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An Atypical Presentation of 11β-Hydroxylase Deficiency: A Family Case Report /Literature Review

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Abstract:
Introduction: Congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders of cortisol biosynthesis. Enzyme deficiencies lead to chronic adrenal overstimulation and accumulation of steroid precursors. The most common form is 21-hydroxylase deficiency, whereas 11β-hydroxylase deficiency is rare, affecting approximately 1 in 100,000 live births.
Case report: We report a Moroccan family in which both parents carried the non-classic form of 11β-hydroxylase deficiency. The mother presented with moderate hirsutism, while the father was asymptomatic. The condition was first identified following the birth of their second daughter, who presented with a disorder of sex development (DSD) adreneal insufficiency without hypertension.
The genetic study revealed a CYP11β1 mutation resulting in an 11β hydroxylase block in its classic virilising form. Despite genetic counseling, six subsequent pregnancies were pursued with two others affected cases
Management: The mother was treated with hydrocortisone and the girls with hydrocortisone, and feminizing surgery
Conclusion: There is considerable heterogeneity in the clinical presentation of patients with 11β-hydroxylase deficiency. Early diagnosis and treatment are essential to prevent complications and improve long-term outcomes.

Keywords: Congenital adrenal hyperplasia, 11β-hydroxylase deficiency, CYP11β1 mutation

1. INTRODUCTION

Congenital adrenal hyperplasia is a group of autosomal recessive disorders leading to multiple complex hormonal imbalances caused by various enzyme deficiencies in the adrenal steroidogenic pathway. The most frequent form is 21-hydroxylase deficiency [1], whereas 11β-hydroxylase deficiency is rare, accounting for only about 5% of cases and affecting approximately 1 in 100,000 live births. It is particularly prevalent in North Africa and the Middle East [2]. Clinically, it is characterized by hyperandrogenism and hypertension in association with adrenal insufficiency. Diagnosis is suggested by

elevated 11-deoxycortisol and 11-deoxycorticosterone (DOC) levels and confirmed by the identification of CYP11B1 mutations. Management relies on hydrocortisone supplementation, often combined with antihypertensive therapy, while feminizing surgery is reserved for girls with the classic virilizing form. Genetic counseling remains the cornerstone of prevention [1]

We report a Moroccan family in which both parents carried the non-classic form of 11β-hydroxylase deficiency.

2. Family observation

We report the case of a 31-year-old Moroccan woman, born of a non-consanguineous marriage, married and mother of four daughters at the time of initial presentation. She was referred to our institution by a pediatrician following the discovery of a disorder of sex development (DSD) at the birth of her second daughter. The patient had no history of diabetes, hypertension, or any other medical or surgical condition. All pregnancies are detailed in (Table 1).

Clinical examination of the mother after this delivery of the second girl showed normal blood pressure, normal heart rate, and normal body habitus with mild hirsutism. Secondary sexual characteristics were complete (Tanner stage V breasts). External genitalia were normal, without clitoromegaly. There were no frontal bossing, voice deepening, or DSD features. Laboratory investigations revealed normal serum sodium, potassium, and glucose, but adrenal insufficiency was demonstrated (baseline 8 a.m. cortisol 5.9 µg/dl, rising to 12.5 µg/dl one hour after Synacthen; 17-hydroxyprogesterone at 0.82 ng/ml one-hour post-stimulation) Hydrocortisone 15 mg/day was initiated, given the absence of high blood pressure 21β-hydroxylase deficiency was first suspected.

Subsequent genetic analysis of the second daughter performed at our university hospital excluded CYP21A1 mutations and instead revealed a missense mutation in exon 6 (54%) and a deletion in exon 8 (40%), consistent with compound heterozygous pathogenic variants in CYP11B1, confirming classic virilizing 11β-hydroxylase deficiency. Further genetic testing of the parents identified heterozygous mutations in CYP11B1 on chromosome 8, consistent with non-classic 11β-hydroxylase deficiency. Genetic counseling was provided, emphasizing the autosomal recessive inheritance and the importance of prenatal diagnosis. Despite this, the patient subsequently conceived four more times.

The sixth pregnancy was first assessed at 8 weeks of amenorrhea. SRY testing at 8 and 12 weeks was negative. Prenatal dexamethasone was started after informed consent. At 27 weeks, maternal oral glucose tolerance test was normal. Chorionic villus sampling was proposed but could not be performed.

