Patricia Bretones, Benjamin Riche, Emmanuel Pichot, Michel David†, Pascal Roy, Véronique Tardy, Behrouz Kassai, Ségolène Gaillard, Delphine Bernoux, Yves Morel, Pierre Chatelain, Marc Nicolino and Catherine Cornu*, for the French Collaborative CAH Growth Study Group

Growth curves for congenital adrenal hyperplasia from a national retrospective cohort

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Abstract

Background: In congenital adrenal hyperplasia (CAH), adjusting hydrocortisone dose during childhood avoids reduced adult height. However, there are currently no CAH-specific charts to monitor growth during treatment. Our objective was to elaborate growth reference charts and bone maturation data for CAH patients.

Methods: We conducted a retrospective observational cohort study, in 34 French CAH centers. Patients were 496 children born 1970–1991 with genetically proven 21-hydroxylase deficiency. Their growth and bone maturation data were collected until age 18 together with adult height, puberty onset, parental height, and treatment. The mean (SD) heights were modeled from birth to adulthood. The median ± 1 SD and ± 2 SDs model-generated curves were compared with the French references. A linear model for bone maturation and a logistic regression model for the probability of short adult height were built.

Results: Growth charts were built by sex for salt wasting (SW) and simple virilizing (SV) children treated before 1 year of age. In girls and boys, growth was close to that of the general French population up to puberty onset. There was almost no pubertal spurt and the mean adult height was shorter than that of the general population in girls (– 1.2 SD, 156.7 cm) and boys (– 1.0 SD, 168.8 cm). Advanced bone age at 8 years had a strong impact on the risk of short adult height (OR: 4.5 per year advance).

Conclusions: The 8-year bone age is a strong predictor of adult height. It will help monitoring the growth of CAH-affected children.

Keywords: adult height; bone maturation; congenital adrenal hyperplasia; growth.

†Deceased
***Corresponding author: Catherine Cornu,** Université Claude Bernard Lyon 1, Lyon, France; INSERM, CIC1407, Bron, France; Service de Pharmacologie Clinique, Hospices Civils de Lyon, Bron, France; Hospices Civils de Lyon – Centre d'Investigation Clinique INSERM CIC1407/UMR5558 Hôpital Louis Pradel 28, Avenue du Doyen Lépine Bron 69677, France, Phone: +33 (0)4 72 35 72 31, E-mail: catherine.cornu@chu-lyon.fr
Patricia Bretones and Emmanuel Pichot: Service d'Endocrinologie Pédiatrique, Hospices Civils de Lyon, Bron, France; and Hôpital Femme Mère Enfants, Hospices Civils de Lyon, Bron, France
Benjamin Riche and Pascal Roy: Université Claude Bernard Lyon 1, Lyon, France; Service de Biostatistique, Hospices Civils de Lyon, Lyon, France; and CNRS UMR 5558, Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique-Santé, Villeurbanne, France
Michel David, Pierre Chatelain and Marc Nicolino: Service d'Endocrinologie Pédiatrique, Hospices Civils de Lyon, Bron, France; Hôpital Femme Mère Enfants, Hospices Civils de Lyon, Bron, France; and Université Claude Bernard Lyon 1, Lyon, France
Véronique Tardy: Hôpital Femme Mère Enfants, Hospices Civils de Lyon, Bron, France; Université Claude Bernard Lyon 1, Lyon, France; and Endocrinologie moléculaire et maladies rares, Hospices Civils de Lyon, Bron, France
Behrouz Kassai: Université Claude Bernard Lyon 1, Lyon, France; CNRS UMR 5558, Laboratoire de Biométrie et Biologie Évolutive, Équipe Evaluation et modélisation des effets des médicaments, Villeurbanne, France; INSERM, CIC1407, Bron, France; and Service de Pharmacologie Clinique, Hospices Civils de Lyon, Bron, France
Ségolène Gaillard: INSERM, CIC1407, Bron, France
Delphine Bernoux: INSERM, CIC1407, Bron, France; Service d'Endocrinologie Pédiatrique, Hospices Civils de Lyon, Bron, France; and Hôpital Femme Mère Enfants, Hospices Civils de Lyon, Bron, France
Yves Morel: Université Claude Bernard Lyon 1, Lyon, France; and Endocrinologie moléculaire et maladies rares, Hospices Civils de Lyon, Bron, France

Introduction

Congenital adrenal hyperplasia (CAH) is a rare genetic disorder – approximately 1 in 15,000 births [1, 2] – due, in more than 90% of cases, to a 21-hydroxylase deficiency caused by mutations in the *CYP21A2*. There are three disease phenotypes: the most severe life-threatening salt wasting (SW) form, the simple virilizing (SV) form, and the less severe nonclassical (NC) form [3]. In CAH, low cortisol causes high adrenocorticotropic hormone (ACTH) levels which increase cortisol precursors (such as 17-hydroxyprogesterone) and results in androgen excess. In 46, XX-affected girls, this excess induces virilization of the external genitalia during fetal development. In all children, boys and

girls, this excess causes accelerated bone maturation and growth and reduces adult height (AH). In these children, hydrocortisone replacement therapy is very challenging: overdosing results in growth inhibition and excessive weight gain [4], whereas underdosing results in accelerated bone maturation and short AH.

