A Rare Case Report of Congenital Adrenal Hyperplasia: 46XX at Tertiary Care Centre, Visnagar, North Gujarat.

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Abstract

This report presents a rare case of pure classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency in a 22-year-old woman with a 46 XX genotype. The patient exhibited virilism, excessive hair growth, and primary amenorrhea with absent secondary sexual characteristics. The diagnosis was confirmed by 17-hydroxyprogesterone testing and the Synacthen test. Treatment with hydrocortisone and spironolactone was followed by feminization surgery, leading to the development of secondary sexual characteristics, including breast development, a reduction in hirsutism, and the onset of regular menstruation.

Keywords: *Congenital adrenal hyperplasia; 21-hydroxylase deficiency; Virilism; Syacthen test; Feminizing surgery; Hydrocortisone; Spironolactone*

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Date of Submission: 25 October 2023
Date of Revision: 18 November 2023
Date of Acceptance: 29 December 2023

Introduction

The most prevalent type of congenital adrenal hyperplasia (CAH), which is a collection of autosomal recessive illnesses, is 21-hydroxylase deficiency, which is defined by enzyme abnormalities in the adrenal steroidogenesis pathway. The disorder is caused by mutations in the CYP21A2 gene, that codes for an enzyme called 21-Hydroxylase[1] which results in a high level of adrenal androgens or inadequate synthesis of cortisol and aldosterone. Due to excessive testosterone exposure during pregnancy, females with the severe type of classic 21-hydroxylase deficiency have virilized external genitalia at birth. This illness can have serious long-term health effects and potentially fatal adrenal crises if left untreated.

The uncommon appearance of a 22-year-old woman with pure classical virilizing CAH is described in this case report, underscoring the difficulties in diagnosis, treatment, and clinical care. To guarantee transparency and completeness, the report is prepared in accordance with the CARE criteria.[2]

Case Presentation

In her adult life, a 22-year-old woman from a non- consanguineous marriage visited our outpatient department. Her preliminary consultation with our team was for atypical sexual development (excessive hair growth) amenorrhea and unclear genitalia which dates back to the time her mother found a genital bud at birth. Upon reviewing her medical history, no evidence of maternal exposure to androgens during pregnancy or salt loss syndrome was discovered. She

visited numerous gynecologists for her issue, but she never obtained a satisfactory response. She eventually came to us about her issue. The clinical examination revealed excessive amounts of body hair growth, no breast growth, and a male morphotype.

The genital examination demonstrated a pair of distinct orifices below the clitoris (Prader II), non-fused smooth pigmented and symmetrical genital folds, clitoromegaly with peniform aspect that measured broadly around 5.5 cm in length and 2 cm in width, and no evidence of gonad palpation at the inguinal and fold levels (Fig 1 and 2). Her subjective Ferriman and Galleway Score of 29 indicated significant hirsutism, which was linked to virilization symptoms.

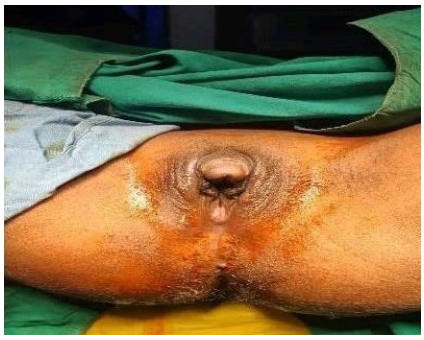

Fig 1 Pre-treatment photograph showing symmetrical, non-fused, pigmented vaginal folds, clitoromegaly with penniform appearance, and two distinct orifices beneath clitoris.

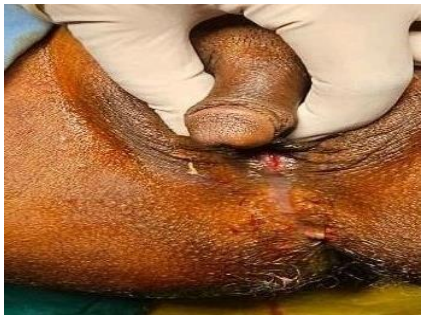

Fig 2: Pretreatment Photograph showing clitoromegaly and Pinniform appearance.

On 50 mitoses, the biological exploration using modal of karyotypes demonstrated a karyotype 46, XX, with testosterone levels of 367.55 ng/ml (CMIA), progesterone was 23.3ng/ml and estrogen (E2) was 3.3 pg/ml while DHEA 752.5 µg/dl (CMIA), and 17OH Progesterone subsequently synacthene stimulation T60 min: 354 ng/ml (VN< 10 ng/ml, radioimmunology), cortisol level was low, measuring 52 g/ml (CMIA). A hypoplastic uterus with uniform contours measuring 42 x 21 x 17 mm and macropolycystic ovaries measuring 23 mm on the left and 24 mm on the right were discovered by pelvic ultrasonography. An abdominal MRI scan revealed hypertrophy of the adrenal glands but no other abnormalities.

