Longitudinal analysis of growth and puberty in 21-hydroxylase deficiency patients

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Longitudinal analysis of growth and puberty in 21-hydroxylase deficiency patients


Aims: To evaluate growth from diagnosis until final height (FH) in 21-hydroxylase deficiency patients. Methods: A retrospective longitudinal study was performed. Only patients treated with hydrocortisone and fludrocortisone (in case of salt wasting) were evaluated. This resulted in a sample of 34 (21 male, 13 female) salt wasting patients (SW) and 26 (13 male, 13 female) non-salt wasting patients (NSW). Auxiological data were compared to recent Dutch reference values.

Results: In the first three months of life, the mean length SDS decreased to −1.50, probably because of the high average glucocorticoid dose (40 mg/m²/day). FH corrected for target height (FHcorrTH) was −1.25 and −1.27 SDS in females and males, respectively. Patients treated with salt supplements during the first year, had a better FHcorrTH (−0.83 SDS). In NSW patients, FHcorrTH was −0.96 and −1.51 SDS in females and males, respectively. In SW and NSW, age at onset of puberty was within normal limits, but bone age was advanced. Mean pubertal height gain was reduced in males. Body mass index was only increased in NSW females.

Conclusion: In SW, loss of final height potential might be a result of glucocorticoid excess in the first three months and sodium depletion during infancy. In NSW, loss of FH potential was caused by the delay in diagnosis. In SW and NSW, the advanced bone age at onset of puberty (undertreatment in prepubertal years) resulted in loss of height gain during puberty. The effect of intensive sodium chloride support in early infancy should be examined prospectively. Neonatal screening is required if the height prognosis in NSW patients is to be improved.

PATIENTS AND METHODS

Patients
A retrospective longitudinal study on growth and puberty was performed in patients with 21-hydroxylase deficiency treated by paediatric endocrinologists from diagnosis until final height. Patients treated with prednisone or dexamethasone for longer than six months were excluded. With the above mentioned criteria, 60 patients were available for further evaluation. Clinical salt wasting was apparent in 13 females and 21 males, whereas 13 females and 13 males were clinically non-salt wasting. Patients were defined as having salt wasting when they had clinical salt loss resulting in a serum sodium concentration below 130 mmol/l and a severe increased plasma renin activity (PRA) at time of diagnosis. In some individual cases, diagnosis was delayed, although salt wasting was apparent from the first month of life. Median (range) age at diagnosis was 3.7 (0–61) days in females and 21.9 (5.9–178) days in males. Patients were defined as non-salt wasting when they were diagnosed after the age of 6 months, never had a serum sodium below or equal to 130 mmol/l, were never treated with salt supplementation, and had a normal (n = 14) or slightly increased PRA (n = 12).

Patients were treated with hydrocortisone, divided into three doses. In 85%, half of the daily dosage was given in the evening (distribution: 1/4–1/4–1/2) and in 10% a 2/5–1/5–2/5 daily regimen was given. Thirteen patients (nine SW) were initially treated with cortisone acetate for 4.4 (0.6) years. Fludrocortisone acetate was used by SW and NSW patients. Seventeen of 34 salt wasting patients received salt supplementation in the first year of life.

Abbreviations: BMI, body mass index; CAH, congenital adrenal hyperplasia; FH, final height; FHcorrTH, FH corrected for target height; FHSDS, final height standard deviation score; HSDS, height standard deviation score; LSDS, length standard deviation score; NSW, non-salt wasting; SDS, standard deviation score; SW, salt wasting; TH, target height; THSDS, target height standard deviation score

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Seven patients (two SW) with early puberty were treated with triptorelin (GnRH agonist) 3.75 mg/month intramuscularly for 3.9 (1.9) years and were evaluated separately.

### Methods

The study was based on a retrospective longitudinal growth registration from patient records. To measure length (until 2 years of age) a measuring table was used on a horizontal plane. Height was measured using a Harpenden stadiometer. Both were expressed as length or height standard deviation score for chronological age. The 1996–97 Dutch height standards were used as reference data after the age of 2 weeks. Determination of final height was based on completion of pubertal maturation with a height increment of less than 0.5 cm/year. Final height was expressed as SDS using the population average at 21 years of age. Parental height served to calculate target height (TH) for each patient, with a correction for secular trend: (midparental height ± 6.5 cm) + 4.5 cm. TH was converted into THSDS using Dutch standards for final height.

Pubertal maturation was recorded according to Tanner’s stages. Onset of puberty was defined as testicular volume ≥4 ml in males and breast stage 2 in females. Age at onset of puberty and age at menarche were compared to recent Dutch data (10.7 years in females, 11.5 years in males, menarche at 13.15 years). In Dutch reference values, mean (SD) bone age at onset of puberty was 9.71 (0.61) years in females and 11.03 (0.64) years in males (TW2-RUS).

Precocious puberty was defined as the onset of puberty before the age of 8 years in females and 9 years in males.

