The Indian Journal of Pediatrics (June 2019) 86(6):496–502
https://doi.org/10.1007/s12098-018-02848-6

ORIGINAL ARTICLE

Growth Pattern and Clinical Profile of Indian Children with Classical 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia on Treatment

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Received: 6 September 2018 / Accepted: 20 December 2018 / Published online: 30 January 2019

Abstract

Objective To prospectively assess the growth parameters in a cohort of children with classical 21-hydroxylase deficiency congenital adrenal hyperplasia, comprehensively profile their clinical data and evaluate the prevalence of testicular adrenal rest tumors among affected boys.

Methods Children with congenital adrenal hyperplasia aged 0–18 y were prospectively followed up for six mo to 2 y (mean follow-up: 17 ± 6 mo). Baseline data were obtained by interviewing parents and from clinic records. Anthropometry, biochemical parameters, X-ray for bone age, and ultrasound scrotum (in boys >5 y) for testicular adrenal rest tumors were performed.

Results Among the 81 children (32 boys, 49 girls), two-thirds (57) had salt-wasting and the remaining had simple virilizing type and the mean age at enrolment was 6.2 ± 4.9 y. The overall height standard deviation score was −0.6 (−2.0 to 0.8) with a greater compromise in children in the age groups 0–2 y and > 10 y and those with salt-wasting type. Overall, 25 (31%) children had short stature and 45 (55.6%) had growth velocity below the reference range. Bone age advancement beyond 2 standard deviation score was seen in 46% of children assessed. Testicular adrenal rest tumors were detected in 5 out of 21 boys (23.8%).

Conclusions The auxological pattern observed in this homogenously-managed Indian pediatric cohort with congenital adrenal hyperplasia highlights that infancy and peri-pubertal age groups are the most vulnerable, reiterating the importance of diligent growth monitoring. The high prevalence of testicular adrenal rest tumors merits the incorporation of annual ultrasound in the follow-up protocol of these patients.

Keywords CAH · Height · Height velocity · Bone age · Testicular adrenal rest tumors · TART

Introduction

Congenital adrenal hyperplasia (CAH) is a spectrum of inherited defects in enzymes of adrenal steroid biosynthesis, the commonest being 21-hydroxylase deficiency in around 90% of all cases [1]. Glucocorticoid replacement therapy, though largely effective in managing crises and limiting virilization, is far from perfect. Inadequate steroid therapy results in androgen excess due to suboptimal central axis suppression and substrate diversion, causing bone age advancement and reduced final height; whereas, in overtreatment, growth is suppressed by the direct growth-inhibiting action of glucocorticoids. The difficulty in maintaining the fine balance between this endogenous hyperandrogenism and exogenous hypercortisolism makes CAH a great therapeutic challenge to the treating physician aiming at growth optimization [1, 2]. Most existing studies have shown that the growth in these children is lower than population standards as well as their own genetic potential [3, 4]. When juxtaposed with the prodigious international literature on this subject, the need for contemporary Indian data becomes explicit [5–8]. This study reports the clinical profile of a homogenously managed cohort

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of Indian children with classical 21 hydroxylase deficiency CAH and their prospectively-assessed growth pattern. The prevalence of testicular adrenal rest tumors (TART) among affected boys older than 5 years has also been investigated.

Material and Methods

This is a longitudinal ambispective single-center cohort study conducted at Pediatric Endocrinology Clinic, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi between August 2015 and July 2017. The study was approved by the Institute Ethics Committee. Children in the age group 0–18 y who had classical 21-hydroxylase deficiency CAH were enrolled after obtaining informed consent from parents and assent from children older than 10 y. They were followed up for a mean duration of 17 ± 6 mo (minimum of 6 mo to a maximum of 2 y). For children enrolled before six mo of age, follow-up till one year of age was ensured. CAH was diagnosed on the basis of standard hormonal/ genetic tests [2]. All children in the growing phase were treated with hydrocortisone as per guidelines [2], the dose of which was titrated based on clinical [physical examination, growth velocity (GV) and bone age] and biochemical parameters [17-hydroxy progesterone (17OHP) and testosterone], while serum electrolytes, blood pressure and plasma renin activity (PRA) (when available) were used for titrating the mineralocorticoid dose.

