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Mayer-Rokitansky-Küster-Hauser Syndrome: Where Does Gynaecological Pathology End and Renal Disease Begin? The Value of a Comprehensive View. Two Case Reports with Adult Onset Kidney Disease and A Review of the Literature

Case reports

Martina Catania[1,3], Micaela Petrone[2], Francesca Tunesi[1,3], Giancarlo Joli[1], Romina Bucci[1,3], Rodolfo Rivera[4], Liliana Italia De Rosa[1,3], Kristiana Kola[1,3], Marta Vespa[1,3], Giorgia Grecchi[2,3], Stefano Salvatore[2,3], Massimo Candiani[2,3], Paolo Manunta[1,3], Giuseppe Vezzoli[1,3], Maria Teresa Sciarrone Alibrandi[1]


Martina Catania

1 Vita Salute San Raffaele University, 20132 Milan, Italy
2 O.U. Obstetric and Gynecology, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
3 O.U. Nephrology and Dialysis, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy
4 O.U. Nephrology and Dialysis, Ospedale Pio XI, ASST Brianza

Corresponding author:
Francesca Tunesi
U.O. Nefrologia e Dialisi, IRCCS Ospedale San Raffaele, Università Vita Salute San Raffaele
Via Olgettina 60
20132, Milano, Italia
Tel +39 02 2643 3993
E-mail: tunesi.francesca@hsr.it

ABSTRACT

Background. Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare congenital condition marked by agenesis or hypoplasia of the upper female reproductive tract. While it is typically recognized for its reproductive implications, renal anomalies – such as unilateral renal agenesis or ectopic kidneys – are also frequent but often underdiagnosed. Recent findings suggest shared embryological origins between the genital and urinary systems, supporting the need for a broader diagnostic and therapeutic perspective.

Case Description. We describe two cases of women with MRKH syndrome diagnosed in adolescence, in whom renal anomalies were detected only in adulthood. Both patients developed hypertension and progressive renal dysfunction in their 30s, revealing previously unrecognized congenital malformations: one with renal dysplasia, the other with unilateral agenesis and compensatory hypertrophy. These cases emphasize how renal involvement in MRKH can remain silent for years and highlight the importance of early and continuous uro-nephrological surveillance.

Conclusion. MRKH syndrome should be considered a systemic disorder involving both reproductive and renal systems. The traditional classification into Type I and Type II may not reflect the full clinical spectrum. A multidisciplinary approach – including gynecology, urology, and nephrology – is essential for timely detection and management of renal complications. Regular follow-up, even in asymptomatic patients, can prevent or delay chronic kidney disease. Greater awareness of renal risks in MRKH is vital to improving long-term outcomes and ensuring truly comprehensive care.

KEYWORDS: Mayer-Rokitanksy-Küster-Hauser syndrome, CAKUT, GREBL1, HNF1B, WNT4

Key findings

Patients with Mayer-Rokitanksy-Küster-Hauser (MRKH) syndrome should be investigated also for urinary tract abnormalities and kindney function involvement.

What is known and what is new?

MRKH patient often experience undiagnosed renal abnormalities, leading to chronic renal failure and hypertension

Regular uro-nephrological follow-up aids in the timely detection of renal complications, enabling prompt interventions and better patient outcomes.

What is the implication, and what should change now?

Comprehensive care ensures MRKH patients receive adequate education and awareness regarding potential renal problems, susceptibility to urinary infections, and the importance of blood pressure monitoring. Enhanced patient knowledge leads to proactive management and improved long-term renal health.

Introduction

Mayer-Rokitanksy-Küster-Hauser syndrome (MRKH) is a rare genetic disorder with a prevalence of 1:5000 females born alive. It is characterized by an abnormal embryonic development that compromises the formation and fusion of Müller or paramesonephric ducts even in the presence of a healthy karyotype 46, XX.

Typically, this condition causes aplasia of the fallopian tubes, the uterus (partial or complete), and the most part (almost the upper 2/3) of the vagina resulting in a blind vaginal vault. Because embryogenesis is governed by fine control mechanisms during the first weeks of pregnancy, interference with this regulation could account for the various systemic disorders commonly found in these patients.

In terms of the disease's localization, two types can be distinguished: type I, or the typical form, which is exclusively marked by uterovaginal aplasia (56-72%), and type II, or the atypical form (28-44%), which affects other organs on a systemic level, most notably the urinary system with a percentage higher than 40% [1].

A severe variant of the atypical form is termed MURCS (Mullerian agenesis, Renal agenesis and Cervicothoraic Somite anomalies) [2, 3] and is associated with multiple abnormalities such as:

- malformations of the kidney and upper urinary tract including renal agenesis ipsilateral to Mullerian duct aplasia, renal ectopia in pelvic location, renal hypoplasia, horseshoe kidney, dromedary kidney;
- skeletal malformations of the spine including scoliosis;
- hearing impairment and deafness either of sensorineural origin or due to stapedial ankylosis;
- cardiac malformations; especially valve defects

In a small cohort of MRKH type II patients, severe malformations of the gastro-intestinal tract such as tracheoesophageal fistula/esophageal atresia, anal atresia and renal abnormalities as well were

identified and defined as VACTERL (Vertebral defect, Anal atresia, Cardiac defect, Tracheoesophageal fistula/Esophageal atresia, Renal defect, Limb defect) [4].

