



# Experience with Congenital Adrenal Hyperplasia in Tripoli Children's Hospital, Libya

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## Abstract

Congenital adrenal hyperplasia (CAH) denotes a group of autosomal recessive disorders. Its clinical spectrum varies from classical CAH (CCAH) to nonclassical CAH. It may be a simple virilizing form or salt-wasting type. The study described the clinical presentation, treatment modalities, and sequelae of CAH, including its effect on patient growth during long-term follow-up. A case series study was conducted on patients with CAH who attended and followed up in the Endocrine Clinic in Tripoli Children's Hospital from January 1, 2000 to December 31, 2018. The presentation and the last visit captured demographic and clinical features at the time of diagnosis, types of CAH (classical vs. nonclassical), investigations, treatment details, and height. All patients underwent biochemical testing and hormonal assay, including adrenocorticotropin hormone (ACTH), 17-hydroxyprogesterone (17-OHP), and plasma renin activity (PRA) levels before and after treatment. Fifty-eight patients were included; 38 (65.5%) were female, age at presentation in 94.8% ranged between 1 day and 10 years, with a mean age of  $2.3 \pm 1.1$  years. Ambiguous genitalia was the presenting feature in 55.2 and 84% of total and female patients, respectively. Salt wasting was present in 37.9%. Of 32 female patients with ambiguous genitalia, only 11 (34.4%) out of them and 19% of all patients had a surgical correction. The mean and standard deviation of height at diagnosis was  $78.327 \pm 31.070$ , and the last visit after treatment was  $108.345 \pm 31.781$ . The relation between the date of birth and height throughout follow-up for those at last visit with age ranges from 13 to 18 years old, their mean and standard deviation of height was  $135.650 \pm 29.286$ , and for patients who were less than 13 years at last visit, the mean and standard deviation of height was  $101.079 \pm 32.121$ ;  $p$ -value = 0.003. The Z-scores were calculated and showed that about eight patients were positively above the average mean of the population. Biochemical disturbances were improved after treatment, including sodium, potassium, and glucose in CCAH type;  $p$ -value < 0.001. Hormonal findings included levels of ACTH, 17-OHP, and PRA; all levels were reduced with treatment;  $p$ -value < 0.001. In this single-center series, most of our patients with biochemical and hormonal abnormalities were normalized with hormonal replacement and limited surgical correction of females with ambiguous genitalia.

## Keywords

- CAH
- classical CAH
- nonclassical CAH
- adrenal crisis
- genital ambiguity

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## Introduction

Congenital adrenal hyperplasia (CAH) includes inherited enzymatic deficiencies that lead to abnormal cortisol synthesis. The impaired cortisol production nullifies the negative feedback to the hypothalamus and pituitary gland. This subsequently leads to excessive adrenocorticotropin hormone (ACTH) production.<sup>1</sup> The most common form of CAH is due to 21-hydroxylase deficiency, which accounts for more than 90% of CAH cases.<sup>2</sup> CAH includes the classical CAH (CCAH) and nonclassical CAH (NCCAH). CCAH presents with salt-wasting or the simple virilizing form that manifests at birth and/or in the neonatal period. The NCCAH form is a less severe form of the disorder that lacks genital ambiguity, is not immediately life-threatening, and presents later in life.<sup>3</sup> Increased androgen production often leads to peripheral precocious puberty in CAH. Chronic hyperandrogenemia causes central precocious puberty by affecting the hypothalamus leading to reduced adult height and advanced bone age.<sup>4</sup> By showing the insufficient synthesis of cortisol, aldosterone, or both in conjunction with a buildup of precursor hormone concentrations, CAH is diagnosed. A high serum concentration of 17-hydroxyprogesterone (17-OHP) occurs in 21-hydroxylase deficiency, low serum aldosterone concentrations, hyponatremia, hyperkalemia, and elevated plasma renin activity indicate hypovolemia. Excess serum concentrations of 11-deoxycortisol result in 11 $\beta$ -hydroxylase deficiency. Pelvic ultrasonography, bone age, karyotype, and genetic mutation analysis may also be needed to confirm the diagnosis.<sup>5</sup> Management of CAH is quite challenging, especially in developing countries.<sup>6–8</sup> Glucocorticoid replacement inhibits ACTH overproduction. Adrenal suppression reduces androgens production, averting further virilization, slowing growth acceleration, and bone age advancement to a more normal rate. Thus, allowing a normal onset of puberty and maintaining adequate sodium balance. Suppression of adrenal activity in 11 $\beta$ -hydroxylase deficiency leads to the remission of hypertension.<sup>9</sup> Current guidelines for CAH treatment are flexible but emphasize the importance of minimizing potential iatrogenic Cushing syndrome. However, adequate adrenal androgen suppression is often challenging without using supraphysiologic doses of glucocorticoids with adverse effects.<sup>10</sup> There are scanty studies regarding CAH presentation and clinical outcome in Libya; hence, we wished to describe the clinical presentation, treatment modalities, and sequelae of CAH, including its effect on patient's growth in the extended, follow-up, in those who reach nearly adult age.