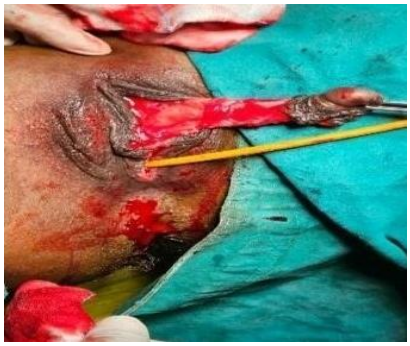

Fig 3: Illustrates the size of the clitoris, with a peniform aspect measuring 5 cm by 2 cm,

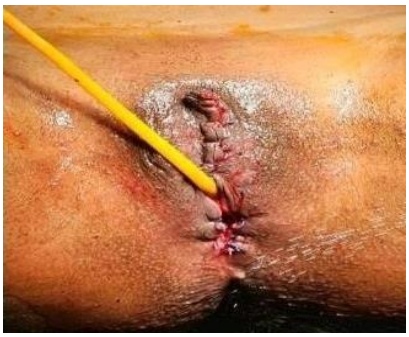

Fig 4: Clitoris appearance following clitoroplasty

Therapeutically, hydrocortisone replacement at a dosage of 10 mg at 8 am and 5 mg at 5 pm was to be administered in addition to dexamethasone at a dose of 0.5 mg/d at night. After three months she observed breast growth which was corresponding to stage S2 of Tanner, the clinical examination revealed a minor decrease in hirsutism, a Ferriman and Gallaway score of 25 versus 29, and smaller in size clitoris measuring 5.5 cm against 5 cm. On a biological level, the 17 OHP went back to 168.6 ng/ml, and the

testosteronemia dropped to 1.12 ng/ml from 3.69 ng/ml. At this point, the patient was admitted for vaginoplasty and clitoroplasty procedures. The surgery went smoothly and efficiently (Fig 3 and 4). Normal anatomical communication was established between the cervix and vagina. To avoid vaginal restenosis, she was encouraged for self-introduction of vaginal mold once a day.

Discussion

A collection of autosomal recessive illnesses known as congenital adrenal hyperplasia are brought on by total or partial abnormalities in one of the numerous steroidogenic enzymes that the adrenal glands use to synthesize cortisol from cholesterol. Steroid 21-hydroxylase, an enzyme encoded by the CYP21A2 gene, is deficient in over 95–99% of all CAH patients.[3] According to data from millions of babies screened globally, 1 in 10,000 to 1 in 20,000 live births had classic CAH.[4,5] With an estimated prevalence of one case per 200 people to one case per 1000 people, non-classic CAH is widespread throughout the world.[6]

The ambiguous genitalia associated with genetic females (46,XX) in neonates (Classical CAH) exemplify clitoromegaly and labioscrotal fusion. Signs and symptoms of dehydration, vomiting, weight loss, and shock (in extreme cases) are typical during a salt-wasting crisis. Early pubarche and advanced bone age are present in children, who have tall stature initial stages but subsequently short as a result of early epiphyseal closure. Adolescents and adults with non-classical CAH exhibit hyperandrogenism symptoms and indicators, including female infertility, hirsutism, acne, and irregular menstruation.

Lack of 21-hydroxylase, a cytochrome P-450 enzyme necessary for the adrenal cortex's synthesis of cortisol and aldosterone, is caused by mutations in the CYP21A2 gene. This enzyme's deficit causes a domino effect. The overproduction of pituitary corticotropin, which results from low cortisol, causes the adrenal cortex to enlarge and increases the release of cortisol precursors, specifically 17OHP, and adrenal steroids, the primary one being D4-androstenedione. In the target cells, this androgen can subsequently undergo metabolism to produce testosterone and dihydrotestosterone.[7]

A complicated genomic structure is intimately linked to the genetic pathways causing 21-OH deficiency. Although there are more than 200 known CYP21A2 gene mutations, over 90% of HCS cases are caused by a small number of these changes, either by gene conversion or uneven recombination. CYP21A2 point mutations account for 70–75% of cases. Large deletions connected to an uneven recombination process or abnormal segregation during meiosis account for 20% of cases. De novo mutations are linked to 21-OH deficiency in 1%–2% of instances. Real-time quantitative PCR is used for molecular diagnosis, employing distinct primer pairs that are unique for the CYP21A2 gene and not the CYP21A1P pseudogene. Point mutations are then found by sequencing.[8]

Two phenotypes, simple virilizing (SV) and salt wasting (SW), are indicative of the classic form. The age of finding, sex, and type of HCS all affect the clinical presentation. Ambiguous external genitalia are present in all patients with classic 21-OHD.[9] Rarely, like with our patient, the diagnosis of the classic pure virilizing type is established late in childhood, adolescence, or adulthood. In most cases, the diagnosis is made at birth. Because hyperandrogenism disrupts the gonadotropic axis, it can lead to anovulation or dysovulation, which can cause irregular menstruation, irregular cycles, or even infertility.[10] Any patient who presents with oligomenorrhea and/or hyperandrogenism should have the diagnosis brought up. With

severe hirsutism, a male morphotype, primary amenorrhea, no breast development, and a peniform clitoris, the clinical picture in our patient was highly suggestive. The ovaries, fallopian tubes, and uterus all develop normally. In addition to confirming the existence of female genitalia, pelvic ultrasonography often reveals the emergence of micropolycystic ovaries as a result of hyperandrogenism. This should not be confused with micropolycystic ovary syndrome, which is an elimination diagnosis. In our instance, macropolycystic ovaries measuring 23 mm on the left and 24 mm on the right were discovered by pelvic ultrasonography beside this evaluation of bone age was done using a left- hand's X-ray.

