Case Report

Pure gonadal dysgenesis (46 XX type) with a familial pattern

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Abstract

46, XX gonadal dysgenesis without the phenotype of Turner's syndrome is described as "pure". Although, previous investigations obtained that commonly gonadal dysgenesis did not cause breast development as a result of low levels of circulating estradiol. However, in this study, we aimed to report a familial pure gonadal dysgenesis with and without normal secondary sexual characteristics. In this study, we reported three siblings with pure gonadal dysgenesis with and without normal secondary sexual characteristics. The elder two sisters had a normal female phenotype and the youngest had amenorrhea with no breast development (B1) and pubic hair. In addition, it seems that the absence of pubic hair occurred due to delayed constitutional puberty. According to results, it seems that clinicians should consider different presentations for pure gonadal dysgenesis with familial pattern.

Key Words: 46 XX, family, gonadal dysgenesis, siblings

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INTRODUCTION

Primary amenorrhea could be diagnosed if a patient has normal secondary sexual characteristics but no menarche by 16 years of age.[1,2] Also, if a patient had no secondary sexual characteristics and no menarche, primary amenorrhea could be diagnosed even in 14 years of age. Secondary amenorrhea is the absence of menses for 3 months in women with previously normal menstruation and for 9 months in women with previous oligomenorrhea. According to previous investigations, secondary amenorrhea is more common than primary type.[3,4]

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46, XX gonadal dysgenesis without the phenotype of Turner's syndrome is described as "pure". It is characterized by the presence of primary amenorrhea with or without normal secondary sexual characteristics. It is often presented without normal secondary sexual characteristics such as breast development.[5]

The initial evaluation should include careful medical history taking, physical examination and appropriate laboratory examinations. The history highlighted the examinations based on growth charts, exercise and nutritional habits, drugs' consumption, family history and an extensive review of systems. Also, height, weight, tanner staging and external genitalia were assessed through physical examination. The goal of the physical examination was to determine the presence of a uterus and occurrence of breast development and estrogen stimulation.[6]

Furthermore, the level of follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH)

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and prolactin (PRL) had been evaluated by laboratory examinations. As the differential diagnosis was exhaustive, it could be helpful for compartmentalizing the causes into hypothalamic, pituitary, ovarian and lower organs disorders.[7]

In this study, we aimed to report a familial pure gonadal dysgenesia with and without normal secondary sexual characteristics.

CASE REPORT

In a family consisting nine siblings of non-consanguineous parents, three sisters aged 22, 17 and 13 years presented complaints of amenorrhea [Table 1].

The 13-year-old girl mentioned no secondary sexual characteristics. The 17-year-old girl showed secondary characteristics without previous history of hormone therapy.

Also, the 22-year-old girl with the diagnosis of gonadal streak showed secondary characteristics. She mentioned hormone therapy which could be probably contraceptives (LD and HD) after marriage for her infertility. By hormone administration, she delivered a baby.

The elder two sisters had a normal female phenotype and the youngest had amenorrhea with no breast development (B1) and pubic hair. Although, absence of pubic hair was a question for investigators, it could be mentioned due to delayed constitutional puberty. Furthermore, according to physical examination, deafness was not mentioned. The laboratory results noted high level of FSH and LH and low level of estradiol in all three girls. In addition, sonography indicated gonadal streak.

DISCUSSION

Clinicians apply laboratory test results and karyotype analysis to diagnose patients with amenorrhea and no secondary sexual characteristics.[2] In our study, one patient mentioned the absence of secondary sexual characteristics by 14 years of age and two others reported lack of menarche by 16 years. Androgen insensitivity syndrome is the common diagnosis in patients with breast development and minimal or no pubic hair (i.e. patient is phenotypically female but genetically male with un-descended testes).[1] Therefore, we performed ultrasonography to evaluate uterus and ovaries and results showed gonadal streak and normal uterus. As, even in Soyer syndrome (XY), normal uterus could be noted and for further evaluation, we indicated Karyotyping as a mandatory step.

In patients with normal secondary sexual characteristics including pubic hair, we performed MRI and ultrasonography to evaluate gonads and to rule out the Müllerian agenesis, because the congenital absence of a vagina and abnormal uterine development usually causes approximately 15% of primary amenorrhea.[8] Also, it has been thought that the etiology involved embryonic activation of the anti-Müllerian hormone which could resulted in malformation of female genital tract.[9]

In laboratory finding, FSH and LH levels were high which mentioned hypergonadotropic hypogonadism (elevated FSH and LH levels) as a result of gonadal dysgenesis or premature ovarian failure in patients with primary amenorrhea.

Turner's syndrome (45, XO karyotype) which is the most common form of female gonadal dysgenesis indicates physical characteristics such as webbed neck, widely spaced nipples and short stature. Also, mosaicism occurs in approximately 25% of patients with Turner's syndrome.[10] In our patients, when results indicated a hypergonadotropic hypogonadism, we considered the possibility of a gonadal dysgenesis, which was confirmed by the karyotyping and resulted in 46 XX. Therefore, as patients didn't mention turner's symptoms and 46 XX karyotype was acquired; consequently 46 XX pure gonadal dysgenesis was indicated as the final diagnosis. Laboratory findings didn't roll out the mutations in LH and FSH receptor, therefore, it can be considered as a limitation in this study.

However, commonly gonadal dysgenesis did not cause breast development as a result of low levels of circulating estradiol. However, Our results indicated that our patient is pure XX gonadal dysgenesis and was consistent with the Marrakchi *et al.,* which indicated development of secondary sexual characters in a six patients follow-up.[11] Also, Nazareth *et al.*

Table 1: Clinical and hormonal profile of the affected siblings

Age	Height	Upper to lower segment ratio	Tanner	LH Normal range: <7	FSH Normal range: 3-20	Estradiol Normal range: 25-75	Imaging	Karyotype
13	154	0.90	B1 p1	60.8 U/L (high)	169 U/L (high)	5 pg/mL (low)	Gonadal streak	46 XX
17	152	0.89	B3 p2	80.8 U/L (high)	120 U/L (high)	7 pg/mL (low)	Gonadal streak	46 XX
22	150	0.85	B4 p3	101.8 U/L (high)	98 U/L (high)	6 pg/mL (low)	Gonadal streak	46 XX

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone

described consistent results in four 46 XX siblings affected by pure gonadal dysgenesis syndrome. They believed that inheritance of gene in these cases was autosomal recessive and limited to the female sex.[12]

Furthermore, Namavar-Jahromi *et al*. presented three sisters with 46, XX PGD, who were born from a first cousin marriage. They mentioned that, two of these sisters developed ovarian tumors and both of them showed the pathological result of dysgerminoma with syncytiotrophoblastic giant cells. They were examples of tumorigenesis in PGD without an identifiable Y chromosome and They obtained that malignant degeneration of the streak gonads should be considered in the patients with 46, XX PGD.[13] According to results, it seems that clinicians should consider different presentations for pure gonadal dysgenesis with familial pattern. Usually tumorigenesis occurs in patients with identifiable Y chromosome, however malignant degeneration of the streak gonads in the patients with 46, XX pure gonadal dysgenesis can also be noted. Therefore, prompt diagnosis and follow-up should be recommended.

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