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Mayer- Rokitansky- Kuster- Hauser Syndrome (MRKH SYNDROME)- An Unusual Case of Primary Amenorrhoea

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Mayer- rokitansky- kUster- hauser syndrome (MRKH Syndrome); Uterine aplasia; Amenorrhoea, secondary sexual characters; Dyspareunia

Abbreviations:

MRKH: Mayer- Rokitansky- KUster- Hauser Syndrome; MURCS: Müllerian Renal Cervico-thoracic Somite; MRI: Magnetic Resonance Imaging; BMI: Body Mass Index; CAIS: Congenital androgen insensitivity syndrome; FSH: Follicle-stimulating hormone; LH: Luteinising hormone; HIV: Human Immunodeficiency Virus; WNT: Wingless Related Integration Sign

1. Abstract

The onset of mestruation is a significant milestone of sexual maturation in a girl child. Although there are numerous causes of primary amenorrhoea, Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also known as Müllerian aplasia is one the extremely rare cause of primary amenorrhoea which is usually picked up by suitable imaging technique like Magnetic Resonance Imaging (MRI). MRKH is a rare congenital disorder that is characterised by aplasia of the uterus and upper part of the vagina with normal secondary sexual characters and a normal female karyotype (46, XX). The diagnosis is often made during adolescence following investigations for primary amenorrhea and has an estimated prevalence of 1 in 4500 live female births. MRKH syndrome is classified as type I (isolated utero-vaginal aplasia) or type II (associated with extra-genital manifestations also called Müllerian Renal Cervicohoracic Somite (MURCS) association). No specific treatment is known for this entity except for vaginoplasty for sexual gratification.

A case of MRKH Syndrome is reported here where a 16 year old female child presented with primary amenorrhoea. The diagnosis was made initially on clinical suspicion by normal growth with normal secondary sexual characters with failure to achieve menstruation at the age of 16 years, which was confirmed later by MRI Pelvis showing absence of uterus and normal ovaries and blind vaginal canal was visualised and no other renal or spinal anomalies noted. Karyotyping done revealed normal karyotype, 46 XX [1].

2. Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also called Müllerian aplasia, is a rare congenital disorder resulting from failure of urogenital development with an estimated incidence of 1/4500 live female births. Embryologically, the uterus is formed by the Mullerian ducts that are paired tubes abutting the urogenital ridge giving rise to the upper portion of the female reproductive tract. Failure of proper development of the upper female urogenital tract results in a wide spectrum of anatomical abnormalities of the genitourinary system. Mullerian agenesis, also known as Mayer-Rokitansky - Kuster - Hauser syndrome (MRKHS), is characterised by absence or aplasia of the uterus, cervix, and/or upper vagina without or with associated urological and other organ system involvement (MRKHS type I versus type II, respectively) [1].

Depending on the particular structures affected and the severity of involvement, such abnormalities may be detected at birth or may go clinically unnoticed until there is absence of menarche or complaints of dyspareunia/sexual dysfunction with attempted sexual

activity [2]. Vaginal agenesis during embryological development often leads to complete absence of the vagina if not the remnant of a small vaginal dimple in adults [2]. Here, we report an case of MRKHS in an otherwise healthy, unmarried, sexually inactive girl who presented at age 16 with primary amenorrhea and was found to have aplastic uterus, absent endometrium and absent cervix along with blind lower vagina with well developed secondary sexual characters. Informed consent was obtained from the patient to use her medical information for this case report.

3. Case Report

A 16-year-old female child belonging to Ghaziabad, Uttar Pradesh, presented with her mother with chief complaint of never having a menstrual period. There was no history of tubercular contact in the patient. Other family history was unremarkable. Female was not sexually active. There was no other relevant past history. There was no relevant drug history or history of any substance abuse. On examination her vital signs were within normal limits and her body mass index (BMI) was 25.51. Child had mild pallor with no icterus or lymphadenopathy, no signs of organomegaly or thyromegaly. Breasts were well- developed with no masses, tenderness, or discharge. Sexual Maturity Staging or Tanner Staging suggested Stage-5. Rest Systemic Examination was within normal limits. No cardiac abnormality was detected. No spinal anomaly detected. No evidence of webbed neck, broad chest, widely spaced nipples or cubitus valgus, nail dysplasia, low hairline, narrow or high arched palate or short fourth metacarpals or metatarsals. Child was evaluated for primary amenorrhoea based on the history. She had never been previously evaluated by a gynaecologist. Gynaecological examination showed no lesions and normal adult female pubic hair pattern, Tanner stage V. The cervix was not palpable or visualised. The uterus was not palpable and no adnexal masses were appreciated. Per vaginal examination revealed a blind vagina measuring 1.5 cm in diameter, no bleeding or discharge. The urethra was normal in appearance. Child had undergone biochemical evaluation previously at local clinics which revealed Hb- 12 gm%, Total Leucocyte Count- 8200, Differentials - Polymorphs- 58%, Lymphocytes- 34%, Eosinophils- 6%, Monocytes- 2% and ESR- 25 mm/hr, RBC- 4.53 million/cubic metre, Platelet count- 2.86 lac/cumm, Blood sugar- 87.6 mg/dl, Mantoux test revealed a highly positive result with an induration of 35 x 40 mm after 48 hours with 5 TU, Chest Xray- suggestive of left lower zone heterogenous infiltrates, HIV serology- Negative and Hepatitis B and C markers were also negative.

