

## ORIGINAL ARTICLE

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

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**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). Auxological 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 ( $40 \text{ mg/m}^2/\text{day}$ ). FH corrected for target height ( $\text{FH}_{\text{corr}}\text{TH}$ ) was  $-1.25$  and  $-1.27$  SDS in females and males, respectively. Patients treated with salt supplements during the first year, had a better  $\text{FH}_{\text{corr}}\text{TH}$  ( $-0.83$  SDS). In NSW patients,  $\text{FH}_{\text{corr}}\text{TH}$  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.

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Congenital adrenal hyperplasia (CAH) is, in more than 90% of cases, caused by a 21-hydroxylation defect in the adrenal cortex.<sup>1</sup> Biochemically, this results in low serum concentrations of aldosterone and cortisol, and increased 17-hydroxyprogesterone (17OHP) and androstenedione concentrations. Clinically, there are two major types of CAH: a severe classic (early onset) form; and a milder non-classic (late onset) form.<sup>2</sup>

In classic CAH, 75% of the patients have the salt wasting (SW) and 25% the non salt-wasting variant (NSW).<sup>1</sup> Male infants have no clinical signs at birth, and in the NSW form, diagnosis is often delayed until pseudoprecocious puberty is apparent.<sup>3,4</sup> In female patients, CAH is suspected shortly after birth if there is genital ambiguity, ranging from slight clitoromegaly to complete masculinisation. The non-classic (late onset) form of CAH is a milder form of 21-hydroxylase deficiency, and is diagnosed later in life. The clinical features resulting from androgen excess can occur at any age.

Final height in early and late onset patients has been reported as diminished (156.4–162.0 cm in females and 167.8–173.6 cm in males).<sup>4,7</sup> In these studies a wide variety of dosages and types of glucocorticoids and mineralocorticoids were given. Growth during puberty was reported to be subnormal in males and normal in females.<sup>8</sup>

The objective of this study was to evaluate longitudinal growth and puberty in Dutch CAH patients on a regimen of hydrocortisone and fludrocortisone acetate from diagnosis until final height.

## 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  $130 \text{ mmol/l}$  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  $130 \text{ mmol/l}$ , 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;  $\text{FH}_{\text{corr}}\text{TH}$ , 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

**Table 1** Treatment and treatment monitoring in children with CAH according to clinical manifestation and gender at age 0–18 years

	Age (y)	Males		Females	
		SW (n=21)	NSW (n=13)	SW (n=13)	NSW (n=13)
Glucocorticoids* (mg/m <sup>2</sup> /day)	0–0.25	39.7 (26.1)		44.9 (35.0)	
	0.25–2	17.9 (7.9)		24.9 (11.2)	
	2–10	15.4 (4.6)	17.9 (6.4)	15.0 (4.3)	13.7 (5.9)
	10–18	14.4 (3.9)	14.8 (3.4)	12.9 (3.7)	13.2 (5.1)
Androstenedione treatment scores†	2–6	0.08 (0.6)	0.29 (0.47)	0.19 (0.6)	0.19 (0.4)
	6–10	0.16 (0.56)	0.31 (0.63)	0.21 (0.61)	0.13 (0.43)
	10–18	0.13 (0.71)	0.22 (0.47)	0.35 (0.67)	0.21 (0.68)

Results expressed as mean (SD).

\*Glucocorticoid dose in mg/m<sup>2</sup> = (A+B)/m<sup>2</sup>. A = hydrocortisone dose per day (mg) or cortisone acetate dose per day (mg/1.25); B = fludrocortisone acetate dose (100 µg = 1 mg hydrocortisone effect).

†All androstenedione concentrations were compared to reference values for age and sex expressed as treatment scores. They were scored as “normal” (0), “above normal” (1), or “below normal” (–1), indicating adequate treatment, undertreatment, or overtreatment, respectively.<sup>16</sup> No distinction was made in the severity of over and under treatment. For each child, the average treatment score was calculated annually. SW, salt wasting; NSW, non-salt wasting.