Bone maturation was determined from radiographs of the left hand and wrist using the method of Greulich and Pyle. As Dutch bone age reference values were only available and according to TW2-RUS, bone age scores in CAH patients according to Greulich and Pyle (G&P) were compared to the bone age scores according to TW2-RUS.

The BMI (weight/height²) was compared to Dutch reference values.

The cortisone acetate dosage was converted into an equivalent hydrocortisone dose by dividing the cortisone dose (mg) by 1.25. The glucocorticoid effect of 100 µg Fludrocortisone acetate was equated to 1 mg hydrocortisone. The glucocorticoid dose in µg was calculated as follows: hydrocortisone dose (mg) + Fludrocortisone acetate dose in µg/100.

All androstenedione concentrations were compared to reference values for age and sex and expressed as treatment scores. They were scored as “normal” (0), “above normal” (1), or “below normal” (−1) indicating adequate treatment, undertreatment, or overtreatment, respectively. No distinction was made in the severity of over and undertreatment. For each child, the average treatment score was calculated annually.

### RESULTS

#### Treatment

Table 1 presents data in age categories concerning treatment and treatment monitoring. In the first three months of life, all salt wasting patients were treated with high dose glucocorticoids (39.7–44.7 mg/m²/day). Females continued to have high doses afterwards until the age of 1 year. Fludrocortisone dose was on average 100 (40) µg/day. Mean (SD) androstenedione treatment scores were 0.18 (0.66) in SW patients and 0.22 (0.64) in NSW patients.

#### Growth

Table 2 presents data from diagnosis to adulthood and fig 1 shows the average length/height SDS over time. In SW, length SDS at diagnosis (at a mean age of 11 days in females and 44 days in males) was below average according to Dutch reference values. In the first three months of life, the mean LSDS decreased to −1.5 in both sexes. In females height SDS (HSDS) increased to −0.6 at the age of 9.5 years and decreased thereafter to −0.85. In males HSDS was maximal at the age of 11 years (−0.08) and decreased afterwards to −1.63. FH was 1.25 SDS and 1.27 below target height SDS in females and males, respectively.

Seventeen of 34 salt wasting patients were treated with additional salt supplements 2.5 (3.0) mmol/kg/day from 0.19 (0.15) years until 0.9 (0.38) years of age. The fludrocortisone dose was similar: 104 (60) µg/day in the salt supplemented group versus 92 (32) µg/day in the non-salt supplemented group. The glucocorticoid dose was different: 27 (19.9) mg/m²/day in the salt supplemented group versus 22.3 (16.8) mg/m²/day in the non-salt supplemented group (p < 0.002). Mean length SDS at the age of 2 years was higher in the salt supplemented group: HSDS −1.0 (0.8) versus −1.56 (0.86). FH corrected for TH was also higher in the salt supplemented group: TW2-RUS.
In a multiple regression analysis, FHSDS showed a positive correlation with THSDS (p < 0.001) and with salt supplementation during the first year of life (p < 0.003).

In NSW, mean HSDS at diagnosis was +0.2 SDS in females and +3.0 SDS in males at a median age of 2.4 and 6.2 years, respectively. FH was 0.96 SDS and 1.51 SDS below target height SDS in females and males, respectively. In a multiple regression analysis, FHSDS showed a positive correlation with THSDS (p < 0.001) and a negative correlation with age at diagnosis (p < 0.01). High androstenedione levels between 6 and 10 years of age, indicating undertreatment, also showed a

Table 2  Auxological characteristics of children with CAH according to clinical manifestation and gender

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SW (n=20)</td>
<td>NSW (n=9)</td>
<td>SW (n=12)</td>
<td>NSW (n=12)</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>0.12 (0.11)</td>
<td>4.9 (2.4)</td>
<td>0.03 (0.05)</td>
<td>3.1 (2.9)</td>
</tr>
<tr>
<td>Length/height at diagnosis (SDS)</td>
<td>−0.85 (0.93)</td>
<td>3.0 (0.9)</td>
<td>−0.27 (0.97)</td>
<td>0.2 (0.7)</td>
</tr>
<tr>
<td>Age at onset of puberty (y)</td>
<td>11.8 (1.5)</td>
<td>11.2 (1.5)</td>
<td>10.6 (0.84)</td>
<td>10.4 (1.3)</td>
</tr>
<tr>
<td>Height at onset of puberty (SDS)</td>
<td>−0.50 (0.89)</td>
<td>0.86 (0.56)</td>
<td>−0.66 (0.75)</td>
<td>−0.2 (0.94)</td>
</tr>
<tr>
<td>HSDS at onset of puberty</td>
<td>−1.07</td>
<td>−1.13</td>
<td>−1.16</td>
<td>−1.17</td>
</tr>
<tr>
<td>Bone age at onset of puberty [G&amp;P]</td>
<td>12.5 (1.5)</td>
<td>13.6 (1.0)</td>
<td>11.2 (1.1)</td>
<td>11.5 (1.7)</td>
</tr>
<tr>
<td>Height gain during puberty (cm) *</td>
<td>21.1 (6.8)</td>
<td>19.6 (7.7)</td>
<td>22.4 (5.3)</td>
<td>21.1 (9.1)</td>
</tr>
<tr>
<td>Final height SDS</td>
<td>−1.63 (1.3)</td>
<td>−1.2 (1.0)</td>
<td>−0.85 (0.82)</td>
<td>−0.78 (1.4)</td>
</tr>
<tr>
<td>Target height SDS</td>
<td>−0.35 (0.87)</td>
<td>0.31 (0.8)</td>
<td>0.40 (0.56)</td>
<td>0.18 (0.85)</td>
</tr>
<tr>
<td>SDS FH corrected for TH</td>
<td>−1.27 (0.94)</td>
<td>−1.51 (0.7)</td>
<td>−1.25 (0.72)</td>
<td>−0.96 (1.3)</td>
</tr>
</tbody>
</table>