A meta-analysis reviewed AH data until 2008 and confirmed height loss: the mean AH in SW and SV patients was – 1.38 SD-score (– 1.56 to – 1.20), even in recent studies. However, patient heterogeneity limits the reliability of these meta-analytic estimates [5, 6]. The management of CAH-children requires a strict monitoring of growth. While specific growth charts exist for Turner syndrome, Prader-Willi syndrome, or achondroplasia [7–9], charts are lacking for CAH. Child-growth monitoring is currently based on bone maturation and AH prediction with reference to healthy children [10]. The aim of this article was to generate CAH-specific growth charts and a bone maturation model from a cohort of genetically proven CAH cases followed from birth to adulthood by specialized centers sharing common French patient-management rules.

Materials and methods

Patients

CAH patient files were provided by pediatric endocrine clinics in France. The criteria for inclusion were birth between 1970 and 1991, genetically proven CAH, regular follow-up (at least one follow-up visit per year from birth to adulthood). The criteria for exclusion were bone dysplasia, any chronic disease affecting growth, and growth hormone treatment. A centrally performed genotyping allowed CAH classification into SW, SV, or NC. The data were retrospectively aggregated into a database that includes neonatal data, parents' heights, CAH genotype, growth data, and treatment data. All left wrist X-rays for BA assessment were centrally read by a single independent investigator with Maturos® software based on Sempé's method [11]. Growth data (EP) were recorded every 6 months during the first 2 years of life and during the "pubertal period" (8–14 years) but yearly between the ages 2 and 8 years and after age 14 years, though the patients were usually seen every 3–6 months. A yearly collection was deemed sufficient for modeling purposes between the ages 2 and 8 years and after age 14 years. Independently, we also recorded the age at puberty onset (i.e. breast Tanner stage II in girls or testicular volume greater than 3 mL in boys) [12–14]. Adult height (AH) was defined as (i) the height recorded after age 20 in boys or 18 in girls; (ii) the height recorded when bone age (BA) was ≥ 18 years in boys and 16 years in girls (99.6% of AH) (10); or (iii) the height measured after growth velocity drop to ≤ 1 cm/year [14]. The total pubertal growth spurt was calculated as the difference between AH and the height at puberty onset. The data on treatment included the age at treatment onset, the dose of hydrocortisone (mg/day) and its changes during the first 2 years of life and every 6 months thereafter, the dose of 9-alpha-fludrocortisone (μg/day), and the dose of salt supplement (mg/day). The dose of hydrocortisone was also calculated in mg/m^2/day. The body surface area was calculated using Bailey and Briars formulas [15]. The average drug dose over a given time interval was calculated as the integral of the doses per m^2 weighted by the treatment duration. The calculation of the mean hydrocortisone dose between 0 and 2 years was restricted to patients whose treatment started before age 6 months. The average pubertal dose was defined as the average dose over ages 10–14 years in girls and 12–16 years in boys. We chose not to record hormonal data because of the heterogeneity across centers regarding the schedule of measurement (before or after treatment administration) and the hormone assays. Instead, we analyzed carefully and homogeneously bone maturation data, which are indirect markers of androgen excess and treatment imbalance. The use of gonadotrophin-releasing hormone agonists (GnRHa) or cyproterone acetate (CA) was also collected with the dates of onset and end of treatment. The Z scores were defined in comparison with the French population [16]. Computer data management and quality controls were performed using Clininfo® software.

