Italian Journal of
Gynæcology & Obstetrics
March 2019 - Vol. 31 - N. 1 - Quarterly - ISSN 2385 - 0868

# Mayer-Rokitansky-Kuster-Hauser syndrome: associated anomalies in a cohort of 77 patients

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## ABSTRACT

**Objective:** Mayer-Rokitansky-Kuster-Hauser is a syndrome with significant extragenital manifestations not entirely known so we programmed to evaluate all patients with a new diagnosis of MRKH syndrome who presented at our institute and completed the extensive diagnostic protocol proposed in consideration of past scientific literature.

**Study Design:** Retrospective observational study including 77 women with a new diagnosis of Mayer-Rokitansky-Kuster-Hauser syndrome who underwent an extensive diagnostic protocol (pelvic ultrasound scan, urinary tract ultrasonogram, pelvic magnetic resonance imaging scan, spinal radiographs, audiometry test, echocardiography) in our referral center.

**Results:** We found extragenital anomalies in 63/77 women (81.8%), urinary tract anomalies in 20/77 (25.9%), skeletal anomalies in 50/77 (64.9%), cardiac anomalies in 22/77 (28.6%), auditory defects in 14/77 (18.2%).

**Conclusions:** Mayer-Rokitansky-Kuster-Hauser is a complex syndrome with extragenital manifestations suggesting a developmental origin of the defect and the need of an extensive diagnostic protocol for its management.

**Keywords:** Mayer-Rokitansky-Kuster-Hauser syndrome; mullerian anomalies; MURCS; renal agenesis; utero-vaginal agenesis.

## SOMMARIO

**Obiettivo:** Mayer-Rokitansky-Kuster-Hauser è una sindrome caratterizzata da importanti manifestazioni extragenitali non sempre completamente identificate. L'obiettivo di tale studio risiede pertanto nel valutare le pazienti afferenti al nostro ambulatorio con nuova diagnosi di sindrome - MRKH proponendo loro un accurato protocollo diagnostico composto da un'ecografia pelvica, un'ecografia del tratto urinario, una risonanza magnetica nucleare, un RX della colonna vertebrale, un test audiometrico, un'ecocardiografia.

**Disegno dello studio:** Abbiamo condotto uno studio retrospettivo osservazionale su 77 donne con nuova diagnosi di sindrome - MRKH, sottoposte al protocollo di valutazione ambulatoriale sopra descritto.

**Risultati:** Sul campione indagato sono state identificate anomalie extragenitali in 63/77 pazienti (81.8%). In particolare, in 20/77 (25.9%) anomalie del tratto urinario, in 50/77 pazienti (64.9%) anomalie scheletriche, in 22/77 (28.6%) anomalie cardiache e in 14/77 (18.2%) difetti uditivi.

**Conclusioni:** Mayer-Rokitansky-Kuster-Hauser è una sindrome caratterizzata da manifestazioni extragenitali suggerendone l'origine complessa e quindi la necessità di un esteso protocollo diagnostico per la sua gestione.

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*DOI: 10.14660/2385-0868-107*

## INTRODUCTION

Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is characterized by congenital aplasia of uterus and vagina (class Ie of the American Fertility Society) in women showing normal female karyotype, ovarian function and development of secondary sexual characteristics[1,2]. It occurs in 1/4000-5000 female births, the majority of cases being sporadic even if familiar cases have been reported[3-8]. The mode of inheritance seems to be autosomal dominant with an incomplete degree of penetrance and variable expressivity of a single mutant major developmental gene or of a limited chromosomal imbalance undetectable at standard karyotype[8].

The extent of MRKH syndrome is variable. It is classified into two types depending on the presence of additional associated anomalies: type I (typical or isolated), and the more frequent type II (atypical or associated)[8,9]. The latter comprehending also MURCS association (Mullerian duct aplasia, Renal dysplasia and Cervical Somite anomalies) and Gres (Genital Renal Ear Syndrome)[9-11].