Results expressed as mean (SD).

Patients treated with triptorelin were excluded.

*In healthy children, bone age [G&P] at onset of puberty (10.7 years in females, 11.5 years in males) was approximately 1.5 years retarded.11 SW, salt wasting; NSW, non-salt wasting; HSDSba, height SDS for bone age.

Figure 1  Longitudinal length and height SDS registration in patients (n = 60) with congenital adrenal hyperplasia according to reference values of Dutch children.9 Length SDS before the age of 2 years is recorded as height SDS. In non-salt wasting females there is an interruption in the mean HSDS at the age of 6.5 years, due to inclusion of four newly diagnosed late onset CAH females. Final height was expressed as SDS using the population average at 21 years of age. HSDS at 21 years was not corrected for target height.

In SW, mean HSDS at diagnosis was +0.2 SDS in females and +3.0 SDS in males at a median age of 2.4 and 6.2 years, respectively. FH showed a positive correlation with THSDS (p < 0.001) and with salt supplementation during the first year of life (p < 0.003).
Bone maturation
Table 2 and fig 2 present bone age and delta bone age/chronological age. The bone age scores (n = 126) according to G&P were compared to the bone age scores according to TW2-RUS in CAH patients. The mean (SD) bone age scores according to G&P were 0.8 (0.6) years younger compared to TW2-RUS scores in all age categories. In SW patients, at the age of 2 years, bone maturation according to G&P was approximately 2.3 years accelerated compared to bone age at onset of puberty of healthy reference values. In NSW, bone age was advanced at time of diagnosis. At onset of puberty, bone age (G&P) was approximately 3.2 years accelerated compared to bone age at onset of puberty of healthy reference values.

Body mass index
In SW patients, during childhood and at FH mean BMI was not significantly different from reference values. In NSW patients, mean BMI during childhood was not increased, but females had a significantly increased BMI at final height (25.2 (6.3); p < 0.001). In a multiple regression analysis with BMI at FH as dependent variable and glucocorticoid dose and androgen concentrations as independent variables, we could not find any significant association.

DISCUSSION
Length SDS decreased from −0.27 in females and −0.87 in males at diagnosis until it reached −1.5 at 3 months of age. Although there may be some inaccuracy in determination of length in young infants, loss of height potency in the first three months seems to be apparent. In this period of rapid growth, reduction of growth velocity has considerable consequences. Growth retardation might be caused by the high mean glucocorticoid dose of approximately 40 mg/m²/day during this period. Previous studies showed that an early overdose with glucocorticoids (>30 mg/m²/day) resulted in loss of height SDS and final HSDS. Treatment with a lower dose of glucocorticoids may be advantageous for final height, even if the adrenal androgen production is not optimally suppressed, as observations of Thilen et al indicated that growth during the first year is not very sensitive to androgens. In addition to glucocorticoid excess, sodium depletion could be another factor resulting in loss of height potential. In the Netherlands, treatment schedules with or without salt supplementation are used in the treatment of CAH infants. Salt wasting infants treated with salt supplements showed an HSDS at the age of 2 years, which was 0.5 SDS higher (p < 0.003). The requirement for sodium in normally growing infants is approximately 1 mmol/kg/day, the amount provided by human milk. However, in CAH patients with increased natriuresis, supplementation of 2–3 mmol/kg sodium may prevent sodium chloride deficiency. Sodium chloride deficiency may result in depletion of the extracellular volume as the mineralocorticoid effect of fludrocortisone is less with reduced sodium supply. The role of the maintenance of sodium balance on growth has been shown previously, but no comparable data on the additional role of sodium supplementation on HSDS in fludrocortisone treated CAH patients are available. To support this mechanism in CAH patients, a prospective study on the role of salt supplementation and treatment during infancy should be performed.

In the prepubertal period between 6 and 10 years, androgen excess (undertreatment) resulted in an advanced bone age increase final height. FHSDS corrected for TH was −2.2 (0.75) in the four non-salt wasting males.
The non-salt wasting female patients were slightly overweight. An increase in muscle mass as seen in prolonged androgen exposure may play an additional role in these females.

REFERENCES


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