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Review

Puberty in patients with aromatase disorders

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Abstract

Aromatase encoded by *CYP19A1* is a microsomal enzyme that converts androgens to estrogens. *CYP19A1* loss-of-function because of biallelic mutations leads to aromatase deficiency, whereas *CYP19A1* overexpression because of genomic rearrangements results in aromatase excess syndrome. These aromatase disorders exert various effects on sexual maturation and stature growth during puberty. Specifically, aromatase deficiency is associated with aberrant linear growth, ovarian cysts, metabolic symptoms, and virilization, whereas aromatase excess syndrome causes prepubertal or peripubertal onset gynecomastia and bone age advancement with or without mild hypogonadism. The pubertal phenotypes of aromatase disorders likely reflect the accumulation or deficiency of sex hormones, as well as perturbed gonadotropin secretion.

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Introduction

Aromatase is a microsomal cytochrome P450 enzyme that converts testosterone to estradiol (E_2) and androstenedione to estrone (E_1) (Figure 1) [1,2]. The enzymatic activity of aromatase determines the balance between androgens and estrogens in individuals of both sexes. The aromatase gene, *CYP19A1* on 15q21.2, is expressed in several tissues including the placenta, ovary, brain, bone, and skin [1,2]. *CYP19A1* expression is tightly regulated by multiple tissue-specific promoters [1,3].

Loss-of-function mutations of *CYP19A1* cause aromatase deficiency characterized by androgen accumulation in women and estrogen deficiency in both men and women [4]. In contrast, overexpression of *CYP19A1* results in aromatase excess syndrome (AEXS) characterized by estrogen excess in men and less significantly in women [5]. This review article introduces the molecular and clinical characteristics of aromatase deficiency and AEXS, with special focus on the pubertal phenotypes of the affected individuals.

Aromatase deficiency

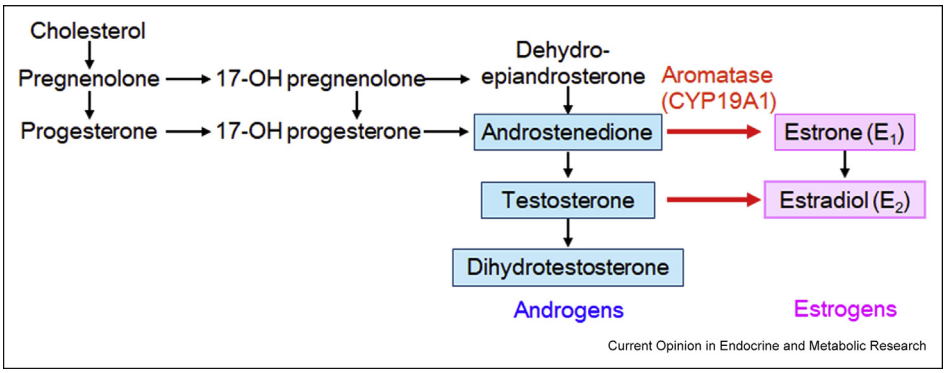
Aromatase deficiency is a rare autosomal recessive disorder caused by homozygous or compound heterozygous loss-of-function mutations in *CYP19A1* (Table 1) [1,2]. After the first report in 1991 [4], more than 40 patients with this condition have been reported ([6–23] and several other reports). Known pathogenic *CYP19A1* mutations include missense, frameshift, indel, and splice site variants, which are widely distributed in the coding exons. In addition, a 600 bp deletion and a 27 bp duplication in *CYP19A1* were also reported [20,21]. Most of these mutations likely cause complete or nearly complete loss of aromatase activity [20], whereas p.F234del and p.R435C were shown to retain 16–19% and 0.7–1.5% *in vitro* enzymatic activities, respectively [19,20]. These two variants have been linked to a relatively mild pubertal phenotype in women [2,19,20].

Clinical features of male patients with aromatase deficiency

The most characteristic feature of male patients with aromatase deficiency is continuous increase in height after puberty, along with genu valgum, unfused epiphysis, and osteopenia or osteoporosis [14]. The lack of growth arrest after puberty results in a tall stature in adulthood (Figure 2) [18]. Such skeletal features likely arise from E_2 deficiency in the bone tissues because it is known that in physiological conditions, bone maturation and mineralization are mediated primarily by E_2 [24,25]. Indeed, similar skeletal changes were observed in male patients with estrogen insensitivity because of mutations in the estrogen receptor alpha gene [26].

Male patients with aromatase deficiency usually exhibit normal male-type external genitalia at birth and

Figure 1



The function of aromatase. Aromatase converts androgens (blue) to estrogens (pink).

Table 1

Molecular and clinical characteristics of aromatase deficiency and aromatase excess syndrome.