Anomalies associated to MRKH syndrome include mainly urinary tract defects (unilateral renal agenesis, renal hypoplasia, ectopic kidneys, horshoe kidney) and skeletal defects, particularly of the spine (scoliosis, vertebral anomalies, Klippel-Feil association, rib malformations, spina bifida and, rarely, face and limb malformations)[2,12-16]. Hearing impairments (conductive deafness for middle ear malformations as stapedial ankilosis, sensorineural defects, dysplasia of the auditory meatus, malformed ears) and heart defects (sporadic reports of aorto-pulmonary window, atrial septal defect, conotruncal defects as pulmonary valvular stenosis or Tetralogy of Fallot) are less commonly reported[7,16-22].

Past scientific literature has plenty of contributions, which have tried to describe the anomalies associated to MRKH syndrome[2,13,23,24,25]. Such studies are inadequate due to the small sample of size of patients considered to the clear limitations of diagnostic examinations.

In our observational study we analyzed the results of an extensive diagnostic protocol applied to a cohort of 77 patients diagnosed with MRKH syndrome. Our aim is to systematically define type, frequency and distribution of main anomalies associated to MRKH syndrome.

## MATERIALS AND METHODS

In our retrospective observational study, we programmed to evaluate all patients with a new diagnosis of MRKH syndrome who presented at our institute (referral center for MRKH syndrome) between January 2005 and December 2012 and completed the extensive diagnostic protocol proposed in consideration of past scientific literature.

In the selected period, we diagnosed 98 new cases of MRKH syndrome candidates for our study, but only 94 women gave their consent to the study. Of these women, 77 were included into the study, having completed the extensive diagnostic protocol planned within the due date (December 2013).

This study obtained the approval from the ethics committee of our institutions.

Clinical criteria for diagnosis of MRKH syndrome were: primary amenorrhea, normal external genitalia, normal axillary and pubic hair, absence of at least the superior two thirds of the vagina and of the median uterine structures, in a woman with a normal female karyotype.

Our extensive diagnostic protocol included: clinical examination, pelvic transabdominal ultrasound scan, pelvic magnetic resonance imaging scan (to confirm the diagnosis of MRKH syndrome and obtain detailed information on pelvic anatomy, useful in case of surgical treatment), urinary tract ultrasonogram (to evaluate the presence of urinary tract anomalies, reported in the 25% of cases of MRKH syndrome, particularly before surgical correction of the syndrome), echocardiography, spinal radioghaphs (to evaluate the presence of relevant defect reported, even if rarely, in association to MRKH syndrome in past scientific literature, particularly before surgical correction of the syndrome), audiometric test (to evaluate the presence of auditory defects reported, even if rarely, in association to MRKH syndrome in past scientific literature) .

All results were reported in clinical records and systematically evaluated by the same authors group.

Of the 77 patients included in the study, 47 underwent also an endoscopic examination of pelvic anatomy at the moment of surgical creation of neovagina by the same surgeon (author L.F.): 12 according to the modified laparoscopic Vecchietti procedure, 35 according to Davidow procedure. Finally, retroperitoneal masses representing pelvic displacement of kidneys were investigated. 15 patients underwent functional method (Frank) for neovaginal creation and 15 were waiting for corrective surgery at the moment of recruitment.

Confidence intervals (95% IC) for estimated proportions were calculated.

## RESULTS

At the moment of recruitment, mean age of patients was 21.3 year-old. They were all Caucasian. No familiar cases were present.

Urinary tract anomalies were found in 20/77 women (25.9%, 95% IC 16.2-35.6), in the 75% of cases (15/20) associated with defects of other systems (**Table 1**). Particularly, unilateral renal agenesis was found in 11/77 women (14.3%, 95% IC 6.6-22), representing the 55% of all urinary tract anomalies: five cases of single right kidney, four cases of single left kidney, two cases of single pelvic kidney. Other findings were: horseshoe kidney in 4/77 women (5.2%, 95% IC 0.3-10.1) with pelvic horseshoe kidney in 2/77 cases; dislocated kidney in 8/77 women (10.4%, 95% IC 3.6-17.2) with two unilateral pelvic kidney, two single pelvic kidney, two horseshoe pelvic kidney, two unilateral ptosic kidney; hypoplasic kidney in 1/77 woman.

