

Congenital adrenal hyperplasia in Tunisia: clinical characteristics and management from a monocentric retrospective study

Hyperplasie congénitale des surrénales en Tunisie : caractéristiques cliniques et modalités de prise en charge d'après une étude rétrospective monocentrique

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ABSTRACT

Background: Congenital adrenal hyperplasia (CAH) represents a spectrum of autosomal recessive disorders of adrenal steroidogenesis. In Tunisia, the lack of systematic neonatal screening and the high rate of consanguinity may lead to delayed diagnosis and more severe presentations. **Objective:** The objective of this study was to describe the clinical, genetic, therapeutic, and evolutionary characteristics of children with CAH in a pediatric Tunisian center. **Study design:** A retrospective descriptive study was conducted over a 15-year period in the Pediatric Department of Habib Bougatfa Hospital, Bizerte, Tunisia. All children with a confirmed diagnosis of CAH were included. **Results:** Eleven patients were included. Consanguinity was reported in 7 cases. One patient was diagnosed prenatally. The median age at postnatal diagnosis was 30 days. The main diagnostic circumstances were disorders of sex development (DSD) (n=6), failure to thrive (n=2), and salt-wasting crisis (n=2). 21-hydroxylase deficiency was the most frequent etiology (8/11), followed by P450 oxidoreductase deficiency (n=2) and StAR-related lipoid CAH (n=1). All patients received standard hormonal replacement therapy (hydrocortisone, fludrocortisone, sodium). Surgical management was required for four patients with DSD. During follow-up, three patients developed adrenal crises, while growth and pubertal development were normal in most cases. **Conclusion:** CAH remains a complex disorder that requires early diagnosis and multidisciplinary management. The findings underscore the value of molecular diagnosis and the need for heightened clinical suspicion to ensure timely management, particularly in countries where neonatal screening is not yet implemented.

Keywords: Congenital Adrenal Hyperplasia, Cytochrome P450 Oxidoreductase Deficiency, Deficiency of 21-Hydroxylase, Disorders of Sex Development, Prenatal Diagnosis

RÉSUMÉ

Problématique : l'hyperplasie congénitale des surrénales (HCS) représente un ensemble de maladies autosomiques récessives affectant la stéroïdogenèse surrénalienne. En Tunisie, l'absence de dépistage néonatal systématique et le taux élevé de consanguinité peuvent entraîner un retard diagnostique et des formes cliniques plus sévères. **Objectif :** l'objectif de cette étude était de décrire les caractéristiques cliniques, génétiques, thérapeutiques et évolutives des enfants atteints d'HCS suivis dans un service de pédiatrie en Tunisie. **Méthodes :** une étude rétrospective descriptive a été menée sur une période de 15 ans au sein du service de pédiatrie de l'hôpital Habib Bougatfa de Bizerte, en Tunisie. Tous les enfants ayant un diagnostic confirmé d'HCS ont été inclus. **Résultats :** onze patients ont été inclus. Une consanguinité était retrouvée dans sept cas. Un patient a été diagnostiqué en période prénatale. L'âge médian au diagnostic postnatal était de 30 jours. Les circonstances diagnostiques étaient les anomalies du développement sexuel (n=6), le retard staturo-pondéral (n=2) et le syndrome de perte de sel (n=2). Le déficit en 21-hydroxylase était l'étiologie la plus fréquente (n=8), suivi du déficit en P450 oxydoréductase (n=2) et du déficit en protéine StAR (n=1). Tous les patients ont reçu un traitement hormonal substitutif (hydrocortisone, fludrocortisone) associé à la supplémentation sodée. Une prise en charge chirurgicale était nécessaire chez quatre. Au cours du suivi, trois patients ont présenté des épisodes d'insuffisance surrénalienne aiguë, tandis que la croissance et le développement pubertaire étaient sans anomalies dans la majorité des cas. **Conclusion :** l'HCS demeure une pathologie complexe nécessitant un diagnostic précoce et une prise en charge multidisciplinaire. Ces résultats soulignent l'intérêt du diagnostic moléculaire ainsi que la nécessité d'un haut niveau de suspicion clinique afin de permettre une prise en charge rapide, en particulier dans les pays où le dépistage néonatal n'est pas encore instauré.

