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Diagnosis and Timely Treatment of Salt-Wasting Congenital Adrenal Hyperplasia-Case Report and Literature Review

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Abstract: ***Congenital adrenal hyperplasia (CAH) encompasses autosomal recessive disorders marked by cortisol biosynthesis defects, often leading to androgen excess and adrenal crisis. The classical form, primarily caused by 21-hydroxylase deficiency, constitutes the majority of cases. This report presents a three-week-old female with ambiguous genitalia and electrolyte imbalances, ultimately diagnosed with the salt-wasting form of CAH. Clinical features, diagnostic measures, therapeutic strategies, and prognosis are discussed in light of current literature, emphasizing the necessity of early detection and multidisciplinary care in such life-threatening endocrine conditions.***

Keywords: congenital adrenal hyperplasia, 21-hydroxylase deficiency, ambiguous genitalia, adrenal insufficiency, pediatric

1. Introduction

Congenital adrenal hyperplasia (CAH) refers to a group of inherited steroidogenesis disorders characterized by mutations affecting enzymes involved in the synthesis of cortisol and, in some cases, aldosterone. The fundamental pathophysiological consequence is cortisol deficiency, with insufficient negative feedback on the pituitary gland, which produces an increased secretion of adrenocorticotropic hormone (ACTH) and excessive stimulation of the adrenal cortex, with hyperplasia and increased androgen synthesis (1,2). Ninety-five percent of cases are due to mutations in the CYP21A2 gene, which encodes the enzyme 21-hydroxylase (3). Allelic heterogeneity determines a broad phenotypic spectrum ranging from the classic salt-wasting form, which constitutes a life-threatening neonatal emergency, to non-classical forms, which manifest in late childhood, adolescence, or adulthood with symptoms of mild hyperandrogenism (4).

The global incidence of classic CAH is estimated between 1:10,000 and 1:15,000 live births, although in certain populations it reaches up to 1:5,000 (5). Its distribution is variable and depends on genetic and geographic factors, being more prevalent in populations of European origin and less common in African and Asian populations. The non-classical form can have a prevalence of 1:1000, making it one of the most common endocrinopathies (6).

Clinically, classic CAH is divided into two main phenotypes:

- Salt-wasting form (75% of cases): characterized by primary adrenal insufficiency with hyponatremia, hyperkalemia, dehydration, and risk of hypovolemic shock in the first weeks of life.
- Simple virilizing form (25%): with sufficient aldosterone production to prevent salt-wasting crises, but with progressive virilization in girls and signs of hyperandrogenism in both sexes (7).

Non-classical forms, formerly called Late Onset, are usually diagnosed later and present with hirsutism, severe acne, menstrual irregularities, or infertility, which leads to differential diagnoses with polycystic ovary syndrome. They may even present with pubertal developmental variants such as precocious puberty (8).

Early diagnosis is crucial. The discovery of ambiguous genitalia at birth in girls should immediately lead to suspicion of CAH, whereas in boys, whose genitalia may appear normal, the first manifestation can be a potentially fatal adrenal crisis in the first weeks of life (9). 17-hydroxyprogesterone (17-OHP) measurement is the cornerstone of diagnosis, and its implementation in neonatal screening programs has allowed for the detection of presymptomatic cases, significantly reducing mortality (10,11).

Treatment for CAH has the following fundamental objectives:

- Replacing deficient hormones (cortisol and, in severe cases, mineralocorticoids).
- Preventing adrenal crisis and metabolic complications.
- Suppressing excessive androgen production to allow for adequate growth and pubertal development.
- Providing comprehensive long-term support that includes endocrinological, surgical, reproductive, and psychosocial aspects (12).

In recent decades, therapeutic advances have transformed the approach to this condition. The development of pediatric and modified-release liquid hydrocortisone formulations, as well as research into gene therapy and gene editing, open up prospects for a more physiological and possibly curative approach in the future (13). Likewise, the debate over early genital surgery in 46, XX patients reflects the ethical evolution in current medicine, which recognizes the importance of informed consent and patient autonomy (14).

