EXTENSIVE CLINICAL EXPERIENCE

Absence of Increased Height Velocity in the First Year of Life in Untreated Children with Simple Virilizing Congenital Adrenal Hyperplasia

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Context: In congenital adrenal hyperplasia (CAH), elevation of adrenal androgens leads to accelerated growth and bone maturation with compromised adult height.

Objective/Patients: The objective of the study was to analyze retrospectively early growth and bone maturation in 17 untreated simple virilizing (SV) CAH patients.

Setting: The study was conducted at Radboud University Nijmegen Medical Centre.

Interventions: Growth data were collected until time of diagnosis. Height was expressed as height SD score and corrected for target height. Bone maturation was determined and expressed as bone age acceleration.

Main Outcome Measures: Growth pattern and bone maturation were measured before the diagnosis.

Results: In the term group (n = 11), there was no increase in height SD score and corrected for target height in the first year of life [−0.1 SD/yr; 95% confidence interval (CI) −0.5, 0.3] with a consecutive significant (P < 0.001) increase up to 0.9 SD/yr (95% CI 0.7, 1.0). In the premature group (n = 3), there was a catch-up growth of 1.6 SD/yr (95% CI 0.9, 2.3) in the first year followed by a growth of 1.1 SD/yr (95% CI 0.9, 1.5) in the following years. There was a positive linear correlation between bone age acceleration and age of diagnosis (r = 0.8).

Conclusions: Height velocity and bone maturation are not increased in untreated children with mild forms of SV CAH in the first year of life. After this period there is a progressive increase in height velocity and bone maturation in strong relation to the duration of androgen exposition. This observation has implications for the dose of glucocorticoids to be used in SV CAH patients in the first year of life. (J Clin Endocrinol Metab 91: 1205–1209, 2006)

CONGENITAL ADRENAL HYPERPLASIA (CAH) is one of the most common autosomal recessive endocrine disorders with an incidence of the classical form at 1:10,000 (1, 2). In most cases, the disease is caused by 21-hydroxylase deficiency. As a result of the enzyme deficiency, the synthesis of cortisol and mostly also that of aldosterone is impaired. Consequently, the secretion of ACTH by the pituitary gland increases, leading to hyperplasia of the adrenal cortex and excess of androgen production. The gene encoding for 21-hydroxylase is well known, and the diagnosis CAH can be easily confirmed by mutation analysis. There is a strong genotype-phenotype correlation reported to be up to 80–90% (3–5).

The clinical symptoms of CAH depend on the degree of enzyme deficiency. In the most severe form, the classic salt wasting (SW) form, the enzyme activity is less than 1% leading to prenatal virilization in female patients and life-threatening SW in both sexes. An enzyme activity of 1–5% is enough to preserve aldosterone synthesis leading to the classic simple virilizing (SV) form. In most of the male cases with the SV form of CAH, patients are not detected in the neonatal period but present after several years with signs of androgen excess leading to pseudo-precocious puberty with increased growth velocity, pubic hair development, and enlargement of the external genitalia. The mildest form of CAH, the late-onset type, can present also with pseudo-precocious puberty, irregular menstruation, hirsutism, and infertility. This form of CAH can be easily missed, especially in male patients. The treatment of CAH consists of substitution of cortisol to prevent Addison crisis and suppress the adrenal androgen overproduction. In the SW form, aldosterone also has to be substituted as well.

The growth pattern of treated children with SW or SV CAH is described in several studies (6–10). It is well known that adrenal hypersecretion of androgens causes increased growth velocity and bone age acceleration. Therefore, adequate suppression of androgens by treatment with glucocorticoids is important; however, oversuppression resulting in Cushing syndrome and growth retardation has to be avoided. Previous reports on the growth pattern in children with CAH suggested that the height velocity is not increased in the first years of life, even in the untreated patient group (11–13).
We therefore investigated retrospectively our group of patients with SV CAH retrospectively to define their growth pattern before the diagnosis. Furthermore, we evaluated the age of the onset of symptoms, the presence of associated clinical features, and the bone maturation at the time of the diagnosis.

Patients and Methods

Patients

We evaluated 17 patients with SV CAH (11 males and six females). None of the patients was treated with glucocorticoids before the time of diagnosis. Two patients (no. 12 and 13) are sisters.