## Patients and Methods

This case series study was conducted in Tripoli Children Hospital, Tripoli, Libya, at the Endocrine Unit, on patients diagnosed with CAH and seen in the outpatient clinic between January 1, 2000 and December 31, 2018. Children aged 1 day to 18 years with a diagnosis of CAH were included. All males and females diagnosed with CAH were proved clinically by detailed history, complete physical examination,

and laboratory investigations. Results of plasma renin, ACTH, 17-OHP (Bioscientia, Germany and Cerba, France), urea, Na, K, and blood glucose levels before and after treatment were retrieved. Ultrasonography of adrenals and gonads and karyotyping in girls with ambiguous genitalia were done. Exclusion criteria: Patients with insufficient data, missed follow-up for more than 3 years.

Data regarding demography, clinical presentation at the time of diagnosis, and type of CAH (CCAH or NCCAH) were collected. A CCAH was defined as a condition with early presentation of symptoms in the first year of life, mainly as a salt wasting, adrenal crisis, or simple virilizing form. NCCAH is a less severe form of the disorder. It lacks genital ambiguity, is not immediately life-threatening, presents later in life, remains asymptomatic, or is misdiagnosed as a different disease.<sup>3</sup> Investigations, treatment details, and height were collected at the presentation and the last visit. All patients underwent biochemical testing for 17-OHP levels to assess the adequacy of therapy. Bone age assessment with the left hand and wrist X-ray using the Greulich–Pyle method was done in all children above 1 year of age. Short stature was defined as the height of 2 or more standard deviations (SDs) below the population mean.<sup>11</sup> 17-OHP levels between 1 and 12 ng/mL were considered appropriate; values below 1 ng/mL indicate suppression and overtreatment, and values above 12 ng/mL are suggestive of undertreatment.<sup>12</sup>

Blood pressure (BP) measurement is done before the treatment, an additional risk factor associated with CAH. High BP is defined as BP measurements persistently between the 95th and 99th percentile for age and sex.<sup>13</sup> Low BP is defined in numerous guidelines using the 5th percentile of systolic BP in healthy children as a cutoff for hypotension in children aged < 18 years.<sup>14</sup>

The data were analyzed using the Statistical Package for Social Sciences version 22. Descriptive analysis was used for continuous variables as mean and SD, while categorical data were presented as frequency and percentage. The chi-square test was used to compare the frequency difference of categorical data. Paired-samples test was used to compare the mean difference before and after treatment of continuous and normally distributed data. At the same time, the Wilcoxon signed ranks test was used for not normally distributed data. Statistical significance was set at  $p < 0.05$ .

## Results

The study showed that out of 58 patients, 65.5% were female, with a male-to-female ratio of 1:1.9, age at presentation in 94.8% of them ranged between 1 day and 10 years. The mean age was  $2.3 \pm 1.1$  years, and the mode was  $2 \pm 1.1$  years. The original city is Tripoli, with 36.2%. Family history was positive in 55.2%, and consanguinity was present in 67.2%. The classical type of CAH comprises 60.3% of patients (**Table 1**).

Ambiguous genitalia was the presenting feature in 55.2% (60.0% of CCAH; 47.8% of NCCAH); total number of females was 38; ambiguous genitalia was 32 female (84%). Salt wasting was more evident in 51.4% of patients with CCAH than those with NCCAH (17.4%);  $p$ -value = 0.009. Precocious

