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CASE REPORT

Two rare forms of congenital adrenal hyperplasia, 11β hydroxylase deficiency and 17-hydroxylase/17,20-lyase deficiency, presenting with novel mutations

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Abstract

Background Congenital adrenal hyperplasia (CAH) is a rare autosomal recessive disorder caused by deficiency of various enzymes responsible for adrenal steroidogenesis. 11-Beta-hydroxylase deficiency (11βOHD) and 17-hydroxylase/17,20-lyase deficiency (17OHD) are rare causes of CAH.

Methods/results We hereby present a 65-year-old man with 11βOHD and a 33-year-old woman with 17OHD. The man with 11βOHD presented with peripheral precocious puberty and hypertension at age 15 years, fathered two children but developed complications of chronic glucocorticoid therapy on long-term follow-up. Interestingly, his younger sister had been diagnosed with the same condition at age 19 and had later given birth to four children while on glucocorticoids. Exome sequencing of the *CYP11B1* gene detected the previously reported pathogenic mutation T318T (c.954G > A [p.Thr318Thr]) on one of the alleles and a novel mutation, R123G (c.367C > G [p.Arg123Gly]), on the other in a highly conserved region of the *CYP11B1* gene. The woman with 17OHD presented with severe hypokalemia at age 22 years against a background of primary amenorrhea and lack of development of secondary sexual characteristics. She was heterozygous for a previously recognized mutation, R125Q (c.374G > A [p.Arg125Gln]), and a novel single base-pair deletion, G337fs (c.1010delG [p.Gly337Valfs*82]), which creates a frameshift with a new stop codon in the last exon of the gene, making it a likely pathogenic variant.

Conclusion Recognition of novel mutations is clinically significant and will contribute to the understanding of the phenotype-genotype relationship of these rare disorders in the future. It also highlights successful fertility outcomes in 11βOHD which have not been well documented in the literature so far.

Keywords 11 Beta-hydroxylase deficiency · 17-Hydroxylase/17,20-lyase deficiency · Congenital adrenal hyperplasia · Fertility · Long-term outcome

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Introduction

Congenital adrenal hyperplasia is a rare autosomal recessive disorder. The genetic mutations lead to enzymatic defects and, hence, abnormal adrenal steroid biosynthesis [1, 2]. 21-Hydroxylase deficiency (21OHD) is the most common form of CAH, accounting for 90–99% of all cases, followed by 11β-hydroxylase deficiency (11βOHD), which is found in 0.2–8% of cases, while rare variants include 17α-hydroxylase/17,20-lyase deficiency (17OHD) and 3β-hydroxysteroid dehydrogenase deficiency [3–6].

11βOHD is caused by mutations in the *CYP11B1* gene located on chromosome 8q24.3 encoding for the 11β-

hydroxylase enzyme. The *CYP11B1* gene has nine exons which encode for 503 amino acids (OMIM#202010). Certain ethnic groups (such as Moroccan Jews) and geographical locations (Saudi Arabia and Turkey) have been found to have a higher incidence of 11βOHD [7].

Mutations in the *CYP17A1* gene affect the activity of 17α-hydroxylase and 17,20-lyase in the adrenal cortex. The *CYP17A1* gene is located on chromosome 10q24.32 and is responsible for 17-hydroxylase and 17,20-lyase activities (OMIM#202110). The gene consists of eight exons encoding for 508 amino acid protein [8]. Similar to 11βOHD, there appears to be a founder effect with 17OHD and hence a higher frequency of mutations has been reported in specific ethnic groups [9].

Unlike 21OHD, there is limited evidence to document any correlation between the disruptive impacts of genetic mutations on the level of activity of 11β-hydroxylase and 17α-hydroxylase/17,20-lyase enzymes. Moreover, data on fertility and long-term outcomes are very scarce. Hence, ongoing clinical studies are required to assess the genotype-phenotype correlation for 11βOHD and 17OHD and their long-term outcomes.