The diagnosis SV CAH was based on clinical and biochemical criteria (i.e., elevated levels of 17-hydroxyprogesterone and androstenedione, abnormal urinary steroid profile, ACTH stimulation test) and was confirmed by mutation analysis (see Table 1). SW crisis has not been reported in any of the patients.

The I172N mutation, which is associated with the SV form of CAH, was detected in all but one patient (no. 16) in at least one allele. Four patients were homozygous for the I172N mutation. Patient 16 with the clinical features of the SV form of CAH had a homozygous deletion/conversion, which is typically associated with the SW form of CAH. Three patients were born prematurely (no. 10, 13, and 14).

Clinical features and growth analysis

The age of diagnosis and clinical symptoms were obtained from the patients’ medical records. The growth data from birth to the first presentation in our clinic were collected from the well-baby clinical reports. The growth data from birth to the first pre-diagnosis time of the diagnosis was determined according to the atlas of Greulich and Pyle corrected for target height (HSDS-THSDS). Bone maturation at the time of diagnosis was assessed according to the national references (14) and corrected for target height (HSDS-THSDS). Bone maturation at the time of diagnosis was determined according to the atlas of Greulich and Pyle and expressed as bone age acceleration (BAc = bone age – calendar age).

Statistical analysis

Because only limited data for the height (HSDS-THSDS) of untreated patients were available for the age over 4 yr, we limited our analysis to the period 0–4 yr. To account for the longitudinal character of the study, linear mixed models with random factor patient were used for the analysis of the growth.

In a preliminary analysis, the statistical model was selected by including the fixed effects age, prematurity, sex, and the interaction between age and the other factors in the model. Because the relationship between age and HSDS-THSDS may not be linear, age was included as a spline function with knots at 1 and 2 yr of age. This analysis showed a strong interaction between age and prematurity; therefore, the growth of the premature and mature children was analyzed separately. It also showed that a spline function with only one knot at 1 yr could adequately describe the data. Such a function consists of two straight lines, one for the growth during the first year after birth and another one for the growth between the age of 1 and 4 yr. As a result, in the final analysis, the model included the fixed effects age up to 1 yr, age over 1 yr, and sex. This model was used to derive estimates for the growth during and after the first year.

Simple linear regression analysis was performed to evaluate the relationship between BAc and age at diagnosis. Ninety-five percent confidence intervals were calculated. The significance level for statistical testing was set at $P < 0.05$ (two sided).

Results

Clinical presentation and growth analysis

The data on the clinical presentation are summarized in Table 1. Fifteen of the 17 children presented with increased growth velocity. The age of reported growth acceleration was 18 months or older. The other two patients (no. 16 and 17) were detected at the age of 17 months and 23 months and presented with clitoral hypertrophy and pubic hair development without a history of increased height velocity. Pubic hair was noted in 11 children. At the time of the diagnosis, enlargement of external genitalia was found in 11 children (seven boys and four girls). Acne was detected in only two patients. Axillary hair or hirsutism was not reported in any of the patients.

The median age of onset of the first symptoms was 28 months (range 12–46 months) in girls and 51 months (range 18–86 months) in boys.