Mots-clés : Hyperplasie congénitale des surrénales, Déficit en oxydoréductase P450, Déficit en 21-hydroxylase, Troubles du développement sexuel, Diagnostic prénatal

Abbreviations : CAH, congenital adrenal hyperplasia; DSD, disorders of sex development; POR, P450 oxidoreductase; StAR, steroidogenic acute regulatory protein; 17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotrophic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; MLPA, multiplex ligation-dependent probe amplification.

BACKGROUND

Congenital adrenal hyperplasia (CAH) represents a group of autosomal recessive disorders characterized by enzymatic defects in the adrenal steroidogenesis pathway. The resulting accumulation of steroid precursors upstream of the enzymatic block produces a wide spectrum of clinical manifestations, ranging from life-threatening salt-wasting crises in neonates to disorders of sex development (DSD) and later-onset hyperandrogenic symptoms [1,2].

With an estimated incidence of 1 in 14,000 to 18,000 live births, 21-hydroxylase deficiency is by far the most prevalent form, accounting for over 95% of all CAH cases [3,4]. However, CAH is a genetically heterogeneous condition. Deficiencies in other enzymes, such as 11 β -hydroxylase, 3 β -hydroxysteroid dehydrogenase, P450 oxidoreductase (POR), and steroidogenic acute regulatory protein (StAR), constitute rare but clinically significant variants.

In Tunisia, as in many regions with a high prevalence of consanguinity, the relative frequency and presentation of these rare enzymatic defects may differ from populations reported in international studies. Moreover, the diagnostic journey for a child with CAH in a specific healthcare setting is shaped by local resources, including access to specialized hormone assays and molecular genetic testing. While national neonatal screening for 21-hydroxylase deficiency is not yet universally established, the clinical recognition of CAH in our country remains heavily reliant on astute clinical suspicion based on classic presenting signs such as DSD, failure to thrive, or acute adrenal crisis [5].

The objective of this study was to describe the clinical, biochemical, genetic, and therapeutic characteristics of CAH in a cohort of Tunisian children.

METHODS

This was a retrospective, descriptive, single-center study conducted in the Department of Pediatrics at Habib Bougatfa University Hospital in Bizerte, Tunisia over a period of 15 years from January 2011 to December 2025. We included all children (aged 0 to 18 years) with a confirmed diagnosis of CAH who were followed in our department during the study period. The diagnosis of CAH was established based on a combination of clinical manifestations (salt-wasting crisis, dehydration, DSD, or signs of hyperandrogenism), elevated levels of precursor hormones according to the suspected enzymatic block and genetic analysis when available.

Data collection

Data were collected using a pre-established form that included socio-demographic information, medical history,

clinical findings, laboratory investigations, therapeutic management, and outcomes. All patients underwent a complete physical examination and a biological assessment including renal function tests, serum electrolytes, urinary electrolytes, blood gas analysis, and karyotyping. DSD were classified according to the Prader scale [6]. Hormonal assays, abdominopelvic ultrasonography, and genetic testing were performed based on clinical and anamnestic indications (Diagram 1). Assays included 17-hydroxyprogesterone (17-OHP), cortisol, adrenocorticotrophic hormone (ACTH), dehydroepiandrosterone (DHEA), androstenedione, testosterone, pregnenolone, aldosterone, plasma renin activity, 11-deoxycorticosterone (DOC), and 11-deoxycortisol. Measurements were conducted using standard immunoassay techniques at the Laboratory of Biochemistry and Hormonal Analysis, Pasteur Institute of Tunis, or accredited private laboratories, with age- and sex-specific reference ranges. Genetic testing by multiplex ligation-dependent probe amplification (MLPA) was performed at the Medical Genetics Department, Farhat Hached University Hospital, Sousse, Tunisia.