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.<sup>9</sup> 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.<sup>9</sup> TH was converted into THSDS using Dutch standards for final height.<sup>9</sup>

Pubertal maturation was recorded according to Tanner's stages.<sup>10</sup> 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).<sup>9</sup> 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).<sup>11</sup>

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 (n = 607) and TW2-RUS (n = 126).<sup>12,13</sup> As Dutch bone age reference values were only available 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.<sup>11,12</sup>

The BMI (weight/height<sup>2</sup>) was compared to Dutch reference values.<sup>14</sup>

The cortisone acetate dosage was converted into an equivalent hydrocortisone dose by dividing the cortisone dose (mg) by 1.25.<sup>15</sup> The glucocorticoid effect of 100 µg fludrocortisone acetate was equated to 1 mg hydrocortisone.<sup>15</sup> The glucocorticoid dose in mg 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.<sup>16</sup> No distinction was made in the severity of over and undertreatment. For each child, the average treatment score was calculated annually.

## Data analysis

Results are expressed as mean (SD) or as median (range) where indicated. Multiple regression analysis was used to determine factors influencing final height SDS in SW and NSW. The following independent variables were taken: THSDS, age at diagnosis, treatment with hydrocortisone or cortisone acetate, glucocorticoid dose in mg/m<sup>2</sup>/day, treatment score, and bone age at onset of puberty. Glucocorticoid doses and treatment scores were analysed in age categories.

## 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/m<sup>2</sup>/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/m<sup>2</sup>/day in the salt supplemented group versus 22.3 (16.8) mg/m<sup>2</sup>/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