Here we describe the clinical phenotype, fertility, and long-term outcomes of a male (XY) with 11βOHD (and briefly his sister) and a female (XX) with 17OHD, both of whom were found to have a novel mutation each, with the aim of adding further knowledge to the currently existing literature on these rare disorders.

Case presentation

11β hydroxylase deficiency

A 65-year-old Caucasian male was referred to the Endocrine outpatient department. He was born of a non-consanguineous marriage and had frequent infections in early childhood. He went on to have early adrenarche and a pubertal growth spurt at the age of 5 years and reached his adult height (162 cm) by the age of 9 years. He was observed to have hypertension at age 15 years. He was diagnosed with classic 11βOHD in Chile at the age of 28 years, but the investigation results were not available. His younger sister had precocious pubarche, clitoromegaly, and hirsutism and was diagnosed at age 19 in Chile with 11βOHD. Later, after being on glucocorticoids, she had four daughters. Since diagnosis, the male had been on dexamethasone 0.5 mg once daily. The benefits of glucocorticoid replacement therapy included reasonable control of hypertension, no development of testicular adrenal rest tumor (TART) (testicular ultrasound at age 65 was normal), intact fertility (fathered 2 children), and no episodes of acute adrenal crises. On the other hand, he has developed complications of chronic steroid therapy including type 2 diabetes mellitus, obesity, obstructive sleep apnea, and hypogonadotropic hypogonadism.

His most recent investigations while on glucocorticoid replacement therapy are shown in Table 1. Genotype testing was requested to confirm the diagnosis and provide counseling to family members. *CYP11B1* genotyping demonstrated a heterozygous state for the previously recognized mutation, T318T (c.954G > A [p.Thr318Thr]), on exon 5 of the *CYP11B1* gene and a novel missense mutation, R123G (c.367C > G [p.Arg123Gly]), in a highly conserved region of the *CYP11B1* gene. He was advised to change the glucocorticoid regimen. It was suggested that the glucocorticoid regime be changed to manage his metabolic complications but declined.

17-hydroxylase/17,20-lyase deficiency

A 22-year-old female presented to the Emergency Department with acute febrile illness and severe hypokalemia (2.1 mmol/L). This was against the background of primary amenorrhea with lack of development of secondary sexual characteristics. She was born of a non-consanguineous marriage with both parents being of Caucasian origin. She had frequent fainting episodes as a child between 5 and 10 years of age but presented no major developmental or health concerns. There is no family history of delayed puberty or endocrine conditions.

At age 17 years, she was referred for assessment of primary gonadal failure with delayed bone age, elevated gonadotropins (FSH 15 U/L and LH 25 U/L) and low estradiol (< 100 pmol/L). Karyotype testing confirmed 46XX karyotype

Table 1 Biochemical parameters in a patient with 11β-hydroxylase deficiency while on long-term glucocorticoid supplementation given in an unphysiological manner (dexamethasone 0.5 mg once daily)

Plasma parameters	Result	Reference range
Sodium	143 mmol/L	135-145 mmol/L
Potassium	4.2 mmol/L	3.5–4.5 mmol/L
Aldosterone/renin ratio	5.0	0.0–7.0
Renin	74 mU/L	3–40 mU/L
17OHP	<0.1 nmol/L	1.3–8.5 nmol/L
Androstenedione	0.2 nmol/L	0.8–3.1 nmol/L
DHEAS	< 0.5 umol/L	< 7.5 umol/L
Testosterone	6.6 nmol/L	9–35 nmol/L
FSH	0.4 IU/L	1–12 IU/L
LH	0.0 IU/L	1–9 IU/L
ACTH	< 10 ng/L	10–50 ng/L
HbA1c	53 mmol/mol	27–42 mmol/mol

FSH, follicle stimulating hormone; *LH*, luteinizing hormone; *17OHP*, 17-hydroxyprogesterone; *DHEAS*, dehydroepiandrosterone sulfate; *HbA1c* glycosylated hemoglobin

with no chromosomal abnormality. Pelvic ultrasound confirmed a small infantile uterus with visible ovaries. She was started on a low-dose estrogen preparation with resultant irregular bleeding and minimal breast tissue development.

