

Review Article

## Congenital Adrenal Hyperplasia in Saudi Arabia

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### ABSTRACT

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder resulting from a deficiency of one of the enzymes necessary for cortisol synthesis. As a result, decreased cortisol synthesis, increased adrenocorticotropin (ACTH) hormone via negative feedback system and over production of the hormones prior to the enzymatic defect. It is not a rare disorder in Saudi Arabia, where more than 90% of cases are due to 21-hydroxylase deficiency. Variable clinical forms ranging from the severe classical CAH, associated with complete loss of enzyme function to the milder non-classical forms (NCAH) where encounter.

This review presents an overview of the various types of CAH in Saudi Arabia, particularly the most common type 21-hydroxylase deficiency, highlighting its epidemiology, clinical presentation, diagnosis and management.

**Keywords:** Congenital adrenal hyperplasia, cortisol deficiency, Androgen excess, epidemiology, Management, Saudi Arabia.

### INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal disorders that result from the deficiency of one of the enzymes required for cortisol production, (figure 1) and the consequent accumulation of steroid intermediates proximal to the enzyme defect. There is increased adrenocorticotropin hormone (ACTH) secretion which is leading to increased synthesis of adrenal androgens and also cortical hyperplasia.

There are two common and three rare forms of CAH. The common forms are caused by defects in either CYP21A2 (21-hydroxylase) or CYP 11B1 (11-B-hydroxylase). An additional CAH is caused by mutations that affect either the 17 B-hydroxylase, 17, 20 lyase or both activities encoded in the CYP 17 A1 gene. <sup>(1-13)</sup>

In this review, we present an overview of the enzymatic defects resulting

in congenital adrenal hyperplasia in Saudi Arabia, particularly the most common 21-hydroxylase deficiency.

### Epidemiology

In Saudi Arabia, there are no precise data on the prevalence of the disease; however, there are impression fostered by clinical experience and local reports of congenital adrenal hyperplasia that this is not an uncommon disease. <sup>(14-25)</sup> A calculated incidence had been postulated, 1 in 5000, from the number of patients diagnosed with the disease among the deliveries at King Khalid University Hospital (KKUH) Riyadh Saudi Arabia. <sup>(15)</sup> Presently, the limited local newborn screening program supported such data. <sup>(26)</sup>

Newborn screening indicates a world-wide incidence of classical 21-hydroxylase deficiency as 1 in 13000 to 154000 live births. Incidences vary among different populations, ranging from 1 in 600

live births in Yupik Eskimo of Alaska to 1 in 5000 live births in Saudi Arabia and 1 in 23000 lives in New Zealand. The prevalence frequency of non-classical 21-hydroxylase deficiency is considered to be higher, 1 in 1000 in white populations, and even higher among selected groups, such as Ashkenazi Jews. Prevalence of non-classical CAH is 1 in 27, for Ashkenazi Jew, 1 in 40 for Hispanics, 1 in 50 for Yugoslavs, 1 in 300 for Italians, 1 in 282 for Yupik Eskimos of Alaska and 1 in 100 in a heterogeneous New York population. The fertility rate among infertile females with non-classical CAH is reported to be 50%. (27-29)

### Molecular (Genetic) Studies

The phenotype expression of different CAH forms depends on the underlying enzymatic defect. Steroid 21-hydroxylase (CYP 21 A2) and 11 $\beta$ -hydroxylase (CYP 11 B1) deficiencies only affect adrenal steroidogenesis, whereas 17 $\alpha$ -hydroxylase (CYP 17 A1) and 3 $\beta$ -hydroxysteroid-dehydrogenase type 2 (HSD 3B2) also impair gonadal steroid

biosynthesis. p450 oxidoreductase deficiency (PORD) manifests with apparent combined CYP17 A1 – CYP 21A2 deficiency. In contrast to other CAH forms, PORD also causes skeletal malformations and genital ambiguity in both sexes. Three additional enzymatic defects have been traditionally classified as CAH. Steroidogenic acute regulatory protein (star) deficiency results in congenital lipid adrenal hyperplasia (CLAH), and has the unique feature of adrenal and gonadal lipid accumulation. P450 side-chain cleavage (CYP 11A1) deficiency resembles the CLAH phenotype, but patients have normal sized or absent adrenals. Aldosterone synthase (CYP 11B2)

Deficiency manifests with isolated aldosterone deficiency and normal cortisol synthesis. Bearing in mind, genetic testing would assist accurate diagnosis of the affected individuals, it could be also used to identify carriers and, hence, used in genetic counseling. In Saudi Arabia, there were limited studies in this field so far. (19,25,30-33)