Therapeutic management was based on hormonal replacement therapy and surgical correction of DSD. We assessed the patients' progression under treatment (treatment response, growth parameters and pubertal development). Patient confidentiality was maintained throughout the study.

RESULTS

A total of eleven pediatric patients (n=11) with a confirmed diagnosis of CAH were included in the study. The history of parental consanguinity was present in 7 cases. A family history of CAH, indicating a previously affected sibling, was reported for 5 patients. One female patient (46,XX) was diagnosed prenatally at 11 weeks of gestation via chorionic villus sampling, following the identification of an affected older sibling with 21-hydroxylase deficiency. Genetic analysis revealed a CYP21A2 mutation. The pregnancy was managed with maternal dexamethasone therapy, initiated at 9 weeks of amenorrhea and continued until 35 weeks of gestation, when the newborn was delivered. At birth, the infant exhibited no signs of virilization.

For the ten patients diagnosed after birth, the median age at postnatal diagnosis was 30 days (mean 69.5 ± 111.8 days, range 1–360 days). The primary circumstances leading to diagnosis were DSD in six patients, failure to thrive in two patients and acute salt-wasting crisis (presenting with vomiting, dehydration, and electrolyte imbalance) in two patients. On examination, dehydration was noted in three patients, and hyperpigmentation of the external genitalia was observed in one patient (Table 1).

