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Coexistence of Mayer Rokitansky Kuster Hauser syndrome and gonadal dysgenesis in a 46XX girl: A case report.

Hallah Alanazi, Hayat Alrabieah, Lubna Khan*

King Abdul-Aziz medical city, Department of obstetrics and gynecology, reproductive medicine unit, Saudi Arabia, Riyadh.

***Corresponding Author:** Lubna Khan, King Abdul-Aziz medical city, Department of obstetrics and gynecology, reproductive medicine unit, Saudi Arabia, Riyadh.

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Abstract

Introduction

Congenital absence of Mullerian duct derivatives, known as Mayer Rokitansky Kuster Hauser syndrome is a rare condition, It is usually associated with urological and skeletal abnormalities. Its association with bilateral gonadal dysgenesis is extremely rare and appears to be independent of chromosomal abnormalities.

Case report

We are reporting a case of a 17-year-old girl who had presented with primary amenorrhea and absence of secondary sexual characteristics. No other abnormalities were detected on examination. The endocrine evaluation revealed a picture of hypogonadotropic hypogonadism with normal thyroid function. Bone mineral density was less than expected for the patient's age. She has a normal female karyotype 46 XX. Pelvic ultrasound showed no uterus or ovaries. Pelvic MRI showed the absence of the uterus, cervix, vagina, and both ovaries which confirm the diagnosis of Mayer Rokitansky Kuster Hauser syndrome and bilateral ovarian dysgenesis. Brain MRI was normal. Urinary tract abnormalities were excluded as well by MRI.

Hormonal replacement therapy was started as conjugated estrogen to trigger her secondary sexual characteristics and osteoporosis prevention.

Conclusion

The association of Mayer Rokitansky Kuster Hauser syndrome and bilateral ovarian dysgenesis is a rare condition with unknown pathogenesis that is independent of chromosomal abnormalities. The management will be supportive with hormone replacement therapy to develop secondary sexual characteristics and to avoid premature bone loss. Unfortunately, there is nothing much that can be done to improve her fertility potential.

Keywords: MRKH, Gonadal Dysgenesis, fertility

Introduction

Gonadal dysgenesis in females is defined as absent or limited development of the ovaries. As a result of the hypogonadotropic hypogonadism hormonal status of such cases, patients will present with amenorrhea and lack of development of secondary sexual characteristics. It occurs in < 1 in 10,000 women with varied karyotyping which can be 46XX, 45XO, mosaicism, or deletion of a certain part of the X chromosome **[1]**. The clinical presentation can be varied and not the same in all cases. somatic anomalies can present in some cases and absent in others. The inheritance of the forms of 46XX gonadal dysgenesis not associated with somatic malformations is commonly autosomal recessive and more common in consanguineous families. These cases present with normal stature without any Turner's phenotype. Several pleiotropic genes may be involved in 46XX gonadal dysgenesis with somatic malformations. After gonadal dysgenesis, the second most common cause of primary amenorrhea is Mayer Rokitansky Kuster Hauser syndrome (MRKHS) which is characterized by congenital absence or hypoplasia of the uterus and upper two-thirds of the vagina. Females with this syndrome are usually phenotypically and karyotypically normal females with normal developed secondary sexual characteristics and functioning ovaries. MRKHS affects 1 in 4500 newborn girls **[2]**.

The coexistence of gonadal dysgenesis and MRKHS is very rare, though it has been reported in a few cases and appears to be coincidental as not related to any chromosomal abnormalities.

Case report

We report a case of 17-year-old girl who presented to our clinic with primary amenorrhea, short stature, and absence of secondary sexual characteristics. She had a normal neonatal period with normal developmental milestones. No history of trauma, respiratory symptoms, skin lesions, vaginal discharges, or vaginal bleeding was reported. She was medically and surgically free and doesn't report any family history of concern, although there is positive consanguinity between her parents. She has a high intellect and a good academic record.

On examination, there were no dysmorphic features, the height was 147, and the weight was around 40 kg. she had normal BP and cardiovascular examination. Breast development, axillary and pubic hair growth staged as 'Tanner 1'. She had normal external genitalia. Pelvic ultrasound didn't visualize the uterus or the ovaries **(Figure 1)**. The hormonal assay showed hypogonadotropic hypogonadism status with FSH of 51 and LH of 21. Prolactin and TSH levels were normal.