Skeletal anomalies were found in 50/77 women (64.9%, 95% IC 54.3-75.5), isolated in the 42% of cases (21 women with 11 of these reporting only scoliosis and/or pelvic asymmetry) (**Table 1**). The most frequent pathologic finding from spinal radiographs was scoliosis in 31/77 women (40.2%, 95% IC 29.3-51.1), associated to pelvic asymmetry in 12/31 patients. Scoliosis was the only pathologic skeletal findings (isolated and/or associated to pelvic asymmetry) in 24/77 patients (31.2%). In this analysis we did not include reports of scoliotic posture. Isolated pelvic asymmetry was found in 10/77 patients (13%, 95% IC 5.5-20.5), in two cases associated also to limb asymmetry.

Vertebral arch anomalies were diagnosed in 7/77 women (9%, 95% IC 2.3-15.7): five cases of posterior vertebral arch cleft, one case of spina bifida (C6-C7), one case of mild spondylolisthesis (C2-C3) (associated to other cervical arch clefts). Klippel-Feil syndrome was found in 2/77 women (one with associated synostosis of the D3-D4). Transitional vertebrae were detected in 8/77 women (10.4%, 95% IC 3.6-14): lumbosacral transitional vertebrae (lumbarization S1 or hemisacralisation L5) and supernumerary ribs (from L1) in four women, cervical rib (from C7) or mega-apophysis tranversae in C7 in three women, dorsolumbar transitional vertebra in one woman. Spondilosis was reported in 4/77 women (5.2%, 95% IC 0.3-10.1). Intervertebral disc anomalies were found in 3/77 women (3.9%): one rudimentary disc, one discal hernia, one Schmrol hernia. No limbs or teeth anomalies were found at general clinical examination. Complex skeletal anomalies (with associations of 2 or more relevant pathologies) were found in 7/77 patients (9%, 95% IC 2.3-15.7).

Cardiac anomalies were found in 22/77 women (28.6%, 95% IC 18.6-38.6), in the 77.3% of cases associated with defects of other systems (**Table 1**). We found mild valvular anomalies in 20 of these women (26% of all 77 patients, and 91% of women with cardiac anomalies): mitral insufficiency in nine women; mitral and tricuspidal insufficiency in five women (with one patient with associated pulmonary artery

**Table 1.**
*Prevalence of main anomalies associated to MRKH syndrome.*

| Associated anomalies | Patients (%) |
|---|---|
| Skeletal anomalies | 50/77 (64.9%) |
| Scoliosis | 31/77 (40.2%) |
| Pelvic heterometry | 10/77 (13%) |
| Vertebral arch anomalies | 7/77 (11.7%) |
| Transitional vertebrae/ribs anomalies | 8/77 (10.4%) |
| Urinary tract anomalies | 20/77 (26%) |
| Renal agenesis | 11/77 (14.3%) |
| Dislocated agenesis | 8/77 (10.4%) |
| Horseshoe kidney | 4/77 (5.2%) |
| Cardiac anomalies | 22/77 (28.6%) |
| Mild valvular anomalies | 20/77 (26%) |
| Ipoacusy | 14/77 (18.2%) |

dilation); tricuspidal insufficiency in two women; mitral and aortic insufficiency in one woman; mitral, tricuspidal and aortic insufficiency in 1 woman; mitral and pulmonary insufficiency in one woman; pulmonary and tricuspidal insufficiency with mitral prolapse in one woman. In the other two women we found: coronary sinus dilation and aneurisma of the interventricular septum with

**Table 2.**
*Urinary tract anomalies.*

| **Urinary tract anomalies** | **Patients (95%, IC, %)** |
|---|---|
| Monolateral renal agenesis | 17/77 (7-22, 14%) |
| Left kidney agenesis | 5/11 |
| Right kidney agenesis | 4/11 |
| Pelvic only kidney | 2/11 |
| Ectopic kidney | 8/77 (4-17, 10%) |
| Monolateral pelvic kidney | 2/8 |
| Pelvic only kidney | 2/8 |
| Pelvic horseshoe kidney | 2/8 |
| Ptosic monolateral kidney | 2/8 |
| Horseshoe kidnay | 4/77 (0-10, 5%) |
| Hypoplasic kidney | 1/77 (1%) |
| Total | 20/77 (16-36, 26%) |