Birth length corrected for gestational age was greater than

### TABLE 1. Mutation analysis, clinical presentation, and BAc at time of diagnosis in 17 patients with SV CAH

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Mutation analysis</th>
<th>Symptoms at time of diagnosisa</th>
<th>Age at first symptoms (yr:month)</th>
<th>BAc at diagnosis (yr:month)</th>
<th>Birth weight (g) with SDSb</th>
<th>Birth length (cm) with SDSc</th>
<th>Gestational age (wk)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Intron2</td>
<td>I172N</td>
<td>1, 3</td>
<td>6:2</td>
<td>2880</td>
<td>49</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>I172N</td>
<td>R356W</td>
<td>2, 3</td>
<td>1:6</td>
<td>2700</td>
<td>48</td>
<td>40</td>
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<tr>
<td>3</td>
<td>M</td>
<td>Intron2</td>
<td>I172N</td>
<td>1, 3</td>
<td>6:2</td>
<td>3380</td>
<td>0.6 (0.6)</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Del-Conv</td>
<td>I172N</td>
<td>1, 2, 3</td>
<td>3:10</td>
<td>3975</td>
<td>0.7 (0.6)</td>
<td>40</td>
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<td>5</td>
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<td>I172N</td>
<td>I172N</td>
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<td>4:0</td>
<td>3250</td>
<td>0.1 (0.1)</td>
<td>38</td>
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<td>Del-Conv</td>
<td>I172N</td>
<td>1, 2, 3</td>
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<td>I172N</td>
<td>1235N, V237E, M239K</td>
<td>1, 2, 3</td>
<td>2:11</td>
<td>3500</td>
<td>0.3 (0.3)</td>
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<tr>
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<td>M</td>
<td>Del-Conv</td>
<td>I172N</td>
<td>1, 3, 4</td>
<td>5:10</td>
<td>3940</td>
<td>0.7 (0.7)</td>
<td>40</td>
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<tr>
<td>9</td>
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<td>Del-Conv</td>
<td>2, 3</td>
<td>3:5</td>
<td>3850</td>
<td>0.5 (0.5)</td>
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<tr>
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<td>Q318X</td>
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<tr>
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<td>I172N</td>
<td>1, 2, 3</td>
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<td>2350</td>
<td>1.3 (1.3)</td>
<td>36</td>
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<tr>
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<td>F</td>
<td>I172N</td>
<td>I172N</td>
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<td>0.6 (0.6)</td>
<td>37</td>
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<td>I172N</td>
<td>3</td>
<td>2:4</td>
<td>3000</td>
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<td>I172N</td>
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<td>1:11</td>
<td>3300</td>
<td>0.5 (0.5)</td>
<td>40</td>
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</tbody>
</table>

M, Male; F, female.

a Symptoms: 1, pubic hair; 2, enlarged external genital; 3, increased height velocity; 4, acne; 5, axillary hair.

b BAc, Bone age – calendar age.

c SDS was calculated according to Niklasson et al. (33).
−1.3 SDS score (SDS) in all children except for one child (no. 15) with a birth length of −1.3 SDS and early stunting in the follow-up with weight and length decreasing to below −2.0 SDS. Three patients had a birth weight greater than 2 SDS. The growth data of 14 patients with sufficient growth data are summarized in Fig. 1. In the term group (n = 11), there was no significant increase in height velocity in the first year [−0.1 sd/yr; 95% confidence interval (CI) −0.5, 0.3] with a consecutive significant (P < 0.001) increase up to 0.9 sd/yr (95% CI 0.7, 1.0). In premature group (n = 3) there was a catch up growth of 1.6 sd/yr (95% CI 0.9, 2.3) in the first year followed by a growth of 1.1 sd/yr (95% CI 0.7, 1.5) in the following years.

Bone maturation at time of diagnosis was determined in 14 of the 17 patients (Fig. 2). We found a strong positive linear correlation between bone maturation and age of diagnosis (Pearson’s correlation coefficient = 0.8). BA increase was 1.06/yr (P = 0.01).

Discussion

In our group of patients with SV CAH, the most prominent symptoms at time of diagnosis were increased height velocity, pubic hair, and enlargement of external genitalia. These observations are similar to other studies. Surprisingly we did not find any axillary hair development or hirsutism, suggesting a higher threshold for androgens in the axillary region.

Increased height velocity is one of the most prominent symptoms of androgen excess in childhood. In prepubertal CAH patients, failure to suppress adrenal androgens leads to accelerated growth and bone maturation with compromised adult height. Treatment with glucocorticoids aims to suppress ACTH and androgens and to restore normal growth and maturation (1, 6–10).

The results of our study, demonstrating the absence of increased height velocity in patients with SV CAH at least in the first 12 months of postnatal life, suggests the presence of relative resistance to androgen excess. After this period there is a progressive increase of growth velocity and bone maturation in a strong relation to the duration of androgen exposure. Several authors described the lack of growth acceleration in the first year of life as well. Aceto et al. (15) described three girls with CAH and normal height and bone age at time of diagnosis at 21, 24, and 42 months of age without information about longitudinal growth data, parental height, or the type of CAH. Another study by Thilen et al. (12) in 14 children with SV CAH showed no increase in height velocity until the age of 18 months; however, height was not corrected for target height, and no statistical analysis was performed.

A similar growth pattern can be observed in other pathological conditions with high androgen levels like in familial testotoxicosis (16, 17). Also in normal males, the temporary high levels of testosterone at the age of 6 wk to 6 months in their minipuberty seem to have no effect on the growth velocity in boys, compared with girls.

