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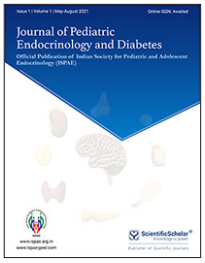
Journal of Pediatric Endocrinology and Diabetes



Case Report

Congenital aromatase deficiency – A virilizing masquerade!

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Received : 20 December 2021
Accepted : 23 February 2022
Published : 03 May 2022

DOI
10.25259/JPED_26_2021

Quick Response Code:

ABSTRACT

Congenital adrenal hyperplasia (CAH) is the most common cause of disorder of sex development in an XX individual. While 21-hydroxylase (CYP21A2) gene mutation is the most common subtype of CAH, aromatase deficiency due to mutations in the gene *CYP19A1* is a rare subtype. We report a 46,XX infant with virilized external genitalia, no clinical signs of glucocorticoid or mineralocorticoid deficiency, normal 17-hydroxyprogesterone and adrenocorticotropic hormone, and high levels of gonadotropins and testosterone with inappropriately low estradiol and ovarian cysts. Based on this clinical and biochemical consortium, next-generation sequencing was advised, in which a novel mutation in the gene *CYP19A1* was identified.

Keywords: *CYP19A1*, Congenital adrenal hyperplasia, Virilization, Hypergonadotropic hypogonadism, 46,XX DSD

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of disorders with abnormal glucocorticoid and sex steroid synthesis with/without mineralocorticoid deficiency. It is one of the most common genetic disorders of steroid synthesis, leading to virilization of a 46,XX fetus *in utero*, 21-hydroxylase (*CYP21A2*) deficiency being the most common enzyme deficiency followed by 3β-hydroxysteroid dehydrogenase and 11-hydroxylase deficiencies.[1]

Aromatase deficiency (AD) is a rare cause of virilization of 46,XX fetus associated with defective sex steroid production without concomitant glucocorticoid production. Antenatal maternal virilization is an important feature of AD, which causes imbalance among sex steroids – testosterone and estradiol in the fetoplacental unit due to enzyme deficiency (*CYP19A1*). We report here a newborn girl with virilization who was diagnosed with AD.

CASE REPORT

A 1-month-old girl, first born baby of a non-consanguineous union, was referred for the evaluation of clitoral enlargement. There was no history of episodes of salt-wasting yet. Antenatally, the mother developed cystic acne and hirsutism during the second trimester; however, there was no history of androgenic drug intake in the antenatal period. There was no family history of any disorder of sex development.

On examination, the baby weighed 3.3 kg (0–−2 SD), with a length of 51 cm (–1 to –2 SD) and blood pressure 60/42 mmHg (50–90th percentile). The labial folds were fused but not hyperpigmented, and there was a single perineal opening depicting Prader Stage 3. There were no

gonads appreciable in the labial folds or the inguinal region. The clitoral length and anogenital ratio were 16 mm (normal <0.9 cm) and 0.65 (normal <0.5) respectively. The systemic examination was unremarkable.

On investigation, the hormonal profile (at 1 month of age) was as follows: Follicle-stimulating hormone (FSH) 70.61 mIU/mL (normal 0.24–14.2), luteinizing hormone (LH) 13.7 mIU/mL (normal 0.02–7.0), total testosterone 1.0 ng/mL (normal 0.2–0.64 ng/mL), and estradiol 10 pg/mL (normal <25 pg/mL). The karyotype was 46,XX with fluorescent *in situ* hybridization test for SRY gene being negative. The pelvic ultrasonography revealed the uterus dimensions as 2.6 cm in long axis (normal prepubertal value is less than 4.0 cm), corpus: cervix ratio <1 (normal prepubertal ratio being <1), and right ovary 2.0 cc with a simple cyst measuring 0.6 × 0.8 × 0.6 cm, while the left ovary was 2.2 cc with a simple cyst measuring 1.8 × 1.8 × 1.3 cm (normal prepubertal ovarian volumes is <1 cc). Basal and adrenocorticotropic hormone (ACTH)-stimulated 17-hydroxyprogesterone (17OHP) values were 0.4 ng/mL and 1.41 ng/mL and were normal for age.

