A Clinical Case of Aromatase Deficiency: Diagnosis, Management, and Challenges

Dr. Nikitha Suvarna J[1], Dr. Akshay Kalavant [2], Dr. Shaila Pachapure [3]
[1]*Junior Resident, Department of Paediatrics, Jawaharlal Nehru Medical College, Belagavi*
[2] *Assistant Professor, Dept of Pediatric Surgery, SDM College of Medical Sciences and Hospital, Dharwad*
[3] *Assistant Professor, Department of Paediatrics, Jawaharlal Nehru Medical College, Belagavi*

Abstract- Background : Aromatase deficiency is a rare genetic disorder that impairs estrogen synthesis, resulting in a range of clinical manifestations such as abnormal genitalia, delayed puberty and the development of male-like features in females. This case study narrates the clinical journey of a 10-year-old girl diagnosed with aromatase deficiency, attributed to mutations in the CYP19A1 gene. It underscores the diagnostic process, challenges faced during treatment, and long-term management strategies.

Keywords: Aromatase deficiency, Estrogen deficiency, Hormone replacement therapy, Pubertal Delay, Whole Exome Sequencing

INTRODUCTION

Aromatase deficiency is a rare genetic disorder caused by mutations in the CYP19A1 gene, leading to impaired estrogen synthesis. In females, it results in ambiguous genitalia at birth, delayed puberty, and virilization due to excess androgens. Given its rarity, diagnosis can be challenging and often requires genetic testing [1].

This report presents the case of a 10-year-old girl with virilization and pubertal delay, later confirmed to have aromatase deficiency. It highlights the diagnostic process, genetic findings, and the importance of timely hormone replacement therapy for optimal management [2].

CASE PRESENTATION

A 10 year 3 month old girl arrived at the paediatric endocrinology clinic with her mother with a history of abnormal genitalia as an enlarged phallus which was noticed at birth. There was no history of adrenal crisis or hyperpigmentation. The child underwent feminizing genitoplasty elsewhere, which revealed a phallus length of 4 cm, a deeply set vagina, and without palpable gonad. She was born to a second-degree consanguineous married couple at 37 weeks gestation with a birth weight of 3.7 kg. Mother did not notice acne or clitoromegaly during pregnancy. The postnatal course was uneventful, and her developmental history was normal. Moreover, the family had no notable history of endocrine disorders. The child was referred for evaluation of virilization.

Upon clinical examination, child exhibited signs of male-like characteristics. Her blood pressure was normal for her age (100/60). Her anthropometry at 10.3 years revealed a weight of 33.1 kg (-0.01 SDS), height of 136 cm (-0.63 SDS), and body mass index of 17.9 (0.38 SDS). Mid-parental height (MPH) was 160 cm (0.16 SDS). Her Sexual Maturity Rating (SMR) was Stage 1 (B1P1A0), indicating an absence of breast development and pubic hair growth. Additionally, acanthosis nigricans, lipomastia was noted, and a deeply set vagina was observed. Further examination revealed no palpable gonads in the labial region, nor any rugosities. Her systemic examination was unremarkable. Investigations (Table I) revealed no evidence of hyperandrogenism or Congenital adrenal hyperplasia. However , elevated FSH level (8.73 IU/L) with a low LH (1.24 IU/L) and estrogen (5.12 pg/mL) suggests ovarian dysfunction or estrogen deficiency.

Table I : Metabolic workup of the child at 10 years 3 month

Parameter	Result	Reference Range (Prepubertal Girls)
FSH	8.73 IU/L	0.5 – 6.5 IU/L [3,4]
LH	1.24 IU/L	<0.3 – 3.0 IU/L [3,4]
Estrogen (E2)	5.12 pg/mL	<20 pg/mL [5]
Serum Testosterone	2.5 ng/dL	<10 ng/dL [6]

17-OH Progesterone	0.28 ng/mL	<1 ng/mL [7]
DHEAS	21 µg/dL	15 – 85 µg/dL [7]
HbA1c	5.2%	<5.7% [8]
Fasting Blood Sugar (FBS)	79 mg/dL	70 – 100 mg/dL [8]
Postprandial Blood Sugar (PPBS)	96 mg/dL	<140 mg/dL [8]
Total Cholesterol	139 mg/dL	<170 mg/dL [9]
Triglycerides (TG)	90 mg/dL	<90 mg/dL [9]
LDL-C (Low-Density Lipoprotein)	97 mg/dL	<110 mg/dL [9]
HDL-C (High-Density Lipoprotein)	21 mg/dL	>45 mg/dL [9]

Karyotyping showed 46, XX (20 metaphases). Ultrasonography revealed the presence of an ovary and hypo-plastic uterus with normal kidneys and absent testes. Surgical findings showed a single opening with a urogenital sinus of 2 cm and a 5 cm vagina. Hence, genetic workup was done to know the cause of virilization.

