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MAYER-ROKITANSKY-KÜSTER-HAUSER (MRKH) SYNDROME IN GIRLS – DIAGNOSIS, TREATMENT AND PSYCHOSOCIAL ASPECTS

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ABSTRACT

Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome is a rare congenital disorder characterized by agenesis or aplasia of the uterus and the upper part of the vagina in otherwise chromosomally and hormonally normal females (46,XX). It affects approximately 1 in 4500–5000 live female births and represents one of the most common causes of primary amenorrhea. Genetic and environmental factors are the main cause of the syndrome, although the pathogenesis is multifactorial. Diagnostics include both imaging tests (such as ultrasound or magnetic resonance imaging) and genetic tests. Therapeutic management is aimed at forming a functional neovagina that allows for comfortable sexual intercourse, achieved through either non-surgical dilation techniques or surgical vaginoplasty, selected according to the patient's preferences and existing indications or contraindications to a given type of procedure. Available reproductive approaches, including uterine transplantation, surrogacy, and adoption, provide women with MRKH syndrome the possibility of achieving motherhood. Psychological assistance is essential, since the diagnosis has a significant impact on a woman's self-esteem, perception of her body, and sense of sexual identity. Multidisciplinary care including medical, surgical, and psychological interventions is vital to achieving the best therapeutic outcomes and enhancing the quality of life of patients with MRKH syndrome.

KEYWORDS

MRKH Syndrome, Amenorrhea, Disorders of Sex Development, Mullerian Aplasia

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Introduction

Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, also referred to as Müllerian agenesis, is described as a agenesis or aplasia of the uterus and the upper part of the vagina in otherwise chromosomally and hormonally normal females. [1] As one of the most common causes of primary amenorrhea, the disease remains a significant clinical challenge due to its complex etiology, diverse clinical presentation, and the influence of quality of life. The disease affects patients on many levels, not only physically, concerning sexual and reproductive functions, but also psychologically - the feeling of not fulfilling one's role as a woman. This review provides an updated overview of MRKH syndrome, including etiopathogenesis, diagnosis, therapeutic options and the consequences for emotional and reproductive health.

Definition and epidemiology

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare congenital disease associated with Müllerian aplasia and characterized by agenesis or aplasia of the uterus and upper part of the vagina in females with a normal female karyotype (46,XX) [1]. The condition occurs in 1 in 4500-5000 live female births [2].

Etiopathogenesis

The etiology of the disease is not fully recognized and multifactorial, including both genetic and environmental factors. Studies show that although most cases are sporadic, there are a significant number of families with multiple affected individuals, suggesting autosomal dominant inheritance with incomplete penetrance and variable expression of clinical features [3,4]. Genetic studies indicate links with a number of candidate genes, such as GREB1L, WNT4, LHX1, PAX8, TBX6 or HNF1B [5]. Furthermore, it has been shown that the frequency of copy number variants (CNVs) in regions such as 1q21.1, 17q12, 22q11.21 and 16p11.2 is higher in patients with MRKH than in the general population [1, 6].

Clinical description

The first clinical signal is a primary amenorrhea with normal and functioning ovaries and normally developed second sex characteristics [7]. Another symptom complained about by patients suffering from this syndrome is dyspareunia caused by the shortened vaginal canal in most cases [8]. Patients with MRKH syndrome often have uterine remnants, which may contain active endometrium. Their presence is associated with the risk of cyclical pelvic pain, hematometra, or the development of endometriosis [9, 10]. Depending on coexisting malformations the syndrome can be divided into two categories: type 1 (56-72%) - isolated, presenting with only genital abnormalities and type 2 (28-44%) with accompanying renal (unilateral agenesis, ectopia of kidneys or horseshoe kidney) and skeletal anomalies (Klippel-Feil anomaly; fused vertebrae, scoliosis) [1, 3, 7]. In some cases MRKH syndrome has been reported with a very severe phenotype such as cardiac defect, anal atresia, oculodentodigital dysplasia, tracheoesophageal fistula/esophageal atresia or absent radius syndrome [11,12].

