ISSN: 2755-0281

Journal of Pediatrics Research Reviews & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Phenotypic Spectrum and Diagnostic Challenges in Non-21-Alfa-Hydroxylase Deficiency Congenital Adrenal Hyperplasia: A Case Series from a Tertiary care Centre

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ABSTRACT

Purpose: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by enzyme deficiencies in adrenal steroidogenesis, with 21-hydroxylase deficiency (21-OHD) being the most common. However, rarer forms such as 11β-hydroxylase (11β-OHD), 3β-hydroxysteroid dehydrogenase type 2 (3β-HSD2), 17α-hydroxylase (17α-OHD), and steroidogenic acute regulatory protein (StAR) deficiency present diagnostic challenges due to variable phenotypes. This study describes the clinical, biochemical, and genetic profiles of non-21OHD CAH cases at a tertiary care centre.

Methods: A retrospective review of 87 CAH patients from 2008 to 2022 identified 13 cases of non-21OHD CAH. Clinical, biochemical, imaging and genetic data were analysed. The diagnosis was confirmed by hormonal assays and next-generation sequencing (NGS)-based genetic analysis.

Results: Among the 13 cases, six patients had 11β-OHD, primarily presenting with precocious puberty, hypertension, and hyperpigmentation, with elevated ACTH, 17-OHP, and suppressed renin levels. Three patients with 3β-HSD2 deficiency were diagnosed in early infancy following salt-wasting crises. 17α-OHD was diagnosed in three adolescent females presenting with primary amenorrhea, tall stature, hypertension, and elevated gonadotropins. One case of StAR deficiency was diagnosed at 45 days of life, presenting with adrenal crisis and severe adrenal insufficiency.

Conclusion: Non-21OHD CAH presents diagnostic challenges due to its varied clinical spectrum. Hypertension and hypokalemia are key differentiators for 11β-OHD and 17α-OHD, while steroid profiling (LC-MS) aids in diagnosing 3β-HSD2 deficiency. However, the most crucial aspect is the early diagnosis, which is a significant factor in preventing complications like hypertensive cardiomyopathy and adrenal crises.

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Received: February 12, 2025; **Accepted:** March 05, 2025; **Published:** August 28, 2025

Keywords: Non-21-OHD CAH, Congenital Adrenal Hyperplasia, Genetic Disorders, Young Hypertension

Introduction

Global incidence of congenital adrenal hyperplasia (CAH) ranges from 1 in 10,000 to 1 in 20,000 births, with a higher incidence of 1 in 5762 in India, with significant regional differences [1,2]. This increased incidence can be attributed to the high incidence of consanguineous marriages within carriers having autosomal recessive inheritance. The most common CAH is due to CYP21A2-- 21alfa hydroxylase deficiency (21 OHD), ranging between 90-95% [3]. The second most common CAH is due to an 11-beta hydroxylase deficiency (11B OHD) [4]. Given the Prenatal Diagnostic Act in India, gender identification prenatally is prohibited, because of which the evaluation of ambiguous genitalia begins after birth. Diagnosing non-21 alfa hydroxylase deficiency CAH (non-21OHD CAH) remains challenging in regions where newborn screening programs are limited [1,2]. Unlike 21-OHD, these rare variants may not present with classic neonatology symptoms but rather manifest later in childhood or adolescence with hypertension, ambiguous genitalia or adrenal crises [5]. Between 2008 and 2022, a total of 87 cases of congenital adrenal

hyperplasia (CAH) were identified at our tertiary care centre during patient evaluations. Among them, 13 children had CAH due to enzyme deficiencies other than 21-hydroxylase deficiency (21-OHD). This case series highlights these disorders' clinical and biochemical heterogeneity, providing valuable insights into their real-world presentation, diagnostic pitfalls and long-term outcomes.

Materials and Methods

Retrospective data of all CAH patients presenting to our institute from 2008 to 2022 were identified, and all patients with a genetically proven mutation other than CYP21A2 were identified as the cause of CAH. Their clinical presentation, biochemical features, imaging, medication, and OP follow-up details were collected and analysed from the medical records. Ethical clearance was obtained from the institutional ethics committee.

