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Case Report

Impact of estrogen replacement on growth, skeletal maturation, bone density and body composition in a girl with novel aromatase gene mutation

Neha Agarwal, Rishi Shukla, Anurag Bajpai*

Department of Endocrinology, Centre for Diabetes Endocrinology and Research, Regency Healthcare Private Limited, Kanpur, Uttar Pradesh, India

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***Correspondence:**
Dr. Anurag Bajpai,
E-mail: dr_anuragbajpai@yahoo.com

ABSTRACT

Aromatase deficiency is a rare autosomal recessive disorder characterized by impaired androgen to estrogen conversion. We report a 13.5-year-old girl initially misdiagnosed as simple virilising 21 hydroxylase deficiency who presented with delayed puberty. Work-up showed aromatase deficiency due to novel mutation in the aromatase gene. Estradiol replacement was associated with increased growth, skeletal maturation, bone density and adiposity. Early estrogen treatment in our case may have prevented metabolic complications and ovarian cysts.

Keywords: Aromatase deficiency, Estrogen, Disorder of sexual development

INTRODUCTION

Aromatase deficiency is a rare autosomal recessive disorder characterized by impaired androgen to estrogen conversion.[1] Its manifestations reflect the effects of estrogen deficiency on one hand and androgen excess on the other, and include atypical genitalia, delayed puberty, primary amenorrhoea, hyperandrogenism, and maternal virilisation during pregnancy.[2-5] Estrogen regulation of epiphyseal fusion, growth, bone mineralization and body composition suggest a multi-system impact of aromatase deficiency. We report the effects of estrogen replacement on growth, skeletal maturation, bone mineralization and body composition in a girl with novel compound heterozygous aromatase mutation, initially misdiagnosed as 21 hydroxylase deficiency.

CASE REPORT

This thirteen-and-a-half-year-old girl presented to our clinic with concerns of delayed puberty. She was born at term to non-consanguineous parents and presented in the neonatal period to a different centre with atypical genitalia. Medical records from that time showed clitoromegaly, labio-scrotal fusion, without palpable gonads. A diagnosis of simple virilising congenital adrenal hyperplasia due to 21 hydroxylase deficiency was made by the treating physician based on 46 XX karyotype and mildly elevated 17-hydroxyprogesterone (17OHP) levels. She was started on hydrocortisone and underwent clitoroplasty at one year of age. 17OHP levels remained low throughout follow-up, prompting a reduction in hydrocortisone doses and gene sequencing for the 21-hydroxylase gene. The genetic study excluded 21 hydroxylase deficiency and led to the discontinuation of hydrocortisone at the age of 12 years. 17OHP levels remained normal after stopping hydrocortisone. She was given estradiol valerate (1 mg daily for four months) by the treating physician at 13 years and referred to our centre two months after stopping estradiol.

At presentation to our clinic (age of 13.5 years), she had a weight of 34.8 kg (-1.98 SDS), height of 149.5 cm (-1.48

SDS), BMI of 15.7 kg/m2 (-1.65 SDS), stage II breast and axillary hair and stage IV pubic hair development. Work-up showed high FSH (98 mIU/l; reference range 3.5-12.5mIU/l) and LH (49 mIU/l; reference range 2.4-12.6 mIU/l), with normal 17-OHP (0.4 ng/ml; reference range 0.1-0.8 ng/ml) and low AMH (less than 0.05 ng/ml; reference range 1.0-4.0 ng/ml) levels. Pelvic ultrasonography showed pre-pubertal endometrial stripe (endometrial thickness 1.7 mm), with normal ovaries with no ovarian cyst. Bone age was delayed at 10.8 years (-2.8 SDS, Bone Xpert assessed Tanner Whitehouse 3 method).

She was reassessed for disorders associated with disorder of sexual development at birth followed by ovarian insufficiency. The mother gave a history of virilisation (acne, voice change, and hirsutism) during pregnancy that resolved post partly. Aromatase deficiency was considered because of maternal virilisation, genital ambiguity at birth, ovarian insufficiency, and delayed bone age. Targeted gene sequencing revealed two novel heterozygous likely pathogenic variants in the aromatase gene (first c343 C>T; p. Arg115Ter in exon 4 causing stop codon and premature truncation of the protein at codon 115 and the second in exon 5 c.552 T>G; p. Tyr184Ter causing the stop codon and premature truncation of the protein at codon 184).

Puberty was induced with low dose estrogen (0.25 mg of estradiol valerate) and titrated to adult dose (2 mg of estradiol valerate) over two years. She developed vaginal bleeding 2.5 years after the onset of treatment. Estrogen replacement increased height (149.5cm, -1.5 SDS to 160.8 cm, +0.6 SDS), body mass index (15.6 kg/m2, -1.65 SDS to 19.7 kg/m2, -0.14 SDS), bone age (11 to 13 years), total body less head BMD Z score (GE Lunar, -0.9 to 0.0) and bioelectrical impedance analyser assessed total body fat (20.1% to 29.7%) over a two year period. Treatment did not affect LH (37 mIU/l), FSH (76.8 mIU/l), and AMH levels (less than 0.01 ng/ml). Metabolic parameters, blood pressure, blood sugar, and lipid profile were normal throughout follow-up. An informed consent was obtained from the parents.

DISCUSSION

Our case highlights the importance of considering aromatase deficiency in an appropriate setting to allow early diagnosis and treatment. False diagnosis of 21 hydroxylase deficiency in our case caused prolonged inadvertent exposure to glucocorticoids.

Aromatase deficiency is frequently misdiagnosed as 21 hydroxylase deficiency in girls with atypical genitalia. Maternal virilisation during pregnancy, due to conversion of non-aromatized androgens to testosterone, is an important pointer to aromatase deficiency and should be enquired in all girls with atypical genitalia.[5]

Persistent FSH elevation in our case may reflect inadequate estrogen dose, as very high estrogen levels (400-600 pmol/L) are required to inhibit gonadotropin levels in aromatase deficiency.[6] The need of high dose estradiol to suppress gonadotropin in the wake of the normal uterine, growth plate and bone mineralization is, however, questionable. Moreover, granulosa cell inhibin B is an important inhibitor of FSH secretion.[7] Exhausted ovarian reserve in our patient due to persistent FSH elevation would have caused inhibin deficiency contributing to FSH elevation. Undetectable AMH levels in our case suggests diminished ovarian reserve.[8] Fetal hyperandrogenism in our case may have desensitised gonadotrophs to progesterone causing post-natal LH elevation. Normal ovarian size and lack of ovarian cysts in our case may be due to early estrogen initiation. High FSH levels cause the development of multiple ovarian cysts that do not progress beyond the initial stage

An increase in skeletal maturation, growth, and bone density with estrogen in our case reiterates its importance in growth plate maturation and bone mineralisation.[6] We did not observe adverse metabolic impact in contradistinction to dyslipidemia and insulin resistance in men and women with aromatase deficiency.[9,10] Early estrogen initiation in our case might have ameliorated the metabolic impact of its deficiency.

CONCLUSION

Our case reiterates the importance of considering aromatase deficiency in the differential of atypical genitalia and provides insights into estrogen's role on gonadotroph, ovarian, growth plate, and bone mineralization. Novel mutations were identified in our case. Further exploration of the multi-system effect of estrogen would unravel pathophysiological insights.

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