Due to her clinical presentation at age 22 years, the possibility of 17OHD was considered and was confirmed on blood (Table 2) and 24-h urine steroid profile. The 24-h urinary steroid profile showed significantly elevated tetrahydrocorticosterone and pregnanediol concentration with a low concentration of cortisol metabolites suggestive of 17OHD (Table 2). She was started on cortisone acetate 12.5 mg twice daily in addition to her low-dose estrogen. Her blood pressure was normal (120/85 mmHg).

At age 33 years, she presented to our clinic for ongoing management. She was observed to be hypertensive with resting blood pressure of 150/100 mmHg. She had previously trialed oral hormone replacement therapy and the oral contraceptive pill with resultant irregular periods which she subsequently self ceased. She had not been in any active relationship and has not conceived till now. *CYP17A1* gene testing was performed and demonstrated that she was heterozygous for a previously recognized mutation, R125Q [(c.374G > A [p.Arg125Gln)], and a novel single base-pair deletion, G337fs [c.1010delG (p.Gly337Valfs*82)], creating a frameshift with a new stop codon in the last exon of the gene. This was hypothesized as having resulted in a truncated protein with altered function and was classified as likely pathogenic. Genetic testing of her mother revealed that she was a carrier of the previously recognized variant, R125Q.

Due to ongoing symptoms of lethargy and low androgens, oral DHEA was scheduled to be commenced.

Table 2 Baseline biochemical parameters in a patient with 17α-hydroxylase deficiency

Plasma parameters	Result	Reference range
Sodium*	127 mmol/L	132–144 mmol/L
Potassium*	2.1 mmol/L	3.2–4.8 mmol/L
FSH*	15 U/L	> 20 U/L (perimenopausal)
LH*	25 U/L	> 20 U/L (perimenopausal)
Estradiol*	< 100 pmol/L	< 200 pmol/L (perimenopausal)
DHEAS*	< 0.5 umol/L	1.0–11.0 umol/L
Androstenedione*	0.3 nmol/L	3.0–10.0 nmol/L
Testosterone*	0.4 nmol/L	0.0–3.5 nmol/L
ACTH**	42.3 pmol/L	2.0–11.5 pmol/L
Aldosterone**	754 pmol/L	140–400 pmol/L
Plasma renin concentration**	11 mU/L	3.3–41 nmol/L
17OHP (baseline)* 17OHP (60 min post ACTH stimulation)	3.0 nmol/L 3.0 nmol/L	0.3–9.9 nmol/L
Cortisol (baseline)* Cortisol (60 min post ACTH stimulation)*	59 nmol/L 70 nmol/L	150–600 nmol/L
DOC (baseline)* DOC (60 min post ACTH stimulation)*	5.2 nmol/L 8.8 nmol/L	0.0–0.8 nmol/L
11-Deoxycortisol (baseline)* 11-Deoxycortisol (60 min post ACTH stimulation)*	1.1 nmol/L 1.1 nmol/L	0.35–6.1 nmol/L
24 h urine androsterone**	<0.6 umol/24 h	1.5–12.0
24 h urine pregnanediol**	7.6 umol/24 h	0.3–2.2 (postmenstrual) 0.6–3.8 (preovulatory) 6.0–19.0 (luteal phase max)
24 h TH-cortisone**	< 0.6 umol/24 h	2.5–12.0
24 h TH-cortisol**	<0.6 umol/24 h	0.7–6.0

The urine steroid profile also showed a significantly elevated concentration of tetrahydrocorticosterone and detectable concentration of 18-hydroxy-tetrahydrocorticosterone but the exact values and reference ranges were not given

FSH, follicle stimulating hormone; *LH*, luteinizing hormone; *17OHP*, 17-hydroxyprogesterone; *DHEAS*, dehydroepiandrosterone sulfate; *DOC*, deoxycorticosterone; *TH-cortisone*, tetrahydrocortisone; *TH-cortisol*, tetrahydrocortisol

*Not on cortisone acetate therapy

**On cortisone acetate therapy

Discussion

In this study, we report on novel mutations in a patient with 11βOHD and in a patient with17OHD. Moreover, we also report on normal fertility outcomes in the patient and his sister with 11βOHD which has rarely been described previously. In addition, the long-term outcomes generally seemed reasonable in all cases.