Results

11-beta hydroxylase deficiency CAH of a total of 87 CAH patients, 13 (14.9%) had non-21 OHD CAH with 5 males (38%) and 8 females (61%) (Table 1). 6 patients among this had 11-beta hydroxylase deficiency, with four phenotypical males (66%) and two females (33%) with a mean age at presentation of 5.7 years, with 3 of them presenting with precocious puberty, 2 with hypertension and one with isolated clitoromegaly. The average height SDS is +1.42, with all patients having BP above the 90th percentile (age-sex-based normative BP) and 4 out of 6 having a BP above the 99th percentile. On presentation, all patients had hyperpigmentation with a median (IQR) ACTH value of 111(59-141) pg/ml. The mean (SD) and median of 8 am cortisol and 17-OHP were 3.98(1.40) mcg/dl and 46.5pg/ml, respectively. 4 out of 6 have hypokalaemia with a mean (SD) value of 3.2(1.02) meq/L. Karyotyping performed on three of the six patients revealed a 46XY pattern, which was consistent with their gonadal and phenotypic sex. Genetic analysis in 4 of 6 revealed homozygous CYP11B1 mutation with predominant involvement of exon 3 in two cases.

Table 1: Clinical, Biochemical and Genetic Profile of Non-21-alfa OHD CAH Patients

Parameter	11-beta hydroxylase deficiency						3-BETA HSD2 OHD			17-alpha hydroxylase deficiency -			StAR deficiency
	CASE-1	CASE-2	CASE-3	CASE-4	CASE-5	CASE-6	CASE-1	CASE-2	CASE-3	CASE-1	CASE-2	CASE-3	
Age at diagnosis	8 years	2 years	2 months	20 years	3 years	6 months	35 days	Prenatal diagnosis	45 days	17 years	16 years	12 years	45 days
Presentation features	Precocious puberty	Precocious puberty	Hypertension, clitoromegaly	Hypertension	Precocious puberty	Clitoromegaly	Dehydration, vomiting	Amniocentesis	Vomiting, dehydration, ambiguous genitalia	Primary amenorrhea, HTN	Primary amenorrhea	Primary amenorrhea, HTN	Vomiting, lethargy, failure to thrive
Height(cm)/ Percentile	145/>97th	95/>97th	90/>97th	150/<3rd	91/3-10th	89/>97th	50/3rd-1st	--/--	55/50th-97th	167/90th-97th	163/90th-97th	172/>97th	60.1/50-97th
Weight(Kg)	42	13	4	60	14	3.5	3	3	3.5	66	73	79	3.0
BP mmHg	270/160	115/70	140/90	180/120	120/70	100/70	59/41	50/40	40/30	160/110	120/80	170/90	40/30
External Genitalia	Male	Male	Female	Male	Male	Female	Female	Female	Male with proximal hypospadias and cordae	Female	Female	Female	Female
Pigmentation	++	++	++	+	++	++	++	-	++	++	++	++	++
Tanner stage	A+, P5, TV-8ml	A+, P4, TV-5ml	A+, P4, B3	A++, P5, TV-10ml	A+, P4, TV-5ml	A+, P4, TV-5ml	A-, P-, B1	A-, P-, B1	A-, P-	A-, B1P1	A-, B1P1	A-, B1P1	A-P-, B1
ACTH (pg/ml)	144	133	50	144	34	89	68	74	60	196	70	301	3367
AM Cortisol (ug/dl)	4.5	6.05	3.5	4.7	3.09	2.04	13.3	15	10	<0.5	<0.5	<0.4	2.1
Sodium	140	136	140	144	133	138	128	130	107	140	140	139	118
Potassium	2.6	2.04	5.0	3.2	2.7	3.72	5.6	4.8	6.95	3.5	4.7	3.7	6
Bicarbonate	25	24	25	25	23	NA	26	25	17	21	22	22	17
17 OHP (ng/ml)	1274	976	19.0	74	4.63	9.57	>12.0	>12.0	>20	0.39	0.22	0.20	0.3
FSH (mIU/ml)	4	2.0	1.01	<0.3	<0.50	NA	NA	NA	NA	52	22	97	NA
LH (mIU/ml)	3	0.26	0.04	<0.07	<0.07	NA	NA	NA	NA	76	68	34	NA
Total Testosterone (ng/ml)	404	<12.9	<12.9	7.35	7.86	5.8	6.15	NA	NA	NA	NA	NA	NA
Karyotyping	46XY	46XY	NA	NA	46XY	NA	46XX	SRY negative in Amniocentesis	46XY	46XX	46XX	46X, del(q12), FISH-SRY+	46XX
Genetic analysis	CYP11B1 homozygous, Exon 5, 6, 2	CYP11B1 Homozygous, Exon 3	CYP11B1 Homozygous, Exon 1	CYP11B1 Homozygous, Exon 3	NA	NA	HSD3B2 Homozygous c.512G>A	HSD3B2 Homozygous c.512G>A	NA	CYP17A1, exon 8	CYP17A1, exon 8	CYP17A1, exon 5	Homozygous mutation of STAR gene