Statistical analyses

Sex-related growth charts were built using exact measurements of age. Smooth reference centile curves were obtained with the LMS method [17, 18]. The method estimates age-specific percentiles using smoothing cubic splines after transformation of the data to approximate normality. The mean height values and their SDs were modeled from birth to age 18 years. The median and the (±1, ±2) SD curves stemming from the models were compared with the French reference curves [16]. Growth charts were built with data on SW and SV children who received treatment before 1 year of age because these charts can be used in children who now benefit from neonatal screening. A mixed linear regression model based on the maximum likelihood estimates was used to model bone maturation taking into account sex, genotype, age at treatment initiation, and the repeated measurements of BA. This model provided predicted BAs at age 8 years [19]. A model for the probability of short AH (more than two SDs below the median French AH) was built using logistic regression. The model included the genotype (SW, SV, or NC) and sex. Potential explanatory variables were sequentially introduced by blocks: parents' characteristics (mother's and father's height), birth characteristics (height, weight, and gestational age), auxological parameters at visits until age 8 years [height, weight, body mass index (BMI), BA, and pubertal stage], environmental characteristics (year of birth, minor or major care center), and treatment characteristics (age at treatment onset, hydrocortisone, fludrocortisone, and salt daily doses, and use of a GnRHa). Variables collected after age 8 years and at puberty were tested as additional factors but not included in the final model because the model is intended for prediction purposes at a young age. The model retained only statistically significant variables (p-value < 0.05).

Results

Patients

Data on 496 CAH patients (208 boys and 288 girls) were retrospectively collected from 34 French centers (28 university hospitals, 4 public non-university centers, and

2 private centers) (Flow diagram in Figure 1). More than half the cases (54%, 266 cases) were recruited from 7 major centers. The patients' characteristics are shown in Table 1. Genotyping allowed form classification (SW, SV, or NC) of all but 51 patients: 11 with rare mutation (enzyme activity not known) and 40 missing genotypes. These patients were classified using the phenotype (age and circumstances at diagnosis, requirement or not for salt and fludrocortisone). The latter classification found 3 SW, 4 SV, and 3 NC forms among the rare mutations and 30 SW, 7 SV, and 1 NC forms among the missing genotypes. Three cases could not be classified and have been excluded from the analyses.

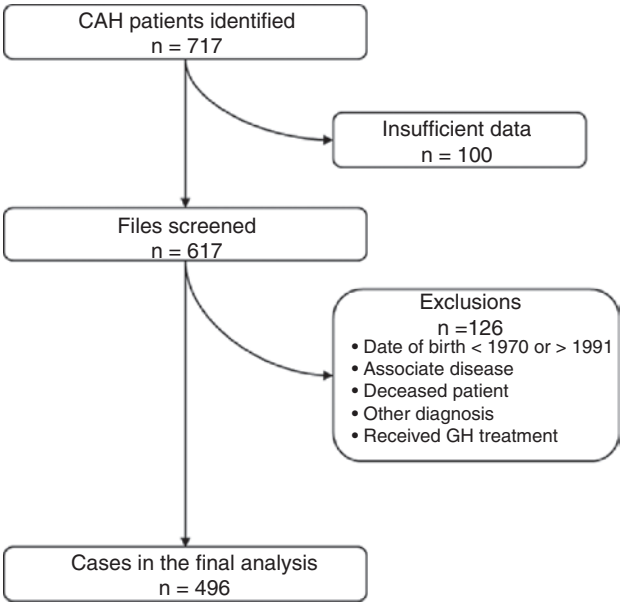

Figure 1: Flow diagram of the patients' recruitment process.

Growth data

Fathers' and mothers' heights were available for 439 and 442 patients, respectively (Table 2). These parents were slightly shorter than the corresponding individuals from the general French population: 161.9 vs. 163.3 cm for women ($p < 0.001$), 174.1 cm vs. 175.3 cm for men ($p = 0.007$) [16]. We recorded, on average, 22.2 height measurements per child (maximum: 26). The data included at least 10 height measurements in 480 patients (96.7%) and validated AHs in 467 patients (94.1%). A set of 5000 BA monitoring radiographies was centrally reviewed for 311 patients (62.7%).

Growth charts were built using data on the 307 children treated before 1 year of age: 156 SW and 28 SV girls (59% of the female cohort) and 110 SW and 13 SV boys (63% of the male cohort. The median-height curves relative to CAH girls and boys were close to those of the general French population until the age of puberty onset (Figure 2A and B) but started to depart from these curves thereafter displaying a dramatic drop in pubertal spurt. This led to a mean AH of −1.2 SD (156.7 cm) in girls and −1.0 SD (168.8 cm) in boys. In the whole CAH cohort, the mean AH depended on the genotype: a more severe genotype was associated with a smaller AH (Table 2). In comparison with the general French population, short AH (< −2 SD score) was seen in 24% of the cohort (22.5% of girls and 26.0% of boys). A major advance in BA was seen at age 8 years with a mean BA of 10 year 2 months in girls and 11 years in boys (Figure 3). The age at puberty onset was similar to that of the general population, except for SV boys and NC girls in whom puberty occurred earlier (Table 2) [11–13]. The mean age at menarche was slightly delayed in SV and SW girls (13 years 8 months ±2 years

Table 1: Characteristics of the study population (n = 496).