Table 1: monitoring of all pregnancies and postpartum follow-up

Pregnancy	First	Second	Third	Fourth	Fifth	Sixth
Consultation time	Not monitored	Second trimester	Not monitored	11 weeks	6 weeks	5 weeks
Sex	Girl	Girl	Girl	Girl	Girl	Girl
Prenatal dexamethasone	No	No	Yes	Yes	Yes	Yes

DSD	No	Yes Prader IV	Yes Prader III	Yes Prader V	No	No
Salt wasting syndrome	No	Yes	Yes	Yes	No	No
Post natal treatement	No	Hydrocortisone +feminizing surgery	Hydrocortisone +feminizing surgery	Hydrocortisone +feminizing surgery	No	No
Genetic result	Normal (retrospective)	missense mutation in exon 6 (54%) and deletion in exon 8 (40%), consistent with compound heterozygous pathogenic variants in CYP11B1, confirming classic virilizing 11β-hydroxylase deficiency	CYP11β1 mutation resulting in an 11β hydroxylase block in its classic virilising form	Not done (died before)	Normal	On going findings
Age now (years)	15	11	7	Died	4	1

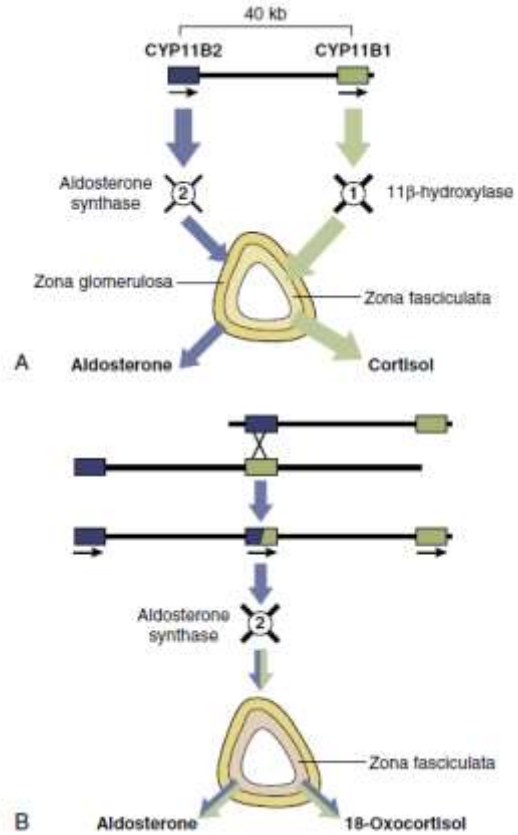
3. Discussion

Since the early 1950s, it has been recognized that the rare patients with congenital adrenal hyperplasia (CAH) who developed hypertension, rather than mineralocorticoid deficiency, were usually affected by 11β-hydroxylase deficiency. This represents the second most common form of CAH, accounting for approximately 5% of cases. Rösler A et al reported that 11β-hydroxylase deficiency is relatively frequent among Jews of North African origin. Over a 39-year period, 38 affected individuals from 25 families were diagnosed; 19 of these families were Moroccan, and in two others, one parent was Moroccan, accounting for 80% of all cases. Demographic studies revealed that most grandparents originated from the Atlas Mountains region. Rösler A et al reported the overall incidence is estimated between 1 in 30,000 and 1 in 40,000 live births, whereas among Moroccan Jews it is considerably higher, ranging from 1 in 5,000 to 1

in 7,000 [3].

This disorder is inherited in an autosomal recessive manner. Two genes encoding 11β-hydroxylase enzymes are located on the long arm of chromosome 8 and share more than 90% sequence homology. CYP11B1 is responsible for 11β-hydroxylase deficiency, whereas CYP11B2 encodes aldosterone synthase. Mutations in CYP11B1 are distributed across the coding region, with clusters in exons 2, 6, 7, and 8. Most known mutations completely abolish enzyme activity, yet the clinical phenotype may vary significantly (Figure 1).

Figure 1: mutations responsible for the 11 B hydroxylase block [2]



Clinically, approximately two-thirds of patients with the severe "classic" form of 11β-hydroxylase deficiency present with arterial hypertension, usually mild to moderate in intensity, which often appears in early childhood [1]. Hypertension is not a constant feature of the non-classic form [2]. What makes our case even more unusual is the absence of hypertension in the entire family, despite the classic deficit in the offspring, and the association of the non-classical form in both parents and the classical form in three daughters.