3-beta-HSD type-2 deficiency CAH Among the three subjects, the first two were siblings-the elder diagnosed at 35 days of life and the younger identified prenatally via amniocentesis. The third subject was diagnosed at 45 days of life. All presented with salt-wasting crises. While birth weight was normal, two had female external genitalia, and one had male genitalia with hypospadias and chordee. Hyperpigmentation was noted in two cases. Mean (SD) ACTH was 67.3 (7.0) pg/ml, cortisol 12.7 (2.5) mcg/dl, and 17-OH progesterone 14.6 (4.6) ng/ml. All had hyponatremia (mean Na = 121 meq/L) and hyperkalaemia (mean K = 5.7 meq/dl). Genetic analysis confirmed

a homozygous HSD3B2 c.512G>A mutation in the siblings. All are on glucocorticoid and mineralocorticoid supplementation 17 alfa hydroxylase deficiency Three female subjects were diagnosed with the condition at 17, 16, and 12 years of age, respectively. All presented with primary amenorrhea, and two exhibited hypertension with mean systolic BP above 160mmhg. All 3 exhibited tall stature with >2SD above MPH. All had female external genitalia and displayed hyperpigmentation at presentation. All had poor secondary sexual characteristics, indicating delayed sexual maturation. All had severe hypocortisolism, with AM cortisol levels below 1mcg/dl. ACTH levels were elevated, with a mean (SD) of 189 (116) pg/ml. 17-OH progesterone levels were low in all cases, with a mean of 0.27 ng/ml. Regarding gonadotropins, all subjects had elevated FSH and LH levels, indicating primary gonadal failure. Had a normal sodium and potassium value with a suppressed renin level. Karyotypic analysis showed 46XX in two subjects, while one had 46X, del(q12), FISH-SRY positive, indicating a structural chromosomal abnormality. Genetic analysis revealed CYP17A1 mutation with 2 involving exon 8 and one exon 5. The BP of one of the subjects was managed with just steroid replacement, while the other two required antihypertensive medication along with steroid supplementation for BP control.

Steroidogenic acute regulatory protein deficiency (StAR) A 45-day-old infant was diagnosed with the condition after presenting with vomiting, lethargy, and failure to thrive. The infant exhibited female external genitalia with no signs of ambiguity and had significant hyperpigmentation with hypotension. The infant was found to have a 46XX karyotype and was diagnosed with a homozygous mutation in the STAR gene, indicating congenital lipoid adrenal hyperplasia. The patient presented with markedly elevated ACTH levels (3367 pg/mL) and low 8 AM cortisol (2.1 µg/dL). 17-OH progesterone levels were suppressed (0.3 ng/mL). Electrolyte abnormalities included hyponatremia (Na = 118 meq/L), hyperkalaemia (K = 6 meq/L), and metabolic acidosis (HCO_3 = 17 meq/L). Plasma renin was mildly elevated (0.99 ng/mL), and aldosterone was undetectable (<10 ng/L). Karyotyping and genetics revealed 46XX and homozygous STAR mutation.

