Congenital Adrenal Hyperplasia: Case report

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Figure 1
Figure 2
Figure 3
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Abstract

Congenital adrenal hyperplasia is an autosomal recessive disease, it can be classic or non classic. Each type could be mild to severe. We report a case of classic virilizing congenital adrenal hyperplasia. Patient underwent surgical correction for ambiguous genitalia and hormone replacement therapy. Proper diagnosis and treatment can enable women with the disease to have a normal sexual, normal menstrual and reproductive life.

Introduction

The term congenital adrenal hyperplasia (CAH) involves a group of autosomal recessive disorders, which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both [1-3]. Steroidogenesis is an essential pathway for the synthesis of steroid hormones in the adrenal cortex: mineralocorticoids, glucocorticoids and androgens, mainly dehydroepiandrosterone (DHEA), and androstenedione [1, 3, 4]. Cholesterol is the key substrate in this pathway which is converted into pregnenolone, the common precursor for all steroid hormones. In the adrenal cortex, this is processed into both glucocorticoids and androgens in zona fasciculate and zona reticularis or into mineralocorticoids in zona glomerulosa [1, 4-6]. In CAH, there are various genetic mutations in the enzymes involved in steroidogenesis. Due to this enzymatic defect, cortisol is under-produced and the negative feedback control on adrenocorticotropic hormone (ACTH) is lost with consequently excess ACTH produced in order to normalize cortisol levels resulting in overproduction and accumulation of steroids precursors prior to the enzyme defect as well as hyperplasia of the adrenal cortex [1, 2, 4-6].

The phenotype of CAH clinical manifestation depends on the degree or type of gene deletion or mutation and the resultant deficiency of the steroidogenic enzyme [7-9]. Two copies of an abnormal gene are required for disease to occur, and not all mutations and partial deletions result in disease [6-9]. The phenotype can vary from clinically unapparent disease to a mild form of disease that is expressed in adulthood to severe disease that results in adrenal insufficiency in infancy with or without virilisation and salt wasting. The low level of cortisol stimulates the pituitary gland to release ACTH [3, 5, 6, 8, 9]. This chronic elevation in ACTH causes hyperplasia of the adrenal cortex, giving the characteristic enlargement of the gland. The clinical presentation of the various forms of CAH depends on the affected enzyme, the residual enzymatic activity, consequences of deficiencies of the end products, and hormonal effects of the elevated precursors [1, 5]. Deficiency of 21-hydroxylase, resulting from mutations or deletions of CYP21A, is the most common form of CAH, accounting for more than 90% of cases [1, 5, 8]. Most of these conditions involve excessive or deficient production of sex steroids and can alter development of primary or secondary sex characteristics in some affected patients. The clinical manifestations of each form of congenital adrenal hyperplasia are related to the degree of cortisol deficiency and/or the degree of aldosterone deficiency [1, 5, 8, 9]. In some cases, these manifestations reflect the accumulation of precursor adrenocortical hormones. When present in large concentrations, these precursors lead to excess androgen production with resultant virilisation, or because of mineralocorticoid properties, cause sodium retention and hypertension [1, 5, 7-9].

CAH clinically divided into classic CAH that includes salt wasting, or simple virilisation, and non-classic disease [5-7]. Patients with the classical form present during the neonatal period and early infancy with adrenal insufficiency with or without salt-losing or as toddlers with virilisation [2, 5-7]. The classical form is the most severe form of CAH due to CYP21A2 deficiency in particular. Females usually have genital ambiguity [5-7]. Approximately 67% of classical CAH patients are classified as salt-losing, while 33% are classified as nonsalt-losing or simple-virilising, reflecting the degree of aldosterone deficiency [1, 2, 5]. Non-classical or late-onset deficiency presents later in life with signs of androgen excess and without neonatal genital ambiguity [6-8]. Clinical features in childhood may include premature puberty and accelerated bone age; adolescent and adult females may be presented with hirsutism, menstrual irregularity, infertility, and acne [3, 4, 9]. On the other hand, some patients with nonclassic CAH remain asymptomatic. This case report mainly focus on classic CAH with no salt wasting or what is known as classic virilizing congenital adrenal hyperplasia [3, 4, 8, 9].
Incidence varies according to the race, but is around 1 in 10–20 thousand live births [1, 2, 6]. It is the most common cause of sexual ambiguity at birth. Main clinical presentation is genital anomalies, which ranges from complete fusion of the labioscrotal folds and a phallic urethra to clitoromegaly, partial fusion of the labioscrotal folds, or both up to precocious pubic hair, clitoromegaly with shallow vagina, or both, accompanied by accelerated growth and skeletal maturation [1, 2, 6, 9]. The other important clinical presentation is with oligomenorrhea, hirsutism, and/or infertility [4, 10, 11].