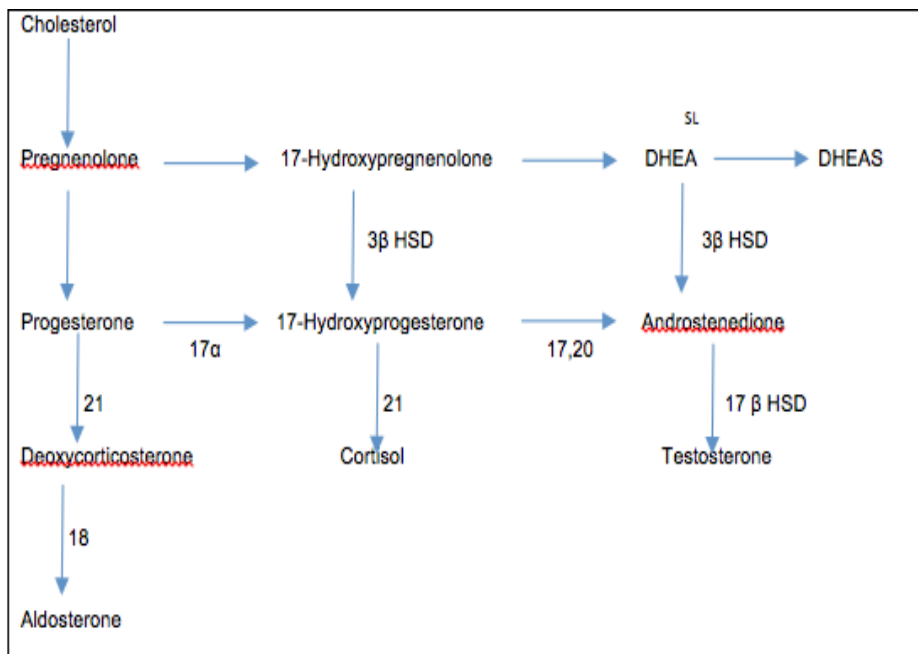


Fig. 1: Schematic structure for biosynthesis of adrenal cortex hormones (glucocorticoids, mineral-corticoids and sex steroid hormone)

### Clinical Presentation

Family history is important in a community with increased consanguineous matings. (34-36) The clinical phenotype of CAH depends on the nature and severity of the enzyme

deficiency. Although the presentation varies according to chromosomal sex, the sex of the neonate with CAH is often initially useless because of the genital ambiguity as in the majority of our patients. In females

with severe CAH due to deficiencies of 21-hydroxylase, 11 $\beta$ -hydroxylase and 3 $\beta$ -hydroxysteroid-dehydrogenase have ambiguous genitalia, i.e., classic virilizing adrenal hyperplasia. Figure 2 Females with milder deficiency of 21-hydroxylase may present later in childhood because of precocious puberty accompanied with advanced growth (simple virilizing adrenal hyperplasia), or even present in adolescence or adulthood with hirsutism and menstrual irregularity, as even infertility (nonclassic adrenal hyperplasia). Female patients with 17 $\beta$ -hydroxylase deficiencies appear phenotypically female at birth, but do not develop breasts or menstruate in adolescence, and even might present with hypertension. Males with 21 $\beta$ -hydroxylase or 11 $\beta$ -hydroxylase have normal male genitalia. In 21 $\beta$ -hydroxylase deficiency, associated with salt-wasting, however, they can present with dehydration and shock (classic salt-wasting adrenal hyperplasia). Males with less severe deficiencies of 21-hydroxylase, present later in childhood with precocious puberty accompanied with accelerated linear growth (simple virilizing adrenal hyperplasia). Males with steroidogenic star deficiency, classic 3 $\beta$ -hydroxysteroid dehydrogenase deficiency or 17 $\beta$ -hydroxylase deficiency generally have ambiguous genitalia or female genitalia; they may be raised as girls and seek medical attention later in life because of hypertension or lack of breast development. (1-9,14-19)

### Diagnostic Studies

Diagnosis must be based on history and physical examination supported by the accumulation of ACTH-stimulated steroid precursors above the enzymatic block, with the exception of lipoid hyperplasia (P450<sub>scc</sub> deficiency) in which almost no steroids are produced. Also, an experienced pediatric radiologist, as part of a multidisciplinary team, plays an important role as the sonographic appearance of the adrenal gland, the cerebriform appearance, is characteristic, (figure 3) and the internal genitalia can be determined. (figure 4) This can be supported by other modalities such

as genitography, computed tomography (CT) scan, and magnetic resonance imaging (MRI). (37-46)

Metabolite such as 17 $\alpha$ -hydroxyprogesterone (17-OHP), androstenedione, dehydroepiandrosterone (DHEA), cortisol testosterone, aldosterone and renin should be assayed to determine the clinical variant of CAH. A profile of steroid metabolites is required to evaluate the clinical cause of CAH. (2-5,11,47,48) Aljurayyan has reported his experience from Saudi Arabia previously. (18,49)



Fig. 2: A newborn baby girl (46 XX) with congenital adrenal hyperplasia due to 21 $\beta$ -hydroxylase deficiency. Note: The fused labioscrotal folds and hypertrophy of clitoris