This report describes the case of an infant with classic salt-wasting CAH, diagnosed based on ambiguous genitalia and electrolyte imbalance in the first weeks of life. The objective is to highlight the importance of early diagnosis and treatment of these patients, in addition to expanding the multidisciplinary approach with other specialties. We complement this with an updated review of the literature.

2. Methodological Design

The methodology for this case report consists of a comprehensive review of the clinical history of a neonatal patient diagnosed with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, a salt-wasting form, combined with a review of relevant literature in databases such as PubMed, Medline, Scopus, SciELO, and Embase. References were selected for clinical relevance, timeliness (within the last 10 years), and relevance to pediatrics.

3. Case Report

Female patient, full-term newborn (39 weeks), product of a controlled pregnancy, with no family history of consanguinity or endocrine disorders.

At birth, the patient's weight was 3200 g, length 50 cm. Ambiguous genitalia were noted, including partial fusion of the labia majora, clitoromegaly (Prader III), and no palpation of gonads in the labia or inguinal canal. The remainder of the initial physical examination was normal. Neonatal screening could not be performed because the test was not available in her country. At 20 days of age, the patient presented with recurrent vomiting, hypotonia, and poor weight gain. The emergency department evaluation revealed hyponatremia (Na: 124 mEq/L), hyperkalemia (K: 6.5 mEq/L), and metabolic acidosis.

The following complementary studies were performed:

Serum 17-hydroxyprogesterone (17-OHP): > 200 nmol/L (normal value < 6).
ACTH: 67 pg/ml
Basal cortisol: 1mcg/ml
Abdominal and pelvic ultrasound: absence of visible uterus, enlarged adrenal glands.
Karyotype: 46,XX.

Based on the clinical and laboratory findings, A diagnosis of classic salt-wasting CAH due to 21-hydroxylase deficiency was established.

Management was initiated with:

IV hydrocortisone (100 mg/m²/day in divided doses).
Oral fludrocortisone (0.1 mg/day).
Oral NaCl supplement (2 mEq/kg/day).

The patient progressed favorably, with electrolyte correction and clinical improvement. A subsequent evaluation by a multidisciplinary team (pediatric endocrinology, genetics, psychology, and pediatric surgery) was scheduled.

4. Discussion

CAH is one of the most relevant inborn errors of steroid metabolism in pediatrics. The case described represents a classic salt-wasting form, which, without early diagnosis, can progress to life-threatening adrenal crisis (1,2).

Pathophysiology and genotype-phenotype correlation

The CYP21A2 gene, located at 6p21.3, has more than 1,000 described mutations, with allelic heterogeneity that explains the clinical variability (3). Clinical severity depends on residual enzyme activity; see Table 1.

Table 1: Clinical severity of CAH

Residual 21-hydroxylase activity	Clinical form	Main manifestations
<1%	Salt loser	Adrenal crisis, ambiguous genitalia, hyponatremia/hyperkalemia
1–5%	Simple virilizing	Ambiguous genitalia, without salt loss
20–50%	Non-classical	Hirsutism, acne, menstrual irregularities, premature pubarche

Source: adapted from Merke & Auchus 2020 (4)

Differential Diagnosis

In newborns with ambiguous genitalia and fluid and electrolyte imbalances, warranting a broad differential diagnosis. Table 2 explains the most common clinical findings for each HPS subtype.

Table 2: Clinical and biochemical variability of HPS types

Entity	Clinical findings	Biochemical findings	Differentiation with HSC
Def. 21-hidroxlayse	XX genital ambiguity, salt loss	↑17-OHP, hyponatremia, hyperK	Diagnosis confirmed with 17-OHP > 200 nmol/L
Def. 11β-hydroxylase	Genital ambiguity XX	↑11-deoxycortisol, hypertension, hypokalemia	Neonatal hypertension difference of 21OH
Def. 3β-HSD	Genital ambiguity in both sexes	↑17-OH pregnenolone, low cortisol	Virilization in XY and XX
Androgen insensitivity	Female genitalia in XY	Normal or elevated testosterone, AMH present	XY karyotype with absence of uterus
Gonadal dysgenesis	Variable ambiguity	Hypergonadotrophic hypogonadism	Gonadoblastomas in some cases

Source: Speiser et al. 2018 (5)

Neonatal Screening

Universal screening based on 17-OHP levels has reduced neonatal mortality, although it has limitations. The introduction of mass spectrometry in second-line therapy improves specificity (7), see Table 3.