**Table 3.**
*Skeletal anomalies.*

| **Skeletal anomalies** | **Patients (95%, IC, %)** |
|---|---|
| Scoliosis | 31/77 (29-51, 40%) |
| Pelvic heterometry | 22/77 (19-39, 29%) |
| Associated to scoliosis | 12/22 |
| Associated to libs heterometry | 2/22 |
| Vertebral arch anomalies | 7/77 (2-16, 9%) |
| Posterior vertebral arch cleft | 5/7 |
| Spina bifida (C6-C7) | 1/7 |
| Spondilolistesis (C2-C3) | 1/7 |
| Transitional vertebrae/ribs anomalies | 8/77 (4-14, 10%) |
| Lumbosacral transitional vertebrae (sacralization L5, lumbarization S1, supernumerary ribs L1) | 4/8 |
| Costal ribs or mega- apophysis tranversae (C7) | 3/8 |
| Dorsolumbar transitional | 1/8 |
| Spondilosis | 4/77 (0-10, 5%) |
| Intervertebral disc anomalies | 3/77 (4%) |
| Rudimentary | 1/3 |
| Hernia | 1/3 |
| Schmrol hernia | 1/3 |
| Klippel – Feil Syndrome | 2/77 (3%) |
| with D3 –D4 synostosis | ½ |
| Total | 50/77 (54- 76, 65%) |

right to left shunt. Auditory defects were found in 14/77 women (18.2%, 95% IC 9.7-26.7), in the 86% of cases associated with defects of other systems (**Table 1**). We found: 8/77 women (10.4%, 95% IC 3.6-14) with conductive hypoacusis, mild in seven cases (two bilateral, four unilateral, one case unilateral associated with controlateral perceptive hypoacusis) and unilateral severe in one case; 3/77 women (3.9%) with mild sensorineural hypoacusis (in two cases bilateral); 4/77 women (5.2%) with mild perceptive hypoacusis (in one case bilateral).

Of all these included in the study, only 14/77 women (18.2%, 95% IC 9.6-26.8) were totally negative at our examinations. The others 63/77 (81.8%, 95% IC 73.2-90.4) had one or more pathologic findings. In 32/77 women (41.6%) anomalies interested only one single system: more frequently the skeletal system in 21/77 women (27%, 95% IC 17.1-36.9), with 11 women reporting only isolated scoliosis; circulatory system in 5/77 women (6.5%, 95% IC 1.1-11.9); urinary system in 4/77 women (5.2%, 95% IC 0.3-10.1), auditory system in 2/77 women (2.6%). Urinary system anomalies were reported more frequently (in 75% of cases) in association with anomalies of other systems. In 31/77 women (40.3%, 95% IC 29.4-51.2) we found association of anomalies from two or more systems and, in 10/77 women (12,9%, 95% IC 5.5-18.4), association of anomalies from three or more systems (12.9%) (**Figure 1**).

**Table 4.**
*Cardiac anomalies.*

| **Cardiac anomalies** | **Patients (95%, IC, %)** |
|---|---|
| Scoliosis | 31/77 (29-51, 40%) |
| Valvular anomalies | 20/77 (16-36, 26%) |
| Mitral insufficiency | 9/20 |
| Mitral and tricuspidal insufficiency | 5/20 |
| Tricuspidal insufficiency | 2/20 |
| Mitral and aortic insufficiency | 1/20 |
| Mitral, aortic and tricuspidal insufficiency | 1/20 |
| Mitral and pulmonary insufficiency | 1/20 |
| Pulmonary and tricuspidal insufficiency, mitral prolapse | 1/20 |
| Coronary sinus dilatation | 1/77 |
| Aneurisma of the interventricular septum | 1/77 |
| Total | 22/77 (19-39, 29%) |

**Table 5.**
*Hypoacusis variants.*

| **Hypoacusis** | **Patients (95%, IC, %)** |
|---|---|
| Conductive hypoacusis | 8/77 (4-14, 10%) |
| Mild bilateral | 2/8 |
| Mild unilateral | 5/8 |
| Severe unilateral | 1/8 |
| Perceptive hypoacusis | 4/77 (5%) |
| Mild unilateral | 3/4 |
| Mild bilateral | 1/4 |
| Sensorineural hypoacusis | 3/77 (4%) |
| Mild unilateral | 1/3 |
| Mild bilateral | 2/3 |
| Total | 14/77 (10-27,18%) |