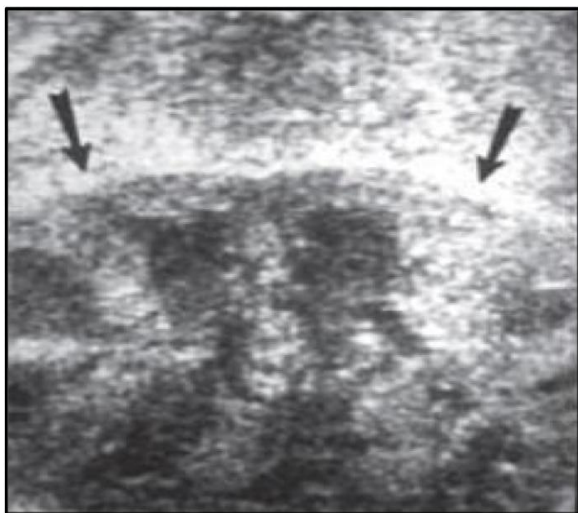


Fig. 3: Abdominal Ultrasonography, showing enlarged adrenal glands, with the typical cerebriform appearance. She was diagnosed to have congenital adrenal hyperplasia due to 21 $\alpha$ -hydroxylase deficiency.

### Management

The initial step in management starts with correct diagnosis. In suspected

individuals, serological studies including chromosomal analysis, if indicated, and various hormonal and biochemical tests to define the nature of deficiency should be undertaken, in addition to the appropriate radiological investigations. The medical therapy (hormonal) aims to prevent the serious consequence of adrenal crisis and shock resulting from cortisol and mineralocorticoid deficiency. Appropriate sex assignment is crucial to prevent the adverse psychological consequences. (50-52) Patients with dehydration, hyponatremia or hypokalemia and a possible salt-wasting form of adrenal hyperplasia should receive an intravenous (IV) bolus of isotonic sodium chloride solution (20 ml/kg) over the first hour, as required, to restore their vascular volume and blood pressure. This dosage may be repeated if the blood pressure remains low. Dextrose must be administered if the patient is hypoglycemic and must be included in the rehydration fluid after the bolus dose to prevent hyperglycemia. After samples are obtained to measure electrolyte, blood sugar, cortisol, aldosterone, and 17 hydroxyprogesterone (17-OHP) concentrations, the patient should

be treated with glucocorticoids based on suspected adrenal insufficiency. Treatment should not be withheld. After the patient's condition is stabilized, treat patient with long term glucocorticoids or aldosterone replacement (or both), depending on which enzyme is involved and on whether cortisol and/or aldosterone synthesis is affected, i.e., oral hydrocortisone, 10-15 mg/m<sup>2</sup>/kg, in 2-3 divided doses, and a stress dose must be given during surgery or severe acute illness. The florinef (9  $\alpha$  Ff) is often administered orally in a dose of 50-200 microg/day accompanied by 1-2 grams of sodium chloride. Suppression of puberty with long-acting gonadotropin-releasing hormone (GnRH) agonists while simultaneously stimulating growth with growth hormone might be indicated. (3-10,12,13,40,53-55)

Surgical correction is a complex clinical situation that requires a multidisciplinary approach. The type of surgical repair performed must be tailored according to each individual patient's anatomy. Reconstruction is generally initiated between the age of 3 and 6 months. (3-10,56-65)



Fig. 4: 1 Pelvic ultrasonography of a patient with 46XX DSD, showing a uterus. She was diagnosed with congenital adrenal hyperplasia, 21-alpha-hydroxylase deficiency.

### Special Issues

Prenatal diagnosis and treatment with oral dexamethasone given to the

mother has been implemented for more than 25 years and was successful in ameliorating genital ambiguity in all pregnancies at 25%

risk for classical CAH. <sup>(66-76)</sup> In utero gene-specific diagnosis guides the treatment of the affected female fetus.

Fertility in females with congenital adrenal hyperplasia due to 21 hydroxylase deficiency reduced especially in classic salt-waster. <sup>(77,78)</sup> Several factors have been suggested such as androgen excess, secondary polycystic ovaries syndrome, and psycho-social factors. Adequate glucocorticoid therapy and improvement of surgical and psychosocial management could contribute to optimize fertility. Majority of our female patients have irregular menstrual cycles and polycystic ovary, however, one with simple virilizing CAH, had successfully conceived with a good outcome. However, fertility in males is poorly studied. While in one series showed normal fertility, others reported substantially reduced fertility. <sup>(79-81)</sup>

Testicular adrenal rest tumours increase with age in CAH. The prevalence of these tumours is variable, ranging from 30-95% of patients depending on the selection of patients and methods of detection. Their impact on fertility has not yet completely established. Four of our six patients whom we studied demonstrated testicular adrenal rest tumours, (unpublished data) and indicated the poor control. <sup>(81-87)</sup> Finally, the future guidelines and strategies in the management of children with congenital adrenal hyperplasia could prevent the long-term consequences of the disease. <sup>(88)</sup>

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