

## Case Report

# Aromatase Deficiency: An Unusual Cause for Primary Amenorrhea with Virilization

K Sudeep<sup>1</sup>, Joison Abraham<sup>1</sup>, Lakshmi Seshadri<sup>2</sup>, MS Seshadri<sup>1</sup>

### Abstract

The most common cause for menstrual abnormality and virilization in children and adolescents would be congenital adrenal hyperplasia. An elevated 17(OH) progesterone is invariably seen in this condition. Aromatase deficiency can also lead to a similar presentation but differs in several aspects. The age of onset of the clinical manifestations, the phenotype, biochemical abnormalities and karyotype help us to arrive at a definitive diagnosis. However sometimes the history is atypical, biochemical abnormalities may overlap between the different conditions and prior treatment may modify the clinical features. We report here a young adult with a late presentation of aromatase deficiency to highlight the differences between the two conditions.

A 27 year old lady presented to us with history of primary amenorrhea and masculine voice. She lacked feminine secondary sexual characters, had eunuchoid body habitus and prominent clitoromegaly. Consanguinity in the parents, a neonatal sibling death and elevated basal 17(OH) progesterone in the patient suggested a possibility of congenital adrenal hyperplasia. But the eunuchoid body habitus raised FSH and lack of response to dexamethasone led to a diagnosis of aromatase deficiency. Variability in the degree of aromatase deficiency is known such that maternal virilization may not occur in pregnancy. Aromatase deficiency should be suspected when a patient presents with primary amenorrhea, absence of female secondary sexual characters, virilization and tall stature with eunuchoid body proportions, and biochemical features of ovarian failure. In our country one should be aware that late presentation and prior treatment may modify disease expression and contribute to the diagnostic challenge.

### Introduction

The commonest cause for virilization and menstrual abnormality in an adolescent girl without electrolyte disturbances or hypotension is simple virilizing congenital adrenal hyperplasia. In our country genital ambiguity at birth is often overlooked and children usually present later with growth disorders or menstrual abnormalities. We report here a patient who presented with primary amenorrhea and virilization due to an unusual cause, aromatase deficiency.

### Case Report

A 27 year old unmarried lady presented to Endocrinology OPD with history of primary amenorrhea. She had noted deepening of voice and pubarche around age 11. She had noticed clitoromegaly much later but did not know that this was abnormal. She did not notice other features of virilization such as hirsutism, frontal balding or masculinization of body habitus. Spontaneous breast development and menarche did not occur. Lack of parental awareness, poor socioeconomic circumstances and lack of education were the causes for late presentation.

She was born of a consanguineous marriage. Her mother had not noticed virilization during pregnancy. The patient was born at term and mother felt that she had 'normal' female external genitalia. There was no history of recurrent vomiting, hyperpigmentation or recurrent hospital admissions in childhood or adolescence, or prior abdominal surgery or inguinal hernia repair. She had normal hearing and female sexual orientation. Her mother had noticed that she was taller than her female siblings. Of the three siblings (one male and two female)

one younger sister died of unknown cause at the age of 10 days. One nephew had died at the age of one month. All her living siblings were married and had children. There was no history of hirsutism or infertility in her relatives.

Evaluation elsewhere one year before presentation showed a hypoplastic uterus on a CT scan, a high total serum testosterone (146 ng/dl) and an elevated 17-OH progesterone (4.6 ng/ml). She was diagnosed to have virilizing congenital adrenal hyperplasia at that time but a trial of dexamethasone for 3 months failed to induce menstrual cycles. She had therefore been prescribed cyclical estrogen-progesterone pills. Normal breast development and regular withdrawal bleeds occurred only while she was on the combination pill.

She was 159 cm tall (Figure 1) with arm span of 170 cm and upper segment and lower segment ratio of 0.89 confirming eunuchoidism. The accurate mid parental height could not be determined in our patient as her father is not alive. Her mother's height is 155 cm and her other siblings are shorter than her. She had a masculine voice. She had a dark complexion but normal blood pressure. Ferriman-Gallwey score was 6/36. Axillary hair was normal and pubic hair was stage 5 with male escutcheon but there was no frontal hairline recession. Breasts were Tanner stage 3. She had prominent clitoromegaly with a clitoral index of 600 mm<sup>2</sup> (Figure 2). Labia were poorly developed but not fused. Urethral and vaginal orifices were seen separately. The gonads were not palpable and no inguinal masses or surgical scars were evident. She was normotensive.

