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Review

Management considerations for the adult with congenital adrenal hyperplasia

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ABSTRACT

The congenital adrenal hyperplasias (CAH) are a group of genetic defects in cortisol biosynthesis, most commonly steroid 21-hydroxylase deficiency (21OHD). With the advent of cortisone therapy in the 1960s and newborn screening in the 1990s, most children with 21OHD now reach adulthood. The needs and concerns of adults with 21OHD overlap with those of children, but the focus and approach shift as these patients reach adulthood. Cohort studies suggest that adults with 21OHD experience significant health concerns such as infertility, obesity, short stature, neoplasia, and bone loss, as well as reduced quality of life. Nevertheless, the spectrum of health status and disease severity is broad, but only some of the reasons for these disparities are known. This review will summarize the current state of knowledge and suggested approaches to management adults with classic 21OHD, plus a few major considerations for adults with nonclassic 21OHD.

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Abbreviations: 17OHP, 17-hydroxyprogesterone; 21OHD, 21-hydroxylase deficiency; ACTH, adrenocorticotropin; AD/T, androstenedione/testosterone ratio; CAH, congenital adrenal hyperplasia; CYP17A1, 17-hydroxylase/17,20-lyase; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TART, testicular adrenal rest tumor.

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1. Introduction

1.1. Types of congenital adrenal hyperplasias

The congenital adrenal hyperplasias (CAH) are genetic deficiencies in the enzymes and cofactor proteins required for cortisol biosynthesis (Fig. 1). Loss of cortisol negative feedback on the hypothalamus and pituitary increases adrenocorticotropin (ACTH) secretion, which leads to adrenocortical hyperplasia and stimulates the adrenal gland to move cholesterol into the steroidogenic pathway for cortisol. With the exception of lipoid CAH, in which the transfer of cholesterol in the mitochondria is impaired, each form of CAH features the accumulation of precursor steroids above the enzyme deficiency. In some cases, these precursors are either biologically active or metabolized to active hormones, and aberrant androgen and estrogen biosynthesis often occurs. Thus, the phenotype of each form of CAH result from a combination of cortisol deficiency as well as variable defects in other steroid hormones, due to blocks in pathways, accumulation of precursors, and spillover to alternate pathways.

1.2. Steroid 21-hydroxylase deficiency

The most common form of CAH is 21-hydroxylase deficiency (21OHD), due to mutations in the *CYP21A2* gene encoding cytochrome P450c21 (also called P450 21A2 or CYP21A2). The severe or classic form (<2% residual activity), which is defined by cortisol insufficiency, occurs in ~1:16,000 newborns (Speiser and White, 2003). The prenatal androgen excess of classic 21OHD causes variable masculinization of the external genitalia in babies with a 46,XX karyotype. In nonclassic 21OHD, a partial enzymatic block (~5–20% residual activity) is not severe enough to cause cortisol insufficiency, and mild-to-moderate androgen excess is manifest postnatally. The defect in 21OHD causes characteristic accumulation of 17-hydroxyprogesterone (17OHP) and progesterone above the block, and diversion of these precursors to androgens (Fig. 2). Children with classic 21OHD have been grouped into "salt wasting" and "simple virilizing" based on spontaneous hypotensive crises without intercurrent illness in the infant; however, this distinction is of no clinical utility in the adult. Adults with classic 21OHD do not have crises spontaneously, but all of them can experience adrenal crises when sick, and most benefit from mineralocorticoid replacement therapy. Genotype does not consistently predict medication needs or ease of control, whereas antecedent control is a better predictor of treatment requirements. Genotyping studies have shown that, in contrast to statistical prediction, about 70% of patients with nonclassic 21OHD who come to medical attention are carriers for a classic 21OHD allele (compound heterozygotes) (Finkielstain et al., 2011).

Classic 21OHD differs from complete adrenal insufficiency (Addison's disease) in that, besides cortisol and aldosterone deficiency, the patients also suffer from severe androgen excess. The lack of negative feedback from cortisol allows ACTH to rise, which stimulates steroidogenesis up to the block, and the accumulating cortisol precursors are shunted to 19-carbon steroids. In nonclassic 21OHD, cortisol production is normal, but at the expense of mild to moderate androgen excess via the same mechanism. Therefore, glucocorticoid and mineralocorticoid therapy in classic 21OHD is given not only to restore fluid and electrolyte balance, but, unlike in Addison's disease, also to provide enough negative feedback to

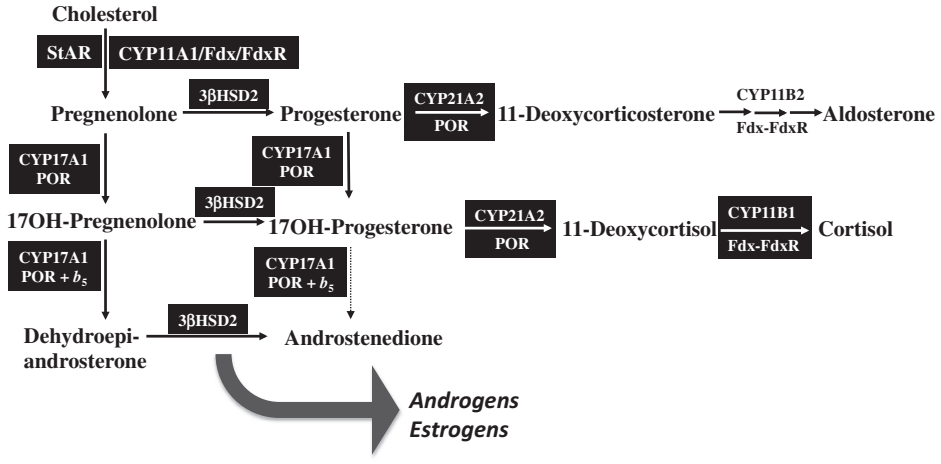

Fig. 1. Adrenal steroid biosynthesis pathways and enzymatic defects causing congenital adrenal hyperplasia (CAH). Deficiency of StAR, the steroid acute regulatory protein, causes lipoid CAH, in which all steroids are low. Deficiency of CYP11A1, the cholesterol side chain cleavage enzyme or P450scc, causes a similar global deficiency of steroids without lipid accumulation in the adrenals. Additional enzyme deficiencies causing various forms of CAH (black boxes with white letters) are 17-hydroxylase/17,20-lyase deficiency (CYP17A1 or P450c17); 3β-hydroxysteroid dehydrogenase/isomerase type 2 deficiency (3βHSD2), P450-oxidoreductase deficiency (POR); 21-hydroxylase deficiency (CYP21A2 or P450c21), and 11-hydroxylase deficiency (CYP11B1 or P450c11β). The electron transfer proteins for the mitochondrial cytochrome P450 enzymes in the CYP11 family are ferredoxin and ferredoxin reductase (Fdx and FdxR, respectively), and cytochrome b_5 (b_5) increases the 17,20-lyase activity of CYP17A1, which has poor efficiency for the conversion of 17-hydroxyprogesterone to androstenedione (dashed arrow).

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