11βOHD results in elevated levels of steroid precursors, 11-deoxycortisol, and deoxycorticosterone (DOC), which are then shunted to synthesis of adrenal androgens (androstenedione and dehydroepiandrosterone) and resultant low plasma cortisol levels. Patients with 11βOHD present as classic or non-classic CAH. Clinical clues to raise suspicion for 11βOHD include hypokalemic hyporeninemic hypertension and hyperandrogenism [7].

There has been limited evidence until recently regarding genotype-phenotype relationships in patients with 11βOHD owing to the rarity of the disease and the wide variability in the clinical presentation [10]. A large international cohort study of 108 patients from 11 countries examined the clinical, genetic, and structural effects of *CYP11B1* mutations. They reported that patients presented with moderate to severe 11βOHD if found to be compound heterozygote or homozygote for one of the following missense or nonsense mutations: P49L, R141Q, W260X, G267S, L299P, T318M, T318R, A331V, Q356X, A368D, R374Q, V441G, G444D, G446V, and R448H. For example, R374W and R448H/C mutations which caused altered heme binding site were associated with high Prader scores (4/5), severe hypertension, and early skeletal maturation. Also, similar clinical features were noted in patients carrying L299P and G267S mutations which affect enzyme stability. On the other hand, the severity of clinical manifestations did not always correlate with the degree of structural disruption. For example, mutations such as T318M and G379S were associated with high Prader score and advanced bone age, respectively, but only mild hypertension [11]. The previously reported mutation, T318T, detected in our patient was the commonest mutation in both the heterozygous and homozygous state in a Turkish cohort study. The male patients presented with rapid growth, enlargement of penis, and hypertension which was well controlled with steroid treatment, while female patients presented with extreme virilization and hypertension [10]. Preliminary in vitro expression studies of the T318T mutation resulted in undetectable mRNA, supporting the classification as a likely pathogenic variant [12].

Our case had a history of early adrenarche, onset of hypertension at age 15 years, and short adult stature. All these clinical findings have been widely reported with classical 11βOHD. Patients with the non-classical form are mostly normotensive or have high normal blood pressure at the time of diagnosis [13–15]. Moreover, the mutation analysis showed the known pathogenic mutation T318T on one allele and a novel missense mutation R123G in a highly conserved region of the *CYP11B1* gene. Taken together, this suggests a classical phenotype of 11βOHD.

Our case also demonstrates intact fertility in the patient and his sister with 11βOHD. There are only two reports of successful pregnancy in females with 11βOHD [16, 17], while there is very limited information regarding male fertility outcomes in the current literature. Two small case series, including XX males, document moderate to severe azoospermia which points to reduced fertility in this group of patients. Issues concerning fertility in CAH have usually been attributed to TARTs [1, 18, 19]. TARTs are considered to be very common in CAH and the incidence appears to increase with age [1, 18]. Most males with 11βOHD who have had a testicular ultrasound performed seem to be affected by TARTs [7]. Interestingly, our male with 11βOHD did not show any signs of TARTs, in spite of his age, which may explain his good fertility outcome. There are no reports of successful pregnancy outcomes with a father with 11βOHD. However, the lack of fertility success in the literature could be due to under-reporting of cases.

Treatment consists of adequate glucocorticoid replacement to normalize blood pressure and features of hyperandrogenism. Ongoing management of 11βOHD requires close monitoring for development of complications of CAH as well as treatment related complications [7]. In our case the low androgens, ACTH, and gonadotrophin levels together with elevated HbA1c indicated over-replacement with glucocorticoids. The aldosterone to renin ratio was normal, while renin was elevated, which is not a typical finding of 11βOHD. However, over-replacement with glucocorticoids may result in elevated renin levels. The aldosterone synthesis is suppressed in untreated 11βOHD due to down-regulation of the CYP11B2 enzyme in zona glomerulosa but treatment with glucocorticoids will result in normalization of DOC levels and hence normalization of the renin-angiotensin-aldosterone axis [7].