Our patient presented with primary amenorrhea and failure of spontaneous development of secondary sexual characters. Follicle stimulating hormone level (FSH) was done to rule out primary ovarian failure and it was elevated at 80 mIU/ml. Other investigations revealed normal serum electrolytes, a serum total testosterone of 119 ng/dl (normal female range 50 - 100) and

Departments of <sup>1</sup>Endocrinology, <sup>2</sup>Obstetrics and Gynecology, Christian Medical College, Vellore-632 004

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Fig. 1 : The lady with Eunuchoid habitus

serum basal 17-hydroxy Progesterone of 10.6 ng/ml (n 0.11 – 1.2), in the range seen in congenital adrenal hyperplasia. Karyotyping revealed normal 46XX pattern with no detectable Y element on Fluorescent in situ hybridization. As she had been treated with a combination OCP for about 9 months estradiol measurement and skeletal X Rays for bone age were not performed. Tall stature, eunuchoid body proportions, normal response to estrogen-progesterone combination pill, elevated FSH and testosterone led to a diagnosis of aromatase deficiency.

## Discussion

Aromatase deficiency<sup>1</sup> was considered incompatible with life till the first description in 1991 of a Japanese newborn girl with an aromatase P450 gene defect.<sup>2</sup> It is an autosomal recessive condition presenting in girls as disorder of sexual differentiation (46XX DSD) with ambiguous genitalia. Children with this disorder have genital ambiguity at birth<sup>1</sup> but have a normal karyotype. The failure of conversion of androgenic precursors to estrogen in the ovaries leads to androgen excess and estrogen deficiency and the characteristic clinical features in this condition.

The classic clinical features include virilization of the mother during second half of pregnancy, clitoromegaly and posterior labioscrotal fusion of the neonate at birth; unremarkable childhood and absence of growth spurt, absence of spontaneous breast development at the time of puberty and primary amenorrhea. Virilization worsens at puberty as



Fig. 2 : Clitoromegaly

ovarian androgens are produced in response to the normal gonadotropin surge in puberty and the stimulated ovaries may become multicystic. The lack of estrogen leads to tall stature and eunuchoid proportions when these children present later in life. These patients have a delayed bone age and a propensity for osteoporosis due to estrogen deficiency. However the clinical picture may vary depending upon the severity of aromatase deficiency and the clinical picture may be modified by prior treatment with estrogen and progesterone.

Our patient was a virilized female, had a uterus, had elevated basal 17 hydroxy progesterone levels and strikingly elevated testosterone levels. History of parental consanguinity and neonatal sibling death raised the possibility of virilizing congenital adrenal hyperplasia. But the presence of eunuchoid body habitus, tall rather than short stature, failure of spontaneous breast development and a high FSH indicative of ovarian failure pointed to aromatase deficiency. The lack of response to glucocorticoid therapy also negated the diagnosis of simple virilizing congenital adrenal hyperplasia.

An ovotesticular type of disorder of sexual differentiation (True hermaphroditism) the other differential diagnosis to be considered, would have presented with palpable or visible gonads, variable karyotype (46XX / 46XY / Mosaic) , spontaneous breast development and menarche and histological demonstration of functioning ovarian and testicular tissues. However these features were absent in our patient and computed tomography in our patient showed only mullerian structures.