**Table 1** Sociodemographic characteristics of the study population

Characteristics total	Total n = 58	Classical CAH 35	Nonclassical 23	p-Value
Gender				0.969
Male	20 (34.5)	12 (34.3)	8 (34.8)	
Female	38 (65.5)	23 (65.7)	15 (65.2)	
Age				0.011
1 d–10 y	39 (67.2)	28 (80.0)	11 (47.8)	
> 10 y	19 (32.8)	7 (20.0)	12 (52.2)	
Age at first presentation				0.057
1 d–10 y	55 (94.8)	35 (100.0)	20 (87.0)	
> 10 y	3 (5.2)	0	3 (13.0)	
Original city				0.136
Tripoli city and its district	21 (36.2)	10 (28.6)	11 (47.8)	
Outside the capital	37 (63.8)	25 (71.4)	12 (52.2)	
Consanguinity				0.790
Yes	39 (67.2)	24 (68.0)	15 (65.2)	
No	19 (32.8)	11 (31.4)	8 (34.8)	
Family history				0.147
Yes	32 (55.2)	22 (62.9)	10 (43.5)	
No	26 (44.8)	13 (37.1)	13 (56.5)	
Duration of follow-up, median (IQR)				3.500 (4.75)

Abbreviations: CAH, congenital adrenal hyperplasia; IQR, interquartile range. Results are shown as number (percentage).

puberty was the presenting feature in 29.3% (60.9% of NCCAH; 8.6% of CCAH), while a prepubertal state was seen in 91.4% of patients with the classical type and nonclassical type; only 39.1% were in the prepubertal state; *p*-value ≤ 0.001.

BP measurement was normal at the presentation time in 58.6% of all patients. High BP reading was found in 24.2% of all patients; however, hypotension was present in 17.2% of all patients (25.7% of CCAH; 4.4% of NCCAH), *p*-value = 0.100 (→ **Table 2**).

**Table 2** Clinical pattern of the study population

Characteristics	Total n = 58	Classical 35	Nonclassical 23	p-Value
Salt wasting				0.009
Yes	22 (37.9)	18 (51.4)	4 (17.4)	
No	36 (62.1)	17 (48.6)	19 (82.6)	
Ambiguous genitalia				0.362
Yes	32 (55.2)	21 (60.0)	11 (47.8)	
No	26 (44.8)	14 (40.0)	12 (52.2)	
Pubertal assessment				< 0.001
Prepubertal	41 (70.7)	32 (91.4)	9 (39.1)	
Precocious puberty	17 (29.3)	3 (8.6)	14 (60.9)	
Blood pressure at the time of diagnosis (at presentation)				0.100
Normal BP	34 (58.6)	19 (54.3)	15 (65.2)	
Low BP	10 (17.2)	9 (25.7)	1 (4.4)	
High BP	14 (24.2)	7 (20.0)	7 (30.4)	

Abbreviation: BP, blood pressure. Results are shown as number (percentage).

**Table 3** Diagnostic tool of the study population by type of CAH

Characteristics	Total n = 58	Classical CAH 35	Nonclassical 23	p-Value
Ultrasound of adrenals and gonads				0.599
Yes	38 (65.5)	22 (62.9)	16 (69.6)	
No	20 (34.5)	13 (37.1)	7 (30.4)	
Karyotyping study				0.300
Yes	25 (43.1)	17 (48.6)	8 (34.8)	
No	33 (56.9)	18 (51.4)	15 (65.2)	
Bone age before treatment				0.122
Normal	21 (36.2)	14 (40.0)	7 (30.4)	
Advanced	26 (44.8)	12 (34.3)	14 (60.9)	
Delayed	6 (10.4)	4 (11.4)	2 (8.7)	
Not done	5 (8.6)	5 (14.3)	0 (0)	
Bone age after treatment				0.048
Normal	31 (53.4)	21 (60.0)	10 (43.5)	
Advanced	17 (29.3)	6 (17.1)	11 (47.8)	
Delayed	6 (10.3)	4 (11.4)	2 (8.7)	
Not done	4 (6.9)	4 (11.4)	0 (0)	

Abbreviation: CAH, congenital adrenal hyperplasia. Results are shown as number (percentage).

Ultrasound of adrenals and gonads was done in 65.5% of all patients. Karyotyping was done in most females with ambiguous genitalia. Bone age was done before treatment. It was normal in 40.4% and advanced in 34.3% of patients with CCAH, while in patients with NCCAHA, it was normal in 30.4% and advanced in 60.9%; compared with bone age after treatment, it was normal in 60% of patients with CCAH and 43.5% in patients with nonclassical type. When using two-sample sign test to examine the changes in bone age before and after treatment within each type of CAH, the changes were not significant (► **Table 3**).

Glucocorticoid and mineralocorticoid replacement treatment was used more often in CCAH than in NNCAH (85.7% vs.

47.8%,  $p$ -value = 0.002). While glucocorticoids only were significantly more often in NCCAHA than in CCAH ( $p$ -value = 0.002). Among 32 female patients with ambiguous genitalia, only 11 (34.4%) of them and 19% of all patients had perineal surgical correction (► **Table 4**).