	Aromatase deficiency		Aromatase excess syndrome	
	Male	Female	Male	Female
Molecular bases				
Known genetic causes	Mutation in *CYP19A1* exons		Chromosomal rearrangement on 15q21.2	
CYP19A1 function/ expression	Loss-of-function		Overexpression	
Phenotype				
Salient clinical feature	Tall adult height	Virilized genitalia at birth	Gynecomastia	Mostly asymptomatic?[a]
Pubertal sexual development	Normal?	Variably impaired	Normal or impaired	Normal or precocious?[a]
Bone age	Delayed	Delayed	Advanced or normal	Advanced or normal?[a]
Other common features	Metabolic symptoms	Ovarian cysts, (Metabolic symptoms)[b]	None	None?[a]
Blood endocrine findings (in peripubertal or postpubertal patients)[c]				
FSH	High	High	Low	No data
LH	Normal or high	Normal or high	Normal or low	No data
Testosterone	Variable	High	Normal or low	No data
E2	Barely detectable	Extremely low	Normal or high	No data

[a] Few data are available for female patients with aromatase excess syndrome. Precocious puberty, macromastia, and short stature were observed in some cases.

[b] Because female patients usually undergo estrogen supplementation from the pubertal age, the frequency of metabolic symptoms remains unknown.

[c] These findings may be absent in prepubertal children.

experience normal sexual maturation during puberty [12]. However, the frequency of cryptorchidism in these individuals appears to be higher than that in the general population [14]. Furthermore, it remains unknown whether the timing of pubertal onset in these patients is completely normal, because mild precocious puberty was observed in one case [11]. Most patients were reported to exhibit spermatogenic failure and infertility, which may be associated with reduced estrogen production in testicular Leydig cells [25,27]. Decreased libido and sexual behavior have also been documented [25]. In addition, metabolic symptoms, such as obesity, insulin resistance, dyslipidemia, acanthosis nigricans, and nonalcoholic fatty liver disease, have frequently been observed in untreated male patients [14,18]. Such metabolic symptoms are predicted to result from E_2 deficiency in local tissues [15,22], although it is also possible that the decrease in aromatase activity itself plays an role in the development of these symptoms [2].

In almost all male patients examined so far, blood follicle stimulating hormone (FSH) levels were constantly increased, whereas E_2 levels were extremely low or undetectable (Table 1) [12,14]. Blood levels of luteinizing hormone (LH) and testosterone were variable; they were elevated or within the normal range, and mildly

Figure 2

Typical growth of patients with aromatase disorders. Models of the growth pattern of patients with aromatase deficiency (the left panel) and aromatase excess syndrome (the right panel) are shown. The black and white dots represent the height and bone age, respectively. The lines depict the mean, ± 1 SD, and ±2 SD of the general population.

reduced testosterone levels were also reported in some cases. High FSH levels in these patients can be attributed to the impaired negative feedback of E_2 on the hypothalamus–pituitary axis [28,29]. Estrogen supplementation therapy usually ameliorates skeletal features, elevated FSH levels, and metabolic symptoms in the patients, indicating that E_2 deficiency is the major cause of such clinical features [14].

Clinical features of female patients with aromatase deficiency

Female patients with aromatase deficiency usually present with markedly virilized external genitalia at birth [2,16,23]. Also, the patients' mothers frequently manifest virilization during pregnancy [10,14]. Fetal and maternal virilization of aromatase deficiency are ascribable to testosterone accumulation in the placenta [20]. Furthermore, a certain percentage of previously reported female patients exhibited progressive virilization during puberty, which is indicative of defective androgen metabolism in the ovary [22]. In addition, female patients often develop ovarian cysts at any time from infancy to adulthood [20]. Enlarged ovaries were also described [13]. This can be explained by continuously high blood levels of FSH (described below) and impaired androgen metabolism in the ovary [20].

During puberty, female patients develop hypergonadotropic hypogonadism [2,19,20]. A substantial percentage of previously reported patients completely lacked sexual maturation at the pubertal ages, whereas some patients manifested spontaneous breast budding as well as regular menses [13,20]. Impaired pubertal sexual maturation is consistent with reduced E_2 production in the ovary [19]. Relatively mild pubertal phenotypes in patients with p.F234del or p.R435C likely reflect partial enzymatic defects of the mutant proteins [2,19,20]. Bone ages were often delayed, and the pubertal spurt was not apparent [20]. In addition, insulin resistance and dyslipidemia were observed in some female patients [20]. However, because female patients with aromatase deficiency usually receive E_2 supplementation from their teens, it remains unknown whether untreated female patients develop skeletal and metabolic abnormalities similar to those in untreated male patients [30]. Moreover, little is known about the fertility and gender identity of female patients with aromatase deficiency.

Endocrine examinations for female patients showed high blood gonadotropin levels, as well as high testosterone levels and low or undetectable E_2 levels. In particular, blood FSH levels were invariably elevated in all patients of various ages, whereas levels of LH and testosterone were variable [23]. The enhanced

responses of FSH and LH to GnRH stimulation suggest defective negative feedback of E_2 on the hypothalamus–pituitary axis [8,31]. Notably, in some cases, high FSH levels and ovarian cysts persisted even after estrogen supplementation therapy [13,32,33]. This indicates that defective androgen metabolism in local tissues, such as the brain and ovary, plays a critical role in the development of these features.