Discussion

Our study indicates that approximately 12% of CAH cases were due to enzyme deficiencies other than 21-hydroxylase deficiency (21-OHD). Although these six cases exhibited clinical features resembling 21-OHD CAH—including precocious puberty in both sexes, virilisation in girls, and hyperpigmentation—relying solely on low cortisol levels, elevated ACTH, and increased 17-OHP could have led to a misdiagnosis.11-beta OHD CAH may be missed in newborn screening programs as the 17-OH progesterone may not be as elevated as in 21-alfa-OHD CAH (4). The key distinguishing factor was blood pressure assessment, which, when compared against age- and sex-matched norms and persistently low potassium levels, guided us toward diagnosing 11-beta hydroxylase deficiency (11β-OHD) [4]. Additionally, measuring plasma renin activity would have further differentiated 11β-OHD from 21-OHD CAH, but this was not performed due to logistical constraints. Distinguishing between these two conditions is crucial, as unnecessary mineralocorticoid supplementation in the former could be harmful to the patient.

All three cases of 17α-hydroxylase deficiency (17α-OHD) were identified during early or late adolescence. This delay in diagnosis is likely because 17α-OHD is not included in routine neonatal screening programs, making it easy to overlook in female children, as it typically presents later with primary amenorrhea or absent secondary sexual development [5]. In contrast, affected males are often diagnosed earlier, as they may present at birth with 46XY disorders of sex development (DSD) and genital ambiguity. A tall adolescent girl with hypertension, primary gonadal failure, hypokalaemia, and suppressed renin levels should prompt suspicion of 17α-OHD [5]. Notably, two of our patients—one with 11β-OHD and another with 17α-OHD—who had discontinued treatment following diagnosis later returned with renal failure and hypertensive cardiomyopathy, underscoring the importance of timely diagnosis and continued medical management

3B-HSD2 has a broad spectrum of clinical presentations as it can present as 46XX and 46XY DSD, causing under-virilisation in boys and virilisation in girls. In our case series, all three subjects presented as salt-wasting crises and male child with hypospadias. Given the presence of hyperpigmentation, elevated ACTH, increased 17-OH progesterone, low cortisol, hyponatremia, hyperkalemia, and metabolic acidosis, this condition can easily be misdiagnosed as 21-hydroxylase deficiency (21-OHD) CAH. However, a comprehensive steroid profile analysis using LC-MS, showing an elevated Δ5/Δ4 steroid ratio (pregnenolone to progesterone) , is crucial for accurate diagnosis [6]. Notably, all three patients entered puberty spontaneously during follow-up. CAH due to StAR deficiency is very rare and usually presents with 46XY DSD, salt wasting, and hypercortisolism involving all 3 pathways of steroid synthesis. The Clinical spectrum of presentation is highly variable.

Conclusion

This study highlights the importance of recognising non-21OHD CAH variants, which often present atypically and can be misdiagnosed due to overlapping clinical features. Hypertension and electrolyte abnormalities are critical clues in differentiating 11β-OHD and 17α-OHD from 21OHD CAH. Steroid profiling using LC-MS following ACTH stimulation is crucial for conforming 3B-HSD2 deficiency, as it reveals an elevated Δ5 to Δ4 steroid ratio [6]. Delayed diagnosis, as seen in 17α-OHD, can lead to significant complications, including hypertensive cardiomyopathy and gonadal failure. Early genetic confirmation, targeted hormonal therapy, and lifelong follow-up are crucial to preventing morbidity and improving patient outcomes. Physicians must maintain a high index of suspicion in atypical CAH cases to ensure timely intervention and appropriate management [7,8].

Funding

No funding was received for the conduction of this study.

Competing Interest

The authors have no competing interest in declaring that it is relevant to the article's content.

Ethics Approval

Ethical approval was waived by the local Ethics committee of Sri Ramachandra University of Health Science because of the study's retrospective nature, and all procedures performed were under routine care.

Consent to Participate

Written informed consent was obtained from the parents.

Consent to Publish

Patients signed informed consent regarding publishing their data.

Data Availability

All data generated during this study analysis has been included in this published article.

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