She had a normal female karyotype 46XX. Brain MRI was normal. Pelvic MRI showed the absence of the uterus, cervix, vagina which had confirmed the diagnosis of Mullerian duct agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome) with bilateral ovarian dysgenesis **(Figure 3)**. Urinary tract abnormalities were excluded as well by MRI. Bone mineral density was found to be less than expected for the patient's age on a BMD scan. Bone age by x-ray (skeletal age) was 14 years with a marked delay in bone maturation **(Figure 2)**.

The echo has been done with normal results. She was also referred to ENT for audiology evaluation which was reported as normal. The patient was started on hormone replacement therapy by conjugated estrogen and was given calcium and vitamin D supplement as well. A few months later the patient was reassessed and found to have an improvement in her height which became 150 cm. Secondary sexual characteristics staged as Tanner 2.

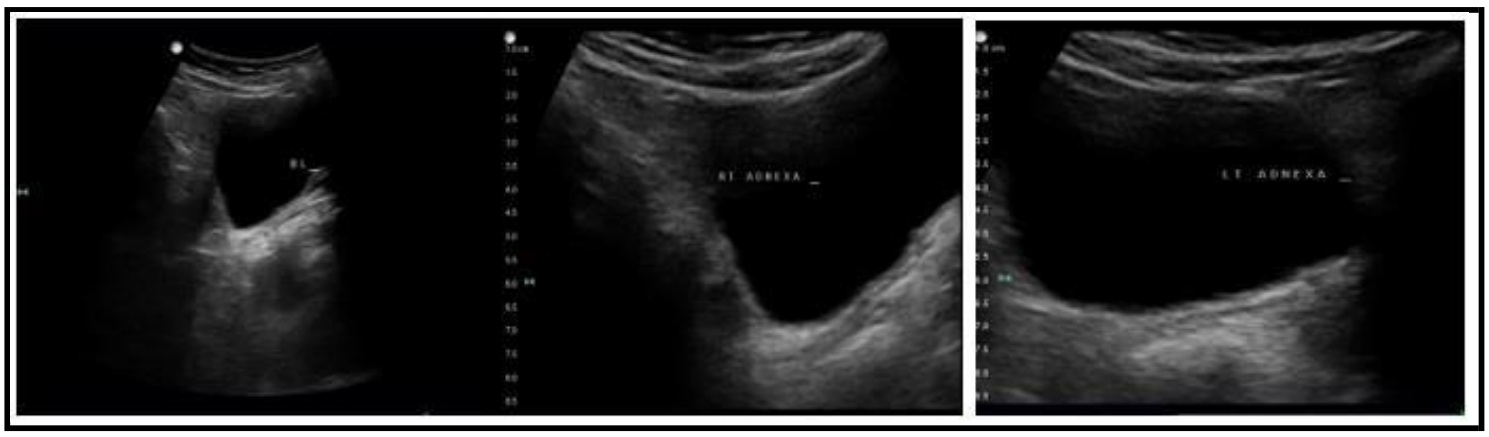

Figure 1: Ultrasound showed absence of uterus and ovaries

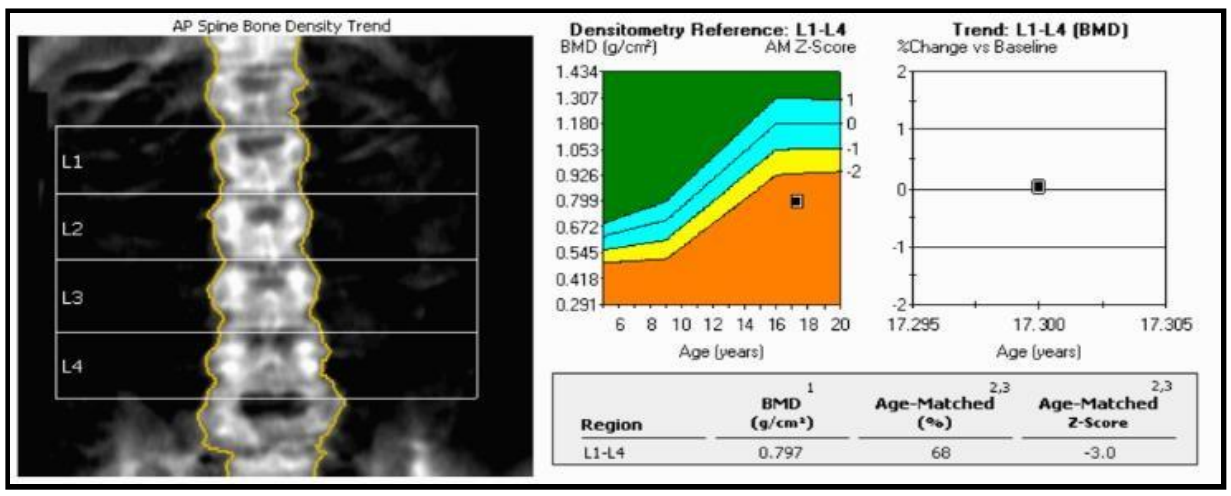

Figure 2: Bone Mineral Density Scan

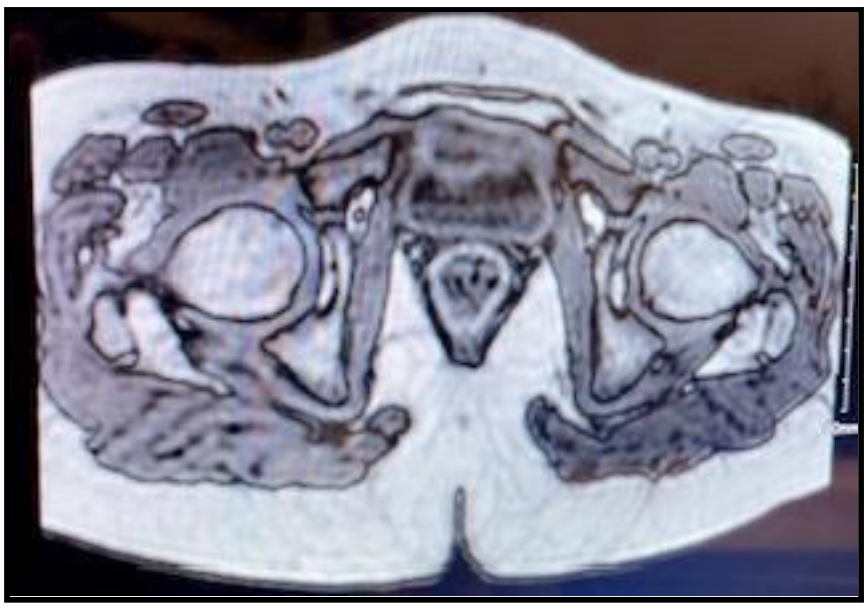

Figure 3: MRI sagittal plane cut showing absence of uterus and ovaries

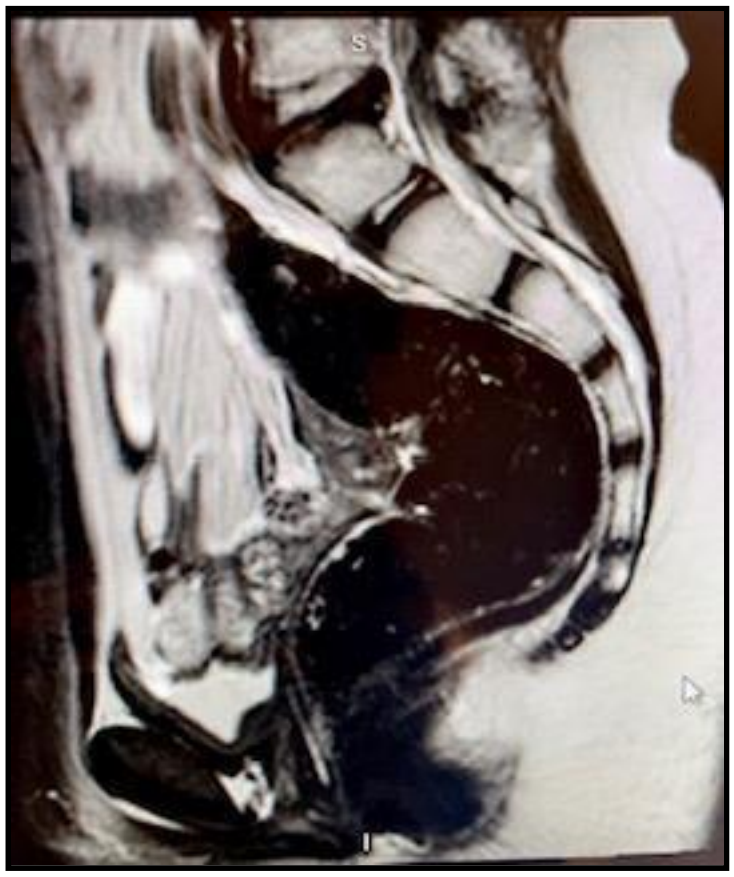

Figure 4: MRI axial plane cut showing bladder and rectum without uterus in-between

Discussion

Mayer Rokitansky Kuster Hauser syndrome is characterized by congenital absence of Mullerian duct derivatives in phenotypically normal females having 46XX chromosomes. The prevalence has been reported as 1 in 4500 female births **[3]**. It is divided by researcher into 2 types:

1- Typical syndrome is characterized by the absence of both the vagina and uterus, leaving only symmetric uterine remnants, normal fallopian tubes, and ovaries.

2- Atypical syndrome which shows asymmetric or absent uterine remnants, hypoplasia, or aplasia of one or both fallopian tubes, and frequently associated anomalies **[4]**.

In 40 % of cases, upper urinary tract malformations are found including unilateral renal agenesis, renal ectopia/hypoplasia, horseshoe kidney, and hydronephrosis. Other malformations reported are Skeletal and cardiac anomalies, auditory defects, and anorectal malformations. Screening for these anomalies by ultrasound and MRI and bone scan is mandatory for all cases of MRKH syndrome. Laparoscopy can be done in some cases for final confirmation **[3]**.

In our case, the diagnosis of typical MRKH was made based on pelvic ultrasound, MRI, and we excluded other anomalies by MRI findings, bone scan, cardiac and auditory evaluation. The exact etiology of MRKH syndrome remains largely unknown although many hypotheses have been speculated. Changes in several genes involved during embryological development during the sixth and seventh week of gestation can give rise to the abnormalities seen in the MRKH syndrome **[5]**. The increased number of cases in familial aggregates raises the genetic cause hypothesis **[6]**. Estrogens and anti-Mullerian hormones are playing a role in Mullerian duct development. During embryonic 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 has been hypothesized to cause MRKH syndrome **[4]**.