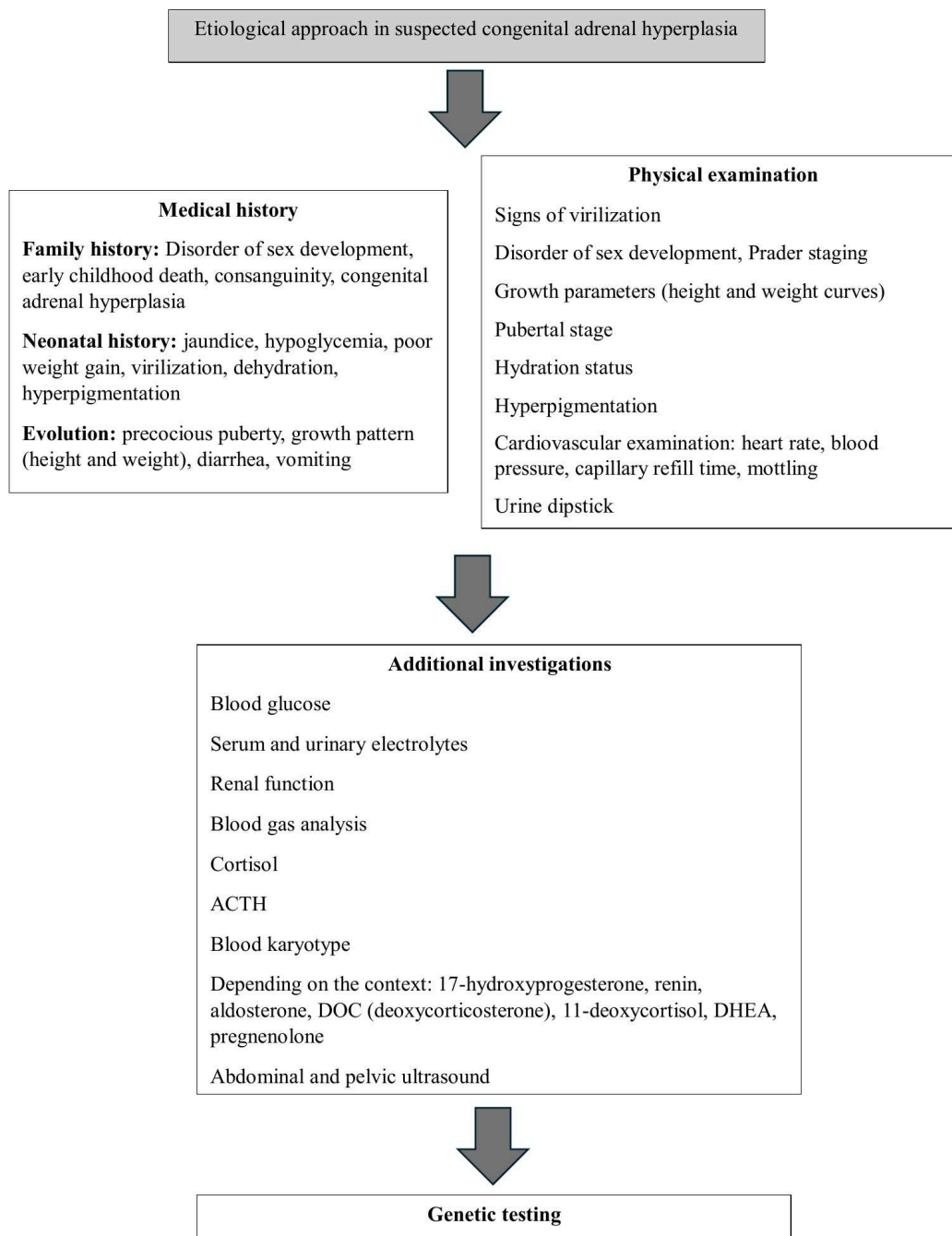


Diagram 1: Etiological approach in suspected congenital adrenal hyperplasia

Diagram 1. Etiological approach in suspected congenital adrenal hyperplasia.

Biochemical analysis revealed hyponatremia associated with hyperkalemia in four patients. The mean serum sodium and potassium levels were 130.5 ± 11.2 mmol/L (range, 113–140 mmol/L) and 5.46 ± 1.79 mmol/L (range, 4–9 mmol/L), respectively. Plasma renin activity was measured in six patients and was elevated in three cases. Hypoglycemia (venous glucose <0.5 g/L) was observed in three patients. Urinary electrolyte analysis showed elevated natriuresis with low kaliuresis in seven patients. No detectable

biochemical abnormalities were identified in three patients. The most frequent etiology was 21-hydroxylase deficiency ($n=7$). POR deficiency was diagnosed in two patients, both with a 46,XX karyotype and Prader stage 4–5, based on a characteristic hormonal profile. Molecular confirmation was not available for this rare variant. The distribution of enzymatic defects within the cohort is summarized in Table 2.

Therapeutic management was based on hormonal replacement therapy, surgical correction of DSD (n=4), and psychosocial support. The declared sex of all patients who underwent surgical management was female. The mean age at surgery was 16.25 ± 3.03 months (range: 12–20 months). Prader staging was 5 in three patients and 3 in one patient.

During the acute phase, patients received hydrocortisone hemisuccinate at 10–15 mg/kg/day divided into four doses, along with fludrocortisone, fluid resuscitation, and correction of electrolyte disturbances. Following stabilization, all patients received maintenance therapy with hydrocortisone (mean dose: 15 mg/m²/day; range: 10–25 mg/m²/day), fludrocortisone (100 µg/day), and sodium supplementation. Gender assignment was consistent with genotypic sex in all patients, with 10 individuals identified as female and one as male. A medical alert card indicating the

diagnosis, current treatment, and situations requiring an increase in glucocorticoid doses was provided to all patients.

The mean follow-up duration was 8.5 ± 4.7 years, with a median of 9 years (range: 0.5–14 years). During this period, three patients experienced a total of eight adrenal crises, all precipitated by intercurrent infections (gastroenteritis or upper respiratory infections). Growth parameters were within normal limits for age in 10 out of 11 patients. All patients who reached pubertal age were female (n=7) and exhibited normal pubertal development, with a mean age at pubertal onset of 11 years (range: 9–13 years). One patient exhibited accelerated growth velocity and signs of precocious puberty secondary to hyperandrogenism, which required an increase in the hydrocortisone dosage to achieve adequate hormonal control.