Pediatric age is a critical period for diagnosing MRKH syndrome, as early identification allows for timely intervention and holistic management. Patients present a normal thelarche and pubarche with normal secondary sexual characteristics in absence of menarche, therefore they consult a gynecologist for primary amenorrhea. Diagnosis is typically made during adolescence before 18 (median age 17.5, interquartile range 16-19) [1]. Patients consult a gynecologist for primary amenorrhea, which is frequently accompanied by cyclic abdominal pain (likely associated with catamenial bleeding of the uterine abdomen, if present, which may progress to haematometra) and dyspareunia/apareunia [5, 6]. The absence of menstrual cycles during puberty may serve as an initial indicator, prompting further investigation. Imaging studies, such as pelvic ultrasound and magnetic resonance imaging (MRI), can provide detailed insights into gynecological and renal structures, aiding in a comprehensive diagnosis. The goal of treatment is to reconstruct the vaginal canal in order to permit them a satisfactory sexual life. This can be accomplished by creating a neovagina by different surgical techniques or through a non-surgical functional method [7].

Conversely, unfortunately patients are typically overlooked for prospective kidney problems because of their young age at diagnosis and early remedial gynecological intervention. Patients rarely undergo an uro-nephrological follow up even if it's well known that congenital kidney and urinary tract abnormalities are the leading cause of chronic kidney disease in individuals under 30 years old and in childhood [8].

In our career as nephrologists, it has occurred more than once to diagnose too late renal anomalies, which are further complicated by more or less severe renal failure degree and hypertension. It's likely that many times, the MRKH found in childhood is not even connected to the diagnosis of renal failure later attributed to renal abnormalities. On the other hand, we believe that early diagnosis is crucial for several reasons:

- Prevention of Complications: Early identification of renal anomalies allows for the prompt management of associated conditions, reducing the risk of complications such as urinary tract infections and kidney dysfunction.
- Individualized Treatment Plans: Tailoring treatment plans to the specific needs of the patient becomes more effective with early diagnosis. This may involve a multidisciplinary approach, including gynecologists, nephrologists, urologists, psychologists, and other specialists, to address both gynecological and renal aspects of the syndrome.

We would like to share our experience of the following two cases of MRKH who developed chronic renal failure, in the absence of other causes, emphasizing the nephrological scenario that can accompany this syndrome and that frequently goes unnoticed in its early stages.

Of the two cases we present, one with early nephrological follow-up has not developed advanced renal failure to date, while the second, diagnosed late in the uro-nephrological setting, experienced an unfavorable renal prognosis.

Case Reports

Case Report 1

43-years-old patient. She was diagnosed with MRKH type II at age 18 and underwent surgical neovagina reconstruction and had a history of repeated urinary tract infections (UTI) dating back to childhood. At the age of 22, abdominal ultrasound and MRI reveal agenesis of the left kidney and

the presence of right kidney in the pelvic area with a defined “dromedary” appearance (Figure 1). She never performed neither an urologic nor a nephrological follow-up until hypertension was discovered at age 37, already in the presence of reduced glomerular filtration rate (GFR) with CKD stage IIIa (eGFR: 68 mL/min) and partially selective proteinuria (0.4 g/L). After beginning ACE I therapy, proteinuria resolved and blood pressure returned to normal. The patient is currently undergoing regular nephrological follow up with slow, but progressive and inexorable decline ofrenal function.

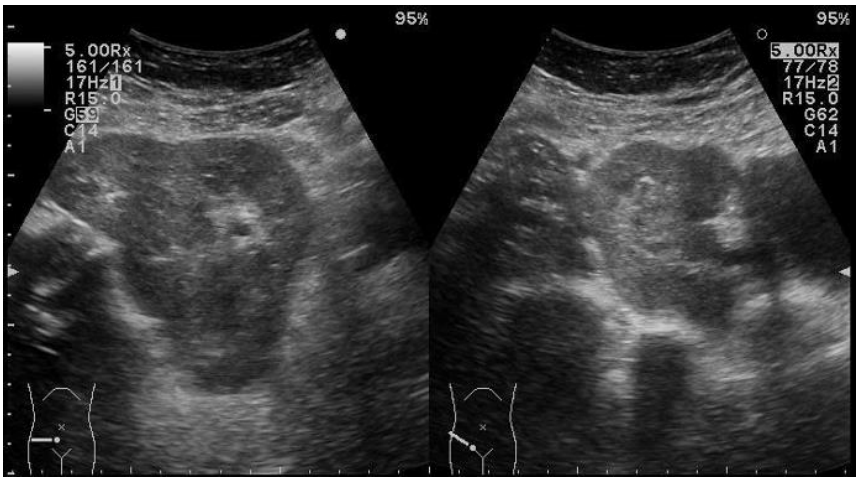

Figure 1. Right kidney in the pelvic area with a defined “dromedary” appearance.

