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Diagnosis and management of classical congenital adrenal hyperplasia

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is among the most common genetic disorders. Deficiency of adrenal steroid 21-hydroxylase deficiency due to mutations in the CYP21A2 gene accounts for about 95% cases of CAH. This disorder manifests with androgen excess with or without salt wasting. It also is a potentially life threatening disorder; neonatal screening with 17-hydroxyprogesterone measurement can diagnose the condition in asymptomatic children. Carefully monitored therapy with glucocorticoid and mineralocorticoid supplementation will ensure optimal growth and development for children with CAH. Genital surgery may be required for girls with CAH. Continued care is required for individuals with CAH as adults to prevent long-term adverse consequences of the disease, including infertility, metabolic syndrome and osteoporosis.

1. Introduction

Congenital adrenal hyperplasia (CAH) is one of the most common genetic disorders, caused by a deficiency of one of the enzymes required for cortisol biosynthesis [1,2]. The most common type is deficiency of the adrenal steroid 21 hydroxylase caused by mutations in the CYP21A2 gene [3,4]. This form accounts for about 95% of cases of CAH and is inherited as an autosomal recessive disorder. The severity of the disorder varies depending on residual enzyme activity, with the salt wasting classical congenital adrenal hyperplasia (SWCAH) having less than 1% residual enzyme activity [5,6]. Individuals affected with CAH require life long care. During infancy the focus is on prevention of adrenal crisis, gender assignment, genital surgery and linear growth. Linear growth, body weight and pubertal development are the concerns for growing children, while fertility and prevention of metabolic syndrome and osteoporosis require attention in older adults.

2. Adrenal steroid biosynthesis

The adrenal cortex has 3 distinct zones: the zona glomerulosa, zona fasciculata and zona reticularis, which produce mineralocorticoid, glucocorticoid and sex steroids, respectively. The adrenal glands secrete glucocorticoid and sex steroids in response to ACTH [7] and are regulated by ACTH, CRH and Arginine-Vasopressin [8,9]. ACTH stimulated androgen secretion is synchronous with cortisol secretion [10]. Cortisol exerts negative feedback both at pituitary and hypothalamus suppressing ACTH, CRH and arginine-vasopressin.

The synthesis of all steroid hormones begins with the conversion of cholesterol to pregnenolone by mitochondrial cytochrome P450scc (cholesterol side chain cleavage enzyme). The rate-limiting step for steroidogenesis is expression of steroidogenic acute regulatory protein (StAR) and cholesterol transport across the mitochondrial membranes where the enzyme, P450scc, converts cholesterol to pregnenolone to initiate steroidogenesis. [11,12]. The clinical features of these disorders are similar. Synthesis of glucocorticoids, mineralocorticoids and sex steroids is impaired, resulting in adrenal failure, severe salt wasting crisis and hyperpigmentation. Phenotypic expression of the external genitalia is female-appearing irrespective of genetic sex [13–15]. Mutations in gene encoding the StAR protein cause lipoid congenital adrenal hyperplasia (lipoid CAH), which is characterized by lipid-laden adrenal glands. The adrenal cortex tends to be smaller in patients with mutations in the gene, CYP11A1, coding for P450scc. Although not widely available, DNA sequence analysis may be the only way to truly discriminate between mutations in StAR and CYP11A1[1].

The class of steroid produced by an adrenal cell is determined by microsomal P450c17, the enzyme that catalyzes both 17α-hydroxylation and 17,20 lyase activity [16,17]. The adrenal zona glomerulosa does not express P450c17 and hence produces 17-

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[1] Tee MK, Abramsohn M, Loewenthal N, Harris M, Siwach S, Kaplinsky A, Markus B, Birk O, Sheffield VC, Pavari R, Hershkovitz E, Miller WL. Varied clinical presentations of seven patients with mutations in CYP11A1 encoding the cholesterol side-chain cleavage enzyme, P450scc. J Clin Endocrinol Metab 2013 Feb;98(2):713-720.

deoxysteroids leading to aldosterone [18]. The adrenal zona fasciculata, which produces cortisol, expresses the 17α-hydroxylase activity, but very little of the 17,20 lyase activity of P450c17. The adrenal reticularis express both the 17 α-hydroxylase and 17,20 lyase activities of P450c17, which are essential for androgen synthesis. Defects in microsomal P450c17 enzyme activity leads to deficiency of both cortisol and sex steroids. Patients with mutations in the gene, CYP17A1, encoding P450c17 manifest mineralocorticoid excess and hypertension. Males may have genital ambiguity or complete sex reversal. Females may present with delayed puberty.

The enzyme 3β-hydroxysteroid dehydrogenase encoded by HSD3B2 converts pregnenolone to progesterone. Deficiency of this enzyme is associated with impaired glucocorticoid and mineralocorticoid production, while DHEA biosynthesis will be unaffected. DHEA is not readily converted to other sex steroids. Thus, this is associated with atypical genitalia in both females and males due to excess androgenic precursors and androgen deficiency, respectively. These patients can present as salt wasters and non-salt wasters, depending on the degree of enzyme activity affected.

