172N conv	SW
30	F	I2G conv	SW
31	F	I2G conv	SW
32	F	I172N I172N	SW
33	F	I172N Q474X	SV
34	F	I2G I2G	SW
35	F	I2G del	SW
36	F	I2G del	SW
37	F	I172N I2G	SW
38	F	del I172N	SW
39	F	I2G I172N	SW
40	F	del I2G	SW
41	F	I2G conv	SW
42	F	I2G conv	SW
43	F	del del	SW
44	F	del I2G	SW
45	F	I2G I172N	SW
46	F	I2G I2G	SW
47	F	I172N R356W	SW
48	F	I2G del	SW
49	F	del W204X	SW
50	F	del del	SW
51	F	R356W I172N	SV

del = Deletion; conv = conversion, I2G = intron 2 splice site mutation; SW = salt-wasting; SV = simple virilizing.

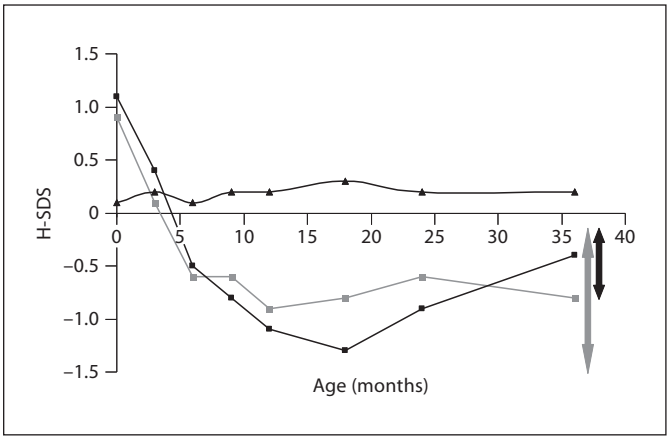

Fig. 1. Growth pattern of CAH patients: course of H-SDS. Black line with boxes: girls. Grey line with boxes: boys. Black line with triangles: reference group. Black arrow: target height girls (mean ± 1 SD); grey arrow: target height boys (mean ± 1 SD).

Statistical analyses were done with the SPSS 10.0 software (2002; SPSS Inc., Chicago, Ill, USA). $p < 0.05$ was considered statistically significant.

Results

The majority of patients were diagnosed with salt-wasting CAH and only 4 patients were classified as simple virilizing CAH. At birth, H-SDS related to gestational age was 1.1 ± 1 in girls, and 0.9 ± 1.5 in boys, respectively. Accordingly, the birth length of both girls and boys with classical CAH was significantly increased when compared with healthy controls. After 3 months, H-SDS decreased significantly to 0.4 ± 0.9 SDS in girls ($p < 0.01$) and to 0.1 ± 1.3 SDS in boys ($p < 0.01$). At 1 year of age, H-SDS further decreased to –1.1 ± 1.8 SDS in girls and –0.9 ± 0.9 SDS in boys ($p < 0.01$). After 3 years, H-SDS was –0.4 ± 1.8 SDS in girls and –0.8 ± 1 SDS in boys, and approached the genetic height potential (target H-SDS of girls: –0.5 ± 0.3, target H-SDS of boys: –0.9 ± 0.7; table 2, fig. 1).

During the first 9 months of age, growth velocity was subnormal in girls (18.2 ± 1.9 cm) and boys (17.3 ± 1.6 cm) when compared to a healthy reference population (girls: 19.0 ± 3.9 cm, boys: 18.7 ± 4.7 cm, Prader et al. [7], $p < 0.05$). During the second and third year of life, growth velocity was in the normal range (growth velocity second year: CAH girls 11.9 ± 1.4 cm, CAH boys 12 ± 1.7 cm vs. reference girls 11.1 ± 2 cm and reference

Table 2. Longitudinal data on H-SDS, BMI-SDS, hydrocortisone dose and 17-OH-progesterone (mean ± 1 SD)

