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Case Report

A Case Report of Familial Mayer-Rokitansky-Küster-Hauser Syndrome (MRKH syndrome) and Literature Review

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Abstract

Introduction:
Atypical Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a congenital disorder characterized by agenesis or aplasia of the uterus and upper part of the vagina in a female with a normal female karyotype (46, XX) with associated extra-genital anomalies such as renal, skeletal, auditory and cardiac malformations. Sporadic cases are common but there is growing evidence of familial cases. We report two cases of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome in siblings from the same family, with their father exhibiting unilateral renal hypoplasia.

Case Description:
A 19-year-old female presented with the complaint of primary amenorrhea. She had undergone patent ductus arteriosus device closure at the age of 6 years. There were no features of hyperandrogenism. Her family history revealed that her father had left renal hypoplasia. On examination she had short stature and scoliosis. She had tanner 5 breast development and pubic hair distribution. She had normal female karyotyping (46 XX) and hormonal profile was within normal range with no abnormalities. Her MRI abdomen and pelvis showed an absent uterus and upper ⅔ of the vagina, single pelvic kidney with normal ovaries. Her younger sister who was 16 years old was also investigated for primary amenorrhea. She was also short and had Tanner stage 5 breast development and normal pubic hair distribution. Her hormonal profile was normal, but pelvic ultrasound revealed bilateral pelvic kidneys, an absent uterus, and bilateral ovaries located in the left and right iliac fossae, suggesting the possibility of MRKH in the sibling as well.

Discussion & conclusion:
MRKH syndrome is the second commonest cause for primary amenorrhea where the aetiology remains controversial. Majority of the cases are sporadic but there is emerging evidence of familial cases of MRKH suggesting a genetic etiology. During the last decade, there has been advancement in the genetic studies related to MRKH syndrome. Understanding the genetics related to MRKH syndrome is of great importance to provide genetic counselling in the clinical setting.

Keywords: Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), primary amenorrhea, utero-vaginal agenesis, familial

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Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a congenital disorder characterized by agenesis or aplasia of the uterus and upper part of the vagina in females with a normal female karyotype (46,XX)[1]. MRKH syndrome is the second commonest cause of primary amenorrhea which accounts for about ~16% of patients with primary amenorrhea [2]. MRKH syndrome is caused by developmental abnormality of the Mullerian duct system, which forms the uterus, cervix and the upper two-thirds of the vagina. It is generally classified into two types, typical (type 1) and atypical (type 2). Typical MRKH syndrome is associated with isolated utero-vaginal agenesis, while atypical MRKH is characterized by utero-vaginal agenesis associated with extra-genital anomalies such as renal , skeletal, auditory and cardiac malformations. The Mullerian hypoplasia, renal agenesis, cervicothoracic somite dysplasia (MURCS) is the most severe form of atypical MRKH syndrome [3]. The prevalence of MRKH syndrome is considered to be in 1 in 5000 live female births [4]. While sporadic cases are common, emerging evidence suggests an increasing trend of familial MRKH syndrome. Other diagnoses presenting with primary amenorrhea and normal secondary sexual characteristics include

congenital absence of the uterus and vagina, isolated vaginal atresia, androgen insensitivity syndrome, transverse vaginal septum and imperforated hymen. In MRKH syndrome, there is normal ovarian function and normal LH and FSH levels. If there is a suspicion of androgen insensitivity syndrome serum testosterone levels should be done. Chromosomal analysis is essential to exclude karyotype abnormalities such as Turner syndrome, gonadal dysgenesis and androgen insensitivity syndrome. Imaging has an important role in diagnosing MRKH syndrome. Transabdominal ultrasonography is the first line imaging modality, but abdominopelvic MRI is more accurate and precise.

There are several reported cases on MRKH syndrome in Sri Lanka. The reported cases include isolated MRKH syndrome as well as cases in which it co-exist with other conditions such as Turner syndrome, gonadal dysgenesis and ovarian tumours. [5],[6],[7],[8] To the best our knowledge there have been no familial cases of MRKH syndrome reported in Sri Lanka.