Treatment usually includes supplying enough glucocorticoids to reduce hyperplasia and overproduction of androgens or mineralocorticoids and providing replacement estrogen [4, 8, 11, 12]. Females with ambiguous genitalia require surgical evaluation and, if needed, plan for corrective surgery. The traditional approach to the female patient with ambiguous genitalia due to adrenal hyperplasia is clitoral recession early in life followed by vaginoplasty after puberty. Surgical reconstruction may not be necessary during the newborn period in mildly virilized girls but may be appropriate in severely virilized girls, and it should be a single stage genital repair [4, 8, 12]. With adequate medical and surgical therapy, the prognosis is good, however, infertility is common [4, 8, 10, 11].

Case report

27 years old single Saudi woman with history of secondary amenorrhea diagnosed as congenital adrenal hyperplasia without salt losing discovered 1 year back. Patient had menarche at age of 13 years once, very little amount of blood and did not come again since the age of menarche. Patient developed sever hirsutism all over the body, hoarseness of the voice, no breast enlargement and she described that she has clitoroegaly which is increased in size progressively since menarche.

Investigations revealed Female Karyotype (46XX), with very high testosterone level as high as 32 nmoL/L (male range). Ultrasound and Magnetic resonance imaging (MRI) of the pelvis showed normal Uterus and Ovaries with no testis (Figure 1, 2).

Patient has 2 sisters of the same parents with the same problem one 32 years old has same finding and underwent surgical correction and another one 11 years she did not need surgery and in hormonal therapy. Also, she has 4 sisters from same father with no abnormality. On the other hand, she has one cousin who had the same abnormalities and correction surgery was done for her, she was followed for few months post surgery, but, since she got married she did not come to follow up.

Patient underwent surgical correction of ambiguous genitalia and started on hormone replacement therapy (HRT). On follow up, Patient reported improvement in the hirsutism and decreased skin pigmentation but patient refusing Laser Therapy. She also, reported good breast development and started to have regular menses. Improvement of her hormonal levels can be seen in (Figure 3).

Discussion

CAH has a wide spectrum of clinical severity depending upon the enzyme deficiency and the residual enzyme activity. Diagnosis of CAH can be done prenatally by villous sampling or amniocentesis for mutational study or by amniotic fluid levels of 17-OHP [1, 2, 6]. Prenatal diagnosis is especially important if both parents had carrier; previous affected child has limited role if the mother herself is affected and in steroid treatment. Diagnosis at birth is done by 17-OHP levels at day 3 of birth. In children and adults, the diagnosis is based on hormonal levels of 17-OHP, testosterone, DHEAS, androstenedione, cortisol, and plasma rennin activity [1, 2, 6, 11].

The incidence of classical CAH is 1:10,000–1:20,000, thus the incidence of carriers in the general population is 1:50–1:71 with a median of 1:60. As such, a patient with classic CAH would be predicted to have a 1 in 120 chance of having a child with classic CAH [8-10].

Treatment of classic virilizing CAH consists of glucocorticoids and genitoplasty [6, 8]. Fertility is reduced in females of CAH because of various reasons like psychosexual problems, inadequate vaginal introitus, coital difficulties, chronic oligo-anovulation, secondary PCOS, and luteal phase defect. Various studies have shown a fertility rate of 35–60 % in classic virilizing CAH [4, 6, 8]. Studies have shown that proper treatment results in spontaneous conception in patients with CAH. It has also been seen that females with CAH give birth to more girls 66% females to 34% boys, the exact reasons for this is not known [2, 4, 8].

Adult patients with CAH have a number of issues due either to the disease or to its treatment. Most of the problems relate to final height, fertility, bone metabolism and psychoneurological issues [2, 4, 8,
Patients with CAH should be regularly followed up from childhood to adulthood by multidisciplinary teams who have knowledge of CAH. Optimal replacement therapy, close clinical and laboratory monitoring, early lifestyle interventions, early and regular fertility assessment and continuous psychological management are needed to improve outcome [5, 8, 10, 11].

**Conclusion**

This is one of the rarely reported cases in Saudi Arabia and in the Arab World. The diagnosis of CAH may be delayed in late childhood, adolescence or adulthood with improper development of sexual milestones and characteristics. A high index of clinical suspicion is necessary when evaluating children and adolescents with sexual infantilism with ambiguous external genitalia. The diagnosis of CAH requires a multidisciplinary approach, but proper diagnosis and treatment can enable these females to have a normal sexual, normal menstrual and reproductive life.

**References**