	Birth	3 months	6 months	9 months	12 months	18 months	24 months	36 months	Target H-SDS	Bone age at 36 months years
Girls (n = 27)										
H-SDS	1.1 ± 1	0.4 ± 0.9*	−0.5 ± 1.2*	−0.8 ± 1.2*	−1.1 ± 1.8*	−1.3 ± 1.4*	−0.9 ± 1.2*	−0.4 ± 1.8*	−0.5 ± 0.3	2.7 ± 0.5
BMI-SDS		0.1 ± 1.7	−0.3 ± 1.4	−0.4 ± 1.3	−0.3 ± 1.3	−0.3 ± 0.7	0.1 ± 0.8	0 ± 1		
HC dose, mg/m^2		10.2 ± 2.3	10.3 ± 3.8	9.6 ± 1.6	10.5 ± 2.2	10.9 ± 2.6	11.1 ± 2.1	12.8 ± 1.9		
17-OH-progesterone, nmol/l		29.9 ± 31	10 ± 11	7.7 ± 7.5	7.7 ± 6	6.7 ± 7.9	20 ± 36	4.7 ± 5.5		
Boys (n = 24)										
H-SDS	0.9 ± 1.5	0.1 ± 1.3*	−0.6 ± 1.2*	−0.6 ± 0.9*	−0.9 ± 0.9*	−0.8 ± 1.1*	−0.6 ± 0.9*	−0.8 ± 1*	−0.9 ± 0.7	2.9 ± 0.5
BMI-SDS		−0.3 ± 1.6	−0.6 ± 1.4	−0.7 ± 1.5	−0.5 ± 1.5	−0.5 ± 1.4	−0.5 ± 1.3	−0.1 ± 1.1		
HC dose, mg/m^2		10.8 ± 3.2	10 ± 3.2	9.3 ± 2	9.6 ± 2.3	10.4 ± 1.9	11.3 ± 1.7	12.1 ± 1.6		
17-OH-progesterone, nmol/l		78.6 ± 117	26.3 ± 39	10.2 ± 8	12.5 ± 18	10.6 ± 6.7	6.4 ± 8.6	17 ± 50		

H-SDS decreases significantly compared to H-SDS at birth (* $p < 0.05$) in boys and girls with CAH. HC = Hydrocortisone.

Table 3. Growth velocity at 9 months, 2 and 3 years of age (mean ± 1 SD)

		CAH patients	Reference population [7]
Growth velocity during first 9 months, cm/year	females	18.2 ± 1.9	19.0 ± 3.9*
	males	17.3 ± 1.6	18.7 ± 4.7*
Growth velocity at 2 years, cm/year	females	11.9 ± 1.4	11.1 ± 2.0
	males	12.0 ± 1.7	11.0 ± 3.5
Growth velocity at 3 years, cm/year	females	8.6 ± 1.4	8.5 ± 1.5
	males	8.1 ± 2.0	8.3 ± 1.3

CAH patients compared to a healthy reference population (* $p < 0.05$).

boys 11.0 ± 3.5 cm; growth velocity third year: CAH girls 8.6 ± 1.4 cm, CAH boys 8.1 ± 2 cm vs. reference girls 8.5 ± 1.5 cm and reference boys 8.3 ± 1.3 cm; table 3).

With hydrocortisone substitution in the low range of general treatment recommendations [10] (1 mg of hydrocortisone 3 times daily during the first 6 months, corresponding to approximately 10 mg of hydrocortisone per m^2 body surface area), in girls the mean plasma 17-hydroxyprogesterone concentration was still elevated at 3 months and subsequently decreased to the treatment goal <18 nmol/l. With the same treatment regimen in boys, the 17-hydroxyprogesterone concentration was elevated at 3 and at 6 months of age and decreased to a mean concentration of 10.2 nmol/l at the age of 9 months. Over 3 years, the mean hydrocortisone substitution dose ranged between 9.3 and 12.8 mg per m^2 body surface area (table 2). One patient suffered from adrenal crisis in the context of gastroenteritis while failing to increase hydrocortisone dose.

At the age of 3 years, bone age was appropriate for chronological age in both girls (2.7 ± 0.5 years) and boys (2.9 ± 0.5 years), indicating that the relatively low dosage of hydrocortisone during the first 6 months did not lead to accelerated bone age.

At 3 months of age, BMI-SDS was 0.1 ± 1.7 in girls and −0.3 ± 1.6 in boys. BMI-SDS remained around the mean over the study period (BMI-SDS at 3 years: 0 ± 1 SDS in girls vs. −0.1 ± 1.1 SDS in boys; table 1).

Discussion

Since newborn screening is available nowadays, diagnosis of CAH is no longer delayed and optimal treatment strategies during the first months of life have become more important.