Characteristic	Girls (n = 288)	Boys (n = 208)	Total (n = 496)
Median year of birth	1984	1984	1984
Born after 1980, n (%)	213 (74.0)	162 (77.9)	375 (75.6)
Mean height (SDS)[a], cm			
Fathers	173.9 (− 0.24)	174.5 (− 0.14)	174.1 (− 0.19)
Mothers	161.6 (− 0.31)	162.3 (− 0.18)	161.9 (− 0.25)
Pre-term birth, n (%)	18 (7.3)	12 (6.7)	30 (7.0)
Twin birth, n (%)	6 (2.2)	7 (3.5)	13 (2.8)
Small for gestational age, n (%)	28 (10.5)	10 (5.2)	38 (8.3)
Mean birth weight, kg (SD)	3.2 (0.5)	3.4 (0.5)	3.3 (0.5)
Mean birth height, cm (SD)	49.6 (2.0)	50.2 (2.2)	49.8 (2.1)
Genotype, n (%)			
Salt wasting form (SW)	164 (56.9)	117 (56.3)	281 (56.7)
Simple virilizing form (SV)	52 (18.1)	63 (30.3)	115 (23.2)
Non-classical form (NC)	72 (25.0)	28 (13.5)	100 (20.2)

[a]SDS, standard deviation score in comparison with the French population.

Table 2: Growth characteristics of patients with known adult height (n = 467).

Characteristic	Girls				Boys			
	SW n = 159	SV n = 51	NC n = 65	All n = 275	SW n = 110	SV n = 57	NC n = 25	All n = 192
Mean adult height, cm	155.5	157.0	161.0	157.1	167.2	168.8	171.3	168.2
SD	6.9	7.1	5.9	7.1	8.5	7.8	8.3	8.4
Standard deviation score[a]	– 1.39	– 1.13	– 0.41	– 1.11	– 1.36	– 1.09	– 0.67	– 1.19
Adult height < – 2 SD, n (%)	51 (32.1)	9 (17.6)	2 (3.1)	62 (22.5)	30 (27.3)	15 (26.3)	5 (20.0)	50 (26.0)
Mean height at 8 years, cm								
Number	148	50	60	258	106	53	23	182
Mean	124.4	126.7	130.9	126.3	127.4	134.5	132.6	130.1
SD	7.1	7.5	6.8	7.9	7.3	7.4	6.3	7.6
Standard deviation score (*)	+0.09	+0.58	+0.46	+0.51	+0.42	+1.81	+1.42	+0.95
Bone age at 8 years								
Number	101	35	41	177	77	46	11	134
Mean	9 years 11 months	9 years 11 months	10 years 11 months	10 years 2 months	10 years 5 months	12 years 0 months	11 years 0 months	11 years 0 months
SD	1 year 8 months	1 year 9 months	1 year 1 month	1 year 7 months	2 years 3 months	1 year 11 months	1 year 1 month	2 years 2 months
BMI at 8 years, kg/m^2								
Number	139	46	37	222	95	49	17	161
Mean	17.48	17.31	17.03	17.37	17.49	17.6	18.15	17.59
SD	2.7	1.74	1.86	2.4	2.46	2.13	1.89	2.31
z-score	1.15	1.15	0.96	1.12	1.0	1.11	1.47	1.08
Mean age at puberty onset, year month								
Number	144	47	56	247	98	52	22	172
Mean	11 years 1 months	10 years 7 months	9 years 8 months	10 years 8 months	11 years 5 months	10 years 7 months	11 years 10 months	11 years 3 months
SD	1 year 9 months	1 year 10 months	1 year 6 months	1 year 10 months	1 year 9 months	2 years 0 months	1 year 8 months	1 year 10 months
Total pubertal height gain, cm								
Number	131	44	48	223	93	50	22	165
Mean	16.6	17.4	21.6	17.8	21.5	23.1	19.0	21.7
SD	7.7	7.4	7.7	7.8	8.7	9.9	6.4	8.9
Mean age at menarche, year month								
Number	139	48	62	249	–	–	–	–
Mean	13 years 10 months	13 years 8 months	12 years 8 months	13 years 6 months	–	–	–	–
SD	1 year 10 months	2 years 0 months	1 year 2 months	1 year 9 months	–	–	–	–
Median age at treatment onset								
Number	148	47	61	257	105	55	23	183
Median	0 year 0 months	1 year 2 months	8 years 3 months	0 year 1 months	0 year 1 month	4 years 3 months	7 years 10 months	0 year 1 months
Upper 75% (Q3)	0 year 1 months	3 years 10 months	9 years 5 months	5 years 3 months	0 year 1 month	5 years 11 months	8 years 10 months	4 years 7 months

[a]Standard deviation score (SDS) in comparison with the French population. SW, salt wasting CAH form; SV, simple virilizing CAH form; NC, non-classical CAH form.