**Table 6.**
*Prevalence of different anomalies in general population.*

| Anomalies | Incidence (general population) |
|---|---|
| Skeletal anomalies | |
| Scoliosis | 2-8% |
| Cervical ribs | 2% |
| S. Klippel –Feil | 1: 50.000 |
| Spondilolistesis | 4-8% |
| Spina bifida | 5: 10.000 |
| Urinary tract anomalies | |
| Renal agenesis | 1: 1.000 |
| Dislocated kidney | 1: 1.200 |
| Horseshoe kidney | 1: 400 |
| Cardiac anomalies | |
| Mitral prolapse | 1-3% |
| Severe perceptive ipoacusy (neonatal) | 1-2: 1.000 |
| Anomalies | Incidence (general population) |

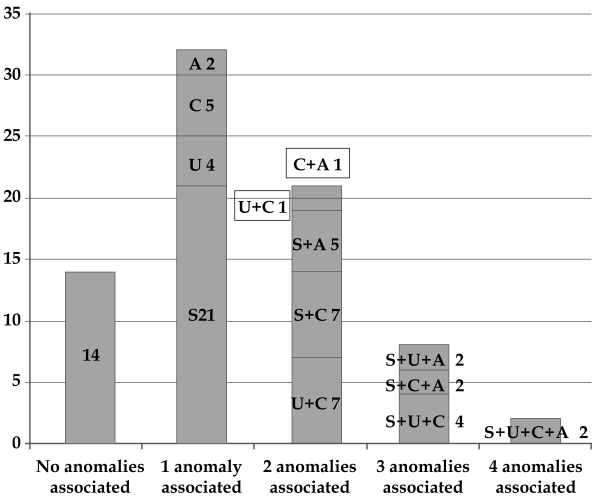


**Figure 1.**
*Distribution of MRKH syndrome associated anomalies (S=skeletal anomalies, U=urogenital anomalies, C=cardiac anomalies, A=auditory problems).*

## DISCUSSION

Our study presents a detailed description of extra-genital malformations associated to MRKH syndrome, and their frequencies, in a large and uniform series of women submitted routinely to an extensive systematic diagnostic protocol. This case series represents a group of 77 patients observed in a relatively short 8-years span from the same research group and assessed with the same instrumental diagnostic approaches for the whole study period.

Past literature has plenty of contributions, including original ones, which have tried to identify malformations associated to MRKH syndrome. In many studies, however, authors analyzed only partially the malformations associated to MRKH syndrome, examining only one single anatomic system (mainly the urinary tract) or using incomplete and not uniform diagnostic methods in their patient series[13,18,20]. At present, mainly four case series considered the association of MRKH syndrome to other malformations of different systems[23,24,13,2]: in 2001, Creatsas, while focusing on therapeutic considerations, provided a superficial and not analytical description of MRKH syndrome associated anomalies: diagnostic examinations were not uniform and cardiac defects never considered[24]; in 2005, trying to describe the extragenital anomalies associated to MRKH syndrome, Pittock and Vuksanovic analyzed 25 patients in a 27-years span, just reviewing patient old charts: diagnostic examinations were not uniform, auditory system was never investigated and only 16 patients had karyotype[13]; in 2006, Peter Oppelt and Renner presented a study that attempt to analyze the clinical aspects MRKH syndrome but their study has several important drawbacks: the case series is heterogeneous because it results from the experience of multiple centers and lacks a uniform diagnostic approach[2].

In fact, it is a retrospective study collecting clinical information by correspondence with physicians, regarding 53 patients evaluated over a long period of time in different institutes and with several clinical data missing for some patients; in 2012, Patricia Oppelt and Lermann, described malformations in a cohort of 284 patients with MRKH syndrome still focusing on genital anatomic variants[23]. Despite the great number of women included, this is a retrospective study without a systematic research of all malformations associated to MRKH syndrome: in fact, only a part (not specified) of their patients have been investigated for associated anomalies without using a uniform diagnostic approach. Accordingly, results of this study cannot be used to describe the real frequency of extra-genital anomalies associated to MRKH syndrome.