According to the consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endo-

crine Society and The European Society for Pediatric Endocrinology, typical hydrocortisone doses during infancy range between 10 and 15 mg/m^2 body surface area, but higher doses up to 25 mg/m^2 body surface area may be necessary initially [10].

From the observation of growth patterns of untreated boys with delayed diagnosis of simple virilizing CAH in the pre-newborn screening era, it has been hypothesized that infants are relatively insensitive to androgen excess [11]. In another synopsis of 17 untreated patients with simple virilizing CAH, growth velocity was not increased during the first year of life. After that period, a progressive increase in height velocity and bone maturation was observed [6]. Therefore, lower doses of hydrocortisone may be sufficient during the first months of life in terms of growth. For this reason we accepted suboptimal hormonal control of CAH at the age of 3 months and continued hydrocortisone substitution at the low end of therapeutic recommendations [10]. Even though metabolic control was definitely not too tight, H-SDS decreased significantly during the first 6 months of life, indicating again that infants are not very sensitive to androgens but may be extremely sensitive to glucocorticoid treatment in terms of growth inhibition. Also during the first 9 months of age, growth velocity was decreased when compared to healthy controls, which might have resulted from the growth suppressing effects of glucocorticoid treatment. Therefore, our relatively low hydrocortisone dose might still be too high during the first year of life. On the other hand, with hydrocortisone substitution at the low end of therapeutic recommendations [10], we do not believe that decreased growth velocity was caused by a glucocorticoid deficient state since only 1 patient suffered from adrenal crisis in the context of gastroenteritis while failing to increase hydrocortisone dose. The fact that H-SDS in the target H-SDS range is reached between the ages of 1 and 3 years suggests that hydrocortisone substitution was sufficient. Another indicator for adequate hydrocortisone substitution in our patients was the age-appropriate bone age at 3 years. The vast majority of patients in our study were classified as having salt-wasting CAH. This is somewhat unusual and may partially explain lower hydrocortisone requirements because patients were additionally treated with fludrocortisone.

In our cohort, birth length was above average in both boys and girls with classical CAH. Significantly increased birth length was also observed in an Italian and Finnish population with classical CAH [12, 13]. Among the patients with classical CAH, those with the salt-wasting form were longer but weighed less than those with the simple virilizing form [12]. 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 [14]. Androgens appear to affect the growth of bone cells, acting both directly and indirectly through the IGF-1 system [15, 16]. Increased expression of IGF-1 and IGF-BP3 mRNA as well as increased IGF-1 and IGF-BP3 concentration were observed after treatment of human osteoblasts with dihydrotestosterone [17]. Interestingly, in our cohort of CAH infants, the birth length of girls was greater than the birth length of boys.

We found H-SDS to decrease significantly during the first year of life in girls and boys with classical CAH. This result is comparable to that of a multicenter study by Hargitai et al. [18] who observed a decline of the general growth trendline to the 10th centile by the age of 1.5 years in girls and boys with salt-wasting CAH.

With relatively high doses of hydrocortisone (19.6–28.2 mg/m^2/day) during the first 2 years of life, Manoli et al. [19] found a negative correlation between hydrocortisone dose and height at 2 years ($r = -0.79$) in patients with salt-wasting CAH diagnosed within the first 2 months of life. Mean height at 2 years was –0.33 SDS in girls and +0.45 SDS in boys. Moreover, height at 2 years showed a positive correlation to final height in this rather timely diagnosed subset of patients.

In a retrospective analysis of the growth inhibiting effects of glucocorticoid treatment in salt-wasting CAH, Stikkelbroeck et al. [20] found that in the interval between 6 and 12 months and between 8 and 14 years of age, there is a dose-dependent negative effect of glucocorticoids on linear growth. Weight and weight for height were not significantly influenced by glucocorticoid dose at any age. The authors conclude that the daily glucocorticoid dose during these intervals has to be adjusted carefully to allow optimal linear growth and adult height.

In summary, we were able to identify a typical growth pattern of patients with classical CAH diagnosed by newborn screening and treated with relatively low doses of hydrocortisone. Suboptimal hormonal control at 3 or 6 months of age does not seem to accelerate bone age and growth due to relative androgen insensitivity of infants at that age. With hydrocortisone substitution between 9 and 15 mg per m^2 body surface area per day, patients were able to achieve H-SDS in the target height range.

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