Diagnosis

Patients presenting with primary amenorrhea should be referred to a specialist in gynecology, pediatric gynecology or disorders in sexual development (DSD). The examination usually includes viewing the female genitalia and examining the introitus/vagina [1]. Various diagnostic techniques may be used, but selecting the appropriate method, the patient’s age and sexual activity status should be taken into account [1, 4]. In most cases, the first method chosen is ultrasound examination which shows the absence of uterus and presence of ovaries [8]. The golden standard method for diagnosis of MRKH syndrome is considered the magnetic resonance imaging (MRI) [1, 4, 8]. The examination provides improved visualization of Mullerian structures, including the presence of uterine remnants and the endometrium within them. Furthermore, the examination allows for the assessment of additional malformations, for example urinary tract and associated organs [13].

Laparoscopy is a rarely used technique in the diagnosis of this condition. It can be used in patients who report chronic pain caused by residual uterine tissue, which requires surgical excision for treatment [1]. Additional tests for differential diagnosis could include karyotype determination or laboratory tests for hormonal disorders, including sex hormone determination [7].

Differentiation

When evaluating primary amenorrhea, it is essential to conduct thorough diagnostic testing to distinguish it from the most frequent underlying causes. The leading genetic cause of delayed puberty and primary amenorrhea is Turner syndrome, characterized by a 45,X karyotype and elevated levels of FSH [4]. MRKH syndrome also shares some of the features typical of Morris syndrome such as typical female phenotype, a blind-ending vagina, absence of the uterus, and normal breast development [1]. Another disease with a similar clinical appearance is 17α-hydroxylase deficiency caused by a mutation in the CYP17A1 gene. Females with a phenotype of 46,XY typically exhibit delayed puberty, amenorrhea, and a lack of secondary sexual characteristics, similar to patients with a phenotype of 46,XX [14]. Female secondary sex characteristics, primary amenorrhea and absence of female primary sex characteristics (uterus and ovaries) may also occur in androgen insensitivity syndrome (AIS), however, the feature that distinguishes it from MRKH syndrome is the level of testosterone [15].

Psychological aspects

The diagnosis of MRKH syndrome is often associated with a strong emotional burden. The majority of patients receive their diagnosis in adolescence, a critical period for the development of body image and sexual identity [1]. Patients may experience shock, sadness, anger and guilt immediately after receiving their diagnosis. Numerous studies show that women with MRKH syndrome are more likely to experience mental illnesses such as depression, phobic anxiety, psychoticism or neuroticism or even suicidal tendencies [16-19]. The attitude towards one's sexuality may also change in patients diagnosed with MRKH syndrome. Despite the normal development of secondary sexual characteristics and ovarian function, the absence of a uterus and vagina may lead to a sense of incomplete femininity, fear of intimacy and reduced self-esteem in a sexual context. Women with MRKHS reported reduced capacity to give or receive sexual satisfaction and had fewer occasions for sexual activity compared to their peers [20]. Another important psychological aspect of patients with MRKH syndrome is their attitude towards their own gender and the related role of parenthood - some women believe Some women felt that being a “true” woman required the ability to bear children [4].

Treatment

The main goal of therapeutic treatment in MRKH syndrome is to enable patients to have painless sexual intercourse by creating a functional neovagina [8]. According to The American College of Obstetricians and Gynecologists (ACOG) guidelines, treatment should initially focus on non-surgical approaches as the preferred option. Vaginal dilation therapy with dilators is associated with a lower risk of complications, less emotional distress, and lower costs [21]. This process involves inserting a dilator of gradually increasing diameter into the existing vaginal pocket daily for approximately 15-20 minutes per day [4]. The methods of inserting a dilator into the vagina include the manual method and the Ingram method which involves placing the dilator on a bicycle seat [22]. Edmonds et al. in their study showed improvement in the vaginal lengthening in over 94% of patients using dilators [23]. The most common side effects of dilation therapy are urinary symptoms, bleeding and pain. The primary recommendations for managing bleeding include applying more lubricant, and using a broader or softer dilator [21]. To relieve pain, it may be helpful to use estriol cream, nitrous oxide and oxygen, diazepam, lidocaine ointment, paracetamol or naproxen [24]. An important element of dilatation therapy is psychological support, which helps patients cope with the emotional challenges associated with treatment [4, 25]. Another way to create a functional neovagina is a vaginoplasty procedure that involves forming a cavity between the bladder and rectum and lining it with different types of autologous grafts [8]. The grafts may be derived from different tissues, including the peritoneum, segments of the bowel, the labia majora or split skin [26-29]. Callens et al. showed that all vaginoplasty techniques had a higher success rate than dilation therapy, both in terms of vaginal lengthening and the ability to have sexual intercourse [30]. Recently, the use of cultured autologous vulvar tissue and tissue-engineered biomaterials has been proposed for vaginoplasty procedures [1]. Some studies have shown that using cells harvested from the vulvar region enables the creation of a functional lining for the neovagina, resulting in favorable anatomical outcomes and improved sexual quality of life for patients [31, 32]. The procedure using tissue-engineered biomaterial graft