During the initial assessment, family and obstetric history, clinical and biochemical findings at initial presentation and medical and surgical treatment details were elicited and checked from the meticulously maintained clinic-records. Auxological parameters were measured prospectively by the same observer (MH) at each three-monthly visit using appropriately calibrated instruments. In children < 2 y, weight and length were measured using infant weighing scale and infantometer (Seca 416, Hamburg, Germany), and in older children, an electronic weight and height scale (Phoenix, Mumbai, India) with a sensitivity of 0.1 kg and 0.5 cm was used. Anthrocal software [9], based on World Health Organisation Multicentre Growth Reference Study [10] till 5 y of age and Indian Academy of Pediatrics 2015 charts [11] for older children, was used for calculation of height standard deviation score (SDS). GV was calculated in cm/ year and compared with available references [10, 12–14]. Prader stage of virilization was assigned to the external genitalia of girls with CAH, with one representing normal female genitalia and five indicating severe virilization [15]. Pubertal stage was documented. Serum 17OHP was measured 6 monthly by enzyme-linked immunosorbent assay (ELISA) (IBL International, Hamburg, Germany). Quantitative determination of serum testosterone and dehydroepiandrosterone (DHEAS) was done using chemiluminescent microparticle assay (Architect 2P13, Abbott Laboratories, Wiesbaden, Germany). Plasma renin activity (PRA) was measured by chemiluminescent immunoassay (DBC-Diagnostics Biochem Canada Inc. Ontario). Morning sample was taken in the erect posture (except for infants) and processed as per standard recommendations [16]. Serum sodium and potassium were measured using ABL 800 Flex (Radiometer medical ApS, Copenhagen, Denmark). Bone age estimation was done using radiograph of left hand and wrist by Gruelich and Pyle method [17] by an experienced pediatric endocrinologist (VJ), who was blinded to the clinical details except for gender. Bone age (BA) to chronological age (CA) ratio was calculated and SDS was computed using population based nomograms [17]. Screening for the presence of testicular adrenal rest tumor (TART) was performed in all boys above 5 y, by an experienced pediatric radiologist (MJ) using a state-of-art ultrasound scanner (Aixplorer, Supersonic Imagine, France) with a high resolution linear transducer of frequency range 5–14 MHz. In children in whom TART was detected, a follow up ultrasound was done after 3 mo.

Qualitative variables were expressed as absolute and relative frequencies, whereas continuous variables were organized as mean ± standard deviation or median (interquartile range). To measure the correlation between variables, Pearson correlation or Spearman rank correlation was used as required. To compare qualitative variables, Chi square test or Fisher exact test was used and for quantitative measures, t test or Wilcoxon test (for two groups) and ANOVA or Kruskal Wallis test (for more than 2 groups) were used according to the distribution of data. *P* values less than 0.05 were considered as statistically significant. Data were analysed using statistical software STATA (14.2) (Stata Corp 4905 Texas USA).

Results

This study included 81 children (32 boys and 49 girls) from 75 families; 27 (37.6%) from Delhi, 19 (24%) from Bihar, 13 (16.5%) from Uttar Pradesh and the rest from Punjab, Haryana and Rajasthan. The clinical and demographic parameters are summarized in Table 1. The mean age at enrollment was 6.2 ± 4.9 y. Around two-thirds of the children (57) had salt-wasting (SW) CAH and one-third (24) had simple virilizing (SV) CAH; with median ages at diagnosis being 11 (0–90) d and 2 (0–11) y, respectively ($p = 0.008$). Consanguinity was present in 12 (16%) families, sibling death in 26 (35%) and maternal history of abortion in 13 (17.3%) families. In children with salt wasting type of CAH, an adrenal crisis in infancy was the commonest presentation (in 48%). Among children with simple virilizing CAH, all girls ($n = 18$) presented with atypical genitalia and all boys ($n = 6$) with precocious puberty. Seventeen girls (35%) had been assigned male gender at birth.