Table 3: Methods for newborn screening for HPS

Method	Advantage	Limitation
17-OHP immunoassay	Fast, low cost	Many false positives in premature babies
LC-MS/MS (mass spectrometry)	High specificity, multianalyte profile	Expensive, requires infrastructure

Source: Speiser et al. 2018Treatment

Classical treatment is based on hydrocortisone and fludrocortisone.

Hydrocortisone is a synthetic glucocorticoid with a structure and action similar to endogenous cortisol, used as replacement therapy for HPS. Its mechanism of action is based on binding to cytoplasmic glucocorticoid receptors, which, upon translocation to the nucleus, regulate the transcription of genes involved in metabolic homeostasis, immunomodulation, and regulation of the hypothalamic-pituitary-adrenal axis. In this context, hydrocortisone serves a dual purpose: it replaces cortisol deficiency—preventing hypoglycemia, cardiovascular disorders, and adrenal crises—and exerts negative feedback on pituitary ACTH secretion, thereby reducing chronic stimulation of the adrenal cortex and, consequently, the overproduction of androgens, which is primarily responsible for virilization and pubertal developmental disorders in these patients (4,15).

Fludrocortisone is a synthetic aldosterone analogue that acts primarily on mineralocorticoid receptors in the distal convoluted tubule and renal collecting duct, promoting sodium and water reabsorption and the excretion of potassium and hydrogen ions, thereby correcting the hyponatremia, hyperkalemia, and metabolic acidosis characteristic of salt-wasting forms of congenital adrenal hyperplasia. In this way, it contributes to the expansion of extracellular volume, stabilizes blood pressure, and reduces hyperactivity of the renin-angiotensin system, constituting a fundamental pillar of replacement therapy in combination with glucocorticoids to also cover concomitant cortisol deficiency (4,5,6).

Table 4: shows the advantages, limitations, and current status of the most commonly used drugs in HPS.

Therapeutic strategy	Advantages	Limitations
Standard oral hydrocortisone	Affordable, known	Cortisol peaks and valleys, risk of overdose
Liquid hydrocortisone	Precise doses in infants	High cost
Modified-release hydrocortisone	Mimicking the circadian rhythm	Not available in all countries
Adjuvant antiandrogens	Better virilization control	Limited pediatric experience
Gene therapy	Healing potential	In research, ethical risks

Table 4: Drugs for managing HPS. Source: Speiser et al. 2018 (5), Turcu & Auchus 2015 (8), Merke & Auchus 2020 (4)

With the advancement of medicine and improved quality of life (physical and psychological), early surgery for ambiguous genitalia in 46, XX girls has gained popularity; however, it remains a matter of debate. Although historically it was performed in the first years of life, today it is recommended to individualize and, in many cases, defer the decision until the patient can actively participate (9,10). Prognosis and Follow-up

Despite advances, CAH remains associated with long-term complications:

- Growth and final height: Overexposure to glucocorticoids compromises adult height (11).
- Central precocious puberty: common due to chronic androgen exposure.
- Fertility: in women, ovulatory dysfunction and polycystic ovary syndrome; in men, testicular adrenal remnant tumors (TART) (12).
- Mental health and quality of life: increased rates of depression and anxiety compared to the general population (13,15).

5. Conclusions

CAH is a complex and potentially life-threatening endocrine disorder if not diagnosed and treated promptly. The case presented illustrates the importance of early recognition of clinical signs and a comprehensive interdisciplinary approach. Universal neonatal screening represents the best strategy for reducing complications and mortality.

6. Future Scope

Our case of CAH seeks to analyze the complexity of this disorder in the neonatal period, the outcome of which is often fatal. Therefore, it is necessary to understand it and know how to implement a targeted care protocol in all hospitals that treat this age group. The scientific community and various medical teams should educate themselves on the importance of prolonging the lives of patients with this type of disorder.

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