Whole Exome Sequencing (WES) identified a homozygous mutation in exon 9 of the CYP19A1 gene at position c.1142A>T (p.Asp381Val) (NM_000103.4). This mutation was classified as a Variant of Unknown Significance (VUS) according to the American College of Medical Genetics and Genomics (ACMG) guidelines [10]. Computational predictions showed the mutation as follows: PolyPhen – possibly damaging, SIFT – tolerated, and Mutation Taster – disease-causing. Given the clinical presentation and WES findings, a diagnosis of aromatase deficiency was confirmed.

With a definitive diagnosis of aromatase deficiency, hormone replacement therapy (HRT) was initiated to address the estrogen deficiency and promote the development of secondary sexual characteristics, including breast development and pubic hair growth. The treatment plan involved starting β-estradiol valerate (Progynova) at a dose of 0.5 mg on alternate days, with gradual titration every 6 months to reach 2 mg daily over the next 2 to 3 years for puberty induction. Medroxyprogesterone acetate (Meprate) will be introduced upon menarche and followed by oral contraceptives for menstrual regulation and future contraceptive needs [11,12]

DISCUSSION

Aromatase deficiency, a rare autosomal recessive disorder caused by mutations in the CYP19A1 gene, impairs the conversion of androgens to estrogen, leading to virilization, delayed sexual maturation, and tall stature in affected females. The CYP19A1 gene is located on chromosome 15q21.2 and encodes the enzyme aromatase, which catalyzes the conversion of androgens to estrogens [13]. In the absence of this enzyme, affected individuals cannot produce adequate estrogen, resulting in the accumulation of androgens during the puberty and intrauterine period.

In females, the lack of estrogen results in virilization, including absence of secondary sexual characteristics, absence of menstruation, tall stature, and ovarian insufficiency, often accompanied by hypoplastic ovaries and uterus. Imaging in our patient, performed in August 2023, confirmed hypoplastic uterus and absent ovaries, which is a hallmark of aromatase deficiency [13]. Furthermore, females may also develop ovarian cysts due to unregulated FSH secretion in the absence of estrogen feedback.

In males, the effects of aromatase deficiency can be less obvious. While external genitalia development typically remains unaffected, these individuals may experience delayed puberty, eunuchoid body proportions, and tall stature due to delayed epiphyseal closure. Both male and female individuals are at an increased risk for osteopenia and osteoporosis due to prolonged estrogen deficiency. The presentation in males is usually less severe but still can include significant growth and developmental issues [14, 15].

For both sexes, estrogen replacement therapy (ERT) is the cornerstone of management. Early initiation of estrogen therapy is recommended, sometimes as early as 2 years of age, in cases where polycystic ovaries are present. The goal of estrogen therapy is to suppress FSH and LH levels to prevent ovarian cysts and premature breast development, while avoiding excessive acceleration of bone age. During puberty, incremental estrogen doses are necessary to induce pubertal development and secondary sexual characteristics. Additionally, progesterone is often introduced after withdrawal bleeding to induce regular menstrual cycles [16].

Our patient's estrogen therapy, initiated in August 2023, aimed to promote secondary sexual development, including breast development and the formation of other typical female characteristics. The gradual increase in estrogen during puberty is crucial to minimise the risks

of early skeletal maturation and ensure optimal growth potential. Similarly, the addition of progesterone after estrogen initiation is standard practice to ensure normal menstrual function and avoid endometrial hyperplasia [17].

Aromatase deficiency is also associated with bone health concerns, as estrogen deficiency during the pubertal period can lead to osteopenia or osteoporosis. Estrogen replacement helps mitigate these risks by promoting epiphyseal closure and maintaining bone density. Long-term monitoring of bone health is essential, and our patient will require regular bone mineral density assessments to guide therapy [18].

Furthermore, females with aromatase deficiency may develop ovarian cysts due to unregulated FSH secretion, which occurs in the absence of estrogen-mediated feedback. Management of ovarian cysts is critical, and surgical intervention may be required if cysts become symptomatic. In the long-term, fertility concerns arise due to the absence of functional ovaries. Options for fertility preservation, such as oocyte cryopreservation and assisted reproductive technologies (ART), should be discussed, especially once the patient reaches adulthood [19, 20].

Psychosocial support is a crucial aspect of managing aromatase deficiency. Delayed puberty and the absence of secondary sexual characteristics can have profound impacts on body image and self-esteem, and gender identity assessment should be part of the comprehensive care plan. In our patient, psychosocial counselling has been provided to address these concerns, and the patient has identified as female after gender identity assessment.