Patients were growing well, and the median (interquartile range) for the duration of follow-up was 3.500 (4.75) years. The mean and SD of height at diagnosis was 78.327 ( $\pm 31.070$ ), and the last visit after treatment was 108.345  $\pm$  31.781 (► **Table 5**). There was a relation between the date of birth and height throughout the follow-up period. Those with a date of birth between 2000 and 2005, their age at last visit ranges from 13 to 18 years old, and the mean and

**Table 4** Treatment modalities of the study population by type of CAH

Characteristics	Total	Classical CAH 35	Nonclassical 23	p-Value
Use of glucocorticoid and mineralocorticoid				0.002
Yes	41 (70.7)	30 (85.7)	11 (47.8)	
No	17 (29.3)	5 (14.3)	12 (52.2)	
Use of glucocorticoid only.				0.002
Yes	19 (32.8)	6 (17.1)	13 (56.5)	
No	39 (67.2)	29 (82.9)	10 (43.5)	
Perineal surgery or surgical correction				0.645
Yes	11 (19.0)	8 (22.9)	3 (13.1)	
No	23 (39.6)	14 (40.0)	9 (39.1)	
Not indicated	24 (41.4)	13 (37.1)	11 (47.8)	

Abbreviation: CAH, congenital adrenal hyperplasia. Results are shown as frequency (percentage)

Note: Significant result ( $p$ -value < 0.05).

**Table 5** Anthropometric findings of the study population before and after treatment

Height	Total N = 58	Classical CAH N = 35	Nonclassical N = 23	p-Value
Height before treatment, mean (SD)	78.327 (31.070)	66.285 (20.618)	96.652 (35.530)	0.002 <sup>a</sup>
Height after treatment, mean (SD)	108.345 (31.781)	94.643 (28.564)	129.195 (24.551)	< 0.001 <sup>a</sup>
Weight before treatment, mean (SD)	6.900 (11.12)	7.880 (6.405)	17.717 (14.198)	0.004 <sup>a</sup>
Weight after treatment, mean (SD)	19.250 (23.00)	20.457 (17.762)	33.595 (16.117)	0.006 <sup>a</sup>

Abbreviations: CAH, congenital adrenal hyperplasia; SD, standard deviation.

<sup>a</sup>Independent-samples *t*-test.

**Table 6** Biochemical findings of the study population before and after treatment

Characteristic	Normal range	At diagnosis (before treatment)	Last visit (after treatment)	p-Value
Sodium (Na), mean (SD)	135–145 meq/L	131.72 (9.42)	139.36 (4.73)	< 0.001 <sup>a</sup>
Potassium (K), mean (SD)	3.6–5.2 mmol/L	5.51 (1.08)	4.37 (0.589)	< 0.001 <sup>a</sup>
Glucose (mg/dL), mean (SD)	< 130 mg/dL	75.07 (20.04)	89.20 (14.44)	< 0.001 <sup>a</sup>
Urea, median	Up to 50 mg/dL	23.0	18.50	0.002 <sup>b</sup>

Abbreviation: SD, standard deviation.

SD of height was  $135.650 \pm 29.286$ , and those with a date of birth after 2005, their age at last visit was less than 13 years, and the mean and SD of height was  $101.079 \pm 32.121$ ; *p*-value = 0.003. The Z-scores were done and showed that about eight patients were positively above the average mean of the population. For example, the z-score of patient number 2 at diagnosis was  $-0.49332$ , which means approximately 0.4933 SDs below the mean of 78.327, and for the same patient at the last visit after 10 years on treatment, the Z-score was 1.89277, which means approximately 1.893 SDs above the average mean of 108.345. This patient's height improved well after treatment (► **Supplementary Material S1**).

Abnormal values of biochemical parameters at presentation, especially in the CCAH type, including sodium, potassium, and glucose, have all improved after treatment and returned to normal values, *p*-value < 0.001 (► **Table 6**). Hormonal findings included levels of ACTH, 17-OHP, and plasma renin, and all the levels were reduced with treatment, *p*-value < 0.001 (► **Table 7**).

