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Mayer-Rokitansky-Kuster-Hauser Syndrome - Case report

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Abstract

This is the report of a teenager student with primary amenorrhea with secondary sexual characteristics. The incidence of Mayer-Rokitansky-Kuster-Hauser syndrome was not clearly established, but studies indicate a variation of 1/4,000 and 1/5,000 live births of the female sex. The syndrome is characterized by aplasia of the Müllerian duct (uterus and upper two-thirds of the vagina) on a person who has karyotype 46, XX with female phenotype characteristic of primary amenorrhea in adolescence. Treatment is usually delayed until the patient is ready to begin sexual activity.

Keywords

Rokitansky syndrome, Mullerian duct, Karyotype, Primary amenorrhea

Abbreviation

MRKH: Mayer-Rokitansky-Kuster-Hauser Syndrome, UNISUL: University of the South of Saint Catherine (Universidade do Sul de Santa Catarina), MIF: Mullerian Inhibiting Factor, MURCS: Mullerian Agenesis, Renal Agenesis, Cervicothoracic Somite Abnormalities, HRA: Hereditary Renal Dysplasia, WES: Whole-Exome Sequencing, SNP: Single Nucleotide Polymorphism, IVF: *in vitro* Fertilization, B/P: Tanner's Criteria for Breast and Pubic Hair Development

Introduction

The normal development of the female reproductive tract depends on the interaction between genetic, hormonal and environmental factors for the differentiation of the Müller and Wolff ducts, and the urogenital sinus1-3. Changing these factors can result in a wide spectrum of abnormalities of the reproductive tract, including imperforate hymen, vaginal agenesis or atresia, incomplete fusion of the Müllerian ducts and Müllerian aplasia1-4. Congenital malformations of female genitalia are often a challenge for doctors, requiring a great knowledge of embryonic development of the genital tract due to the wide variety of possible diagnoses.

Clinical Case

E, 16 years and two months, student, born in Palhoça, Santa Catarina, single, Caucasian, referred to the Clinic of Gynecology and Obstetrics, UNISUL in March 2011 for primary amenorrhea research with presence of secondary sexual characteristics. The larche and pubarche at age 12. Denies chronic diseases, excessive exercise, medications, anorexia, clinical hypothyroidism or hyperandrogenism. No family history of amenorrhea. Mother menarche at age 11 and sister at age 12. Physical examination: weight 49kg, height of 1,67m, female phenotype, symmetrical breasts (B4), the genital examination hairiness gynecoid (P4/P5), rudimentary clitoris, unchanged from inner and outer labia. Pelvic ultrasonography: uterine agenesis or uterine atrophy, cystic formation at the right adnexa, regular, anechoic of 3,3cm. Left ovary with reduced volume for the age group.

Discussion

The Müller and Wolff ducts are essential for the development of the female and male reproductive system, respectively. The mullerian ducts mature to become fallopian tubes, uterus, cervix and upper two thirds of the vagina (lower third is derived from the urogenital sinus), while the Wolff duct degenerates [1,2]. The Urogential sinus and Mullerian ducts, of which the female reproductive system is composed, are conjoined via the mullerian tubercle. The presence of the Mullerian Inhibiting Factor (MIF) or anti-mullerian hormone is the driving force behind maturation of the mullerian ducts to become the above mentioned portions of the female reproductive system. Developmental abnormalities, such as uterine and vaginal agenesis or the duplication of the uterus and vagina are preceded by any disruption in the production of MIF [3-5].

There may be various forms of Müller duct abnormalities, ranging from small anatomical variations to total aplasia. The most common cause of abnormalities is the Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH). It affects up to 90% of women with vaginalagenesis [1,3].

The incidence of MRKH syndrome, on the other hand, was not clearly established, but studies indicate a variation of 1/4,000 and 1/5,000 live births of the female sex [1,4,6].

MRKH syndrome is characterized by aplasia of the Müllerian duct (uterus and upper two-thirds of the vagina) on a person who has karyotype 46, XX with female phenotype characteristic of primary amenorrhea in adolescence. The lower third of the vagina, the ovaries and external genitalia in these cases do not usually have alterations present [1,6]. Approximately 40-60% of patients have renal disorders such as unilateral agenesis, horseshoe kidney, ectopic or bilateral uteropelvic obstruction. In addition, 20% had bone changes, thoracocervical asymmetry, spinal fusion, scoliosis or Klippel-Feil

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syndrome. Cardiac abnormalities and hearing defects can also be encountered1. Occurring less frequently, but also reported in the literature is bilateral femoral hypoplasia [7].