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

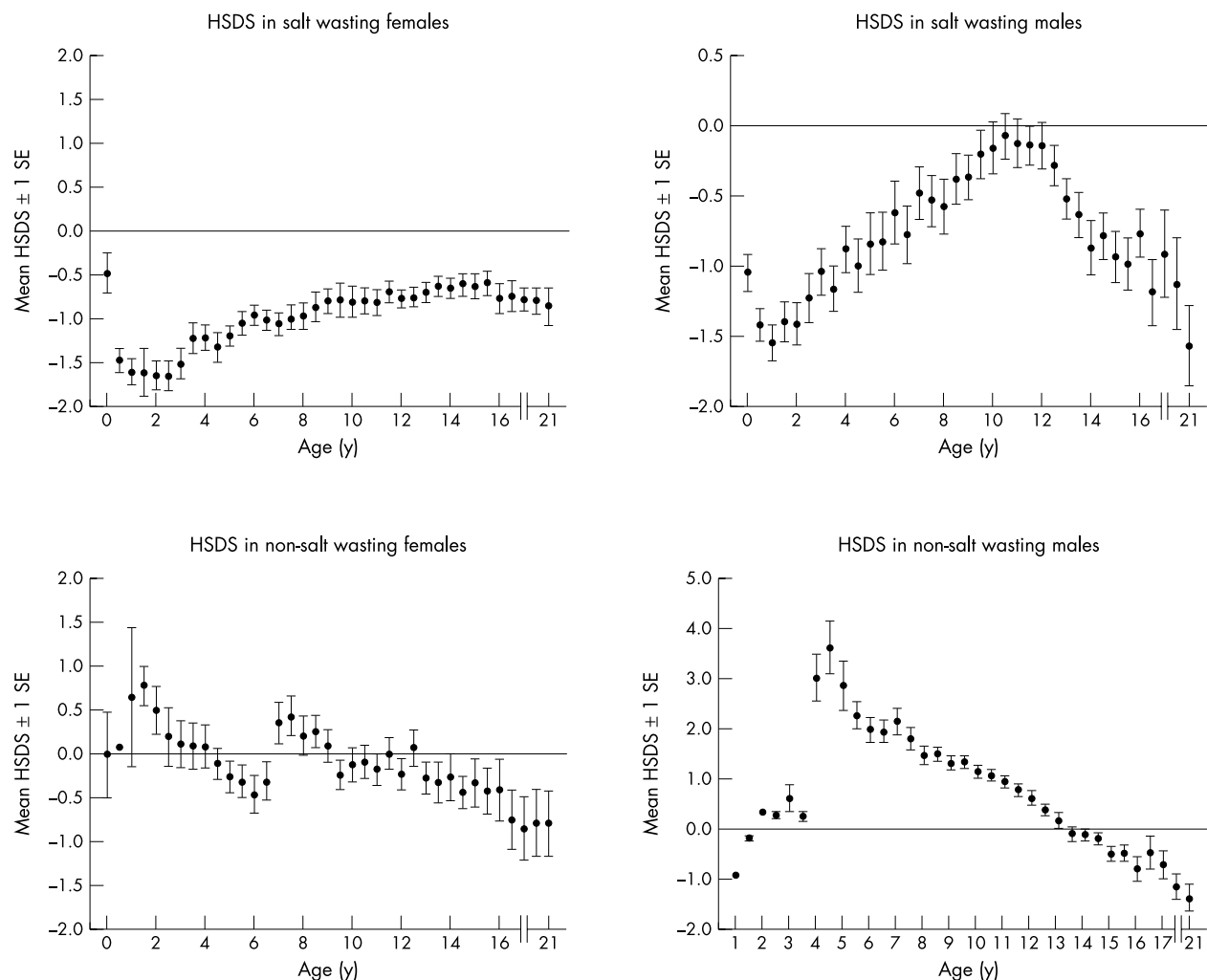
	Males		Females	
	SW (n=20)	NSW (n=9)	SW (n=12)	NSW (n=12)
Age at diagnosis (y)	0.12 (0.11)	4.9 (2.4)	0.03 (0.05)	3.1 (2.9)
Length/height at diagnosis (SDS)	-0.85 (0.93)	3.0 (0.9)	-0.27 (0.97)	0.2 (0.7)
Age at onset of puberty (y)	11.8 (1.5)	11.2 (1.5)	10.6 (0.84)	10.4 (1.3)
Height at onset of puberty (SDS)	-0.50 (0.89)	0.86 (0.58)	-0.66 (0.75)	-0.2 (0.94)
HSDSba at onset of puberty	-1.07	-1.13	-1.16	-1.17
Bone age at onset of puberty (G&P)*	12.5 (1.5)	13.6 (1.0)	11.2 (1.1)	11.5 (1.7)
Height gain during puberty (cm)	21.1 (6.8)	19.6 (7.7)	22.4 (5.3)	21.1 (9.1)
Final height SDS	-1.63 (1.3)	-1.2 (1.0)	-0.85 (0.82)	-0.78 (1.4)
Target height SDS	-0.35 (0.87)	0.31 (0.5)	0.40 (0.56)	0.18 (0.85)
SDS FH corrected for TH	-1.27 (0.94)	-1.51 (0.7)	-1.25 (0.72)	-0.96 (1.3)

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.<sup>11</sup>

SW, salt wasting; NSW, non-salt wasting; HSDSba, height SDS for bone age.