also has a good anatomical (vaginal lengthening) and functional effect (enabling intercourse), but the negative aspect of using this type of material is the cost of the procedure [33]. An alternative to the procedure of creating a neovagina using a transplant may be the laparoscopic Vecchietti vaginoplasty based on progressive passive traction through the external pelvic wall on the retrohymenal fovea with the use of an acrylic "olive"[4]. Unfortunately, this procedure may be associated with an increased incidence of urogynecological problems [34]. It should be remembered that every surgical treatment method carries a risk of postoperative complications such as blood loss, poor response to anesthesia, or the possibility of postoperative vaginal stenosis [8]. Additionally, surgical interventions necessitate postoperative dilatation or sexual activity to preserve sufficient vaginal length and width. According to ACOG recommendations, surgery should only be an option for patients in whom vaginal dilation therapy has not produced the expected results [21].

The issue of fertility and reproduction

Patients with MRKH syndrome due to the absence of uterus or presence of uterus, in which the embryo is unable to implant, are classified within the group of patients with absolute uterine factor infertility (AUFI) [1]. Uterine transplant, surrogacy or adoption are the possible ways for having a child [4]. The first documented case of a uterine transplant followed by embryo implantation that led to pregnancy and the delivery of a baby involved a 35-year-old woman with MRKH syndrome. During the whole pregnancy the woman received immunosuppressive drugs to reduce the risk of transplant rejection. Due to preeclampsia, doctors decided to perform a cesarean section at 31 weeks and 5 days. A healthy boy was born with a normal birthweight for gestational age [35]. A single kidney, frequently associated with MRKH syndrome, is considered a risk factor for preeclampsia, which could explain the elevated incidence of preterm births in these patients [36]. Furthermore, research on organ transplantation has reported a link between preterm birth and the use of immunosuppressive drugs, which are also widely administered in UTx [8]. Since uterine transplantation remains an experimental technique, many women with MRKH syndrome opt for surrogacy instead. A review investigating the reproductive potential of women with MRKH syndrome found that, within a cohort of 140 patients, 125 underwent 369 IVF cycles with gestational surrogacy, resulting in 71 live births [37]. Although many patients with MRKH syndrome desire motherhood and consider surrogacy as a possibility to have a child, in most cases it is not feasible due to the illegality of the procedure in their country [38, 39].

Conclusions

Mayer-Rokitansky-Küster-Hauser syndrome is a rare and complex congenital anomaly. Appropriate diagnostics, including an extensive gynecological interview, imaging tests, and genetic tests, enable early diagnosis and precise treatment planning tailored to the individual patient.When making a final diagnosis, the most common causes of primary amenorrhea should be ruled out. Therapeutic management focuses on restoring sexual function and quality of life, achievable through non-surgical or surgical neovaginal reconstruction, guided by patient preference and psychological suitability. During therapeutic procedures, it is necessary to remember about the psychological aspects of the disease, providing the patient with appropriate support due to the fact that the disease may affect her sense of well-being (self-esteem, body image or sexual identity). Uterine transplantation is available to enable motherhood, but the method is still experimental. To sum up, optimal care for patients with MRKH syndrome relies on a multidisciplinary approach that combines medical, surgical, and psychological support to address both physical and emotional needs.

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