The reason for the lack of increased height velocity of CAH patients in the early life is not well understood.

It is well known that androgens act on the bone mainly after being aromatized to estrogens; however, direct effects are described as well (18, 19). Van der Eerden et al. (20) detected an androgen receptor (AR) in the tibial growth plate of male and female rats with a significant higher expression rate in male than female rats during sexual maturation with increased testosterone levels. They found that testosterone can either up-regulate or down-regulate AR mRNA in a dose-dependent manner (20). The insensitivity of bone to androgens in the first year of life can hypothetically be explained by temporary down-regulating or limited expression of the AR in this period (21).
Another possible explanation of increased growth velocity by sex hormones might be the interference with the GH/IGF axis. Sex hormones, mainly estrogens, increase pulse amplitude and the amount of GH secreted per pulse (22). It is suggested in the infancy-childhood-puberty model that the infancy growth in the first year of life seems to be relatively independent of GH (23, 24). Therefore, in this period any action of androgens by this pathway may not result in increased growth velocity. However, several studies (25, 26) show that GH has some influence also in the first year of life as demonstrated by growth failure of children with congenital GH deficiency.

There are not much data about the effect of androgen excess in utero on prenatal growth and bone maturation. Some studies (6, 27) show that the birth length in patients with CAH is slightly elevated, independent of the degree of virilization in girls or the postnatal androgen levels in boys. Therefore, androgen excess in utero seems to have no strong effect on the prenatal growth and bone maturation. In our patients birth weight and length were mostly within the normal range.

The absence of growth acceleration seems to be independent of the severity of the disease. Personal observations of a patient with SW CAH and urethral valves who was treated only with salt substitution in the first 3 yr of life showed no increase in growth velocity or bone maturation (our unpublished data).

There is no evidence that higher androgens in the first year of life can cause infertility in later years. It is well known that fertility in women with CAH is impaired due to several factors: mechanical factors after genital surgery, adrenal overproduction with disturbing ovarian activity, polycystic ovarian syndrome, or ovarian adrenal rests. It is not known whether higher androgens in the first year of life can also contribute to these factors. Behavioral problems are mostly the result of prenatal exposure of androgens and not of postnatal exposure (28, 29). A prospective study to analyze reproductive problems in this group of patients could be very helpful.

In our population the androgen levels in the first year were not measured because the diagnosis was made in later life. Therefore elevated androgens were not established. It is known that in SV CAH patients androgen levels are elevated in utero and after birth. The 21-hydroxylase activity in this group is less than 5%, leading to elevated serum 17 hydroxyprogesterone and androstenedione levels. This becomes visible in girls with SV CAH, who present with signs of virilization after birth. However, it is just possible that in this situation the androgen levels are not high enough to see any effect on the growth velocity in early life.

Although the reason for the absence of increased height velocity in the first year of life in SV CAH patients is not completely understood, our observations have important implications for the first year treatment of children with CAH. In prepubertal children, the recommended cortisol replacement is hydrocortisone in doses of 10–20 mg/m²d in two or three divided doses (30). This advice is based on the clinical experience with the general premise to use the lowest possible dosage. However, the glucocorticoid dosages used in daily practice in infancy are much higher (9–37.5 mg/m²d) (31). These doses exceed physiological levels of cortisol secretion, which are 6–8 mg/m²d in children and adolescents and are necessary to adequately suppress adrenal androgens and prevent growth acceleration.

However because of the absence of increased growth velocity and bone maturation in the first year of life as demonstrated in our study, suppression of androgens as required in later years to prevent growth acceleration is not necessary, and much lower doses of glucocorticoids are sufficient for adequate treatment. Moreover, in an earlier study (32), we demonstrated the high sensitivity of glucocorticoid with respect to growth retardation, especially in the first year of life. These two arguments augment for a recommendation of using more physiological glucocorticoid doses in early age. Further prospective studies will be done to evaluate the effect of this treatment on growth and fertility in later life.

Conclusion

Our study demonstrates the absence of increased growth velocity and bone maturation in the first year of life untreated children with mild forms of 5V CAH. After this period there is a progressive increase in height velocity bone maturation with a strong correlation with the duration of androgen exposure. This observation has implications for the dose of glucocorticoids to be used in SV CAH patients in the first year of life.

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