The enzyme CYP21A2 converts progesterone to deoxycorticosterone (DOC) and 17-hydroxy progesterone to 11-deoxycortisol. Deficiency of the enzyme CYP21A2 is the most common cause for CAH. CYP11B1 is required for both aldosterone and cortisol biosynthesis. Children with CYP11B1 deficiency can have hypertension (due to accumulation of DOC) in addition to cortisol deficiency. Girls with these two disorders are born with virilized external genitalia due to androgen excess.

3. CAH due to 21-hydroxylase deficiency

Congenital adrenal hyperplasia from 21-hydroxylase (P450c21) deficiency is the most common form of this disease, accounting for about 95% cases of CAH. This enzyme converts 17-hydroxyprogesterone to 11-deoxycortisol and progesterone to deoxycorticosterone, precursors for cortisol and aldosterone, respectively. Cortisol deficiency leads to ACTH excess, which causes accumulation of steroid precursors and adrenal androgens. Androgen excess *in utero* causes virilization of external genitalia, irrespective of the genetic sex of the fetus. Therefore girls with CAH due to 21-hydroxylase deficiency are born with virilized/atypical genitalia.

The incidence of CAH is 1 in 5000–1 in 20,000 individuals in different populations and is an autosomal recessive disorder [1,19]. The CYP21A2 gene and its highly homologous pseudogene are located on the short arm of chromosome 6. The functional gene (*CYP21A2*) and a nonfunctional pseudogene (*CYP21P1*) are located closely adjacent to each other in tandem arrangement with the *C4A* and *C4B* genes encoding for the fourth component of the serum complement. The *CYP21A2* and *CYP21P1* genes consist of 10 exons and show a high homology, with a nucleotide identity of 98% in their exon and 96% in their intron sequences [3,4]. The 21OHD-causing mutations are generated by unequal crossing over or gene conversion events [20,21]. Complete gene deletions, large gene conversions, single point mutations, and an 8-bp deletion have been described [19,22].

About 65–75% of the CAH patients are compound heterozygotes for disease-causing mutations. The clinical expression of CAH correlates with the less severely mutated allele and consequently with the residual activity of 21-hydroxylase [5,23,24].

More than 100 CYP21A2 mutations are known, and about 10 common mutations account for about 90% of cases. There is genotype and phenotype correlation., Siblings with CAH usually, but not always, have similar presentations [25–28]. There is a 25% probability that siblings of an index case also will have CAH. However, we have seen families in which all children were affected. Congenital adrenal hyperplasia is clinically divided into classic CAH, which includes salt-wasting (SW) & simple virilizing (SV) types, and non-classic (NC) disease [29]. Nearly 75% of individuals with classic CAH suffer with aldosterone deficiency from SWCAH [30].

4. Clinical profile

Clinical presentation consists of signs of androgen excess with or without salt wasting. The presence of atypical/ambiguous genitalia suggests the possibility of CAH in girls. There is often increased pigmentation, especially of nipples and genitalia, due to ACTH excess. Other features of SWCAH are failure to thrive, hypovolemia, hypotension, hyponatremia and hyperkalemia, which usually manifest by the 2nd to 3rd week of life. In the absence of newborn screening, SVCAH may go undiagnosed in boys until features of androgen excess manifest. If the disorder is not treated, both girls and boys undergo rapid postnatal growth and sexual precocity. In the case of severe SWCAH, neonatal salt loss and death can occur. About 75% of classic CAH cases suffer aldosterone deficiency with salt wasting. The milder NC-CAH may be asymptomatic or may present at an older age with hirsutism, oligoamenorrhoea or infertility.

Children from countries with suboptimal medical care as political as well as economic instability may present at different ages with diverse problems. They provide valuable information regarding the natural history of the disorder and also emphasize the misery of under-privileged CAH children.

4.1. Case 1

MN was 13 years old when she sought medical attention for hirsutism. She had noticed pubic hair growth years earlier, without breast development, or menarche. She was lean, her hirsutism score (Ferriman-Gallwey Score) was 16, and she had marked clitoral enlargement (Fig. 1). Her plasma testosterone level was 3 ng/ml, which suppressed to 0.4 ng/ml after dexamethasone 6 hourly for 2 days. The diagnosis of CAH was made and she was started on dexamethasone 0.5 mg once daily, which was later reduced to 0.25 mg daily. Breast development was noted in 6 months and menarche occurred 2 years later. Genital surgery was done approximately 5 years later to reduce the size of clitoris. No surgery was required for the vagina since it was found to be of normal size. She did not develop obesity and later had vaginal delivery of a normal girl.

4.2. Case 2

MS was brought for medical advice at the age of 16 years for short stature. He had a male phenotype and was the first born of a non-consanguineous marriage. Genital ambiguity was noted at

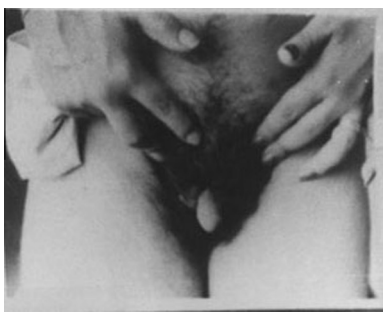

Fig. 1. External gentalia of 13 year-old female with CAH before initiation of steroid therapy. Note the clitoromegaly and masculine pubic hair distribution.