Table 1 Clinical characteristics of enrolled children with CAH. ($n = 81$, 32 boys and 49 girls)

Parameter	Summary statistic n (%)			
Mean age at enrollment (y)	6.2 ± 4.9			
Age distribution of enrolled children*				
• 0–2 y	15 (18.4)			
• 2–5 y	22 (27.2)			
• 5–10 y	22 (27.2)			
• >10 y	22 (27.2)			
Family and Obstetric history*	(n = 75 mothers)			
• Parental consanguinity	• 12 (16)			
• >1 child with CAH alive	• 5 (6.7)			
• Sibling death	• 26 (35)			
• Still births/ abortions	• 13 (17.3)			
	Salt wasting CAH (n =57)		**Simple virilizing** CAH (n = 24)	
	Males (n = 26)	**Females** (n = 31)	**Males** (n = 6)	**Females** (n = 18)
Age at diagnosis*				
• First week of life	07 (27)	18 (58)	–	05 (28)
• 2nd to 4th wk	13 (50)	11 (35)	–	01 (5.5)
• 4th to 12th wk	06 (23)	02 (7)	–	02 (11)
• 3 mo to 1 y	–	–	–	02 (11)
• 1–3 y	–	–	–	07 (39)
• >3 y	–	–	06 (100)	01 (5.5)
Presentation at diagnosis*				
• Only atypical genitalia	–	16 (52)	–	18 (100)
• Only adrenal crisis	24 (92)	–	–	–
• Both genital atypia and crisis	–	15 (48)	–	–
• Detected by newborn screening	2 (8)	–	–	–
• Precocious puberty	–	–	6 (100)	–
Median 17-OHP (ng/ml)**				
• At diagnosis	37.6 (20.0–177.0)		20 (17.0–169.0)	
• During the study period	9.3 (2.0–22.9)		7.5 (1.5–20.0)	
Mean hydrocortisone dose (mg/m^2/day)***				
• At therapy initiation	23.9 ± 13.8		11.9 ± 6.3#	
• During the study period	14.6 ± 3.2		14.9 ± 3.7	
Median dose of fludrocortisone (mcg/day)**				
• At therapy initiation	130 (25–250)		100 (0–250)	
• During the study period	100 (0–250)		90 (0–100)##	

* number in each sub-category (intra-category proportions as percentage within parenthesis); ** Median (inter-quartile range); *** Mean±SD; # $p = 0.0001$; ## $p = 0.03$

CAH Congenital adrenal hyperplasia; *17-OHP 17* hydroxy progesterone

The overall median height SD score was −0.6 (−2.0 to 0.8). As presented in Table 2, the height SD score was significantly lower in children with SW CAH compared to those with SV CAH ($p = 0.006$). There was a greater compromise in stature in the first two years and later during the adolescent phase ($p = 0.001$) (Fig. 1). In the age category 6 mo-2 y (n = 15), the mean growth velocity (GV) was only 4.2 ± 2.6 cm/y against the corresponding age-specific reference of 12–18 cm/y, with all the children having a GV below −2 SD [10]. In the age categories of 2–5 y ($n = 22$) and 5–10 y (n = 22), GV was respectively 4.7 ± 3.9 cm/y and 5.3 ± 4.8 cm/y, with 12 (55%) and 15 (68%) having a GV below 5th centile or − 2 SD, respectively; and 2 (9%) and 3 (13.6%) having GV exceeding +2 SD of the reference range [12–14]. In children >10 y (n = 22), mean GV was 3.7 ± 2.7 cm/y; with 3 (14%) having GV below 5th centile and 4 (18.2%) above 90th centile [14].

