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The Coexistence of Gonadal Dysgenesis and the Mayer-Rokitansky-Kuster Hauser Syndrome in a girl with a 46, XX karyotype: A Rare Case Report

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Abstract

Background: *46,XX gonadal dysgenesis is a rare genetically heterogeneous disorder characterized by underdeveloped or absent ovaries with consequent, impuberism, primary amenorrhea, and hypergonadotropic hypogonadism. Mullerian agenesis or Mayer Rokitansky Kuster Hauser (MRKH) syndrome is characterized by congenital aplasia of the uterus and the upper part (2/3) of the vagina in a woman with normal development of secondary sexual characteristics and a normal 46,XX karyotype. The association of these two conditions is very rare and appears to be coincidental. Clinical Presentation and Intervention: We aimed to report a case of gonadal dysgenesis with MRKH. In this case report, we reported a 18-year-old girl with primary amenorrhea and underdeveloped secondary sexual characteristics. Vaginal examination revealed patent vagina. There were no other associated malformations. Her karyotype was 46, XX. The pelvic ultrasound and abdominopelvic MRI without contrast demonstrated bilateral ovarian agenesis, absence of uterus and upper part of the vagina. Hormonal substitution therapy with oral combined pill was begun. The patient has been under regular follow up for the last 1 years and showed development of secondary sexual characteristics.*

Conclusion: *These two conditions 46, XX gonadal dysgenesis and Mullerian agenesis compromise the prognosis of fertility of young patients. Hormone substitution therapy remains the only therapeutic option. It is aimed at triggering the development of secondary sexual characters and prevent osteoporosis. There remains the unsolved problem of infertility.*

Keywords: *46,XX gonadal dysgenesis, Hypergonadotropic hypogonadism, Mayer Rokitansky Kuster Hauser syndrome, Primary amenorrhea*

Introduction:

Gonadal dysgenesis with female phenotype is defined as the absence or insufficient development of the ovaries. It causes primary amenorrhea with variable hypogonadism or impuberism, depending on the degree of gonadal development. The karyotype can be 46,XX; 45,X0; 46,XY or mosa¨ýcism 45,X/46,XX; 45,X/46,X,del(X)(p22.2); 46,X,i(Xq).[1-3] The Mayer Rokitansky Kuster Hauser (MRKH) syndrome 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. It is the second most common cause of primary amenorrhea after gonadal dysgenesis.[2]

An association between these two conditions is very exceptional and appears to be coincidental, independent of chromosomal anomalies.

Case Report

A 17-year-old female college student, presented with primary amenorrhea and absence of secondary sexual characteristics.

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There was no family history of consanguinity, congenital anomaly, or other members with primary amenorrhea.

She had good cognitive developmental milestones and has average educational performance.

On physical examination, her blood pressure was 120/70 mmHg and pulse rate was 64 b.p.m. Her height was 144 cm, weight 45 kg, and BMI 21.4 kg/m2.

There was no facial dysmorphism, webbing of the neck, high-arched palate, thyroid enlargement, or skeletal deformity found on examination.

Staging of breast development, pubic and axillary hair growth showed Tanner's Stage 1. Gynecologic examination revealed a 1 cm vaginal blind pouch. Female external genitalia were normal. No uterus was palpable on rectal examination.

The endocrinological evaluation revealed hypogonadotropic hypogonadism and the rest of the hormonal parameters were normal (Table: Homone Profile).

Table-I

Hormone Profile

Hormone	Patient value	Lab value
hTSH	1.25uIU/mL	00.47-05.01 uIU/mL
LH	45.10mIU/mL	2.00-105.00 mIU/mL
FSH	78.50mIU/mL	4.00-22.00mIU/mL
Prolactin	44.70ng/mL	2.80-29.20 ng/mL
Estradiol	<2.72pg/mL	26.6-382.00 pg/mL
Testosterone	12.98ng/dl	63.00-120.00 ng/dl

Internal genitalia could not be identified on the pelvic ultrasound (Figure 1) nor on the MRI (Figures 2 and 3). Karyotyping revealed normal 46,XX complement (Figures 4).