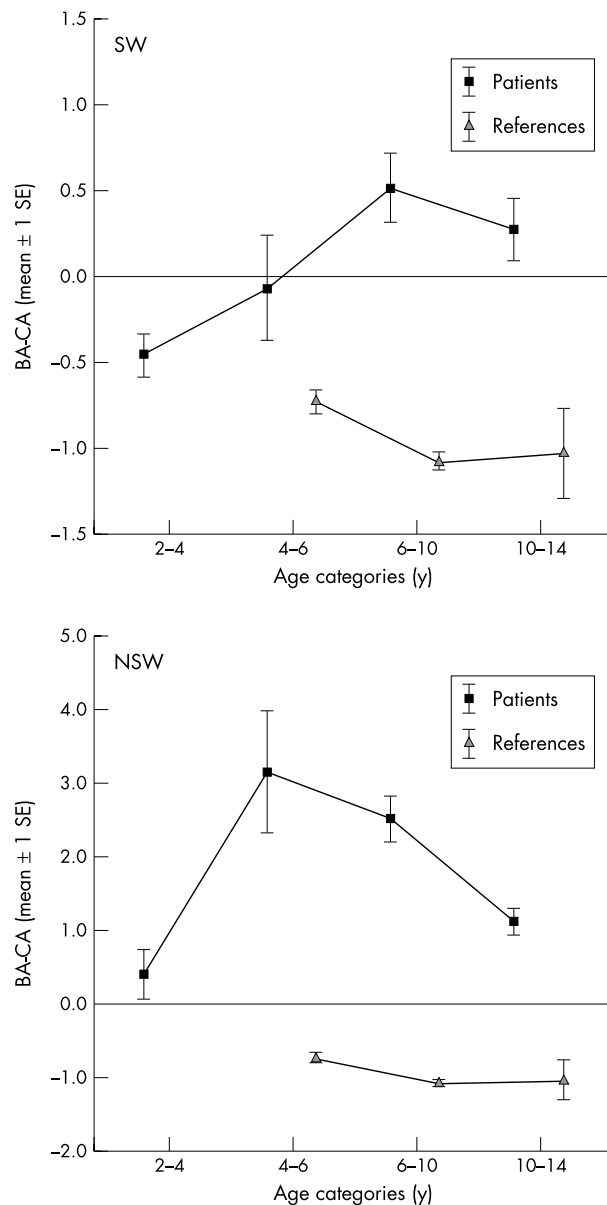


**Figure 1** Longitudinal length and height SDS registration in patients (n = 60) with congenital adrenal hyperplasia according to reference values of Dutch children.<sup>9</sup> Length SDS before the age of 2 years is recorded as height SDS. In non-salt wasting females there is an interruption in the 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.

group:  $-0.83 (0.73)$  versus  $-1.69 (0.81)$  ( $p < 0.003$ ). 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



**Figure 2** The difference between bone age (BA) according to G&P and chronological age (CA) in relation to age categories. The reference values were adjusted from Dutch TW2-RUS reference values.<sup>11</sup> Bone age according to G&P is 0.8 years lower than that according to TW2-RUS (see results).

negative correlation with final height ( $p < 0.001$ ). The dose of glucocorticoids had no significant correlation with FHSDS.

### Puberty

Table 2 presents age and skeletal maturation at onset of puberty and pubertal height gain. In SW and NSW, age at onset of puberty was within normal limits, but bone maturation was advanced.<sup>9</sup> Mean pubertal height gain was 21.1 (6.8) and 19.6 (7.7) cm in SW and NSW males and 22.4 (5.3) and 21.1 (9.1) cm in SW and NSW females, respectively.<sup>17</sup> Menarche occurred approximately 0.5 years later than in the Dutch population, at the mean age of 13.9 (0.96) years in SW and 13.5 (1.32) in NSW.<sup>9</sup> The mean height gain after menarche was approximately 3 cm less than previously reported: 4.1 (2.5) cm in SW and 5.1 (2.8) cm in NSW females.<sup>17, 18</sup>

Six patients (five males (four NSW) and one NSW female) had precocious puberty and one additional SW female patient was treated with triptorelin to postpone puberty in order to

increase final height. FHSDS corrected for TH was  $-2.2$  (0.75) in the four non-salt wasting males.

### 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 retarded. At onset of puberty, bone age (G&P) was approximately 2.3 years accelerated compared to bone age at onset of puberty of healthy reference values.<sup>11</sup> 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.<sup>11</sup>

### 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);  $p < 0.001$ ).<sup>14</sup> 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/m<sup>2</sup>/day during this period. Previous studies showed that an early overdose with glucocorticoids ( $>30$  mg/m<sup>2</sup>/day) resulted in loss of height SDS and final HSDS.<sup>4, 8, 19</sup> 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.<sup>20</sup> In addition to glucocorticoid excess, sodium depletion could be another factor resulting in loss of height potential.<sup>21-24</sup> 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 ( $-1.0$  versus  $-1.56$ ), despite the higher mean glucocorticoid dose during infancy in this group. FH corrected for TH was also higher in the salt supplemented group:  $-0.83$  versus  $-1.69$  ( $p < 0.003$ ). 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.<sup>25</sup> The role of the maintenance of sodium balance on growth has been shown previously,<sup>21, 26-28</sup> 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