The diagnosis of AD was considered in view of the history of antenatal maternal hirsutism, elevated levels of gonadotropins for age, and inappropriately low estradiol levels in the face of high testosterone levels. Clinical exome sequencing by next-generation sequencing yielded a homozygous missense pathogenic variant in exon 9 of *CYP19A1* gene (p.Val370Met) confirming the diagnosis of AD. Based on the literature review, this particular variant has not been reported in 1000 genomes and disease database (ClinVar/Leiden Open Variation Database), research publication, or case reports. The *in silico* predictions of the variant were found damaging by sorting intolerant from tolerant technique.

DISCUSSION

Aromatase deficiency is an uncommon subset of CAH reported in both females and males that were first described in 1991 by Shozu *et al*.[1] It is inherited in an autosomal recessive fashion with homozygous or compound heterozygous mutations in *CYP19A1* gene. Girls with deficiency of the enzyme *CYP19A1* have been diagnosed with manifestations *in utero*, at birth, puberty, or even adulthood. Clinical phenotype varies with gender and age of presentation and may have a wide range of clinical presentation depending on the percentage of enzyme activity preserved and other modifying factors such as non-classic pathways of estrogen synthesis, variability in the core modifiers, or differences in androgen responses.

During intrauterine period, AD at fetoplacental unit manifests with signs of progressive masculinization of the mother in the form of deepening of voice, clitoromegaly, and acne. These antenatal clinical manifestations develop as the placenta cannot aromatize the testosterone and androgens produced by the fetal adrenal glands. The same androgens are also responsible for virilization of 46,XX fetus because of their inability to be aromatized to estrogen. Maternal virilization is not a consistent clinical finding, as even very low functional enzyme activity can prevent the antenatal masculinization.[2]

AD may remain clinically silent during infancy and early childhood, although abdominal pain and ovarian torsion may occur due to ovarian cysts. The ovarian cysts are formed due to the lack of feedback loop regulation of estradiol at the receptors at hypothalamic level. A plausible role of the lowest possible dose of estrogen replacement in childhood to prevent this complication as well as resetting of hypothalamic–pituitary–gonadal axis exists in addition to preventing metabolic complications while being careful to avoid acceleration of bone age, detection of estradiol on ultrasensitive assays, and appearance of early thelarche.[3]

Girls can present for the first time in adolescence with hypergonadotropic hypogonadism and primary amenorrhea if the virilization is subtle. Although majority of peripubertal girls manifest cystic development of ovaries due to chronic gonadotropin (FSH) stimulation, it has been reported that they can have normal ovarian sizes and echotexture without cysts as well. However, hypoplastic ovaries and streak echotexture have also been reported, though the mechanisms are unclear.[4,5]

The fertility prospects are unfavorable for a woman with AD and no successful pregnancies have been reported till date. AD simulates metabolic syndrome-like phenotype comprising central obesity, fatty liver, and insulin resistance.[5-8] The clinical manifestation of 46,XY individuals with AD is usually noticed after the first decade with subnormal bone mineral density and delayed closure of epiphyses, leading to persistent growth into adulthood with extremely tall stature.[9]

CONCLUSION

To identify, patients with AD in pre-pubertal age groups without genetic analysis can be a challenge. There are multiple case reports of misdiagnosis of AD as CAH and the patients being reared as males till diagnosis is established later in life.[9] In the settings with resource constraints, the clinical clues such as genital ambiguity without episodes of adrenal crisis or shock and the biochemical profile with the absence of hypoglycemia, hyponatremia, or hyperkalemia, normal serum cortisol, and 17OHP and ACTH, along with inappropriately elevated FSH, should alert the clinicians to look for a diagnosis other than classical forms of CAH for 46,XX DSD.

The lessons learned during the diagnosis and management of this case included:

- A life-threatening condition such as salt-wasting CAH should not be missed
- AD is an important differential diagnosis in patients with an antenatal history of maternal virilization
- While evaluating a case of 46,XX DSD, especially after ruling out CAH, inadvertent use of steroids should be discouraged until a confirmatory diagnosis is reached.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Kulkarni AJ, Agrawal PC. Congenital aromatase deficiency – A virilizing masquerade! J Pediatr Endocrinol Diabetes 2022;2:31-3.