X-ray of long bones and ultrasound of whole abdomen revealed no genitourinary and skeletal anomalies. There were no other morphological malformations. Hormonal therapy with OCP (ethinylestradiol 0.05mg+Lynestrenol 2.5mg) was started for the development of secondary sexual characteristics and to prevent osteoporosis. After 8 months on her follow up there is development of breast from Tanner stage 1 to Tanner stage 3.

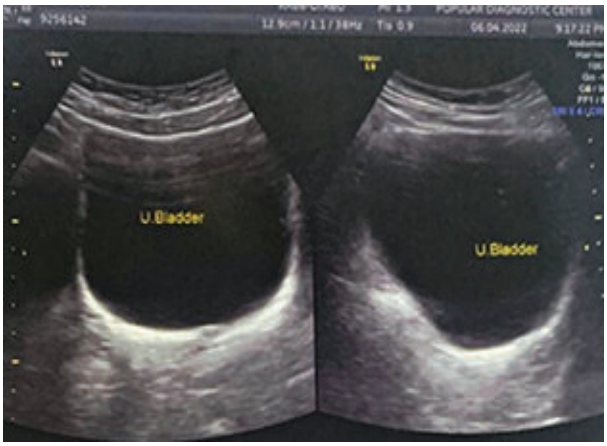

Figure 1: *Ultrasound exam: no uterus identified behind the bladder.*

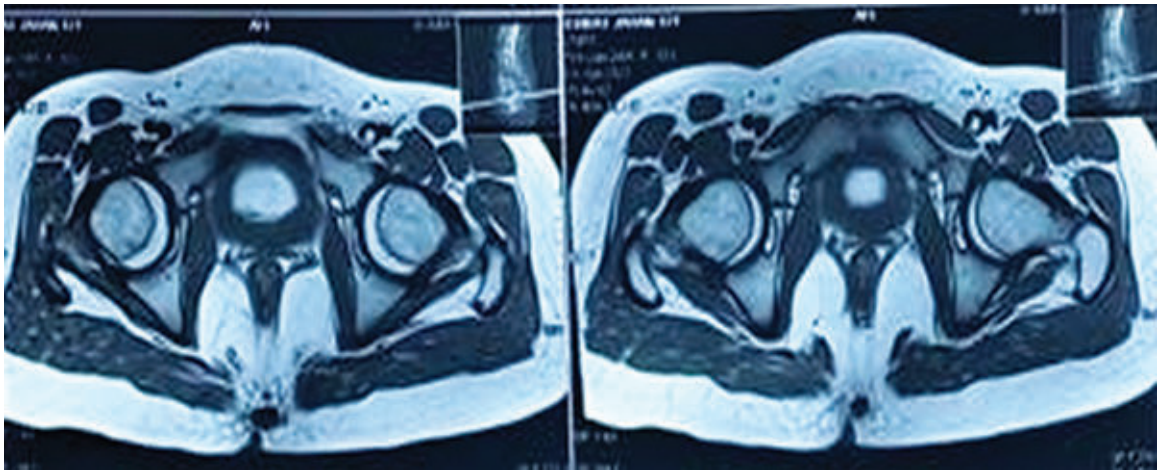

Figure 2: *Magnetic resonance imaging (MRI): axial plane cut showing bladder and rectum without interposition of uterus.*