In light of the patient's presentation, trans-abdominal ultrasound was performed, which revealed bilateral uteri non visualisation, only a streak of mass tissue measuring 39 mm x 9 mm seen, with no endometrium appreciated. The cervix was not imaged. Follicle-containing ovaries were imaged trans-abdominally and were normal in size and appearance bilaterally, definitively excluding the presence of testes and effectively ruling out congenital androgen insensitivity syndrome (CAIS). Right Ovary showing multiple follicles with the largest follicle measuring 15 x 5 mm and a simple cyst of size 35 x 30 mm. No fluid was appreciated in the Cul de sac.

NCCT Abdomen revealed non visualisation of uterus, only streaky soft tissue in the region of uterus with ovaries normal in size with normal follicular appearance and mild mesenteric lymphadenopathy in ileo-caecal mesentery largest measuring 1.3 x 1.1 cm. MRI Pelvis revealed uterine aplasia with bilateral ovaries with normal morphology. The upper one-third of the vagina was absent, while the lower two-thirds were present. Rest study was normal. Together, the findings of primary amenorrhea, normal ovaries and female secondary sexual characteristics, and aplasia of the uterus with absence of the cervix and upper one-third of the vagina, were consistent with a diagnosis of MRKHS. A subsequent biochemical analysis was performed to further support the diagnosis of MRKHS. Levels of estriol, follicle-stimulating hormone (FSH), luteinising hormone (LH), total testosterone, were all within normal limits, again consistent with the diag-nosis of MRKHS (Table 1). Karyotyping was done and revealed normal karyotype (46 XX). Because of the well-known association between MRKHS and anatomical abnormali-ties of the urological system [2], a renal ultrasound was performed, which demon-strated normal bilateral kidneys, no evidence of hydronephrosis, and no evidence of contour deforming mass. Right kidney shows a calculus of size 4.1 mm seen in the upper pole.

Table 1: Biochemical evidence of female phenotype.

Serum marker	Patient value	Reference range
Estriol (ng/mL)	194	43.8-211.0 (Luteal phase)
Follicle stimulating hormone(mIU/mL)	5.2	1.5- 9.1 (Luteal phase)
Luteinising hormone(mIU/mL)	15.28	0.5-16.9 (Luteal phase)
Prolactin(ng/mL)	17.87	5-25 (Female)
Total Testosterone(ng/dL)	32.97	14-76(Female)
Thyroid stimulating hormone(microIU/mL)	2.83	0.25-6.00
Free T3 (pg/mL)	3.53	1.5-4.1
Free T4 (ng/mL)	1.18	0.8-1.9

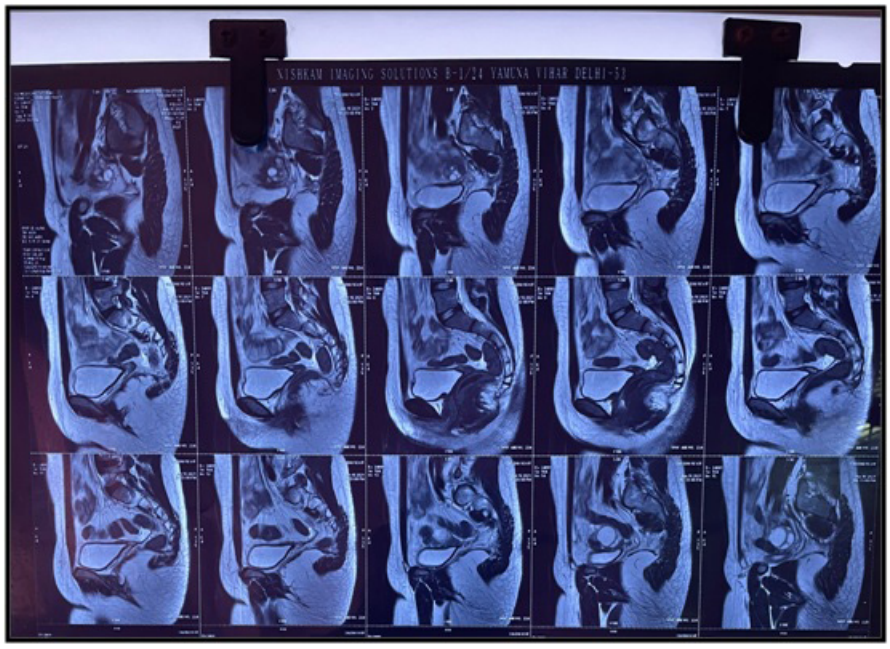

Figure 1: Showing MRI T2 weighted image pelvis ; (A) Blind vaginal sac with absent uterus

Thus, our patient displayed characteristics of MRKHS type I. Upon hearing the diag-nosis, our patient was anxious, especially with regard to future reproductive pro-spects; however she was counselled with her parents present regarding the implica-tions of the diagnosis and reproductive options such as use of a surrogate to carry a pregnancy for her. She expressed gratitude at the end of the encounter for the infor-mation and services provided and was offered follow-up as needed.