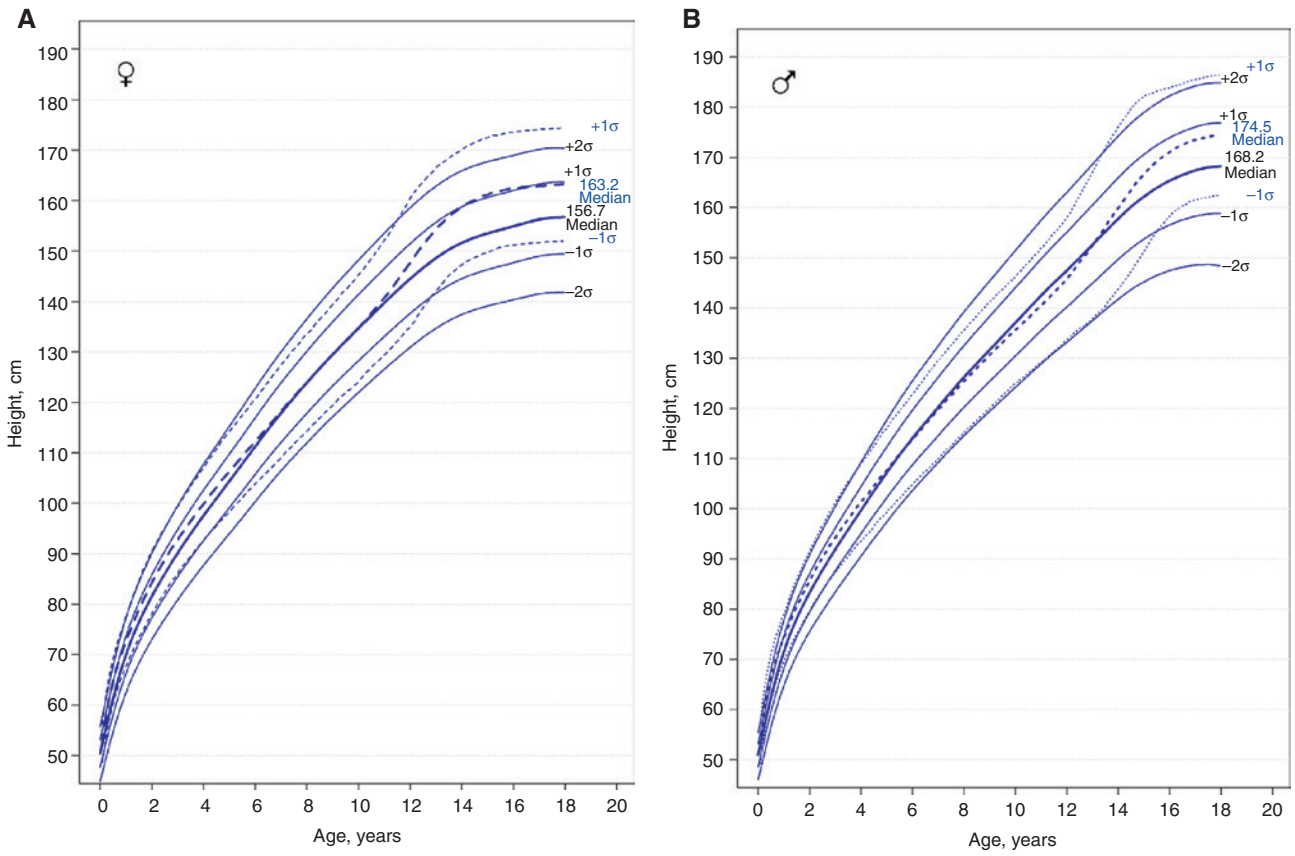

Figure 2: Growth curves relative to the CAH patients, SW and SV forms, treated before age 1 year (bold solid lines), and to the French reference population (bold dotted lines).
The thin solid lines correspond to ±1 SD and ±2 SDs envelopes of the solid lines. The thin dotted lines correspond to ±1 SD envelopes of the dotted lines. (A) in girls; (B) in boys.

