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CASE REPORT

A rare cause of congenital adrenal hyperplasia: Antley-Bixler syndrome due to POR deficiency

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ABSTRACT

Cytochrome P450 oxidoreductase (POR) deficiency is a recently discovered new variant of congenital adrenal hyperplasia. Distinctive features of POR deficiency are the presence of disorders of sexual development in both sexes, glucocorticoid deficiency and skeletal malformations similar to those observed in the Antley-Bixler syndrome.

KEYWORDS

Antley-Bixler syndrome, congenital adrenal hyperplasia, POR deficiency

INTRODUCTION

Congenital adrenal hyperplasia (CAH) comprises a group of inherited autosomal recessive disorders characterised by a defective cortisol biosynthesis, compensatory increases in corticotrophin secretion and adrenocortical hyperplasia. Cardinal symptoms of CAH are adrenal insufficiency, disorders of sexual development (DSD), short stature and infertility.[1] The most frequent cause of CAH is 21-hydroxylase (CYP21A2) deficiency, which is responsible for about 95% of cases (*figure 1*).[2] Other causes of CAH are deficiency of 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2), 17α-hydroxylase (CYP17A1) or 11β-hydroxylase (CYP11B1). Furthermore, two distinctive CAH variants are not caused by defective synthesis of a steroidogenic enzyme, but result from decreased enzyme activity due to the deficiency of an important co-factor. Lipoid CAH is caused by loss-of-function mutations in the gene encoding steroidogenic acute regulatory protein (StAR), which facilitates cholesterol transport from the outer to the inner mitochondrial membrane, thus providing the substrate for steroid biosynthesis.[3] More recently, cytochrome P450 oxidoreductase (POR) deficiency has been identified as a new CAH variant.[4,5]

CASE REPORT

A 19-year-old female was referred for evaluation of irregular menses. As a neonate, she had been examined at the Department of Clinical Genetics for several dysmorphic features. At the time, her karyotype had been documented as 46,XX; a specific diagnosis had not been attained and she had been lost to follow-up. She did not report any other complaints, except for a lack of libido. Her parents were non-consanguineous. At physical examination, blood pressure was 128/64 mmHg, height 182.5 cm (+1.98 SD), body weight 88 kg (+3.1 SD) and body mass index 26.3 kg/m^2 (+1.5 SD). Axillary and pubic hair were sparse. Breast development was normal, but internal labia appeared infantile (Tanner stage: B5,P3). Several dysmorphic features were observed: prominent forehead, midface hypoplasia with depressed nasal bridge, pear-shaped bifid nose, small mouth with high-arched palate, limited supination of forearms, long slender hands, extension contractures of metacarpal joints and irregularly positioned toes.

Hormonal analysis in serum revealed a distinct pattern: 17-hydroxyprogesterone 17 nmol/l (reference: 2.0 to 8.0 nmol/l), androstenedione 0.6 nmol/l (3.0 to 9.6 nmol/l), dehydroepiandrosterone (DHEA) 1.2 μmol/l (3.0 to 13.0 μmol/l), oestradiol 0.09 nmol/l (follicular phase: 0.07 to

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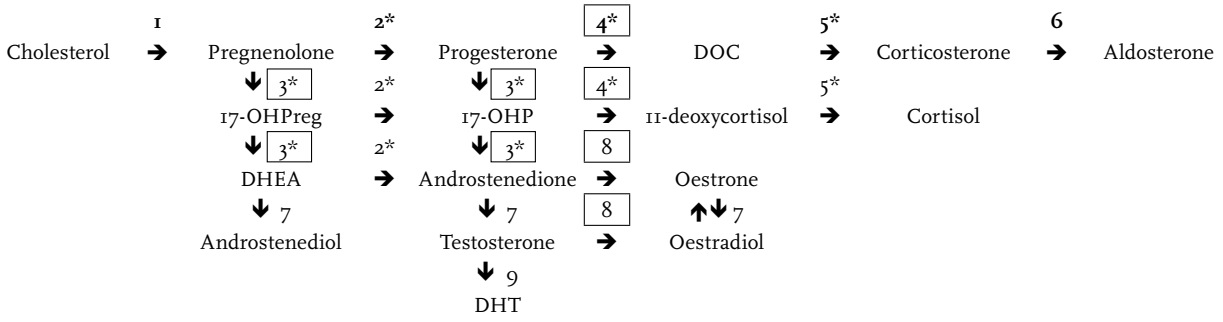
Figure 1. *Schematic overview of adrenal and gonadal steroid biosynthesis and their enzymes.*



Most of these enzymes belong to the family of cytochrome P450 oxygenases (CYP). Steroidogenic acute regulatory protein (StAR) facilitates the movement of cholesterol from the cytosol into the mitochondria, where it is converted to pregnenolone by P450 side-chain cleavage enzyme (CYP11A1). This reaction is the rate-limiting step in steroid biosynthesis. Each number represents a steroidogenic enzyme. Numbers with an asterisk represent enzymes involved in the classical enzyme deficiencies of congenital adrenal hyperplasia. Numbers within a box represent enzymes requiring electron transfer from P450 oxidoreductase. DOC = deoxycorticosterone; 17OHPreg = 17-hydroxypregnenolone; 17-OHP = 17-hydroxyprogesterone; DHEA = dehydroepiandrosterone. 1 = StAR and P450 side-chain cleavage enzyme (CYP11A1); 2 = 3β-hydroxysteroid dehydrogenase (HSD3B); 3 = 17α-hydroxylase/17,20-lyase (CYP17A1); 4 = 21α-hydroxylase (CYP21A2); 5 = 11β-hydroxylase (CYP11B1); 6 = aldosterone synthase (CYP11B2); 7 = 17β-hydroxysteroid dehydrogenase type 3 (HSD17B3); 8 = aromatase (CYP19A1); 9 = 5α-reductase type 2.