Case Presentation

Case 1

A 19-year-old patient presented to the endocrine clinic with primary amenorrhea. She had normal thelarche and pubarche. At the age of 6 years, she had undergone patent ductus arteriosus device closure. She was not on any long-term drugs. Her mother's obstetric history did not reveal exposure to teratogenic drugs or radiation during the pregnancy. Her father's medical history revealed left renal hypoplasia. She had a younger sister of 16 years who was also being investigated for primary amenorrhea. On examination the patient had short stature (148.3 cm). Her BMI was 24.8 kg/m^2 and she was found to have scoliosis. She had normally developed breasts (Tanner stage 5) with normal pubic hair distribution (Tanner stage 5).and normal female external genitalia.. Laboratory investigation results for luteinizing hormone, follicular stimulating hormone, serum oestradiol levels, thyroid stimulating hormone and prolactin levels were within the normal limits. She had normal 46 XX karyotype at genetic testing. Her ultrasound pelvis showed a right side solitary pelvic kidney, but the uterus and the ovaries were not visualized.MRI pelvis showed absent uterus, upper 2/3 of the vagina, renal anomaly (pelvic kidney) and normal ovaries [figure 1, 2] suggestive of atypical Mayer-Rokitansky-Küster-Hauser syndrome.

Case 2

Her 16-year-old sister was investigated for primary amenorrhea. She had normal pubarche and thelarche. Her past medical or surgical history was unremarkable. Physical examination revealed short stature (Height 147 cm). She had Tanner stage 5 breast development with normal pubic hair distribution and normal female external genitalia. Her laboratory investigation results for luteinizing hormone, follicular stimulating hormone, serum estradiol levels, thyroid stimulating hormone and prolactin levels were all within the normal limits. Her pelvic ultrasound revealed bilateral pelvic kidneys, absent uterus with bilateral ovaries in the left and right iliac fossae.

Father of the above two cases was 61 years old and was investigated for renal impairment. He underwent DTPA renal scan and found to have left side small sized kidney and normal right kidney demonstrating moderate functional impairment.

Discussion

Atypical MRKH syndrome is the most frequent form of MRKH, which accounts for approximately 56% of cases [9]. Renal and skeletal malformations are the commonest abnormalities associated with atypical MRKH syndrome. The renal malformations associated with MRKH are unilateral renal agenesis/renal hypoplasia, ectopic kidneys, horseshoe kidney, hydronephrosis etc. (Table 1) . MRKH syndrome associated cardiac malformations are rare. The reported cases of cardiac malformations in the literature include pulmonary stenosis, ostium secundum type atrial septal defect, Holt Oram with aorto-pulmonary window, Tetralogy of Fallot, patent ductus arteriosus with bicuspid aortic valve (Table 2). In our first patient had patent ductus arteriosus for which she had undergone surgery. Skeletal anomalies related to MRKH commonly involve the spine such as scoliosis, isolated vertebral anomalies, Klippel Feil anomaly etc. and less frequently limb extremities [26]. In the reported cases, the elder sibling had scoliosis. The reported auditory defects in the literature are associated with MRKH are conductive deafness due to stapedial ankylosis, dysplasia of the auditory meatus and malformed ears [27].

The exact aetiology of MRKH syndrome still remains unclear. Majority of the cases are sporadic but there is increasing evidence of familial clustering which points

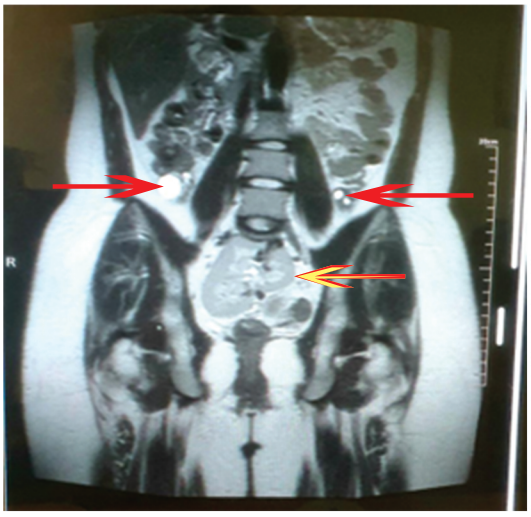

Figure 1: MRI abdomen and pelvis (coronal section) of the case 1(ovaries, single pelvic kidney)