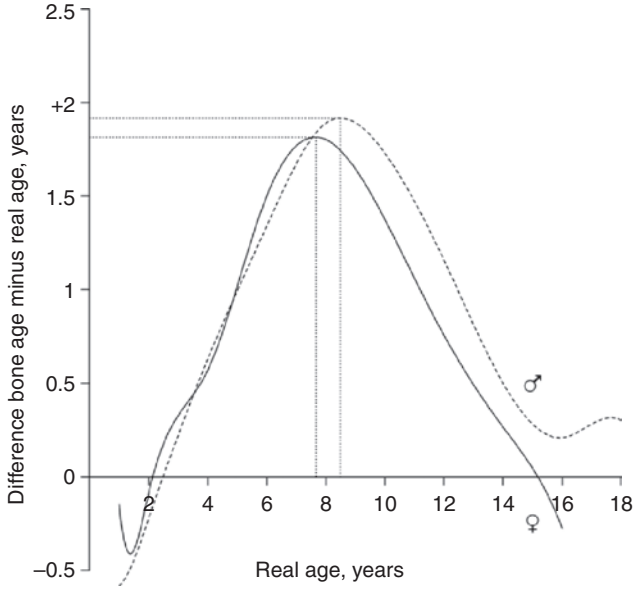

Figure 3: Progress of bone age in patients of genotype SW treated before the age 1 year.

and 13 years 10 months ±1 year, 9 months, respectively). Besides, CAH patients had higher BMI than the general French population: the mean BMI Z-score started to increase by age 2–3 years to reach +1.08 Z-score at 8 years in boys and girls. There was no significant correlation between 8-year BMIs and 2–7 years steroid doses.

Treatment data

Treatment data are shown in Table 3. They were in accordance with the French standard CAH treatment protocol [3]. Fludrocortisone was given to 96.5% of SW patients and 69.4% of SV patients. Salt supplementation was given to 78.8% of SW patients and 22% of SV patients. All patients received hydrocortisone as main glucocorticoid twice daily in 40%, thrice daily in 10%, and at various frequencies according to age in 50% of cases. Seven NC patients received no glucocorticoid. GnRHa were prescribed to 19.5% of all patients; specifically, to 40.4% of

Table 3: Treatment description of patients with known adult height (n = 467).

Treatment and time	Girls				Boys			
	SW n = 159	SV n = 51	NC n = 65	All n = 275	SW n = 110	SV n = 57	NC n = 25	All n = 192
Hydrocortisone, mg/m²/day								
In 0- to 2- years-old children[a]								
Number	106	20	2	128	76	9	3	88
Mean	45.9	40.7	38.8	45.0	44.7	36.2	48.7	44.0
SD	15.0	7.9	5.9	14.1	18.9	6.4	17.1	18.0
In 2–7- years-old children								
Number	147	42	10	199	99	41	6	146
Mean	16.8	16.9	15.2	16.8	17.6	18.3	14.2	17.7
SD	5.0	4.9	4.0	4.9	6.8	5.5	6.2	6.4
During prepuberty[b]								
Number	146	47	42	235	106	54	21	181
Mean	17.4	16.4	13.8	16.5	17.6	16.9	13.7	16.9
SD	5.1	5.0	4.6	5.1	5.4	5.6	4.1	5.4
During puberty[c]								
Number	153	50	54	257	109	53	21	183
Mean	17.8	16.3	11.8	16.3	17.5	16.4	13.2	16.7
SD	4.9	5.6	4.6	5.5	5.5	5.1	7.1	5.7
Fludrocortisone, n (%)	153 (96.2)	38 (74.5)	11 (16.9)	202 (73.5)	104 (94.5)	37 (64.9)	4 (16.0)	145 (75.5)
Salt supplementation, n (%)	120 (75.5)	17 (33.3)	1 (1.5)	138 (50.2)	92 (83.6)	7 (12.3)	3 (12.0)	102 (53.1)
GnRH analogues-Rx, n (%)	17 (10.7)	11 (21.6)	21 (32.3)	49 (17.8)	16 (14.5)	23 (40.4)	3 (12.0)	42 (21.9)
Cyproterone acetate, n (%)	40 (25.2)	17 (33.3)	29 (44.6)	86 (31.3)	21 (19.1)	15 (26.3)	2 (8.0)	38 (19.8)

[a]Minimum duration of 6 months; [b]7–12 years in boys and 7–10 years in girls; [c]12–16 years in boys and 10–14 years in girls. SW, salt wasting CAH form; SV, simple virilizing CAH form; and NC: non-classical CAH form.

SV boys and 32.3% of NC girls. The median age at GnRHa treatment start was 9 years in girls and 9 years 7 months in boys. Those who received GnRHa had a greater mean BA advance than the rest of cohort. The mean BA advance was 2 years 8 months (SD: 14.4 months) in girls and 4 years 2 months (SD: 25.6 months) in boys. The median GnRHa duration was 22 months in girls and 29 months in boys. A total of 124 patients received cyproteron acetate (40 girls and 21 boys with SW form, 17 girls and 15 boys with SV form, and 29 girls and 2 boys with NC form).