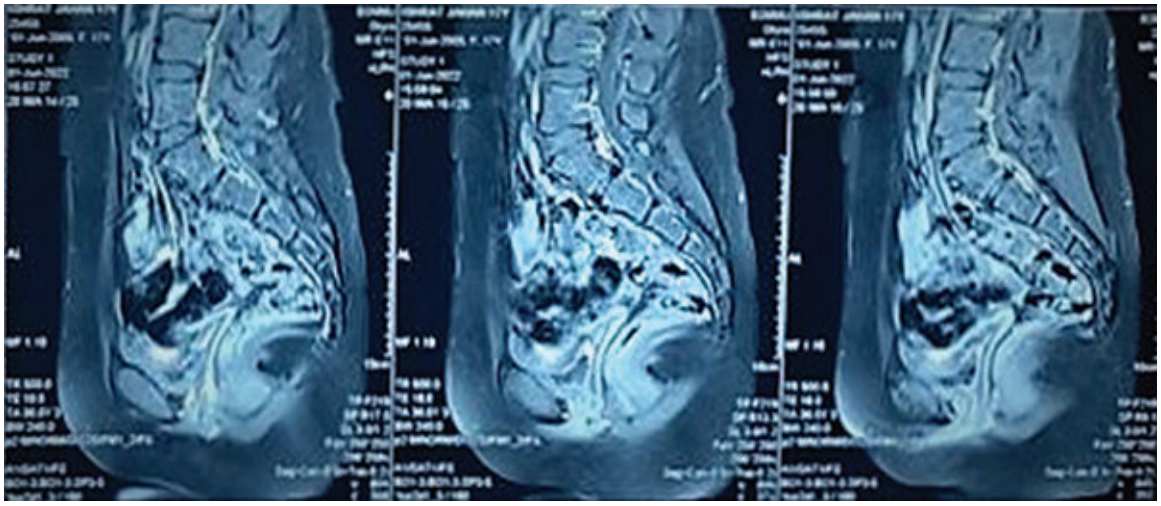

Figure 3: *MRI examination sagittal plane cut: absence of uterus and ovaries.*

Figure 4: *46,XX Karyotype Complement*

Discussion:

The ovaries are embryologically derived from 3 sources: mesodermal epithelium (lining the posterior

or abdominal wall), underlying mesenchymal (embryonic connective tissue), and primordial germcells. The epithelium and mesenchyme proliferate to produce the genital (gonadal) ridge. The primordial germ cells migrate along the dorsal mesentery of the hindgut to the genital ridges and enter the underlying mesenchyme. If the primordial germ cells do not form or migrate into the gonadal area, an ovary will not develop.

Gonadal dysgenesis is the most common cause of primary amenorrhea. 46,XX gonadal dysgenesis is relatively rare form of gonadal dysgenesis and wide variations are seen in its clinical presentation.[4,5] Both sporadic and familial cases show these clinical variations. 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.[6-10]

The mullerian (paramesonephric) ducts develop lateral to the gonads and play an essential role in the development of uterine tubes, uterus, superior part of the vagina and broad ligaments.

MRKH syndrome is characterized by Müllerian 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 typical form (type A) is characterized by absence of both the vagina and uterus, leaving only symmetric uterine remnants, that is normal fallopian tubes and ovaries. The atypical form (type B) usually shows asymmetric or absent uterine remnants, hypo-plasia or aplasia of one or both fallopian tubes, and frequent urinary and skeletal congenital anomalies.

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.[8] The increased number of cases in familial aggregates

raises the hypothesis of a genetic cause.[11] Autosomal dominant trait with an incomplete degree of penetrance and variable expressivity is most likely mode of transmission.[12] 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.[2] 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.[14] The coexistence of these two anomalies was then reported in patients with 45, X, 45, X/46, XX, 46, XX, 46, XY, 45, X/46, Xdic (X), 46, Xi (Xq), 45, X/46, X, del (X) (p11.21), and 46, X, del (X)(pter '! q22:) karyotypes.[1,2,12-18] This finding suggests that the occurrence of neither this association nor Mullerian tract anomalies alone is not related with a specific chromosomal abnormality.[1] Theoretically, an undifferentiated gonad could produce anti Mullerian hormone in earlier embryologic period, leading to a subsequent regression. But this hypothesis cannot be valuable without the presence of the chromosome Y.[2] Karyotype of our patient demonstrated the absence of chromosome Y. All the studies mentioned above revealed that 46,XX gonadal dysgenesis with mullerian agenesis commonly presents with normal female phenotype with primary amenorrhea, impuberism, and hypergonado-tropic hypogonadism with or without somatic malfor-mations are extremely rare.

Conclusion:

The association of gonadal dysgenesis and Mayer Rokitansky kuster hauser syndrome is very rare and appears to be coincidental, independent of chromosomal anomalies. These two conditions compromise the fertility both in the mechanic and hormonal plane. Actually the treatment is based on hormone substitution therapy. The aim of the treatment is to trigger the development of secondary sexual characters and prevent osteoporosis. There remains the unsolved problem of infertility.

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