Serum 17-hydroxyprogesterone, usually stimulated by synthetic ACTH, is still the gold standard for diagnosing CAH. Therefore, the diagnosis is confirmed by a baseline 17 OH progesterone value greater than 2 ng/ml or a concentration >10 ng/ml in the synacthen test.[4] When diagnosing the condition, CYP21A2 genotyping is seen to be a useful supplement to biochemical tests.[3] But in our case because of the patient's financial issues, the genetic investigation could not proceed.

Blocking hyperandrogenism and preventing or managing complications of classic form and its therapy are the two goals of managing it throughout adolescent and adulthood.[11] The most widely used glucocorticoid is hydrocortisone. Other glucocorticoids, including dexamethasone, prednisone, or prednisolone, have longer half-lives and offer a stable replacement action all day. Unfortunately, without a sufficient dosage of glucorticoids, it is difficult to achieve androgen secretion suppression, and as a result, there is a substantial risk of iatrogenic hypercortisolism. Regardless of the regimen, the choice between long-acting glucocorticoids, which have a higher risk of adverse effects, and physiological hydrocortisone, which is well tolerated but has limited control on androgen secretion, remains problematic. Plenadren, a novel slow-release glucocoticoides formulation, was just released, while Chronocort, another, is presently being researched. Although the medication has not yet received approval, this is another modified-release hydrocortisone formulation that is being developed. It is taken twice a day, at bedtime and at waking, and has been demonstrated to imitate normal circadian cortisol levels. In patients with congenital adrenal hyperplasia, a phase II trial showed greater suppression of morning 17-OH progesterone levels (and, consequently, nightly androgen output). Phase III trial results are still pending.[12] In our case, in addition to dexamethasone at a dose of 0.5 mg/d at night, hydrocortisone replacement was to be given at doses of 10 mg at 8 am and 5 mg at 5 pm.

The antiandrogenic effects of spironolactone, an aldosterone antagonist, are seen at doses between 100 and 200 mg/day. It works by blocking androgen receptors and inhibiting 5-α-reductase activity.[11] In our instance, we decided to use 100 mg of spironolactone each day for treatment. A reduction in hirsutism, a reduction in the size of the clitoris, and the onset of breast development were observed as improvements in the symptomatology following three months of carefully managed replacement therapy and anti-androgenic medication.

Apart from this for proper dehydration and electrolyte imbalance in an acute crisis (salt-wasting CAH), intravenous fluids should be administered. IV hydrocortisone should be used for stress dosage to replenish cortisol. Beside this for the management of mineralocorticoid deficit in acute crises, sodium supplementation and fludrocortisone are recommended. Along with mineralocorticoids, glucocorticoids are used in chronic care to replenish cortisol and inhibit excessive androgen production

(e.g., hydrocortisone in children, prednisone in adults). Bone age, blood pressure, and growth are periodically monitored. When it comes to surgical management, femaleizing genitoplasty—ideally done during infancy in females with ambiguous genitalia. Growth abnormalities, puberty progression, and metabolic consequences of steroid medication all necessitate for continual observation. For concerns related to gender identity and quality of life, psychosocial help is crucial.

Complications include - Growth abnormalities spurred by the overt or insufficient usage of glucocorticoids, stress or illness-induced adrenal crisis and psychological effects associated with ambiguous genitalia and fertility. Patients can live normal lives with early diagnosis and proper care. Because of early intervention, newborn screening programs have greatly improved outcomes.

Conclusion

We describe a 22-year-old female patient who sought our consultation due to a sexual development abnormality, primary amenorrhea, and ambiguous genitalia. The diagnosis of congenital adrenal hyperplasia in its classic pure virilizing form remains unchanged at this age, necessitating challenging and specialized medical attention. In order to permit proper growth, female puberty, and good fertility, it is crucial to make the diagnosis as soon as feasible.

Consent: The patient's parents gave their written informed consent for this case report and its associated photos to be published.

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Abbreviations:

CYP21-gene encoding 21-hydroxylase Cytochrome P-450 enzyme
CMIA-Chemiluminescent microparticle immunology
DHEA-dehydroepiandrosterone sulphate
17OPH-17 hydroxyprogesterone
ACTH - Adrenocorticotropic Hormone

How to cite the article:

Alwani M, Nimbalkar P, Halvadia H, Kadikar B, Kaku YD. Rare Case of Congenital Adrenal Hyperplasia: 46XX at Tertiary Care Centre, Visnagar, North Gujarat. JIHR 2024; 1(1): 41-46.