Modeling results

The factors found associated with short AH are shown in Table 4. The logistic regression model underlined the importance of CAH genotype: the odds ratio (OR) for short AH was 7.7 in SV and 10.9 in SW (vs. NC as reference condition). This model underlines the strong impact of advance in BA at 8 years on AH: the OR for short AH was 4.5 per year of BA advance. Other factors significantly associated with short AH were loss in height SD-score at 8 years and shorter parents than the general population. After adjustment for all significant factors, age at treatment onset and treatment doses was not found significantly associated with short AH. Neither of the following variables was found significantly associated with the risk of short AH: intrauterine growth retardation, birth weight, birth height, BMI at 8 years, early puberty, use of GnRHa, center size, and dose of hydrocortisone during the first 2 years or from age 2–7 years. In the multivariate analysis, cyproteron acetate treatment was not found significantly associated with short AH.

The AH predicted from observed height and BA at 8 years according to a model by Bayley and Pinneau [10] was significantly lower than the mean observed AH: on average, −7.4 cm in girls and −2.7 cm in boys ($p < 0.001$). Precisely, the mean predicted AHs were 157.1 cm in girls and 168.2 cm in boys (vs. 150.1 and 165.9 cm according to the model of Bayley and Pinneau).

Discussion

Our main results are that regularly monitored French CAH children from the pre-screening era reach shorter AHs than the general population (mean: −1.4 SD score in SW patients) and present a dramatically advanced 8-year bone maturation that influences strongly the risk

Table 4: Factors associated with the risk of short adult height (n = 277 patients).

Model and variables	n	Odds ratio (95% CI)	p-Value
Final adjusted model			
Genotype			0.031
Non-classical form (NC)	50	1	–
Salt wasting vs. NC	154	10.8 (1.8, 65.0)	0.009
Simple virilizing vs. NC	73	7.7 (1.2;50.2)	0.034
Sex			
Girls	162	1	-
Boys vs. girls	115	1.0 (0.5, 2.4)	0.912
Height at 8 years (per one SD)	277	6.2 (3.4, 11.3)	<0.001
Bone age at 8 years (per one years BA)	277	4.5 (2.7, 7.3)	<0.001
Father's height (per one SD)	277	1.4 (1.0, 2.0)	0.034
Mother's height (per one SD)	277	1.7 (1.2, 2.6)	0.007
Not retained additional variables			
Study center			
Small	132	1	–
Big vs. small	145	1.0 (0.4, 2.2)	0.958
Year of birth (per one year)	277	0.9 (0.9, 1.0)	0.065
Early puberty			
No	246	1	–
Yes vs. no	18	3.8 (0.7, 21.1)	0.121
GnRH analogues and early puberty			0.198[a]
Yes and yes	17	1	–
Yes and no	53	0.4 (0.1, 2.4)	0.306
No and yes	1	–	–
No and no	193	0.2 (0.0, 1.0)	0.051
Average hydrocortisone dosage			
Age 0–2 years (per unit)	139	1.01 (0.97, 1.05)	0.595
Age 2–7 years (per unit)	219	1.04 (0.97, 1.12)	0.265
Fludrocortisone (yes vs. no)	52 (yes)	1.8 (0.4, 9.1)	0.463

GnRH, gonadotropin-releasing hormone; p-value with Wald test of association.

of short AH. However, these children had a noticeably reduced pubertal growth spurt and a high risk of overweight. To our knowledge, this is the largest longitudinal survey of growth in CAH patients. It involved nearly all French CAH reference centers and provides the first CAH-specific height and bone maturation charts for a historic cohort. The major assets of this study are that the 496 CAH patients had regular visits in pediatric centers: 480 (97%) had at least 10 height measurements and 467 (94%) had a validated AH. The CAH management principles developed by David et al. [3] were quite consistently followed. The French treatment protocol was high hydrocortisone doses during the first 2 years of life: 50 mg/m^2/day until day 15, 25 mg/m^2/day from day 15 to day 30 and adjustment on clinical data and biomarkers thereafter. The aim of these initial high doses was a fast reduction of adrenal hyperplasia and hyperandrogenism [3, 20]. In this cohort, the high dose during the first 2 years was found correlated with the 2-year height (rho = – 0.23, $p < 0.001$). However, neither the 2-year height nor the dose during the first 2 years was correlated with AH. All BAs were assessed by the same BA expert and generated CAH-specific BA curves by sex. Because of the dramatic impact of BA on the prediction of AH in CAH, these curves constitute an important tool for patient follow-up and/or drug evaluation. Here, a normal height was achieved circa 8 years of age at the cost of an advanced BA, which compromised AH. Finally, genotyping was performed by a single molecular biology center in 94% of the patients. This allowed studying the relationship between genotype and AH independently from other factors such as the delay to treatment. In previous series, the shortest adults were those diagnosed late with moderate CAH severity [20–23]. Our results reveal the role of the genotype whose severity is associated with the risk of short AH. One limitation of this study is its retrospective design and heterogeneous treatment. In addition, although the study centers were asked to apply a common CAH management protocol [3, 20], treatment adjustments still depended on local medical