Estrogen resistance was not considered as she had developed secondary sexual characters and withdrawal bleeding with cyclical estrogen therapy. Further estrogen resistant females would not show serum testosterone elevation or virilization

Though most of the features fit in with aromatase deficiency in our patient, there were atypical features like infant deaths in the family, lack of maternal virilization during pregnancy, history of 'normal' genitalia at birth, raised 17 OHP and absence of demonstrable cystic ovaries. Two decades earlier, placental aromatase deficiency was considered incompatible with life. However it was soon realized that a number of children with aromatase deficiency survive into adulthood because the lack of expression of aromatase is not absolute but variable in this disorder. Even 1% residual placental aromatase activity of

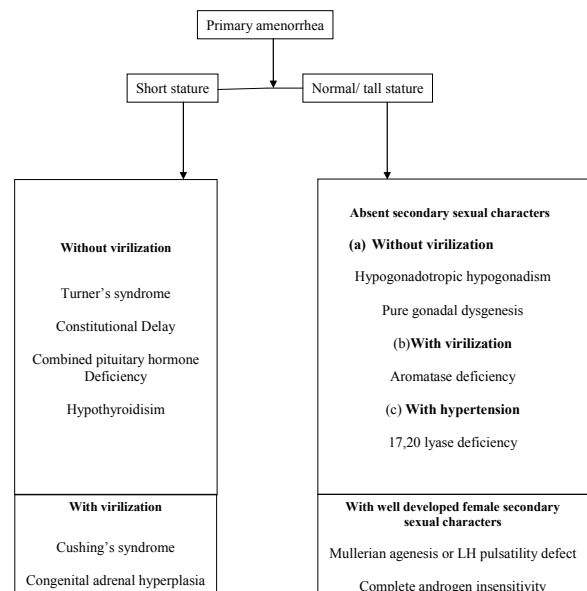
**Table 1 : Similarities and differences between simple virilizing CAH and Aromatase deficiency**

Features	Virilizing CAH	Aromatase deficiency
Genital ambiguity at birth	+	+
Increased pigmentation	++	-
Stature	Short	Tall and eunuchoid
Breast development	Normal	Absent
Menarche	Variable	No spontaneous menarche
Exaggerated virilization at puberty	-	++
17 (OH) Progesterone	↑↑	↑
Testosterone	↑	↑↑
FSH	N	↑↑

wild-type P450arom enzyme seems to be enough to prevent virilization of the mother during pregnancy.<sup>1</sup> This may explain the lack of virilization in our patient's mother during pregnancy.<sup>3</sup> Case reports<sup>2,4</sup> of aromatase deficiency with high 17 OHP due to precursor accumulation secondary to the block in estrogen synthesis indicate that this disorder may indeed be a differential diagnosis for simple virilizing CAH. Even though the elevated 17 (OH) progesterone may mimic virilizing congenital adrenal hyperplasia, patients with aromatase deficiency tend to be tall with delayed bone age. Table 1 summarizes the similarities and differences between the two conditions. The absence of enlarged or cystic ovaries in our patient is probably due to prior long-term treatment with the combination oral contraceptive pill. For the degree of clitoromegaly, except for the voice change and body habitus she lacked other features of hyperandrogenism like hirsutism, acne and labial fusion. This may be due to tissue selective expression of p450arom and or due to variable target tissue sensitivity to androgen.

If parents fail to notice genital ambiguity at birth, the child may be brought for primary amenorrhea and around the expected age of puberty, virilization and primary amenorrhea may dominate the clinical picture as in our patient.

When they are brought for primary amenorrhea, ultrasound reveals hypoplastic uterus and enlarged cystic ovaries if they are untreated but the uterus and the ovaries may be normal sized as in our patient if they have received a combination OCP for sufficient duration of time. These patients respond to estrogen and progesterone treatment with normal breast development and regular withdrawal bleeds. The high FSH level in aromatase deficiency is due to failure of normal follicular development in the presence of estrogen deficiency and androgen excess. Despite elevated testosterone levels psychosexual orientation is female presumably because the serum testosterone levels are only moderately elevated in utero. An approach to primary amenorrhea is given as a flow chart (Figure 3).



**Fig. 3 : A clinical approach to primary amenorrhea**

In summary, aromatase deficiency should be suspected in a normal/tall statured girl with primary amenorrhea, eunuchoid body proportions, failure of spontaneous breast development, virilization, presence of Mullerian structures on ultrasound, high FSH values in the menopausal range, 46XX karyotype and good response to estrogen-progesterone therapy. Maternal virilization during pregnancy may not be noted or reported or may be absent if aromatase deficiency is partial.

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