CASE REPORT

Unusual association of Turner syndrome and Mayer-Rokitansky-Küster-Hauser syndrome

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SUMMARY

Gonadal dysgenesis and Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) are the most common causes of primary amenorrhoea. Patients with gonadal dysgenesis present with primary amenorrhoea and lack of secondary sexual characteristics, which, in contrast, are present in patients with MRKHS. The coexistence of the 2 syndromes has been reported in only a few studies so far. We describe a case of a 15-year-old girl who presented with short stature and primary amenorrhoea. Investigations revealed hypergonadotropic hypogonadism, and absence of the uterus, and upper two-thirds of the vagina, with presence of the rudimentary lower third of the vagina and non-visualised bilateral ovaries on imaging. Karyotyping obtained by lymphocyte culture GTG banding revealed 45X/46XX. The patient was diagnosed as having a rare case of gonadal dysgenesis with MRKH. She was started on growth hormone therapy. The association of these syndromes is uncommon, and has further implications on fertility and pregnancy, affecting the quality of life.

BACKGROUND

Gonadal dysgenesis (Turner syndrome) in females is defined as absent or insufficient development of the ovaries. These individuals can have varied karyotypes in the form of 46XX, 45XO, mosaicism or deletion of a certain part of the X chromosome.¹ Patients usually present with primary amenorrhoea and lack of development of secondary sexual characteristics due to inability of the ovaries to produce sex steroids. The overall incidence is about 1:2500 live birth females.

Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is characterised by an absent or hypoplastic uterus and upper two-thirds of the vagina in phenotypically and karyotypically normal females, with incidence of ~1 case per 5000 newborn females.² A patient with MRKHS has normal secondary sexual characteristics due to normally functioning ovaries.

The association of gonadal dysgenesis and MRKHS, though reported, remains rare.

CASE PRESENTATION

We report a case of a 15-year-old girl who presented to the outpatient department, with reports of inability to gain height after 10 years of age. She was a full term normal vaginal delivery born out of a non-consanguineous marriage. The patient had normal mentation with no behavioural abnormalities and had not attained menarche. There was no history of antenatal stress events, or any chronic

Figure 1 Patient (middle) is shorter than younger and older siblings (from left to right).

illness in the mother or the patient. There was no family history of genetic disease. The patient had been fully vaccinated. Her elder sister and younger brother were healthy and taller than the patient (figure 1).

On examination, her height was 125 cm, weight 38 kg and mid-parental height was 154 cm. She had a short fourth metacarpal of the right hand (figure 2). There was presence of a shield chest with widely placed nipples (figure 3), however, no webbing of the neck and no wide carrying angle at the elbow were present. Her pubic hair and breast

Figure 2 Short fourth metacarpal of the right hand.

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Figure 3 Shield chest.

development were Tanner stage 1. Her blood pressure was 116/70 mm Hg with no difference in upper and lower limbs, and pulse was 72/min. Pulmonary, cardiovascular and abdominal examination was normal.

INVESTIGATIONS

Investigations revealed haemoglobin of 13.3 g%, total leucocyte count 8900 mm³, platelet count 2.44 mm³ and erythrocyte sedimentation rate 12 mm/hour. Lipid profile, liver function and kidney function tests were normal. Her calcium was 9.4 mg/dL (8.7–10.2 mg/dL), phosphorus 5.0 mg/dL (2.5–4.3 mg/dL), alkaline phosphatase of 296 U/L (33–96 U/L) and bone alkaline phosphatase >140 U/L. Hormonal profile showed suppressed intact parathyroid hormone levels of 2.8 pg/mL (8–52 pg/mL), elevated luteinising hormone 33.9 mIU/mL (2–15 mIU/mL) and follicle-stimulating hormone 72.9 mIU/mL (3–20 mIU/mL). Thyroid function tests were normal. Bone age was estimated radiologically to be 8.5–12 years. Ultrasound of the pelvis did not show the uterus and ovaries. MRI of the pelvis revealed absence of the uterus, and upper two-thirds of the vagina, with presence of the rudimentary lower third of the vagina and non-visualised bilateral ovaries (figures 4 and 5). The kidneys on abdomen MRI were normal in size, shape and signal intensity (figure 6). Karyotyping

Figure 4 Mid-sagittal T2-weighted image showing absence of uterine tissue.