About one-third of patients may develop left ventricular hypertrophy and/or retinopathy, and in rare cases death may occur from cerebrovascular accidents or hypertensive nephropathy requiring renal transplantation or pulmonary edema. That is the case of a 5-year-old Moroccan boy diagnosed with congenital adrenal hyperplasia due to 11-hydroxylase deficiency, revealed by disorders of sex development (DSD) and acute pulmonary edema due to severe hypertension [4]

In affected female newborns with the classic form (as in the three daughters of our patient), disorders of sex development (DSD) range from mild clitoral enlargement to severe clitoromegaly with penile urethra and fused labioscrotal folds (Prader staging). The degree of virilization correlates with the proportion of

mutated alleles.

It would be reasonable to assume that the severity of enzymatic deficiency directly correlates with clinical manifestations. If so, biochemical abnormalities (accumulated steroid precursors), cardiovascular complications (hypertension, hypokalemia), and virilization should correlate. However, Ariel Rosler et al. [3] reported a complete dissociation between these parameters. Normotensive patients (with or without elevated 11-deoxycorticosterone) were sometimes severely virilized, as in the three daughters of our family, while others with marked hypertension showed only modest virilization despite relatively low mineralocorticoid excess. This variability may be explained by the specific location of the mutation: CYP11B2 mutations impair aldosterone synthase, leading to higher accumulation of DOC and variable hypertension, whereas CYP11B1 mutations more typically result in cortisol deficiency [2] (Figure 1).

In non-classic forms (as in both parents), clinical features are usually mild hyperandrogenism such as accelerated growth velocity with possible growth retardation, premature puberty, hirsutism, acne, menstrual irregularities (primary or secondary amenorrhea, oligomenorrhea) in adolescent girls, and infertility in women.

The distinctive feature of our case lies in its rich clinical presentation, which differs from one family member to another, with varying stages of Prader and the absence of hypertension—an inconsistent feature, as explained above—and in the incidental discovery of the disease at the birth of the second daughter with DSD, while the mother had only mild hirsutism and had never sought medical consultation. The mother's normal 17-OHP level can be explained by the downstream location of the enzymatic block (unlike 21-hydroxylase deficiency) and by the non-classic form (Table 1).

Because of the severity of the clinical expression, the significant physical and psychological burden in affected girls with DSD, and the high mortality in untreated individuals, genetic counseling is essential. In autosomal recessive inheritance, if both parents are affected by non-classic 11β-hydroxylase deficiency, each pregnancy carries a 25% risk of classic disease. Given a 50% chance of a female fetus, there is therefore a 1 in 8 risk of having a female infant with DSD. In addition, 50% of offspring may inherit the non-classic form and transmit the disease to their descendants, while 25% will be unaffected. In our family, both parents carried the non-classic form: they had one daughter with the non-classic form, three with the classic form, one unaffected daughter, and the mother is currently pregnant with another girl.

Prenatal diagnosis aims to identify fetuses with the classic form. It is indicated in couples with a child affected by the classic form or at risk because both parents are carriers. Fetal sex determination can be performed at 6 weeks of gestation using SRY analysis in maternal blood, with confirmation at 11 weeks; if still negative, chorionic villus sampling is indicated.

Maternal treatment with dexamethasone (20 µg/kg/day in three divided doses, maximum 1.5 mg/day) aims to suppress ACTH and thereby reduce or prevent virilization in affected female fetuses. Unlike hydrocortisone, dexamethasone crosses the placenta because it is not inactivated by placental 11β-hydroxysteroid dehydrogenase. Despite the use of dexamethasone during the third and fourth pregnancies, the girls were born with DSD ➔ Since fetal adrenal activity begins between the 6th and 8th weeks, treatment must be started before 7 weeks of gestation (9 weeks of amenorrhea) to be effective, and continued until the fetus is confirmed to be male (by karyotype or FISH) or genetic analysis excludes disease in a female fetus, otherwise continued until delivery.

However, prenatal dexamethasone therapy does not have formal approval due to limited knowledge of long-term effects. Maternal risks include weight gain, striae, edema, gastrointestinal symptoms, mood changes, and in some cases hypertension, gestational diabetes, and Cushingoid features. Potential fetal

risks include teratogenicity, altered birthweight, possible long-term cognitive impairment [5], structural brain alterations with epigenetic changes [6], and increased aortic stiffness [7].