practices and on patient compliance to the treatment. This compliance could not be assessed but the included children had at least one follow-up visit per year and 62% of them had repeated wrist X-rays (on average, 16 per child), which is a proxy variable for compliance to the treatment. Some children had a very poor BA control (i.e. extreme values on BA curves) but extreme values did not influence the median. Besides, we have chosen not to record hormonal data because of assay and measurement schedule heterogeneity between centers. We considered that height and bone maturation were indirect indicators of treatment balance and analyzed carefully and homogeneously BA data. BA maturation was also considered as an indirect marker of androgen excess and treatment balance. Despite these limitations, this study curves, like other disease-specific growth curves, provide an efficient tool for patient follow-up and should help growth assessment in clinical trials aimed at evaluating growth-promoting drugs [21]. Our results match those of a meta-analysis by Muthusamy et al. [5] on 892 CAH patients (SW and SV forms) diagnosed before age 5 years. In this meta-analysis, only 10 out of the 35 studies included genetically proven cases and the mean AH was – 1.39 SD score in girls and – 1.37 SD score in boys in SW patients (close to the values reported here) and – 0.99 SD score in girls and – 1.04 SD score in boys in SV patients (slightly higher values than in the present cohort). The present study reports an accelerated BA maturation between birth and 8 years. The multivariate analysis showed that an advanced 8-year BA is an independent predictor of short AH (4.5 times greater risk per year of BA maturation advance). This advocates strongly for a well-monitored treatment before age 8 years. The impact of advanced bone maturation in CAH has long been known [1] and found related to an increased adrenal androgen production and a loss of growth potential [21]. This stresses the importance of developing long-acting hydrocortisone formulations [23]. Our series shows that GnRHa was prescribed in 19% of the patients to prevent precocious puberty, in accordance with current recommendations [24]. This prescription was more often reported in SV boys (40.4%) and NC girls (32.3%) with advanced BA. Growth data from children who had received GnRHaor CA were kept to build the curves. This ensured that this population represents adequately the population of CAH children despite a greater heterogeneity. Treatments received by the children in this cohort are described in detail in the Table 4. The present results suggest strongly that the method of Bayley and Pinneau, the commonest tool for AH prediction, is not appropriate in CAH patients [10]; on average, it underestimates AH by 7.4 cm in girls and 2.7 cm in boys. This is in accordance with Bonfig and Schwarz's findings [25]. A more specific prediction tool is thus needed. In accordance with the above-cited meta-analysis [5] but unlike another study [26], we found no association between delayed treatment and small AH. The advance in BA might integrate the effect of late treatment in SV and NC forms. When BA was removed from the model, the effect of late treatment on AH became significant (data not shown). Similarly, several authors have found a better height outcome in patients who received fludrocortisone [26]. They hypothesized that the delay to treatment might be a confounding factor: patients diagnosed early had supposedly salt loss and received fludrocortisone. Our multivariate analysis supports this. Though about 25% of SV girls and 35% of SV boys did not receive fludrocortisone, this factor was not found associated with a higher risk of short AH. This indicates probably that, in our cohort, SV patients with subclinical salt loss received fludrocortisone adequately. We actually promote the use of fludrocortisone in SV patients with subclinical salt loss to normalize plasma renin activity and decrease hydrocortisone dose [27]. Here, a higher pubertal hydrocortisone dose was associated with a slightly higher risk of short AH (OR = 1.1, p = 0.028, results not shown). This may be due to the well-known negative effect of excessive glucocorticoid doses on growth [22, 26]. High hydrocortisone doses may reflect a poorly controlled disease either because of disease severity or secondary to poor compliance to the treatment. The AHs achieved are actually below the average and 20% of adult CAH patients have a short AH (below – 2 DS). Optimizing standard glucocorticoid and mineralocorticoid treatments and improving compliance should be emphasized. The new tools we propose will help optimizing care.

In conclusion, in this large CAH patient series, we report a shorter AH, a reduced pubertal spurt, and an advanced BA at 8 years. Eight-year BA seems to be a strong independent predictor of short AH in CAH patients. Disease-specific charts for height and bone maturation were obtained from a large genetically characterized cohort. These new charts are important tools to monitor the growth of children with CAH. They should also help investigators developing clinical trials aimed at assessing growth-promoting or bone-maturation-delaying drugs [28].

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