Table 2 Auxological parameters of children with CAH ($n = 81$)

Category	N	Height SD score*	p	Growth velocity** (cm/y)	p	BA:CA** (N)	*p*
Overall	81	−0.6 (−2.0 to 0.8)		4.5 ± 3.7		1.3 ± 0.4 (36)	
Type							
Salt wasting	57	−0.7 (−2.2 to 0.8)	0.006	4.5 ± 3.9	0.8	1.2 ± 0.3 (23)	0.05
Simple virilising	24	0.4 (−1.1 to 1.9)		4.5 ± 3.2		1.5 ± 0.5 (13)	
Gender							
Males	32	−1.9 (−3.4 to −0.4)	0.07	3.7 ± 2.8	0.3	1.3 ± 0.5 (19)	0.1
Females	49	−0.1 (−1.4 to 1.2)		5.0 ± 4.0		1.4 ± 0.5 (17)	
Age group							
0–2 y	15	−2.0 (−3.2 to −0.8)	0.001	4.2 ± 2.6	0.7	N.A.	0.04
2–5 y	22	0.2 (−1.2 to 1.6)		4.7 ± 3.9		1.5 ± 0.5 (16)	
5–10 y	22	0.6 (−0.6 to 1.8)		5.3 ± 4.8		1.6 ± 0.5 (7)	
>10 y	22	−1.0 (−2.4 to0.4)		3.7 ± 2.7		1.0 ± 0.1 (13)	

* Median (IQR); ** Mean ± SD

BA: CA Bone age to chronological age ratio; *CAH* Congenital adrenal hyperplasia; *SD* Standard deviation

Bone age assessment was done in a sub-group of 36 children (of the 66 children above 2 y of age). Their mean chronological age was 7.6 ± 2.7 y, while the bone age was 9.8 ± 4.9 y. The mean BA: CA ratio was 1.3 ± 0.4, denoting an overall advancement, which was more marked in the SV group, as seen in Table 2. Further, analysis across age-categories revealed a greater BA advancement among children aged 2–10 y ($p = 0.04$). BA advancement > 2 SD was present in 16 (46%) of the children, 8 (61.5%) having SV, and 8 (34.8%) SW CAH. The hydrocortisone dose and the 17 OHP levels were not significantly different among the children with and without advanced BA.

Of the 21 boys older than 5 y, 5 (23.8%) were found to have hypoechoic lesions in one or both testes (Table 3). The prevalence was higher in SV CAH as 3 out of 6 boys (50%) were affected, compared to 2 out of 15 boys with SW (13%). One of these children was already diagnosed with TART before enrolment. A follow-up ultrasound after 3 mo showed regression

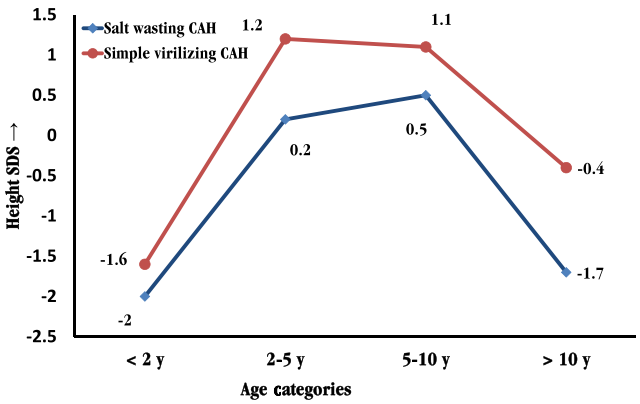

Fig. 1 Age-category wise distribution of Median height SDS in salt wasting and simple virilising CAH. *CAH* Congenital adrenal hyperplasia; *SDS* Standard deviation score

in 60% of the children (3 out of 5). Bilateral tumors were detected only in one child, and the youngest patient with TART was 5.8 y old.

The serum 17 OHP levels at diagnosis for the SW and SV groups were 38 (20–177) ng/ml and 20 (17–169) ng/ml, respectively. The overall median 17-OHP during the study period was 8.0 (5.8–35.7) ng/ml with values within the target range of 1–10 ng/ml in 32%, suppressed in 20%, and high in 48%, respectively, with no difference between the levels in SV and SW children.

