Original Article

Clinical and Hormonal Profile of Classical 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia: Experience from a Tertiary Centre In India

Harshitha Boyareddy, Pramila Kalra, Mala Dharmalingam
Department of Endocrinology, M S Ramaiah Medical College, Bengaluru, Karnataka, India

Abstract

Introduction: Congenital adrenal hyperplasia (CAH) is a rare autosomal recessive disorder requiring treatment with steroids. Both over and under-treatment can have an impact on growth outcomes. **Aims:** The aim of this study was to study the clinical and hormonal profile of a cohort of individuals with classical 21-hydroxylase CAH and to assess the factors influencing growth outcomes in these individuals. **Methods:** In this cross-sectional study, individuals with classical CAH were included. Baseline data were obtained from electronic medical records. Anthropometric measurements and hormonal profiles were assessed. Quantitative variables were expressed as mean ± standard deviation or median (interquartile range) and qualitative variables as percentages. To measure the correlation between variables, Spearman's rank correlation was used. **Results:** Of the 27 patients with classical 21-hydroxylase CAH, 13 had salt wasting and 14 had simple virilizing phenotype. The median height standard deviation score (SDS) of the cohort was -1 SDS (-2.00 to 0.2) with 24% having short stature (height < -2 SDS). There was no significant difference in height SDS depending on the age, gender, type of CAH or onset of central precocious puberty. There was no significant correlation between glucocorticoid dose and height SDS ($r = 0.104$). Obesity was a common finding (40% adults, 41.1% children). However, there was no significant correlation between BMI and glucocorticoid dose ($r = 0.419$). **Conclusions:** Short stature was a significant finding as noted in earlier studies. However, the high prevalence of obesity was a new finding that could not be explained by the dose of steroids alone.

Keywords: 17-OH progesterone, 21-alpha-hydroxylase, ambiguous genitalia, congenital adrenal hyperplasia (CAH), growth outcomes, height, salt wasting

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by a deficiency of the enzymes involved in adrenal steroidogenesis. Of all the enzyme defects, mutations in the 21-hydroxylase gene (CYP21A2) account for 90–95% of cases of CAH.[1] Depending on the severity of the enzyme deficiency, the clinical presentation of CAH varies widely. It ranges from the milder non-classical CAH to the more severe classic CAH. Data regarding the clinical course and growth profile of individuals with CAH are limited. This study aims to understand the clinical and hormonal profile of individuals with CAH and identify factors influencing growth outcomes in these individuals.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_337_22

Material and Methods

Study design

This is a cross-sectional single-centre study with a retrospective component.

Setting

This study was conducted at the Endocrinology Clinic, Ramaiah Medical College, Bangalore, between January 2019 and December 2021.

Address for correspondence: Dr. Pramila Kalra, Professor and HOD of Endocrinology, M S Ramaiah Medical College, Bengaluru - 560 054, Karnataka, India.
E-mail: kalrapramila@gmail.com

Submitted: 31-Aug-2022 **Revised:** 11-Dec-2022
Accepted: 15-Feb-2023 **Published:** 30-Jun-2023

How to cite this article: Boyareddy H, Kalra P, Dharmalingam M. Clinical and hormonal profile of classical 21-hydroxylase deficiency congenital adrenal hyperplasia: Experience from a tertiary centre in India. Indian J Endocr Metab 2024;28:413-6.

Participants

Individuals with classical 21-hydroxylase CAH were included in the study after obtaining informed consent/assent. CAH was diagnosed based on standard hormonal/genetic tests.[2]

Methods

Individuals with classical 21-hydroxylase CAH were included in the study if they had at least one follow-up visit during the study period.

Demographic data, age and clinical presentation at diagnosis and treatment details, including genital reconstruction surgery, family and obstetric history, associated comorbidities and episodes of adrenal insufficiency if any, were collected retrospectively from electronic medical records.

In older children (above 2 years of age) and adults, a Harpenden stadiometer and electronic weighing scale were used to measure height and weight, respectively. For children below 2 years of age, an infantometer and infant weighing scale were used to measure height and weight, respectively. Height SDS was calculated using the WHO/IAP-combined growth chart. Short stature was defined as a height less than −2 SDS. BMI was calculated by dividing weight in kilograms by height in metres squared. For children, overweight/obesity was defined using WHO charts as values above the 85th and 95th centile, respectively. For adults, a BMI of 23 or more was considered overweight and 25 or more was considered obese.