## Discussion

CAH is the most common adrenal disorder. In this study, 58 patients diagnosed with CAH were included with female

predominance; these results are similar to those in Southeast Asia.<sup>15</sup> Female sex predominance was also seen in the Assiut study.<sup>16</sup> However, equal sex distribution was seen in the Nigerian study by Oyenusi et al.<sup>5</sup> The age at presentation of most patients in this study ranged between 1 day and 10 years, with a mean age of around 2 years. In comparison with the study done at Assiut University Children's Hospital by Bakhit et al,<sup>16</sup> according to the age at diagnosis, the cases were in the age range from 1 month to 10 years, with a mean age at diagnosis of 15 months. Positive family history was documented in half of the cases, nearly similar to the Saudi study that showed positive family history in 53.6% related to a high rate of consanguineous marriage.<sup>17</sup> Consanguinity accounts for 67.2% of patients with CAH in the study population compared with a study with no history of consanguineous marriage in Nigeria.<sup>5</sup> Also, the patients in Asian countries where parental consanguinity with CAH ranged from 52.3 to 82%.<sup>16,18–20</sup> CAH is the most common adrenal disorder in childhood and was documented to be the most common cause of ambiguous genitalia in newborns.<sup>21</sup> This was also reflected in the present study in which half of the children presented with genital ambiguity. This concurs with Oyenusi et al, who showed many patients presenting with genital

**Table 7** Hormonal findings of the study population before and after treatment

Characteristic	Normal range	At diagnosis (before treatment)	Last visit (after treatment)	p-Value
Adrenocorticotrophic hormone level (ACTH), median	< 100 pg/mL	83.15	29.00	< 0.001 <sup>a</sup>
Plasma renin activity, median	< 20 pg/mL	259.50	40.85	< 0.001 <sup>a</sup>
17-Hydroxyprogesterone, median	< 2 ng/mL	160.0	14.40	< 0.001 <sup>a</sup>

<sup>a</sup>Wilcoxon signed ranks test.

ambiguity.<sup>5</sup> Several other studies also documented this pattern, where CAH accounted for between 27.5 and 60% of cases of ambiguous genitalia.<sup>22–24</sup> It was reported that a quarter of the female patients required corrective surgery in the study population, which is considered a few in this condition. In contrast, a study by Al Shaikh et al reported that ambiguous genitalia was present in 72% of females, and the majority required corrective surgery.<sup>17</sup> The low percentage in this respect in the present study is perhaps due to a lack of awareness about the disease in the family or limited access to surgery.

Adrenal crisis occurred in about one-third of participants in the present study, which is remarkably lower than in the Oyenusi et al study, which showed that only 18.2% of patients had a salt loss.<sup>5</sup> More than half of the participants have normal BP at presentation, similar to the study of the Children's Hospital in Minneapolis that evaluated 180 pediatric patients with CAH, where results varied between normal and hypertensive levels in 65% of participants and 35% were normotensive.<sup>25</sup>

Hyponatremia and hyperkalemia improved in our study after the replacement of mineralocorticoids and glucocorticoids in the salt-wasting classical type of CAH, in agreement with Canlas and Ponmani.<sup>26</sup>

Bone age was not affected significantly before and after hormonal replacement therapy. Our results not supported by this patients in compared study (Linsu et al) have compromised height predictions due to advanced bone ages at presentation.<sup>27</sup>

We observed good height after treatment in patients who reached near adult age; their height (Z-score) was positively above the average mean of the population. Also, the other patients needed to reach a certain age before any final statement about their height could be reported. Other studies reported between 1977 and 1998 revealed a short final height outcome in patients with CAH. Generally, children with CAH would eventually be short adults and consistently below their genetic potential.<sup>17</sup> Mean final height is often impaired in a study in Northern Ireland over 30 years.<sup>28</sup>

Small sample sizes do not reflect CAH distribution and outcome in the Libyan population. There is a lack of support for research centers to facilitate the determination of enzymatic defects and genetic testing. There is no neonatal screening program available in the country. The lack of documentation in patients' medical records and detailed information limits the number of cases in the study.

## Conclusion

In this single-center series, most of our patients with biochemical and hormonal abnormalities were normalized with hormonal replacement. In the current study, however, minor surgical correction of females with ambiguous genitalia needs to investigate this problem and provide more surgical management for this population. Patients who reach near adult age achieved good height during long-term follow-up. Other patients in the study need close follow-up to assess

their final height. Transitional care clinics are strongly needed to transfer patients to adult services.

## Authors' Contribution

Both authors contributed substantially to the study's design and conduct, drafting and revising the manuscript, and approval of its final version.

## Compliance with Ethical Principles

The Tripoli Children's Hospital Committee approved the study for scientific research, and permission was also obtained from the research and consulting department at the Faculty of Medicine, University of Tripoli for publication. Verbal informed consent was obtained from all participants during their follow-up at the clinic. Data confidentiality was maintained throughout the study, and any resulting publication was anonymous.

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None.

## Conflict of Interest

None declared.

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