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Case Report

Gonadal dysgenesis and the Mayer-Rokitansky-Kuster-Hauser syndrome in a girl with a 46, XX karyotype: a case report

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ABSTRACT

The association of gonadal dysgenesis and Mayer-Rokitansky-Kuster-Hauser syndrome is very rare. Hypofunction of the ovaries can be either primary or central in etiology. It may be caused by congenital failure of development, postnatal destruction (primary or hypergonadotropic hypogonadism), or lack of central stimulation by the pituitary and hypothalamus (secondary or tertiary hypogonadotropic hypogonadism). Mutations of certain genes could result in primary ovarian insufficiency. Diagnosis of the hypergonadotropic hypogonadisim before puberty difficult because most affected patients have no prepubertal clinical manifestations. We report such a case of 17 year old girl who presented with primary amenorrhea and impuberism. The endocrine study revealed hypergonadotropic hypogonadism. The karyotype was normal, 46XX. On USG abdomen infantile uterus was seen and no ovarian structures. On MRI pelvis no definite uterine or ovarian tissues could be seen, only rudimentary vagina is seen. Hormonal therapy with estrogen and progesterone was begun.

Keywords: Gonadal dysgenesis, Mayer-Rokitansky-Kuster-Hauser syndrome, Hypogonadism, Primary amenorrhea

INTRODUCTION

Gonadal dysgenesis in female is defined as absent or insufficient development of ovaries.[1] The patient with gonadal dysgenesis presents with primary amenorrhea and lack of development of secondary sexual characteristics due to inability of ovaries to produce sex steroids. The karyotype in patients with gonadal dysgenesis can be 46XX, 45XO, mosaicism or deletion of a certain part of X chromosome.[1] The Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKHS) is a specific type of mullerian duct malformation characterized by congenital absence or hypoplasia of uterus and upper two thirds of the vagina in both phenotypically and karyotypically normal females with functional ovaries.[2] It is the second most common cause of primary amenorrhea. The disorder is rarely recognized in children because the external genitals are normal, no other abnormalities are visible & growth is normal. At pubertal age, sexual maturation fails to take place. Plasma gonadotropin levels are elevated. Pelvic ovaries revealed streak ovaries.

CASE REPORT

A 17 year old female presented in OPD with complaint of not attained menarche till date. On examination her height 130 cm (<3rd percentile) weight 27.5 kg (<3rd percentile) & no secondary sexual characters. Tanner scale armpit and pubic hair stage I and mammary stage I. her external gonads were normal. On examination, there was no facial dysmorphism, no features suggestive of Turner syndrome like webbing of the neck or wide carrying angle. No skeletal deformity was found.

Investigations

The blood count was within normal range. The endocrine evaluation revealed normal thyroid function (TSH 1.91 microU/L) with hypergonadotropic hypogonadism (S.FSH 84.6 microU/L & S.LH 23.6 microU/L). An abdominal ultrasound revealed the uterus size of 3.01x1.2 cm i.e. infantile uterus with no visible ovaries. On MRI pelvis no definite uterine or ovarian tissues could be seen, only rudimentary vagina is seen suggestive of possibility of primary Mullerian agenesis. Her blood karyotype was 46 XX. The patient was diagnosed as having 46 XX pure gonadal dysgenesis with Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKHS).

Treatment

Replacement hormonal therapy with estrogen and progesterone.

DISCUSSION

46, XX gonadal dysgenesis is a primary ovarian defect leading to premature ovarian failure in otherwise normal 46, XX females due to failure of the gonads to develop or resistance to gonadotropin stimulation. Prevalence is unknown but is thought to be less than 1/10.000. Patients are born as females without ambiguity. However, affected individuals present during adolescence or young adulthood with either delayed or absent puberty resulting in primary or sometimes secondary amenorrhea. The internal and external genitalia are normally developed. Although the underlying etiology of ovarian dysgenesis remains unknown in most cases, several genes have been implicated including homozygous or compound heterozygous inactivating mutations of the Follicle-Stimulating Hormone Receptor gene (FSHR), mutations in the BMP15 gene, and mutations in the NR5A1 gene.[3-7]

If FSH and LH blood levels are low (hypogonadotropic hypogonadism), the most probable explanation is delayed puberty, frequently corresponding to family genetics. Less commonly, amenorrhoea could be due to infiltrative lesions of the hypothalamus or the pituitary gland.

Ropke et al.[8] consider mosaicism in gonadal karyotype as a frequent cause of gonadal dysgenesis, regardless of a normal peripheral karyotype. They strongly recommend testing the karyotype of the gonadal tissue because this information could be extremely useful. In addition, Massin et al.[9] recommend an ovarian biopsy in cases of pure gonadal dysgenesis due to the fact that it is a stronger indicator than pelvic ultrasound for the presence of follicles in the ovaries. These authors think that, in the near future, the ovarian biopsy could help in determining the aetiology and could even provide a therapeutic effect due to the success of in vitro growth of immature oocytes in humans.

MRKH syndrome is characterized by Mullerian duct structures agenesis, vaginal atresia, rudimentary or absent uterus with normal ovaries and Fallopian tubes in females normal from a genetic (46 XX), phenotypic and developmental features. The prevalence has been reported as 1 in 4.500 female births.[10]

The etiology of MRKH syndrome is unknown but it is believed that embryological development is interrupted during the sixth or seventh week of gestation. Since the mesonephros (which give rise to kidneys), the Mullerian ducts, and the skeleton all originate from the mesoderm, it is believed that a deleterious event occurs during this phase of gestation, giving rise to the abnormalities seen in the MRKH syndrome.[11]

Estrogens may influence development of the Mullerian ducts. Absence of anti-Mullerian hormone is also essential for its development. The existence of activating mutations of either the gene for the anti-Mullerian hormone or the gene for the anti-Mullerian hormone receptor, and the lack of estrogen receptors during embryonic development have been hypothesized to cause MRKH syndrome.[12]

The association of gonadal dysgenesis with Mullerian tract anomalies is extremely rare. It was first described by McDonough et al. in a girl with gonadal dysgenesis, duplication of the Mullerian duct system, and a 46, XX karyotype.[13]

CONCLUSION

The association of gonadal dysgenesis and MRKH syndrome is extremely rare. Long-term lack of oestrogens could cause early bone loss and osteoporosis in these patients. In addition, the lack of female sexual hormones represents an important risk factor for neurological, metabolic and cardiovascular health problems. Therefore, these patients would require replacement hormonal treatment with oestrogens and progesterone. This last hormone is required for reducing the risk of endometrial carcinoma, which will increase due to the long-term application of oestrogens without opposition. Sterility is an obvious consequence in patients with premature ovarian failure. Nevertheless, patients could become mothers with proper endometrial stimulation and subsequent implanting of embryos fertilised with donated ovules. An early diagnosis is extremely important in order to promptly begin treatment for the management of symptoms, provide emotional support to the patient and reduce the risks associated with this illness.

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