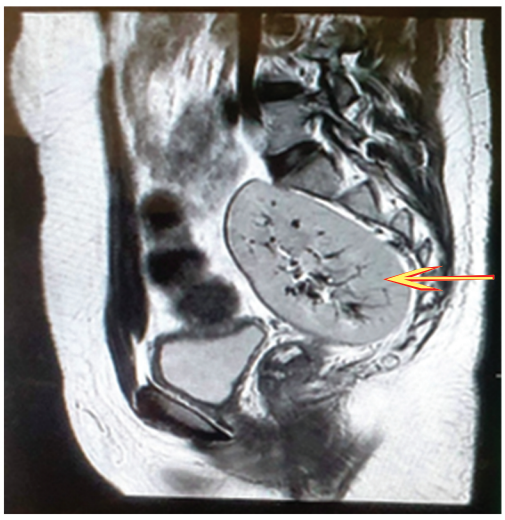

Figure 2: MRI abdomen and pelvis (Sagittal section) of the case 1(single pelvic kidney)

Table 1: MRKH associated renal abnormalities

Unilateral renal agenesis/Hypoplasia [10],[11]
Bilateral renal agenesis [12]
Simple renal cysts [13]
Duplex kidneys [14]
Ectopic kidneys [15],[16],[17]
Hydronephrosis [18]
Renal duplication [19]
Horseshoe kidney [20]

Table 2: MRKH syndrome associated cardiac abnormalities

Pulmonary stenosis [21]
Holt Oram syndrome [22]
Tetralogy of Fallot [23]
Ostium secondum type ASD [24]
PDA and bicuspid aortic valve [25]

out towards a possible genetic cause [28]. The precise pattern of inheritance in the familial cases remains debatable but can be explained by autosomal dominant inheritance with incomplete penetrance and variable expressivity [29]. It was suggested that female carriers develop Mullerian abnormalities, whereas the male carriers do not manifest major defects. However, there is a controversy remaining regarding the male phenotype. Variable expressivity of MRKH syndrome was observed even within the same pedigree. It is believed that epigenetic and in utero environmental factors have a role in modifying the severity of the phenotype. The familial clustering of MRKH was recently reviewed by Herlin et al. They reviewed a total of 67 pedigrees that address 123 cases of MRKH syndrome and 84 non-MRKH relatives with other anomalies. They found renal and skeletal malformations are the commonest like sporadic cases. In our case father of the index case patient had renal hypoplasia. We could not further investigate on the family members as he had no female siblings. Understanding the pattern of inheritance of MRKH is challenging due to a number of reasons. They are the inability of MRKH syndrome patients to have children without assisted reproduction and lack of clinical information about extended family members. Ultrasonographic screening of the relatives is important as majority of the associated anomalies were asymptomatic [30]. In a case of a unilateral agenesis of the kidneys it is important to diagnose the condition early as possible as any insult to the solitary kidney would result in kidney insufficiency. Positive ultrasound findings will help to diagnose familial cases so that genetic counselling and further investigations can be arranged.

Genetics related to MRKH syndrome has become an area of professional research interest during the last decade. Array comparative genomic hybridisation analyses in MRKH syndrome patients had identified recurrent aberrations in chromosomal regions 1q21.1, 16p11.2, 17q12 and 22q11.21 respectively [31],[32],[33]. Increasing number of genes responsible for MRKH syndrome have been identified. They are genes of known importance to urogenital embryologic development such as AMH, AMHR2, WNT, WT1, LHX1, HNF1B, homeobox genes, PAX and etc. [34] and genes causing diseases associated with MRKH syndrome such as GALT [35] and CFTR [36]. It is important to identify the genetic causes of MRKH syndrome to improve the knowledge regarding genetic factors related to human uterovaginal development and to provide better patient care in educating and counselling the patient and the families in the clinical setting. In the reported case we were unable to proceed with genetic testing in our patient due to unavailability of testing in Sri Lanka.

MRKH syndrome has a long-lasting impact on patients and their families with regards to sexual identity, the sexual life, grief of infertility and risk of depression. Proper timely psychological support and counselling is one of the most important in-patient care. There are number of nonsurgical and surgical treatment options suggested for treatment of MRKH syndrome. The treatment options are vaginal dilation or vaginoplasty, the former being the first line option. Uterine transplantation and gestational surrogacy have been used to achieve biological motherhood in developed countries.

Conclusion

Atypical MRKH syndrome is associated with mullerian agenesis and extragenital abnormalities. Sporadic cases are common but there is rising evidence for familial cases. The recent advancement in genetic studies related to MRKH syndrome reveals a heterogenous etiology with the involvement of various genes. Identifying the genetic background of MRKH syndrome is crucial both academically and for genetic counseling and evaluation of asymptomatic family members.

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