Mayer-Rokitansky-Küster-Hauser Syndrome – A Case Report of Genetics and MR Imaging Findings with Short Literature Review

Savina Hadjidekova¹, George Hadjidekov²

¹Department of Medical Genetics, Medical University, Sofia, 1431 Bulgaria

²Department of Radiology, University Hospital "Lozenets, Sofia 1407, Bulgaria

Abstract: The authors describe the clinical and genetic presentation in case of a young female patient with primary amenorrhea and normal development of secondary sexual characteristics, normal external genitalia and functional ovaries. Normal karyotype 46, XX without visible chromosomal anomaly has been observed. MR imaging was confirmatory to the diagnosis of Mayer-Rokitansky-Kuster-Hauser's type 1 (isolated) syndrome (MRKH).

Keywords: Mayer-Rokitansky-Küster-Hauser Syndrome, Genetics, MRI

1. Background

Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is a rare condition characterized by congenital aplasia of the uterus and of two/third superior parts of upper vagina with a normal physiological development of the secondary sexual characters and a normal female karyotype 46 XX (1). It affects at least 1 out of 4500 women. MRKH may be isolated (type I) but it could also be associated with renal, vertebral, and, to a lesser extent, auditory and cardiac defects (MRKH type II or MURCS association) (2). The type I (or isolated type), object of our case report, characterized by a vaginal-uterus aplasia is statistically less frequent than complex type. This congenital disorder without any racial predisposition is often difficult to be diagnosed up to adolescence or at the beginning of adulthood (3)

2. Case

Our case describes a 17 y old female with primary amenorrhea without any associated clinical disorders. The patient presents with developed secondary sexual characteristics compatible with her age. At gynecological examination a single urethral orificium has been observed and no speculum examination was possible to be performed. Magnetic resonance imaging (MRI) has been used to clarify the inconclusive ultrasonography results due to technical difficulties; however no uterus has been found on ultrasound (US). MRI clearly visualizes the normally located ovaries with preserved volume and signal intensity as well as the ovarian tubes. No uterus and vaginal canal have been observed on MRI. The size of the right ovary on axial images was 26/20mm presenting with single follicular cyst measuring 16 mm on long axis and the left ovary dimensions were 19/13mm. The urethra was with normal appearance, measuring 36mm in length. (Figure 1)





Figure 1: A: Sagittal, MRI T2-weighted image without fat suppression: the uterus is not seen in the uterovesical excavation. B, C: Axial and Coronal T2-weighted image without fat suppression: functional ovaries with normal volume and shape, in their original location→, the right ovary presenting follicular cyst (arrow) and rudimentary ovarian tubes. D: Axial, T2weighted image: note the absence of the vagina. E: Axial, T1-weighted image: note the absence of the uterus.

Genetic evaluation revealed karyotype 46, XX, confirming the diagnosis of Mayer-Rokitansky-Kuster-Hauser syndrome. The patient choice for first-line therapy was a nonsurgical option, aiming the creation of a neovagina by applying progressive pressure to the perineum using dilators with gradually larger caliber and grater length, the so-called *Frank's method* (11). These dilators were placed daily on the perineal dimple for about 20 minutes with good initial results.

3. Discussion

Mayer-Rokitansky-Kuster-Hauser appears more and more probably is pathology with a complex and multifactorial etiology. The majority of cases are sporadic (4); however few family cases have been described in the literature (5, 6, 7, and 8) and type I (isolated) is less frequently observed than type II (9). Although no known gene has been linked to this condition and identified yet, the mode of inheritance seems to be autosomal dominant with incomplete penetrance and variable expressivity, suggesting that the prevalence of the syndrome may probably be underestimated (1). Moreover genetic alterations, which affect embryological profile, contribute highly to its determination and recent studies investigate genetic mutations during the early phases of the embryonic development. Some genes like the wingless-type MMTV integration site family member 4 (WNT4) seems surely to be involved, since it plays important role on embryonic female genital development with specific function (10, 13, 14). There have been several assumptions about other involved genes such as Wilms tumor 1 (WT1), PAX2 (thought that the WT1 oncosuppresor may act as repressor of thee transcription of PAX 2), HOXA7-HOXA13 (very important genetic clusters for the correct embryogenesis and pre-B-cell leukemia homebox 1 (PBX1) (15). More recently other candidate genes have been reported - TCF2 (also known as HNF1B that codifies a specific transcription factor for the liver from the family of homeobox containing the double helix motive) and LHX1 (producing a control factor protein for the development of nerve cells and lymphoid tissue). By using the Array-CGH method Ledig et al. have identified three regions (1q21.1, 17q12 and 22q11.12) suggesting that HNF1B and LHX1 could be involved in the determinism of MRKH syndrome, after having identified recurrent deletions and missense mutations (16). In other studies the authors found some imbalances which are concerned with those and others chromosomal regions 1q21.1, 17q12, 22q11.12 and Xq21.31 with LHX1 and KLHL4 been the candidate genes identified in this case. The presence of the same alterations in a phenotypic normal mother of a patient with MRKH syndrome has raised the assumption of an incomplete penetrance and/or variable expressivity (17). Vaginal agenesis might also be associated with a reduced activity of