Among the various proposed ratings6, the MRKH syndrome may be (according Oppelt et al. [8]):

a) Typical MRKH: isolated uterovaginal aplasia or hypoplasia

b) Atypical MRKH: uterovaginal aplasia or hypoplasia + renal malformation uterovaginal or hypoplasia + ovarian dysfunction

c) MURCS syndrome: uterovaginal aplasia or hypoplasia + renal, skeletal and heart malformation

In a meta-analysis of 521 cases of MRKH, Oppelt et al8 found that 64% of patients had the typical form, 24% atypical and 12% had MURCS syndrome.

The following research should be conducted: 1) systemic form, with imaging tests such as pelvic MRI, pelvic ultrasound and hormone dosage of follicle-stimulating hormone, luteinizing hormone, testosterone and estradiol; and 2) depending on the associated symptoms by radiographs, audiogram, electromyogram, pelvic laparoscopy [6].

The differential diagnosis is based on a comparative analysis of several syndromes that have similar defects. One is Vater syndrome, which shares similar clinical symptoms, such as renal and vertebral abnormalities. However, in these cases, in addition to symptoms found in MRKH syndrome, tracheoesophageal fistula (70%) and anal atresia (80%), and uterovaginal dysplasia are rare1.

Another differential diagnosis is Winter syndrome, described in the literature as renal syndrome, and genital abnormalities in the middle ear. Initially, it is found as bilateral stenosis of the external auditory canals in young patients, but the diagnosis is made after the primary appearance of amenorrhea, and having common findings of unilateral renal agenesis and distal vaginal atresia (which differs from MRKH syndrome) [1].

In addition an investigation should also be done for the occurrence of hereditary renal dysplasia (HRA). In HRA, the unilateral or bilateral renal agenesis can be found in members of the same family, but it is rare to find Müllerian duct changes. When these are present, they are small, being evident by the presence of didelphic uterus (didelphic uterus) or unicornuate uterus (unicornuate), which can be surgically corrected to allow pregnancy. There is no HRA in association with bone and auditory malformations [1].

Recently researchers have been attempting to identify novel causative genes of isolated Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome using whole-exome sequencing (WES) together with single nucleotide polymorphism (SNP) array. A genetic study was performed on seven unrelated women over a 2-year period. The research team found that the gene loss-of-function variants OR4M2 (olfactory receptor, family 4, subfamily M, member and PDE11A (phosphodiesterase 11A) in addition to deletions at 15q11.2, 19q13.31, 1p36.21, and 1q44 are potential commonly altered regions in patients with type 1 MRKH. Although additional research and validation is necessary, this study has established the viability of identifying potential common causative genetic abnormalities in patients with type 1 MRKH syndrome using WES and SNP arrays [9].

Treatment is usually delayed until the patient is ready to begin sexual activity. This is a serious physiological problem, in fact, they are often associated with somatic and psychosocial disorders such as depression, requiring psychological monitoring [1,3].

The restorative treatment may or may not be surgical, but the method chosen must be adapted to individual needs, the patient's motivation and available options [1,3].

According to the literature, a large number of techniques were used for the creation of a neovagina. The colon and rectum, peritoneum, skin autograft and even muscle flaps and fasciocutaneous have all been used to correct this anomaly. The Vecchietti method especially, which consists of continuous pressure applied to the vaginal area by an acrylic sphere pulled from the abdomen has been used frequently in Europe over the last 20 years. The vaginoplasty is the surgical technique of choice [1,3,10].

Restorative treatment, whether surgical or nonsurgical can allow the patient to have normal sexual function. Reproductive options do exist for patients diagnosed with MRKH syndrome. Although most MRKH patients have a rudimentary nonfunctioning uterus, a small percentage (2-7%) do have a uterus with a functioning endometrium. These patients although a small percentage do have the potential to carry a pregnancy. A case has been reported of a woman whom had type 1 MRKH syndrome and a functioning uterus, initiate a pregnancy using In Vitro Fertilization (IVF), successfully carry a pregnancy and via cesarean section, give birth to a healthy baby [11]. In the past patients with a nonfunctioning or absent uterus, gestational surrogacy was the only option to have a genetically related offspring. However, in September 2014, nearly two years after a successful uterus transplantation, a woman in Sweden gave birth to a healthy male baby. Both the transplantation and birth performed by a medical team headed by Prof. Mats Brännström, MD, marks the first ever live-birth after uterus transplantation. This success demonstrates live uterus donation as a possible viable treatment for patients with MRKH syndrome [12].

Conclusion

The diagnosis and treatment of MRKH syndrome can be difficult. Considering the varying presentation of MRKH and numerous treatment options, it is important that each case be individualized.

This patient was given all pertinent information regarding MRKH syndrome as well as treatment options. After everything was explained to the patient and her family, it was decided that due to her age, she would continue regular followups at the clinic until which time she starts having sexual activity.

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