The mean doses of oral hydrocortisone at the initiation of therapy were 23.9 ± 13.8 mg/m^2/d and 11.9 ± 6.3 mg/m^2/d in the SW and SV groups, respectively. During the study period, the hydrocortisone dose in the two groups was similar at 14.6 ± 3.2 mg/m^2 and 14.9 ± 3.7 mg/m^2, respectively. Children < 2 y were noted to have received a higher median steroid dose than those >2 y (16.1 ± 3.3 *vs.* 14.1 ± 3.3 mg/m^2/d; $p = 0.02$). Forty-five (79%) children with SW CAH and 13 (54%) children with SV CAH received the oral mineralocorticoid fludrocortisone in doses ranging from 25 to 250 mcg/d. Apart from steroids, 10 children (12.3%) had received gonadotropin releasing hormone (GnRH) analogs for an average duration of 1.5 ± 0.8 y; and 6 children (7.4%) had received the anti-androgen Flutamide for an average of 1.9 ± 0.7 y. The incidence of adrenal crises among children on treatment in this cohort during the study period (using a working definition 'an acute state of health impairment requiring intravenous glucocorticoid administration and hospital admission') was 1 per 100 patient-years with nil mortality [18].

Among the 49 girls in this cohort, five were not advised genitoplasty, 24 had undergone surgery at enrolment and 7 underwent surgery during the study period. The mean age at surgery was 2.4 ± 1.9 y, and the commonest procedure was a

Table 3 Individual characteristics of children detected to have TART

Enrolment number	22	23	02	09	25
Type of CAH	SV	SV	SV	SW	SW
Age at diagnosis (y)	11	3	7	0.08	0.06
Age at TART detection (y)	11	5.8	9.4	16.6	11.2
Tanner Stage	3	2	3	5	2
Dose of hydrocortisone (mg/m^2)	12[a]	13.5	11	16[a]	12.7
Dose of fludrocortisone (mcg/day)	–	–	–	25	100
Additional therapy	–	–	GnRH analog	GnRH analog for 3 y	GnRH analog for 2 y; Flutamide
Compliance	Late diagnosis	Regular	Regular	Regular	Regular
Size of testes (ml)					
Right	6.0	1.7	2.5	6.0	2.0
Left	3.5	1.9	2.4	6.5	2.1
Laterality	Right	Right	Left	Bilateral- near mediastinum	Right-near mediastinum
Size of lesion(s) mm	19.8 × 12.4	Diffuse	Multiple small	Right- 11 × 9 Left- 6 × 4	10
Sonological characterization	Heterogeneous; extensive vascularity	Diffusely altered echogenicity	Tiny echogenic foci	Hypoechoic with foci of calcification	Hypoechoic
Repeat USG at 3 mo for regression	Rt 12 × 7 mm focal lesion with calcification	Normal echogenicity	Same findings	Persisting	3 mm single lesion[b]
Whether MRI confirmed	+	–	–	+	–

[a] Dexamethasone as hydrocortisone equivalent

[b] Next ultrasound done at 6 mo confirmed no focal lesions in bilateral testes

CAH Congenital adrenal hyperplasia; GH Growth hormone; GnRH Gonadotropin releasing hormone*; MRI* Magnetic resonance imaging*; SV* Simple virilizing*; SW* Salt wasting; *TART* Testicular adrenal rest tumors; *USG* Ultrasound

single-stage vaginoplasty with vestibuloplasty and clitoroplasty (in 87%). Among the unoperated girls, 15 (60%) had Prader stage 2 genitalia while the rest had higher stages.

Discussion

The present study demonstrated an overall median height SDS of −0.6 (−2.0 to 0.8) in a regularly followed-up cohort of Indian children with CAH. Short stature (height SDS < −2) was present in 25 (31%) of the children. A conspicuous compromise in stature was noted in the first two years as well as during the peri-pubertal period, while the stature was on the higher side during mid-childhood, with height SDS > +2 in 6 out of 44 children (13.6%) in this age group. However, this is an effect of androgen excess as corroborated with the maximum advancement of bone age in this age-group (BA: CA ratio of 1.6 ± 0.5), and hence does not translate to an improved final height. The observed growth pattern was in alignment with that reported in existing literature [6, 19–23]. A possible explanation for the growth faltering in the first two years of life in this cohort is the relatively higher steroid dose prescribed in this age group due to a perceived risk of dyselectrolytemia and hypoglycemia, and more frequent courses of stress doses (3 times the usual dose of hydrocortisone for 2–4 d) used by parents during minor illnesses. The second period with notable growth impairment was >10 y [1, 19, 21–23], possibly related to the advanced bone age, precocious puberty and early growth spurts before the age of 10 y [19].