Table 1. Circumstances of diagnosis and clinical examination findings

	Number of cases (n)
Circumstances of diagnosis	
Prenatal diagnosis	1
Disorders of sexual differentiation	6
Poor weight gain	2
Diarrhea and vomiting	2
Clinical abnormalities	
Hyperpigmentation	1
Dehydration	3
Prader classification of DSD	
Prader 5	4
Prader 4	2
Prader 3	1
Prader 2	1

Table 2. Genotypic and phenotypic features of enzymatic defects in patients with postnatal diagnosis

Enzymatic deficiency	Clinical form	Karyotype	Molecular study	Hormonal assessment
21-hydroxylase deficiency (n=7)	• Salt-wasting syndrome (n=6) • Simple virilizing form (n=1)	• 46,XX (n=6) • 46,XY (n=1)	• Large homozygous deletions of CYP21A2 (n=4) • Q318X mutation in CYP21A2 (n=1) • Double mutation Q318X/V281 in CYP21A2 (n=1)	• Elevated 17-hydroxyprogesterone (mean=78 µg/l; range [11–257 µg/l]) • Elevated ACTH (mean=824 ng/l; range [178–2400 ng/l]) • Elevated plasma renin activity (mean=223 pg/ml; range [130–400 pg/ml])
P450 oxidoreductase deficiency (n=2)	• DSD, Prader 4 (n=1) • DSD, Prader 5 (n=1) • No bone deformities	• 46,XX (n=2)	Not performed	• Elevated 17-hydroxyprogesterone (mean=63 µg/l) • Elevated pregnenolone (mean=232 ng/dl) • Normal ACTH (mean=34 ng/ml) • Normal plasma renin activity (mean=53 pg/ml)
Lipoid adrenal hyperplasia due to StAR defect (n=1)	• Salt-wasting syndrome (n=1)	• 46,XX (n=1)	Not performed	• Low 17-hydroxyprogesterone (=0.04 µg/l) • Low cortisol (=19 nmol/l) • Elevated ACTH (=240 ng/l) • Low DHEA (=0.25 µg/dl) • Low aldosterone (=9 pmol/l) • Plasma renin activity at the upper limit of the normal range (118 pg/ml) • Low 11-deoxycorticosterone (DOC) (=9 ng/dl) • Low 11-deoxycortisol (0.05 µg/dl)

Normal values: Cortisol 166–507 nmol/l; ACTH 7.2–63.3 ng/l; 17-hydroxyprogesterone 0.3–2 µg/l; Plasma renin activity 18–120 pg/ml; Pregnenolone 10–75 ng/dl; DHEA 5–50 µg/dl; Aldosterone 164–2929 pmol/l; 11-deoxycorticosterone (DOC) 10–60 ng/dl; 11-deoxycortisol 5–50 µg/dl.

DISCUSSION

This single-center case series describes the clinical, biochemical, and therapeutic spectrum of CAH in a cohort of 11 Tunisian children. Our study has several limitations inherent to its design. The retrospective nature and small sample size limit the generalizability of the findings and preclude robust statistical comparisons. Furthermore, the unavailability of genetic confirmation for the rare forms (POR and StAR) is a constraint, although the diagnoses were strongly supported by characteristic clinical and biochemical phenotypes.

The clinical presentation of our cohort aligns with the series described in the literature [1,7]. DSD were the most frequent circumstance, followed by life-threatening salt-wasting crises and failure to thrive. This pattern underscores the persistent diagnostic challenge: the window between birth and the potential onset of an adrenal crisis is often narrow. The median age at diagnosis of 30 days in our postnatal cases strongly argues for the systematic implementation of neonatal screening for 21-hydroxylase deficiency, a proven strategy to reduce morbidity and mortality by enabling pre-symptomatic diagnosis [8]. In its absence, our results showed that a high index of clinical suspicion, particularly in the presence of DSD or a positive family history, remains the cornerstone of timely intervention.

Tunisian series consistently report a high rate of consanguinity and a predominance of classic forms, particularly salt-wasting phenotypes, similar to our findings. These studies also describe recurrent CYP21A2 pathogenic variants in Tunisian patients [5,9]. Our results are in line with these observations, suggesting that genetic factors related to founder effects and cultural practices, such as consanguinity, may contribute to the prevalence and clinical severity of classic CAH in Tunisian populations.