4. Conclusion

MRKHS represents a spectrum of urogenital anomalies arising from failure of the up-per female reproductive tract (Mullerian duct derivatives) to properly form during embryogenesis. In cases of MRKHS type I, patients exhibit varying degrees of con-genital aplasia of the uterus and upper vagina, without extra-gynaecological involve-ment and with normal secondary sexual characteristics [2] The typical presentation in this condition is primary amenorrhea. Some women may present with cyclical ab-dominal pain, and gynecological examination may reveal absent or rudimentary vagi-na[2]. MRKH syndrome is a form of Mullerian abnormality also known as Mullerian aplasia. It is caused by embryonic growth failure resulting in agenesis or underdevel-opment of the vagina or uterus or both [3]. The ovaries are of a different embryologic origin and they are normal in structure and function; thus, patients with this syndrome usually appear normal on physical examination, with normal height and secondary sexual characteristics. The labia majora, labia minora, clitoris, hymen and distal por-tion of the vagina are usually present because this portion is of a different embryonic origin.

Cases of MRKHS type II involve renal, vertebral, auditory, and/or cardiac defects in addition to the aforementioned gynaecological anomalies.

There are two subtypes of MRKH: the typical and the atypical forms [4]. The typical form is characterised by laparoscopic/laparotomy findings of Mullerian remnants and normal fallopian tubes. The atypical form shows asymmetric hypoplasia of one or two buds, possible dysplasia of the fallopian tubes with one or more of the anomalies, such as unilateral or bilateral renal agenesis, ectopic kidneys or horseshoe kidneys in 40–60% of cases. Other abnormalities include cervicothoracic (asymmetric, fused or wedged vertebrae, scoliosis and Klippel–Feil anomaly), hearing defects and varying degrees of digital anomalies. The most severe form of the atypical form is referred to as Mullerian renal cervical somite association [4, 5]. The diagnosis is confirmed mainly with imaging modalities of ultrasonography and magnetic resonance imaging. These help to definitively characterise the anatomy. The preferred ultrasonography is the three-dimensional mode. Laparoscopy is considered when the earlier mentioned mo-dalities have not yielded adequate information or in the treatment of rudimentary uter-ine horns [6].

Karyotyping is also needed in establishing the diagnosis of MRKH syndrome as it helps in differentiating it from the other clinical conditions that appear similar in ap-pearances such as androgen insensitivity syndrome and 17α-hydroxylase syn-drome [7]. However, the absence of hypoplastic thumbs and a short neck strengthened the diagnosis of MRKH syndrome [4].

Here, we report a case of a woman with MRKHS with a blind lower vagina measur-ing 1.5 cm along with uterine aplasia on MRI pelvis and hormonal profile suggestive of a female phenotype whose only complaint was primary amenorrhea.

While most cases of MRKHS are sporadic, a subgroup of patients has been shown to harbour mutations in WNT family genes [9]. Given the well-established role of WNT signalling in cellular pro-

liferation, dysregulation of this pathway in our patient may have contributed to her phenotype, although this remains unknown at present.

The management of this condition involves the exclusion of other clinical malfor-mations that will hinder the well-being of this patient. The treatment is multidiscipli-nary and involves surgical and nonsurgical treatment options including the creation of a neovagina to have a normal sex life. Vestiges of the uterus can be removed to avoid the development of endometriosis [10]. The timing of the surgical or nonsurgical crea-tion of the neovagina should be planned for when the woman is emotionally mature and expresses the desire for correction. Surgery aims to create a vaginal canal in the correct axis of adequate size and secretory capacity to allow intercourse. A procedure commonly done involves dissection of space between the rectum and the bladder, placement of a mould into the space covered with a split-thickness skin graft. After healing, serial dilation is done to prevent skin graft contracture. A neovagina can also be created laparoscopically. Other forms of grafts that can be used include buccal mu-cosa, bowel mucosa and amnion [7]. Routine gynaecological care is expedient in women undergoing therapy to optimise and maximise the care. In conclusion, MRKH syndrome is a rare anomaly of the Mullerian duct. The absence of sexual and reproductive health education, combined with the cultural shame of dis-cussing issues relating to genitals and sexuality results in a lack of communication and delayed diagnosis. An absence of or "missing" education on this diagnosis, and "missing" education for health professionals results in poor communication and often humiliating and negative experiences for the young women. The cultural pressures to bear children impacts on their capacity to have romantic relationships and marriage. Public awareness of this condition is necessary via mass media. Education regarding this condition needs to be included in the medical undergraduate and postgraduate curriculums. Patients should be equipped with appropriate knowledge of their condi-tion especially aspects of fertility and sexual function. Frank discussion regarding physical aspects of sexual intercourse should be initiated early and not kept to be 'just before marriage'[11] Despite the clinical management options available, the distress of having such a condition is better managed with support from psychologists, coun-sellors and a strong social and family support group.

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