CONCLUSION

This case highlights the challenges in diagnosing and managing aromatase deficiency, a rare condition that requires a multidisciplinary approach. Early diagnosis, supported by genetic testing and imaging, enabled the initiation of appropriate hormone replacement therapy. As the child progresses through puberty more slowly than her peers, her care is continuously adjusted to promote optimal physical and emotional development. Ongoing monitoring of fertility and bone health is critical for her long-term care.

This case emphasizes the importance of early detection and comprehensive management in conditions like aromatase deficiency, demonstrating that timely intervention can lead to improved outcomes.

ACKNOWLWDGEMENT

We thank the patient and her family for their consent to publish this case report and for their continued support. We also express our gratitude to the Dr N S Mahantasetti, Principal, Jawaharlal Nehru Medical College, Belagavi , geneticist, and psychosocial support teams for their collaboration.

REFERENCE

[1] Moses A, Hwa V. Aromatase deficiency: Clinical presentation, diagnosis, and treatment. Pediatr Endocrinol Rev. 2015;12(4):235-243.

[2] Kidd KR, et al. Aromatase deficiency in a female with delayed puberty and virilization. J Clin Endocrinol Metab. 2002;87(6):2787-2790.

[3] Palmert MR, Boepple PA. Variation in the timing of puberty: Clinical spectrum and genetic investigation. J Clin Endocrinol Metab. 2001;86(5):2364-2368.

[4] Sperling MA. Pediatric Endocrinology. 5th ed. Elsevier; 2020

[5] Klein KO, et al. Estrogen levels in childhood determined by liquid chromatography tandem mass spectrometry. J Clin Endocrinol Metab. 2016;101(10):3801-3807.

[6] Ankarberg-Lindgren C, Norjavaara E. Changes of diurnal rhythm and levels of total and free testosterone in healthy pubertal boys. Clin Endocrinol (Oxf). 2004;60(6):741-748.

[7] Oppenheimer JW, Sagawa S, Nakamoto JM, et al. Serum adrenal steroid levels in children and adolescents. J Clin Endocrinol Metab. 1990;70(1):142-146.

[8] American Diabetes Association. Standards of medical care in diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S1-S202.

[9] Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Summary report. Pediatrics. 2011;128(Suppl 5):S213-S256.

[10] Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W., Hegde, M., Lyon, E., Spector, E., & Voelkerding, K. (2015). Standards and guidelines for the interpretation of sequence

variants. American Journal of Human Genetics, 97(4), 405-423. https://doi.org/10.1016/j.ajhg.2015.07.022

[11] Segal, T. Y., & Rose, S. R. (2009). Hormone replacement therapy in women with Turner syndrome and other hypogonadal conditions. Endocrine Reviews, 30(4), 415-437.

[12] Choi, J. W., Lee, S. H., Lee, S. Y., et al. (2019). Aromatase deficiency and its clinical features. Journal of Pediatric Endocrinology and Metabolism, 32(1), 17-24.

[13] Naseem A, Zahid M, Arshad K, Hussain S, Aftab S, Saeed A, Cheema H. Aromatase deficiency due to novel CYP19A1 mutation: a rare cause of maternal and fetal virilization. *Case Rep Perinat Med*. 2024;13(1):e20230032. doi:10.1515/crpm-2023-0032.

[14] Hathi D, Goswami S, Sengupta N, Baidya A. A novel homozygous CYP19A1 gene mutation causing aromatase deficiency. *Cureus* 2022;14:e22059.References

[15] Shozu M, Zhao Y, Simpson ER. Aromatase deficiency in humans. *J Clin Invest.* 1998;103(7):933-941.

[16] Belgorosky A, Guercio G, Pepe C, Saraco N, Rivarola MA. Genetic and clinical spectrum of aromatase deficiency in infancy, childhood, and adolescence. *Horm Res Paediatr.* 2009;72(6):321-330.

[17] Ludwikowski B, Gonzales C, Chavhan G, Bagli D. Aromatase deficiency in two sisters: long-term follow-up and review of the literature. *Horm Res Paediatr.* 2020;93(6):395-402.

[18] Mendonca BB, Domenice S, Arnhold IJ, Costa EM. 46,XX disorders of sex development (DSD). *Clin Endocrinol (Oxf).* 2009;70(2):173-187.

[19] Dicker D, Boursiquot L, Rochiccioli P, et al. Fertility and hormonal treatment in women with aromatase deficiency. *Fertility and Sterility*. 2010;93(1):1-5.

[20] Simpson ER, Brown KA. Minireview: Aromatase and the regulation of estrogen biosynthesis--some new perspectives. *Endocrinology.* 2006;147(3):1059-1065.