Figure 5 Axial T2-weighted image shows absence of uterine and ovarian tissue.

obtained by lymphocyte culture GTG banding revealed 45XO/46XX.

TREATMENT

Following the diagnosis, the patient was started on replacement therapy with recombinant growth hormone (GH) (0.05 mg/kg/day subcutaneously) after endocrinology consultation. She has currently been on therapy for 12 months and is doing well.

OUTCOME AND FOLLOW-UP

The patient has been on GH therapy for 12 months and has achieved a growth velocity of 10 cm/year, without showing signs of complications from treatment.

DISCUSSION

Gonadal dysgenesis is the most common cause of primary amenorrhoea and absent secondary sexual characteristics.³ This may

Figure 6 Both kidneys are normal in size, position and signal intensity.

Table 1 Review of published cases showing association of Turner syndrome and Mayer-Rokitansky-Küster-Hauser syndrome

	Author (year)	Age of presentation (years)	Karyotype	Ovaries	Uterus	Fallopian tubes	Consanguinity
1	Bhandari and Chaudhary (2015) ⁴	17	46XX	Agenetic	Absent	NR	Absent
2	Bialka <i>et al</i> (2016) ⁵	17	46,X/X(q10)	Dysgenetic	Hypoplasia	NR	Absent
3	Kebaili <i>et al</i> (2013) ⁶	21	46XX	Agenetic	Absent	Absent	Absent
4	Viral <i>et al</i> (2013) ⁷	21	46XX	Agenetic	Absent	Absent	Absent
5	Bousfiha <i>et al</i> (2010) ³	19	46XX	Dysgenetic	Absent	Absent	Absent
6	Tatar <i>et al</i> (2009) ²	2 sister (34 and 23)	46XX	Agenetic	Hypoplasia	Hypoplasia	Present
7	Zaman and Nisar (2009) ⁸	2 sisters (22 and 13)	46XX	Dysgenetic	One absent The other, rudimentary	Hypoplasia	Present
8	Güvan <i>et al</i> (2008) ⁹	17	45,X/46,X delX (p11.21)	Agenetic	Absent	NR	Absent
9	Kumar <i>et al</i> (2007) ¹⁰	18	46XX	Right side, Agenetic	Absent	NR	Absent
10	Colombani <i>et al</i> (2007) ¹¹	15	46XX	Dysgenetic	Absent	N	Present
11	Marrakchi <i>et al</i> (2004) ¹²	19	46XX	Dysgenetic	Absent	N	Absent
12	Plevraki <i>et al</i> (2004) ¹³	6 patients	46XX with testis specific protein 1-Y linked gene (in Patient 1 and 4)	Patient 1: left side, Agenetic Patient 6: Agenetic	Patient 1: hypoplastic uterus with symmetrical uterine buds, with no endometrium Patient 6: uterus, symmetrical hypoplastic	Patient 1: left fallopian tube, absent Patient 6: both fallopian tubes were symmetric, but hypoplastic	Absent
13	Kaya <i>et al</i> (2003) ¹⁴	17	46XX	Left Agenetic	Absent	Right, normal Left, hypoplastic	Absent
14	Aydos <i>et al</i> (2003) ¹⁵	19		Agenetic	Rudimentary	NR	Absent
15	Mégarbané <i>et al</i> (2003) ¹⁶	2 sisters	46XX	Dysgenetic	Hypoplasia	Hypoplastic	Present
16	Gorgojo <i>et al</i> (2002) ¹⁷	17	46XX	Agenetic	Absent	Absent	Absent
17	Ting and Chang (2002) ¹⁸	22	45x/46x, del(X) (p22.22)	Dysgenetic	Absent	Rudimentary	Absent
18	Güitrón-Cantú <i>et al</i> (1999) ¹⁹	19	45,X/46,Xdic(X)	Agenetic	Absent	N	Absent
19	Güitrón-Cantú <i>et al</i> (1999) ¹⁹	19	45,X/46,Xdic(X)	Agenetic	Absent	N	Absent
20	Oyer <i>et al</i> (1994) ²⁰	Neonate	46XX	Agenetic	Defects in Müllerian derivatives	NA	Absent
21	Aughton (1993) ²¹	NA	46XX	Dysgenetic	Absent	Absent	Absent
22	Alper <i>et al</i> (1985) ²²	16	NA	Dysgenetic	Absent	NA	Absent
23	Al-Awadi <i>et al</i> (1985) ²³	2 sisters (18 and 16)	46XX	One Agenetic The other, dysgenetic	Hypoplastic	One, absent, The other, hypoplastic	Present
24	De Leon <i>et al</i> (1984) ²⁴	NA	46,X,i(Xq)	Agenetic	Absent	NR	Absent
25	Levinson <i>et al</i> (1976) ²⁵	17	46XX	Agenetic	Absent	Absent	Absent