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the galactose-1-phosphate uridyl transfer enzyme (GALT) (18). It might be also a strong correlation between the activator mutations in the gene for anti-Mullerian hormone (AMH) or in its receptor (AMHRII) and the potential cause

of development of MRKH syndrome (19). Partial duplication of pseudoautosomal Xpter region 1, which contains homebox gene for short height (SHOX), may be involved in the genesis of this condition (20) (**Table 1**).

Table 1: Genes involved in MRKH syndrome, from "GeneCards: the human gene compendium" (3,21)).
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Gene	Chromosome	Cytogenetic band	Beginning	End	Size	Orientation
WT1	11	11p13	32,409,321 bp from pter	32,457,176 bp from pter	47,856 bases	Negative filament
WNT4	1	1p36.23-p35.1	22,443,798 bp from pter	22,470,462 bp from pter	26,665 bases	Negative filament
PAX2	10	10q24	102,505,468 bp frompter	102,589,698 bp frompter	84,231 bases	Positive filament
HOXA7	7	7p15.2	27,193,335 bp from pter	27,196,296 bp from pter	2,962 bases	Negative filament
HOXA13	7	7p15.2	27,235,022 bp from pter	27,239,725 bp from pter	4,704 bases	Negative filament
LHX1	17	17q12	35,294,499 bp from pter	35,301,912 bp from pter	7,414 bases	Positive filament
HNF1B	17	17cen-q21.3	36,046,434 bp from pter	36,105,237 bp from pter	58,804 bases	Negative filament
KLHL4	Х	Xq21.3	86,772,715 bp from pter	86,925,050 bp from pter	152,336 bases	Positive filament
SHOX	Х	Xp22.33; Yp11.3	585,079 bp from pter	620,146 bp from pter	35,068 bases	Positive filament

MRI is a non-invasive technique providing a more sensitive and specific diagnosis than ultrasonography, especially in incomplete and inconclusive US findings. MRI benefits of increased spatial and tissue resolution which improves the assessment of subperitoneal structures and detects the presence rudimentary horns and ovaries. It can be used to image the spine if vertebral anomalies are suspected. Furthermore, MR urography (MRU) is an excellent imaging modality for visualization of both the reproductive and th urinary anatomy, as well as for function and to search for associated renal and skeletal malformations. The uterine aplasia is best characterized on sagittal images, while vaginal aplasia is clearly demonstrated on transverse images (12).

Treatment will usually include appropriate management of the physical findings associated with MRKH syndrome and psychological counseling and support before and throughout treatment support for the emotional issues that often accompany the diagnosis. Despite the major developments in reconstructive surgery, female patients seem to be weighed by a very disabling pathology under an anatomic, physiological and psychological profile.

For this reason non-surgical method have recently gain advantages over surgical treatment as preferable method of choice as in our patient thus requiring time and motivation. However, compliance may be poor in patients with a vaginal dimple or no vagina, because these patients may experience discomfort and abandon the dilatation.

4. Conclusion

Mayer-Rokitansky-Kustler-Hauser syndrome consists of vaginal aplasia with other mullerian duct abnormalities (10). The diagnosis is essentially clinical. However, the normal medical examination should be confirmed with genetic tests for determination of the karyotype, pelvic ultrasound and magnetic resonance imaging for better assessment of the internal anatomy. MRKH syndrome penetrance varies, as does the involvement of other organs and systems, which determines the type of the disorder. MRI is the best imaging method in the diagnostic work-up of this condition due to the lack of ionizing radiation, the better contrast and tissue resolution providing excellent images of superficial and deep tissue planes. New studies in genetic and

embryological field will continue to be carried out, in order to clarify etiology better and open up new possible therapeutic decisions (3). Surgical and non-surgical treatment options are present in order to assure normal sex life and future expectations concerns the possibilities for uterine transplantation.

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