As expected, 21-hydroxylase deficiency was the most prevalent etiology, with the severe salt-wasting form predominating. This overrepresentation of severe classic forms is a common recruitment bias in hospital-based series, as mild or non-classic forms are less likely to be referred to a tertiary pediatric endocrinology unit [10]. Hormonally, this condition is characterized by markedly elevated 17-OHP levels, low cortisol, and, in salt-wasting forms, decreased aldosterone with elevated plasma renin activity. Molecular analysis in our cohort revealed large CYP21A2 deletions and the Q318X mutation. According to the Tunisian study by Ben Charfeddine et al., the most frequent point mutations were p.Q318X (26%), large deletions (22%), and p.V281L (12%) [5].

A notable feature of our series is the inclusion of three patients with rare enzymatic defects: two with POR deficiency and one with lipoid CAH due to a StAR defect. The diagnosis of POR deficiency, suggested by the triad of 46,XX DSD, a hormonal profile mimicking combined 21- and 17 α -hydroxylase deficiencies (elevated 17-OHP and pregnenolone with normal ACTH), and the absence of salt-

wasting, illustrates the complexity of CAH [11]. The StAR defect case, presenting with profound salt-wasting in a 46,XX female without virilization, is a classic but rare presentation of this most severe form of CAH, resulting from a global impairment of steroidogenesis [2]. The hormonal profile in this patient was characteristic, showing very low levels of cortisol, aldosterone, DOC, pregnenolone, 17-OHP, DHEA, and 11-deoxycortisol, with elevated ACTH, reflecting the complete block in adrenal steroid synthesis. Plasma renin activity may be normal or only mildly elevated, particularly in early stages or partially compensated forms, and should therefore be interpreted in conjunction with electrolyte balance [12,13]. The presence of these rare variants in a small cohort underscores the genetic heterogeneity of CAH and the importance of advanced hormonal profiling to guide diagnosis when molecular resources are limited.

Prenatal diagnosis is indicated for families with an index case of 21-hydroxylase or 11 β -hydroxylase deficiency. It allows for anticipation of neonatal management and maternal dexamethasone treatment to reduce fetal hyperandrogenism and prevent virilization in female fetuses [14]. In our series, prenatal diagnosis was achieved in one case through identification of a homozygous CYP21A2 mutation. The absence of sexual differentiation anomalies at birth is consistent with published data.

Systematic neonatal screening for 21-hydroxylase deficiency, implemented in over 50 countries, allows early detection of severe forms before the onset of salt-wasting adrenal crises, as well as non-classic forms, thereby reducing morbidity and mortality [8].

The therapeutic management of our patients adhered to international consensus, with hydrocortisone, fludrocortisone, and sodium supplementation constituting the mainstay of treatment for all cases [7,14]. The occurrence of adrenal crises in three patients exclusively triggered by common infections highlights a persistent risk even under replacement therapy. This aligns with recent data identifying intercurrent illnesses as the primary trigger for acute decompensations and reinforces the critical need for proactive "sick-day rules" education for families [11].

Monitoring relies on clinical assessment (growth, pubertal development, hydration status, signs of glucocorticoid excess, and hyperandrogenism), hormonal evaluation, urinary electrolytes, and bone age assessment [14]. Literature data suggest that, under treatment, final height may be reduced (due to both corticosteroid therapy and hyperandrogenism), whereas pubertal development is generally unaffected [10]. This underscores the importance of good treatment adherence. In our series, only one patient exhibited accelerated growth with precocious puberty.

CONCLUSION

Our study shows that CAH in Tunisian children is associated with high consanguinity and both common (21-hydroxylase) and rare enzymatic defects (POR, StAR). Early neonatal

screening is crucial in countries without a national program to prevent adrenal crises. Molecular testing is essential for atypical forms, and multidisciplinary follow-up ensures optimal growth, pubertal development, and quality of life.

Patient and family education on treatment adherence and "sick-day rules" remains key to preventing crises.

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