Aromatase excess syndrome

AEXS is an extremely rare autosomal dominant disorder caused by heterozygous genomic rearrangements of chromosome 15 (Table 1) [34,35]. After the initial report in 2003 [5], about 30 cases have been reported [36–44]. Pathogenic chromosomal rearrangements leading to AEXS include inversions and submicroscopic deletions, which create chimeric genes consisting of the coding region of *CYP19A1* and promoters of widely expressed neighboring genes [5,41]. Furthermore, submicroscopic tandem duplications encompassing the coding region or promoters of *CYP19A1* have also been identified in patients with AEXS [42]. The formation of chimeric genes is predicted to result in ectopic expression of *CYP19A1*, whereas tandem duplications likely increase *CYP19A1* expression only in the native aromatase-expressing tissues [42]. Therefore, inversions and deletions lead to more severe phenotypes than duplications.

Clinical features of male patients with AEXS

The most characteristic feature of male patients with AEXS is prepubertal or peripubertal onset gynecomastia [34,35]. Gynecomastia is a nonspecific symptom resulting from an imbalance between estrogens and androgens [45,46]. Thus, several conditions other than AEXS, such as mutations in the androgen receptor gene or exposure to estrogenic chemicals, can also cause gynecomastia [45–47]. AEXS is one of the major cause of hereditary gynecomastia. Gynecomastia in AXES patients can be attributed to the increased conversion of testosterone to E_2 in the testis and other tissues [5]. Moreover, the prepubertal onset of gynecomastia implies that adrenal androgens also serve as a substrate for estrogen production [43]. The degree of breast budding in AEXS patients varies from Tanner stage 2 to stage 4 [41]. Severe gynecomastia was occasionally subjected to surgical removal or aromatase inhibitor treatment [5,45].

Male patients with AEXS usually show normal external genitalia at birth and normal fertility in adulthood [34,35]. Most patients experience normal sexual maturation during puberty, whereas mildly impaired masculinization, such as relatively small testes and scarce facial hair, has been observed in some patients [34,35]. Subnormal masculinization of such patients can be primarily ascribed to decreased FSH secretion [41], whereas increased testosterone metabolism may also contribute to this feature to some extent. Advanced bone age in childhood and short stature in adulthood because of estrogen exposure of the bone are characteristic features of AEXS, although these features are not shared by all patients [5,41,42]. Thus far, gender incongruousness has not been described in male patients with AXES, indicating that estrogen exposure during the fetal period does not affect male sexual development of the brain.

Reportedly, adolescent and adult male patients with AEXS invariably manifested FSH-dominant hypogonadotropic hypogonadism [5,41]. Blood FSH levels were low at baseline and poorly responded to GnRH stimulation. The low FSH levels can be ascribed to the negative feedback of E_2 on the hypothalamus and/or pituitary [28,29]. Blood E_2 levels were above or within the normal range, whereas testosterone levels were usually low normal or markedly decreased. Previous studies have revealed that E_2/testosterone ratios are invariably elevated in adult patients, although these ratios vary in prepubertal children. Blood E_1 levels were elevated in all male patients examined [41].

Clinical severities of male patients are correlated with the types of genomic rearrangements [42]. Specifically, patients with inversions showed a relatively early (prepubertal) disease onset, severe gynecomastia, markedly advanced bone age, and short adult height. Significantly elevated blood E_2 levels were often observed in these patients. In contrast, patients with duplications exhibited relatively mild gynecomastia with a late (pubertal) onset and normal adult height. These patients showed normal or only slightly elevated E_2 levels. Patients with deletions manifested an intermediate phenotype. These results imply that the clinical severity of male patients is determined primarily by the expression levels of *CYP19A1* [41,42].

Clinical features of female patients with AEXS

There are only a few reports of female patients with AEXS [37,38]. Women with AEXS may lack conspicuous clinical manifestations, although various features indicative of estrogen excess, such as macromastia, precocious puberty, irregular uterine bleeding, enlarged uterine size, and short adult height, have been described in some cases. Thus far, the growth patterns and endocrine profiles of women with AEXS have poorly been investigated.

Additional notes for aromatase and puberty

Lee *et al.* [48] have suggested that a tetranucleotide repeat polymorphism in the *CYP19A1* promoter is associated with precocious puberty in women. Furthermore, Stueve *et al.* [49] have linked the degree of *CYP19A1* promoter methylation to the pubertal timing in urban

girls. Hence, it is possible that not only aromatase deficiency and AEXS but also relatively minor changes in *CYP19A1* expression levels can affect sexual maturation during puberty. This notion awaits further validation.

Conclusions

Aromatase disorders exert various effects on pubertal sexual maturation and growth pattern in patients or both sexes. Specifically, aromatase deficiency is associated with aberrant linear growth, virilization, ovarian cysts, and metabolic symptoms, whereas AEXS results in gynecomastia and bone age advancement with or without mild hypogonadism. Such pubertal phenotypes of aromatase disorders likely reflect the accumulation or deficiency of sex hormones, imbalance between estrogens and androgens, and perturbed FSH secretion.

Conflict of interest statement

Nothing declared

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