In the 6 children of present cohort who had attained final height, the height SD score was −2.0 (−2.4 to −0.6). This is slightly lower than that reported by a meta-analysis including 35 studies till 2008 (*viz.,* −1.37) [3] and more recent studies (−1.9 to +0.6) [24, 25].

The median hydrocortisone dose in present cohort conformed to existing standards [2], but was significantly higher in children less than 2 y old. Several studies have reported the negative effect of supra-physiological doses of glucocorticoid on height [20, 23, 24, 26]. The results in an exclusively newborn-screening detected cohort of children treated with lower doses of hydrocortisone (10 mg/m^2/d) showed that though growth velocity decreased slightly during the first 9 mo, the height SD score then approached the genetic height potential with an appropriate bone age to chronological age at 3 y and no intervening episodes of crises [26], suggesting that the use of this lower dose of hydrocortisone may help in improving the growth in this age group. However, adequately-powered prospective trials are needed, to form the basis of steroid-dosage recommendations in children with CAH (as underscored in a recent Cochrane review [27]) and to authenticate the utility of parameters currently used in therapy monitoring [2] such as 17OHP.

Testicular adrenal rest tumors are benign testicular masses that arise from aberrant adrenal cells that had apparently trailed the testes in their embryological descent. These cells proliferate in response to high adrenocorticotrophic hormone concentration, and can cause infertility [28]. Optimization of steroid therapy can lead to regression of the lesions if detected early [2]. Worldwide, six studies in children with CAH have reported their prevalence ranging from 14% and 50% [28–30]. The prevalence of TART in boys above 5 y ($n = 21$) in present cohort was 23.8%. Half of the boys with simple virilizing CAH ($n = 6$) were detected to harbor them. All the five children with TART were pubertal, with 4 of them having central precocious puberty. It is noteworthy that salt-wasters were detected at a later age, but they had lesions near the mediastinum of the testis, reflecting a greater risk for later infertility due to seminiferous tubule obstruction [28].

A few points of concern were identified from the clinical profile of the cohort. Firstly, there was a female preponderance in this cohort, as well as in previous Indian cohorts [5, 8], indicating that in the absence of universal newborn screening, boys with CAH are being missed [2]. Because of the same reason, the diagnosis of SV CAH was significantly delayed leading to advanced skeletal maturity, precocious puberty and possibly a higher prevalence of TART. Thirdly, the fact that 35% of girls in this contemporary cohort were assigned wrong gender at birth calls for sensitization of medical personnel. Finally, the strikingly high number of families in present cohort with multiple affected children and previous sibling deaths highlights the need for strengthening genetic counseling and prenatal diagnostic services.

Conclusions

Growth in Indian children with CAH on treatment is still far from satisfactory. There is an overall bone age advancement, prominently in mid-childhood, and especially among children with simple virilizing CAH. Roughly, one-fourth of the boys with CAH have testicular adrenal rest tumors. Based on the findings from this study, the recommendations put forth are– more stringent growth monitoring, especially in infancy, annual screening ultrasound scrotum in all boys with CAH and implementation of universal newborn screening for CAH so that the complications arising from delayed or missed diagnosis can be avoided. Further long-term, pan-Indian studies covering the entire growth period are recommended.

Acknowledgements Mr. Brijesh Kumar and Ms. Kalpana Kunj performed the laboratory assays for this study and their contribution is acknowledged.

Compliance with Ethical Standards

Conflict of Interest None

Source of Funding The study was funded by MD thesis grant of Indian Council of Medical Research (Grant No: 3/2/Oct2015/PG_Thesis_HRD).

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