### Key messages

- Linear growth in SW patients with CAH is poor during the first two years of life, and contributes to loss of final height potential
- While this growth pattern may be due partly to glucocorticoid excess, sodium depletion is a possible contributory factor
- The effect of intensive sodium chloride support in early infancy should be examined prospectively
- In NSW patients with CAH, loss of final height potential is related to acceleration in bone maturation during delay in diagnosis. Neonatal screening for CAH will substantially improve the height prognosis of NSW patients
- In both SW and NSW patients, bone age advance at the onset of puberty, attributable to undertreatment during the prepubertal years, accounted for a decrease in height gain during puberty

(G&P) of approximately 2.3 years at onset of puberty in comparison to healthy children at the same chronological age. Skeletal sensitivity to sex steroids is maximal during childhood and decreases with advancing age.<sup>29</sup> In our study, in the prepubertal period the acceleration in bone maturation was more pronounced than statural growth (HSDSba less than -1.0 SDS). Accelerated bone age at onset of puberty negatively influences height gain during puberty as reported by Bourguignon.<sup>30</sup>

Pubertal height gain seems to be lower than previously reported on longitudinal growth in normal children, although no recent comparable reference values were available.<sup>9, 31, 32</sup> Pubertal height loss was more pronounced in males. No substantial reduction of duration of growth was found. Loss of height potential during puberty seemed to be caused by a lower peak height velocity.<sup>8</sup> In females, menarche occurred approximately six months later than in Dutch girls, resulting in an increase of duration of growth. The growth hormone IGF-I axis was not responsible for the loss in final height potential during puberty as normal to increased serum levels of IGF-I during puberty in treated CAH patients were found.<sup>33</sup>

In non-salt wasting patients, females were diagnosed earlier than NSW males with a less advantaged bone age and better height prognosis. In males, loss of final height was more pronounced because of late diagnosis. Prolongation of androgen excess induced true precocious puberty in 30% of the male patients. Despite treatment with triptorelin,  $FH_{corr,TH}$  was approximately 0.8 SDS below  $FH_{corr,TH}$  in non-salt wasting males without true precocious puberty. With the introduction of neonatal screening for CAH, non-salt wasting males may also be diagnosed within the first weeks of life.

In recently performed studies, final height was recorded between 156.4 and 162.1 cm in females and between 167.8 and 173.6 cm in males.<sup>4, 7</sup> In our study, mean final height was better (165.1 in females and 172.8 in males), but the relatively good final height may be a result of the fact that the Dutch population is the tallest in Europe. However, the FHSDS (not corrected for target height) in the Finnish study was comparable with our results, but also with the worst results in NSW males.<sup>4</sup> Adult height corrected for target height SDS is the best parameter in the comparison between results. However, definitions of target height vary, depending on whether a correction for secular trend is included.

The development of overweight may be a clinical problem in the long term management of 21OHD.<sup>5, 34</sup> Overweight is defined as a BMI >25 kg/m<sup>2</sup> and obesity as a BMI >30 kg/m<sup>2</sup> in adulthood.<sup>14</sup> The increase in BMI from childhood to adulthood as reported in CAH patients was associated with an increase in fat mass as seen in glucocorticoid excess.<sup>34</sup> A relation was reported between obesity and severe overtreatment (>30 mg hydrocortisone equivalent/m<sup>2</sup>). Patients are now

treated with lower hydrocortisone dosages (15–25 mg/m<sup>2</sup>), but there are still reports of obesity in adulthood.<sup>5, 34, 35</sup> In our population, the mean glucocorticoid dose (including fludrocortisone) between 2 and 18 years was 14.6 (4.8) mg/m<sup>2</sup>. A mean BMI at final height was found below the overweight cut off. These findings suggest that a glucocorticoid replacement dose mimicking the normal cortisol production rate may reduce the risk of obesity in these children.<sup>36, 37</sup> 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.

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