Tanners (SMR) sexual maturity rating was used to assess pubertal development at each visit. The Prader scale was used to measure the degree of virilization of external genitalia in girls with CAH.

All individuals were treated with glucocorticoids as per standard guidelines.[2] The dose of glucocorticoids was titrated based on clinical parameters including physical examination and growth velocity and biochemical parameters including serum 17-hydroxy progesterone and serum testosterone. In individuals on mineralocorticoids, the dose was adjusted using serum electrolytes and blood pressure examination.

Serum 17-OH progesterone measured using a chemiluminescent immunoassay was used to assess the adequacy of therapy at every follow-up visit. Serum 17-OHP levels between 4 ng/ml and 12 ng/ml were considered optimal; values below 4 ng/ml were considered suppressed and indicative of over-treatment and values above 12 ng/ml were considered high and indicative of under-treatment.

Statistical methods

Quantitative variables were expressed as mean ± standard deviation or median (interquartile range) and qualitative variables were expressed as percentages. To measure the correlation between variables, Spearman's rank correlation was used. To compare qualitative and quantitative variables, non-parametric tests including the Mann–Whitney test and Kruskal–Wallis test were used, as the distribution of data is unknown. *P* values less than 0.05 were considered statistically significant. Data were analysed using the statistical software SPSS Version 19.0. (Armonk, NY: IBM Corp).

Ethical aspects

The study was approved by Ramaiah Medical college ethics committee vide letter no MSRMC/EC/SP-6/04-2021 on 27April 2021. Written informed consent or assent wherever applicable was taken. The procedure followed the guidelines laid down in the Declaration of Helsinki 1964 and as revised later.

Results

Twenty-seven individuals with classical 21-hydroxylase CAH were included in this study. The clinical and demographic data are summarized in Table 1. Thirteen (48.1%) had a salt-wasting (SW) and 14 (51.9%) had a simple virilizing phenotype. Thirty-seven per cent of the cohort (n = 10) were adults at the time of data collection. Twenty-two patients were born of consanguineous marriages and there were three sibling pairs. There were six miscarriages of unknown cause and two infant deaths in this cohort.

Clinical presentation at diagnosis

In individuals with SW CAH, the most common clinical presentation was an adrenal crisis for males and genital ambiguity for females, respectively. However, one girl had severe genital ambiguity (Prader stage 4) and was assigned the male gender at birth. She presented to us with a NSW crisis in infancy. She was subsequently reassigned to the female gender and underwent female genital reconstruction surgery.

Table 1: Clinical profile of individuals with CAH (n=27)

Parameter	Frequency, n (%)			
CAH phenotype				
a. Salt wasting (SW)	13 (48.1)			
b. Simple virilizing (SV)	14 (51.9)			
Age distribution (in years)				
a. 0-2	3 (11.1)			
b. 2-10	10 (37)			
c. 10-18	4 (14.8)			
d. >18	10 (37)			
Gender distribution	SW and SV			
a. Male	7 6			
b. Female	6 8			
Mode of presentation at diagnosis	SW M	F	SV M	F
a. Adrenal crisis	5	1	–	–
b. Ambiguous genitalia	–	5	–	7
c. Diagnosis by newborn screening	2	–	–	–
d. Precocious puberty	–	–	6	–
e. Short stature	–	–	–	1
Family history	n=24 mothers			
a. Consanguinity	22 (91.6)			
b. Abortion/Stillbirth	6 (25)			
c. Sibling with CAH	3 (12.5)			
d. Sibling death	2 (8.3)			

SW: Salt wasting, SV: simple virilizing, M: males, F: females

In individuals with SV CAH, all girls presented with atypical genitalia and all boys with precocious puberty (onset of pubic hair and increase in phallic length). One girl with SV CAH, who was assigned male gender at birth, presented in late adolescence with short stature. USG abdomen revealed Mullerian structures and the karyotype was 46XX. She preferred male identity and subsequently underwent hysterectomy and bilateral salpingo-oophorectomy and is currently on testosterone replacement.