In our study, we observed a considerable frequency of patients with MRKH syndrome and associated anomalies compared to previous studies (81.8% versus 44.7% in Oppelt 2012) and general population, with a high prevalence of patients reporting different combinations of two or more (renal, skeletal, cardiac and auditory) anomalies (40.3% versus 13.4% in Oppelt 2012). Generally, scientific literature on MRKH syndrome reports associated malformations in up to 64% of patients[26]. Possible explanation of this finding is that, in our series, all patients have been systematically submitted to an extensive and sensitive diagnostic protocol, which have highlighted a great number of previous undetected anomalies.

In particular, compared to previous studies, in our patients we found a high prevalence of skeletal anomalies (64.9%), of different variants already known in association to MRKH syndrome. Moreover, our series reported a significant frequency of cardiac anomalies (28.6%, mainly valvular defects with mild insufficiency) and hearing loss (18.2%, in the half of cases of conductive type): previous data on this association being very limited and anecdotal.

Also urinary tract anomalies represent a common finding in our patients series (26%), as previously reported in literature. Differently from frequencies of other anomalies investigated (that are higher in our study), our frequency of urinary tract anomalies is comparable to the one of previous studies. This is probably due to the fact that the association of urogenital anomalies was better known into the past and, accordingly, urinary tract has always been more extensively investigated compared to others systems. This enforces the idea that our patients do not have an improbable and unfortunate selective bias explaining their increased frequencies of associated anomalies. Probably, this is due only to the systematic and meticulous diagnostic workup targeted to the diagnosis of anomalies associated to MRKH syndrome.

A restriction of this study is the sample size, limiting the identification of anomalies occurring in association to MRKH syndrome at a rate lower than 4%.

The spectrum of all these anomalies associated to MRKH syndrome could suggest a developmental origin of the defect, involving systems closely related during embryogenesis[10,27]. Specifically, MRKH syndrome can be attributed to an initial defect of the intermediate mesoderm that, normally, originates the urogenital system. An anomaly into the nephrogenic cord, at the level of the mesonephric ducts (or Wolffian ducts), could prevent the normal differentiation of the definite kidney from the metanephros through the failure of the formation of the ureteral bud and, contemporary, could inhibit the regular development of the paramesonephric ducts (or Mullerian ducts) which, normally, in the women are responsible for the constitution uterus, tubes and the superior part of the vagina (absent in the MRKH syndrome). Likewise, during embryogenesis, a defect of the intermediate mesoderm could influence the differentiation of some other closely adjacent structures, developing from somites of the paraxial mesoderm (like the axial skeleton and internal ear) and of the lateral mesoderm (like the heart). However, the precise pathogenetic mechanism at the base of MRKH syndrome is still unknown. The choice of the diagnostic protocol to use in the management of patients with MRKH syndrome should consider the information deriving from the present study. In our institution, we have decided ethically to propose an extensive diagnostic protocol to all patients with MRKH syndrome, in consideration of the high association of this syndrome with extragenital anomalies, which could have relevant therapeutic implications in a lifetime. Patients with a new diagnosis of MRKH syndrome, moreover, are generally very young women, which could particularly benefit of information deriving from the extensive diagnostic examinations: the early diagnosis of an anomaly, in fact, can allow its correct and prompt clinical management. For example, the diagnosis of a unilateral renal agenesis in a patient with MRKH syndrome allow to schedule an annual urological

follow-up to check renal functioning, to give adequate antibiotics prophylaxis for urinary tract infections and to suggest particular attentions in case of surgical creation of a neovagina (above all if the only kidney is pelvic). The diagnosis of a mild mitral insufficiency, to do another example, permits to give an appropriate antibiotic prophylaxis for endocarditis at surgical operations and to plan a follow-up for the evaluation of the (possible) progression of the pathology in the adult age.

We have to underline, in fact, that in the present study we have not analyzed a long-term follow up of patient anomalies, and so it is not possible to describe their specific evolution.

In conclusion, this study investigates extensively the extragenital anomalies associated to MRKH syndrome, highlighting its extreme complexity and underlining the need of an adequate extensive diagnostic protocol in its management.

## DECLARATION OF INTEREST

The authors report no conflict of interest or financial support.

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