0.53 nmol/l), luteinising hormone 6.15 IU/l (2.1 to 14.0 IU/l) and follicle-stimulating hormone 10.0 IU/l (1.8 to 9.6 IU/l). In addition, urinary gas chromatography/mass spectrometry (GC/MS) demonstrated decreased metabolite excretion of androgens and elevated metabolite excretions of progesterone, 17-hydroxyprogesterone and corticosterone. Serum cortisol before and after intravenous administration of 250 µg cosyntropin (synthetic $ACTH_{1-24}$) was 375 and 425 nmol/l, respectively (normal response >500 nmol/l). An abdominal MRI demonstrated cystic enlargement of her right ovary, but was otherwise normal. Sequencing of the POR gene revealed a missense mutation in exon 4 (g.26404A>G, p.T142A) of one allele and a frameshift mutation in exon 10 leading to a stop codon (g.30843dupC, p.Y376LfsX74) in the other allele. Treatment with oestradiol-dydrogesterone and DHEA was instituted and hydrocortisone coverage for medical stress situations was advised.

DISCUSSION

POR deficiency has only recently been identified as a separate CAH variant. The first patient was described in 1985, representing a 46,XY newborn with DSD and impaired steroid biosynthesis compatible with defective activities of CYP21A2 and CYP17A1.[6] The underlying mechanism, however, remained elusive for many years. DNA analysis of CYP21A2 and CYP17A1 revealed no mutation.[7,8] Sequencing of the POR gene became feasible through its description in the human genome project, resulting in the identification of POR gene mutations in these patients.[4,5] Until now, more than 40 mutations have been found in about 70 cases with POR deficiency. The POR gene is located on chromosome 7q11.2 and consists of 15 exons. It encodes a flavoprotein which facilitates electron transfer from NADPH to microsomal bound cytochrome P450 enzymes, including the steroidogenic enzymes CYP21A2, CYP17A1 and CYP19A1.[9] A variety of inactivating mutations have been described, including missense, frameshift and splice site mutations.[1] The missense mutation in our patient was also present in her father and has been described before.[10] The frameshift mutation represented a *de novo* mutation and has not been described in a previously reported patient.

Clinically, POR deficiency is characterised by DSD, glucocorticoid deficiency and skeletal malformations. In contrast to other CAH variants, DSD may be present in both sexes. Male undervirilisation is readily explained by inhibition of CYP17A1, leading to decreased production of androgens. Female virilisation despite low circulating androgen levels is a more puzzling finding that might be explained by the presence of an alternative pathway towards androgen synthesis which is only active during foetal life.[4] The glucocorticoid deficiency is often partial, and should be actively sought for by performing a cosyntropin stimulation test. Skeletal malformations closely resemble those observed in Antley-Bixler syndrome with features such as craniosynostosis, brachycephaly, midface hypoplasia, radiohumeral synostosis, radio-ulnar synostosis, choanal atresia or stenosis and multiple joint contractures.[4,11] These are probably caused by impaired

synthesis of cholesterol and retinoic acid metabolism, both of which play a crucial role in the regulation of foetal bone development and growth. Antley-Bixler syndrome is genetically heterogeneous and can also originate from autosomal dominant inherited mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene, which are not accompanied by abnormalities in steroid biosynthesis.[8] Recently, ovarian cysts have been described in several girls with POR deficiency.[12,13] These may be driven by high gonadotropins, but possibly also by impaired CYP51A1-mediated production of meiosis-activating sterols due to mutant POR.[12]

The diagnosis of POR deficiency is established by urinary steroid profiling with GC/MS, which reveals a characteristic accumulation of pregnenolone and progesterone metabolites, combined with low androgen metabolites and increased 17-hydroxyprogesterone metabolites. If urinary steroid profiling is not directly available, the combination of an increased serum 17-hydroxyprogesterone level with low serum levels of sex steroids may suggest the presence of POR deficiency. However, analysis of serum steroids may be misleading, as several combinations of serum steroids have been described.[14] As in our patient, an increased excretion of corticosterone metabolites might be present, reflecting the preferential inhibition of CYP17A1 over CYP21A2, which has been described in certain POR mutations.[15] Treatment consists of sex hormone replacement and regular hydrocortisone treatment or stress coverage only, depending on the degree of adrenal insufficiency. In addition, genetic counselling should be offered and orthopaedic management of the skeletal malformations might be indicated in some patients.

CONCLUSION

POR deficiency is a recently recognised CAH variant characterised by distinctive features such as DSD in both sexes and skeletal malformations. Urinary steroid profiling should be considered in all patients with features of Antley-Bixler syndrome.

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