Treatment

All the children in our cohort are on hydrocortisone replacement except a 9-year-old boy who is on prednisolone after he developed central precocious puberty despite a high dose of hydrocortisone. The median hydrocortisone dose of our cohort was 12.2 mg/m^2/day (range: 8–14.3 mg/m^2/day). Four adults are on prednisolone and one is on dexamethasone as they had persisting hyperandrogenism while on hydrocortisone. All patients with SW phenotype and four individuals with SV phenotype are on fludrocortisone.

Growth outcomes

The overall median height SD score of our population was −1.0 (−2.00 to 0.2) with 24% having short stature (height < −2 SDS). As depicted in Table 2, the height outcomes were not significantly different among different CAH phenotypes, age groups, gender or individuals with central precocious puberty. There was no significant correlation between the dose of hydrocortisone and height SD (r = 0.104).

Four patients had suppressed 17-OH progesterone values while 10 had elevated 17-OH P. There was no difference in height outcomes in those with and without good biochemical control (P = 0.258).

Four adults (40%) were obese, of whom three were on prednisolone. On the contrary, seven children (41.1%) were obese. There was no significant correlation between BMI and the dose of hydrocortisone (r = 0.419).

Table 2: Factors influencing height outcomes in individuals with CAH

Category	*N*	Height SD score Median (IQR)	*P*
Overall	27	−1.0 (−2 to 0.2)	
CAH phenotype			
SW	13	−1.2 (−1.7 to 0.1)	0.576
SV	14	−1.0 (−2.15 to 0.65)	
Gender			
Male	13	−1.2 (−2.8 to 0.425)	0.697
Female	14	−1.0 (−1.425 to−0.25)	
Age			
0-2	3	−1.4 (−2.00 to−1.4)	0.07
2-10	10	−1.0 (−1.2 to 0.6575)	
10-18	4	−0.06 (−1.6 to 0.67)	
>18	10	−1.4 (−2.7 to−1.0)	
Central precocious puberty			
Yes	5	0.2 (−2.2 to 0.875)	0.126
No	22	−1.2 (−2.0 to−0.3)	

Comorbidities

Coexisting comorbidities included hypothyroidism in four individuals (14.8%) and biliary atresia in one boy.

Metabolic and reproductive complications

None had hypertension or diabetes in our cohort. Five children (18.5%) received GnRH therapy for central precocious puberty (four SV, one SW) for a mean duration of 1.9 ± 0.8 years. There were five episodes of adrenal insufficiency in three children who required hospitalization and IV glucocorticoid administration. One male patient was identified with testicular adrenal rest tumour during evaluation for infertility. Of the five adults who are married in our cohort, one conceived naturally. Two of them have children via assisted reproductive techniques.

Discussion

The prevalence of SW and simple virilizing phenotypes is nearly equal in our cohort (SW: SV – 1:1.07). Few studies from developing countries including India had a predominant simple virilizing phenotype.[3,4] However, the SW phenotype is nearly twice more common in developed countries.[5,6] A meta-analysis from China reported a 3.25 times higher prevalence of SW phenotype diagnosed by newborn screening.[7] The lack of universal newborn screening probably explains the lower prevalence of SW type. Employing newborn screening in families with a history of CAH or with bad obstetric history helped identify two male infants with SW CAH in our cohort. This highlights the importance of newborn screening, especially in populations at high risk.

Girls with SW phenotype present with genital ambiguity at birth and hence are more likely to be diagnosed than boys. This explains the female preponderance in previous studies.[3,4,8] However, there was near equal gender distribution in our study. The use of newborn screening helps identify male infants with CAH who might otherwise be missed.[9,10]

A significant proportion of girls are assigned male gender at birth due to severe genital ambiguity. It ranged from 14%,[6,11] study to as high as 35% in a recent study.[4] In our cohort, one child with severe genital ambiguity (Prader 4) presented with SW crisis. The other child, who had an SV phenotype and was reared as male, presented with short stature at 16 years. This is an uncommon presentation of CAH and highlights the importance of proper gonadal examination before gender assignment.