Gonadal dysgenesis with a female phenotype is defined as the absence or incomplete development of the ovaries and is the most common cause of primary amenorrhea and absent secondary sexual characteristics. In the literature, it was found in different karyotypes like 45XO, 45X/46XX, 45X/46X, dic(X), 46XX, and 46XY **[7]**. Our case is 46XX which is a relatively rare form of gonadal dysgenesis. The underlying etiology of ovarian dysgenesis is still unknown although several genes have been implicated, including homozygous or compound heterozygous inactivating mutations of follicle-stimulating hormone receptors, and mutations in BMP15 and NR5A1 **[8]**.

The coexistence of Mayer Rokitansky Kuster Hauser syndrome and gonadal dysgenesis has been reported in the literature but is extremely rare. A literature review found 29 reported cases of the concomitant presence of these two abnormalities **(Table 1)**.

Table 1: Summary of published cases of coexisting gonadal dysgenesis and MRKHS

Case	Author	Year	Age at presentation (years)	Karyotype	Uterus	Ovaries	Fallopian tubes
1	Arnab Nandy et al.	2019	12	46 XX	Hypoplastic	Agenetic	Absent
2	Ioris et al.	2019	17	46 XX	Rudimentary Uterine with cervix and normal vagina	Dysgenetic	Normal
3	Manne C et al.	2016	20	46XX	Absent	Agenetic	NR
4	Meena et al.	2016	15	45X/46X X	Absent	Agenetic	NR
5	Białka et al.	2016	17	46X/X (q10)	Hypoplastic	Dysgenetic	NR
6	Bhandari and Chaudhary	2015	17	46XX	Absent	Agenetic	NR
7	Kebaili et al.	2013	21	46XX	Absent	Agenetic	Absent
8	Viral et al.	2013	21	46XX	Absent	Agenetic	Absent
9	Bousfiha et al.	2010	19	46XX	Absent	Dysgenetic	Absent
10	Tatar et al.	2009	2 sisters (34 and 23)	46XX	Hypoplastic	Agenetic	Hypoplastic
11	Zaman and Nisar	2009	2 sisters (22 and 13)	46XX	One absent, other rudimentary	Dysgenetic	Hypoplastic