Parents must therefore be fully informed of the benefits and risks of prenatal dexamethasone therapy and be involved in the decision-making process regarding its use.

In our family, the mother was informed of all the risks associated with dexamethasone and consented to its use during her last four pregnancies.

Preimplantation genetic diagnosis (PGD) remains a good alternative to prenatal treatment with dexamethasone in some countries, it requires an in vitro fertilization approach and enables implantation only of embryos without the specific genetic disorder. It may present ethical challenges. The preferred approach to obtain DNA for PGD is a biopsy at day 5-6 from the trophectoderm of the blastocyst when it comprises about 120 cells.The disadvantage for autosomal recessive disorders is that only the oocyte is assessed and the paternal allele is not included in the assessment [1].

Table 1: Comparative table between the different epidemiological, clinical, paraclinical and therapeutic parameters of 21 and 11 B hydroxylase block (abbreviation: HTA: arterial hypertension, DOC: 11 deoxycorticosterone, 17 OHP: 17 hydroxy progesterone, FC: classic form, FNC: non-classic form; OGE: external genital organs).

		21-hydroxylase deficiency	11β-hydroxylase deficiency
Incidence		FC: 1/10000 to 1/20000	FC: 1/100000
		FNC : 1/200 to 1/1000	FNC : unknown
Clinic	Sexual differentiation disorder	FC : hyperandrogenism in girls	FC : same
		FNC : no	FNC : same
	Post-natal virilisation	FC : Major hyperandrogenism in newborns and girls with retarded growth and weight and virilisation of the OGE (Prader score). In boys: retarded growth and weight	FC : same
		FNC : minor hyperandrogenism in adolescents and women: hirsutism, cycle disorder, amenorrhoea, acne, RSP In boys: RSP	FNC : same
	Salt wasting syndrom	FC : yes	FC : no
		FNC : no	FNC : no
	Adrenal insufficiency	FC : yes	FC : yes
		FNC : yes, somtimes no	FNC : same

	HTA	FC : no	FC : 2/3 yes, 1/3 no
		FNC : no	FNC : non constant
	Fertility	FC : difficult according to surgery feminisation and Prader rating	FC : same
		FNC : possible	FNC : possible
Biology	DOC	↙	↗↗
	11 desoxycortisol	↙	↗
	Potassium	↗	↙
	17 OHP	FC : ↗↗ > 50 µg/dl	FC and FNC ↗ > 10 µg/dl
		FNC : ↗ > 10 µg/dl	sometimes normal
	Cortisol	↙	↙
	Corticosteron	↙	↙
	Renin	↗	↙
Genetics	Autosomal recessive diseases	Chromosome 6 mutations in CYP21A2	Mutations on chromosome 8 of CYP11B1/ CYP11B2
Treatement		FC : feminisation surgery	FC : same
		FNC : hydrocortisone	FNC : hydrocortisone sometimes antihypertensive

The management of 11β-hydroxylase deficiency requires a multidisciplinary approach. Treatment primarily relies on hydrocortisone (10–20 mg/m²/day), which addresses adrenal insufficiency, controls hyperandrogenism, prevents hypertension, and may improve fertility.
In cases of hypertension resistant to hormonal therapy, antihypertensive treatment may be indicated (nicardipine, spironolactone, central-acting agents, or even beta-blockers), along with correction of hypokalemia if necessary.
Surgical management is indicated for girls with the classic form presenting virilization of external genitalia, ideally within the first month of life. Psychological support is also essential to mitigate the psychosocial and psychosexual impact of the condition.
Patients with CAH reported lower quality of life, particularly in the pain/discomfort and anxiety/depression domains. Based on this, it's recommended the early involvement of psychologists in a multidisciplinary team approach, pre-marital screening, and the implementation of awareness programs for people diagnosed with CAH in communities with high consanguineous mating [8].

4. Conclusion

Disorders of steroidogenesis represent a group of rare diseases. There is considerable heterogeneity in the clinical presentation of patients with 11β-hydroxylase deficiency. It remains difficult to discuss, especially in non-classical forms, in the absence of high blood pressure and sexual differentiation disorders. Early diagnosis and treatment are essential to prevent complications and improve long-term outcomes. Comprehensive genetic counseling remains the most effective strategy for preventing classic forms associated with significant psychological impact, and in the most severe cases, mortality

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