The human 17α hydroxylase enzyme catalyzes two enzymatic reactions, namely 17α hydroxylation and 17,20-lyase reaction. It is responsible for 17α-hydroxylation of pregnenolone and progesterone as well as conversion of 17-hydroxypregnenolone to DHEA and to a lesser extent 17-hydroxyprogesterone to androstenedione [8]. This results in elevated corticosterone, DOC, and progesterone with concomitant low levels of cortisol, 11-deoxycortisol, DHEA, and 17-hydroxyprogesterone. The 17,20-lyase activity of CYP17A1 and presence of 17–20 hydroxysteroid substrates are essential for adrenal and gonadal synthesis of androgens and estrogen. The patients frequently present at later age with hypertension, hypokalemia, and sexual infantilism (male pseudo hermaphroditism in 46XY or primary amenorrhea in 46XX). Amenorrhea results from estradiol deficiency [20].

Lack of virilization is a salient feature differentiating 17OHD from other forms of CAH. Another interesting feature of 17OHD is lack of clinical features of cortisol deficiency despite low serum cortisol levels. This is explained by the accumulation of corticosterone which substitutes cortisol and hence these patients rarely present with adrenal crises [20].

The incidence of 17OHD is unknown but has been estimated to be around 1:50,000. [21] However, this is probably an over-estimation, since two large national cohorts with 203 and 612 CAH patients, respectively, did not find any cases of 17OHD [5, 6]. The *CYP17A1* gene is located on chromosome 10q24.32 and is responsible for 17α-hydroxylase and 17,20-lyase activities. The gene consists of 8 exons encoding for 508 amino acid protein [8]. A 57 kDa polypeptide is translated from the 1.6kB coding region of the *CYP17A1* gene. The protein resides in the smooth endoplasmic reticulum and along with P450-oxidoreductase co-factor catalyzes 17α-hydroxylase and 17,20-lyase reactions. Over 100 mutations in *CYP17A1* have been reported to date for combined 17α-hydroxylase/17,20-lyase deficiency [20]. Mutational "hot spots" have been identified in certain ethnic groups suggesting a founder effect [9]. These groups include the Japanese (phenylalanine 53 deletion) [22], the Chinese (Y329 frameshift and D487-F489 deletions) [23], the Spanish-Portuguese in Brazil (R362C and W406R) [21], the Canadian Mennonites, and Dutch Frieslanders (duplication of four nucleotides at amino acid 478) [24]. The mutation R125Q found in our patient has been demonstrated to completely disrupt 17α hydroxylase and 17,20-lyase activity in an in vitro expression study. The patient was a compound heterozygote for R125Q and R416H and was diagnosed at age 15 years with hypertension, hypokalemia, and delayed puberty [25].

Treatment consists of glucocorticoid replacement at the lowest possible dose with the aim of reducing DOC production and consequently resulting in better blood pressure and potassium control. Mineralocorticoid receptor antagonists such as spironolactone and eplerenone are ideal agents to control hypertension. Appropriate sex steroid replacement regimes, i.e., estrogen with progestin in 46XX/46XY phenotypic females and testosterone replacement in 46XY phenotypic males, are required during adolescence for pubertal induction and during adult life to avoid metabolic complications of hypogonadism [9, 20]. Bianchi et al. recently reported the first case of successful singleton live birth with IVF in a woman with 17OHD, using her own oocytes, but there is no report of successful live birth without IVF [26]. Thus, the fertility potential is very low and our case did not have any children.

In conclusion, we report two novel mutations causing 11βOHD and 17OHD along with the clinical, biochemical, and genetic findings in each of these cases. We also report successful fertility outcomes in both a male and female patient from the same family with 11βOHD. Our clinical reports may help to identify genotype-phenotype correlations in the future.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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