Case	Author	Year	Age at presentation (years)	Karyotype	Uterus	Ovaries	Fallopian tubes
12	Güvan et al.	2008	17	45X/46, X delX (p11.21)	Absent	Agenetic	NR
13	Kumar et al.	2007	18	46XX	Absent	Right side, Agenetic	NR
14	Colombani et al.	2007	15	46XX	Absent	Dysgenetic	Normal
15	Marrakchi et al.	2004	19	46XX	Absent	Dysgenetic	Normal
16	Plevraki et al.	2004	6 patients	46XX with testis specific protein 1-Y linked gene (in patient 1 and 4)	Patient 1: hypoplastic uterus with symmetrical uterine buds, with no endometrium Patient 6: uterus, symmetrical hypoplastic	Patient 1: left side, Agenetic Patient 6: Agenetic	Patient 1: left fallopian tube, absent Patient 6: both fallopian tubes were symmetric, but hypoplastic
17	Kaya et al.	2003	17	46XX	Absent	Left Agenetic	Right, normal Left, hypoplastic
18	Aydos et al.	2003	19	46X, del (X) (pter- -> q22:)	Rudimentary	Agenetic	NR
19	Mégarbané et al.	2003	2 sisters	46XX	Hypoplasia	Dysgenetic	Hypoplastic
20	Gorgojo et al.	2002	17	46XX	Absent	Agenetic	Absent
21	Ting and Chang	2002	22	45X/46X , del(X) (p22.22)	Absent	Dysgenetic	Rudimentary
22	Güitrón-Cantú et al.	1999	19	45,X/46, Xdic(X)	Absent	Agenetic	Normal

Case	Author	Year	Age at presentation (years)	Karyotype	Uterus	Ovaries	Fallopian tubes
23	Oyer et al.	1994	Neonate	46XX	Defects in Müllerian derivatives	Agenetic	NR
24	Albelardo et al.	1999	19	45x/46,xdic(x)	Absent	Agenesis	Normal
25	Aughton	1993	NA	46XX	Absent	Dysgenetic	Absent
26	Alper et al.	1985	16	NA	Absent	Dysgenetic	NR
27	Al-Awadi et al.	1985	2 sisters (18 and 16)	46XX	Hypoplastic	One agenetic, other dysgenetic	One absent, other hypoplastic
28	De Leon et al.	1984	NA	46,X,i(Xq)	Absent	Agenetic	NR
29	Levinson et al.	1976	17	46XX	Absent	Agenetic	Absent

* MRKUS: Mayer Rokitansky Kuster Hauser syndrome, NR: not reported.

The exact genetic mechanisms that underlie the association of Mayer Rokitansky Küster Hauser syndrome with 46XX gonadal dysgenesis are not known **[9]**. In 1976, Levinson et al. reported the first case of MRHKS in a patient with bilateral gonadal absence and was associated with left sided double ureter **[10]**. The age of presentation of most of the reported cases was adult age, like our case. Some of the cases had hypoplastic or rudimentary uterus (6 cases). Urological and skeletal abnormalities were reported in a few cases **[1,4,10-16]**. In our case, we excluded any associated abnormalities.

The presence of these two conditions will compromise the patient's chances to have her biological children. The only treatment modality will be the use of hormonal replacement therapy to trigger and maintain secondary sexual characteristics and to prevent osteoporosis.

Conclusion

The association between Mullerian duct anomalies (Mayer Rokitansky Kuster Hauser syndrome) and gonadal dysgenesis is a rare event and appears to be a coincidental association and not related to any genetic abnormality. The condition will not only compromise the patient's fertility potential but also will have a great psychological and social impact on her life.

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