N, normal; NA, not available; NR, not reported.

arise from an early defect in primordial follicle formation or a defect in differentiation of the ovaries. Patients usually present with short stature and have streak or immature ovaries. Other features classically described include webbed neck, low set ears, shield-like chest, broadly placed nipples, cubitus valgus, lymphoedema of hands and feet, nail dysplasia, genu valgum, etc. There is no clear association with any established risk factors,

maternal age, or familial inheritance pattern. Diagnosis is established on the basis of karyotype analysis. Deletion of the whole (45X) or part of one X chromosome will invariably be the basis of the definitive diagnosis. GH therapy should be considered in all girls with Turner syndrome whose height is below the 95th centile and who do not exhibit significant catch-up on growth charts. Oestrogen therapy in these patients can help in sexual

development and bone maturation. In vitro fertilisation using donor oocytes has been successfully employed with good pregnancy outcomes for these patients.

Müllerian agenesis, on the other hand, presents with normal secondary sexual characters and developmental anomalies of the female genital tract including an absent/malformed uterus and upper two-thirds of the vagina (MRKHS syndrome). However, due to different embryonic origin, the lower third of the vagina is always present. It is also associated with urogenital, skeletal or dental defects and other dysmorphias. These individuals have normal female genotype 46 and XX, and they ovulate normally. The most common presentation is primary amenorrhoea. The levels of luteinising hormone and follicle-stimulating hormone are normal due to normally functioning ovaries. Diagnosis is established on the basis of clinical findings, MRI of the pelvis and/or laparoscopy and karyotype analysis. However, MRI of the pelvis is preferred over diagnostic laparoscopy as it is non-invasive, gives better soft tissue contrast resolution and multiplanar capability, and is cost effective. With appropriate reconstructive surgeries (creating a neovagina), these patients can have a normal sex life.

This rare association of the two syndromes has been described in 25 published case reports so far.^{2–25} A brief summary of presentation is shown in table 1.

It is difficult to postulate a common theory for coexistence of these two anomalies in the same patient. Mutations of the gene encoding the anti-Müllerian hormone receptor (AMH-R) and the lack of oestrogen receptors during embryonic development have been hypothesised to cause MRKH syndrome.¹⁷ However, mutation in neither AMH nor AMH-R has been found. This combination of Turner syndrome and MRKH is a double blow to the patient, with very poor chances of conception. Hormone substitution therapy remains the only therapeutic option; it aims at triggering the development of secondary sexual characters and preventing osteoporosis. However, the unsolved problem of infertility remains.¹²

Learning points

- It is important to consider Turner syndrome in all cases of short stature and primary amenorrhoea.
- Early diagnosis of the condition might help in sensitising caregivers to understand the importance of instituting hormonal therapy for feminisation and bone health during adult life to improve the quality of life.
- Coexisting Müllerian agenesis in these patients can jeopardise the chances of future pregnancy as they are associated with structural abnormalities of the uterus and vagina.

Contributors AM was the chief author and investigator and takes full responsibility for the publication. MKD supervised the writing and proofread the manuscript. RD provided input on the radiological images.

Competing interests None declared.

Patient consent Obtained.

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