The median hydrocortisone dose of our cohort was 12.2 mg/m^2/day (range: 8–14.3 mg/m^2/day) which conformed to existing standards.[2] However, one child with poor control despite a high dose of hydrocortisone is on a trial of prednisolone therapy for 6 months.

Forty per cent of adults and 41.1% of children in our cohort were obese. In a study including 89 children and

adolescents with CAH, the BMI SDS of the whole group ranged from −2.7 to + 4.3. Glucocorticoid dose, chronologic age, advanced bone age and parental obesity were significant contributors.(12) However, our study saw no significant association between BMI and glucocorticoid dose. The high prevalence of obesity in our cohort cannot be explained by the rising global trend in obesity alone. Prospectively analysing a larger cohort might identify other significant contributors.

The height outcomes in our study are in agreement with a recent study that reported an overall median height SDS of −0.6 (−2.0 to 0.8) with 31% of the children having short stature. The adult height SD of our cohort −1.4 (−2.7 to −1.0) also confirms to what is reported in the above study (−2 SD) and a few other recent studies (−1.9 to +0.6 SD). No significant association was found between glucocorticoid dose and height outcomes. However, the lack of longitudinal data on the dose of glucocorticoids and the adequacy of biochemical control limits the interpretation of these height outcomes. Also, the onset of central precocious puberty and treatment with GnRH analogues influences height outcomes.

Despite the above limitations, this study highlights a few points of concern. Until newborn screening becomes universal, screening for CAH in families with unexplained infant deaths or a family history of CAH is important and might reduce the potential mortality associated with missing cases.

Second, ensuring adequate compliance and stress dosing helps reduce the prevalence of central precocious puberty and adrenal insufficiency, respectively.

Third, the high prevalence of obesity in this cohort despite optimal doses of hydrocortisone emphasizes the importance of prevention and management of nutritional obesity.

A prospective study with a larger sample size may help to better analyse various factors influencing metabolic and height outcomes. This in turn will help to optimize treatment strategies.

Acknowledgements

None.

Authors contribution

HB, PK and MD conceptualized and designed the study. HB and PK did the data acquisition and statistical analysis. All authors contributed to study execution and drafting the manuscript and finalizing the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr Rev 2000;21:245-91.
2. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, *et al*. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An endocrine society clinical practice. J Clin Endocrinol Metab 2018;103:4043–88.
3. Kovacs J, Votava F, Heinze G, Solyom J, Lebl J, Pribilincova Z, *et al*. Lessons from 30 years of clinical diagnosis and treatment of congenital adrenal hyperplasia in five middle European countries. J Clin Endocrinol Metab 2001;86:2958-64.
4. Meena H, Jana M, Singh V, Kabra M, Jain V. Growth pattern and clinical profile of indian children with classical 21-Hydroxylase deficiency congenital adrenal hyperplasia on treatment. Indian J Pediatr 2019;86:496–502.
5. Maiti A, Chatterjee S. Congenital adrenal hyperplasia: An Indian experience. J Paediatr Child Health 2011;47:883-7.
6. Bajpai A, Kabra M, Menon PS. 21-Hydroxylase deficiency: Clinical features, laboratory profile, and pointers to diagnosis in Indian children. Indian Pediatr 2004;41:1226-32.
7. Li Z, Huang L, Du C, Zhang C, Zhang M, Liang Y, *et al*. Analysis of the screening results for congenital adrenal hyperplasia involving 7.85 million newborns in China: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 2021;12:624507.
8. Belinda G, Vinay D, Moolechery J, Mathew V, Anantharaman R, Ayyar V, *et al*. Congenital adrenal hyperplasia - Experience from a tertiary center in South India. Indian J Endocrinol Metab 2012;16(Suppl 2):S385-6.
9. Grosse SD, Van Vliet G. How many deaths can be prevented by newborn screening for congenital adrenal hyperplasia? Horm Res 2007;67:284-91.
10. ICMR Task Force on Inherited Metabolic Disorders. Newborn screening for congenital hypothyroidism and congenital adrenal hyperplasia. Indian J Pediatr 2018;85:935–40.
11. Rajendran UD, Kamalarathnam C. Clinical profile, predictors of death and anthropometric follow-up in neonates with classical 21-Hydroxylase deficiency. J Clin Diagn Res 2018;12:SC06-9.