Case report 2

52-year-old patient. Diagnosis of MRKH type II at age 18, with following neovagina reconstruction surgery. Several episodes of UTI. Also in this instance, an uro-nephrological follow-up was not performed, and at the age of 42, it was found that the patient had II-degree arterial hypertension in addition to CKD IV stage (eGFR 20 ml/min/1.73m^2). On this occasion ultrasound revealed left renal agenesis. Kidney function progressively worsened, ending up to terminal uremia and the need of peritoneal dialysis at 46. The patient is currently on the waiting list for kidney transplant.

Discussion

Our aim in reporting these clinical cases is to highlight the importance of a multidisciplinary long-term follow-up that has to include urologists and nephrologists in females with MRKH.

Considering that CAKUT is the most common cause of chronic kidney disease in patients under the age of 30 and in childhood [8], intuitively, from a uro-nephrological standpoint, this syndrome should not be disregarded because of its frequent association with severe renal defects. Moreover, there is still much to be clarified regarding the genetics of this disease and its probable overlap with other renal abnormalities.

According to several genetic studies, the axial skeleton and urinary tract are involved because they both derive from intermediate mesoderm of the embryo. Disturbances in gastrulation can in fact interfere with migration and differentiation of paraxial (cervical vertebrae), intermediate (urogenital structures) and lateral mesoderm (appendicular anomalies). From a genetic perspective, the etiology is still unknown, particularly in relation to the infertility-causing nature of the disease and the impossibility of vertical gene mutation transmission. Analysis of familiar forms suggests an autosomal dominant inheritance with incomplete penetrance [9, 10]; however, the vast majority of cases are due to sporadic mutations. Through Chromosomal microarray analysis and Next Generation Sequencing (NSG) technologies, a number of disease-related gene variants have been

studied over time. These systems have made it possible to detect anomalies in the number of copies of chromosomal regions as well as variations in single nucleotides.

Some of these have picked nephrologists' interest due to their prevalence in patients with concomitant kidney abnormalities. The first gene to show a strong association with MRKH type II syndrome is GREBL1, identified in 2017. Growth Regulation by Estrogen in Breast cancer 1-like (GREB1L) is a gene regulated by androgen which acts as a coactivator of the retinoic acid receptor (RAR) gene and plays a fundamental role in the development of the vestibulocochlear apparatus, the urogenital tract and the ventricular system. Variants of this gene have been found in both familial and sporadic MRKH [1, 11, 12].

In our experience as an Italian tertiary referral center, 30% of affected women present anomalies in the structure and position of their kidneys, most commonly renal agenesis, a single kidney in the pelvis, or horseshoe kidney. These data are consistent with what reported in international literature [13].

The 2 cases that we have reported have been diagnosed as Type II; although they didn't have any other major alteration in other districts. Indeed, they had significant kidney anomalies, both functional and anatomical, without any other informative malformations. We cannot rule out the possibility that Type I and Type II are more intertwined than expected, with Type I exhibiting a different, lower degree of malformations that occasionally go undetected. Instead of considering two distinct diseases, it is possible that we are dealing with the same one with a wide range of clinical manifestations on a grayscale, caused by more than one single factor or mutation, likely overlapping with other renal anomalies.

The majority of systemic reviews on this disease have collected data without distinguishing between Type I and Type II and using Whole Genome Sequencing. Except for the obvious one as GREB1L, others may be considered such as WNT4 or HNF1B. WNT4 plays a key role in female reproductive structure and renal development as well [14]. HNF1B though is more of a gene regulating gene, so a lot of anomalies might fall under its domain, probably in a not so much specific way. Its deletion/intragenic mutations are the most frequently identified genetic cause of renal and urinary tract congenital anomalies; however, it is also expressed in the genital tract during the early stages of embryonic development [15]. There is certainly still more to learn about etiopathogenetic, including how genital and renal defects are related. Given the similarity in genital and urinary embryogenesis, it would be intriguing to determine shared genetic traits. Definitely more common ground exists than anticipated and its clarification could mark a substantial change, perhaps even in clinical practice. Now from a purely clinical standpoint the significance of uro-nephrological monitoring derives from several factors: first and foremost, the evidence that all women with MRKH type II and associated renal abnormalities develop chronic renal failure of varying degrees with age. In many cases, renal disease progresses insidiously until it manifests in its later stages, bringing it to the nephrologist's attention when drug therapy cannot slow its progression and renal replacement therapy must be started, as mentioned above. In the second analysis, it should be noted that the progression of renal insufficiency coincides with the appearance of secondary factors such as arterial hypertension and urinary tract infections. These conditions are typically treated by a general practitioner without additional diagnostic and specialistic procedures. Once the vaginal canal is created through a surgical and functional approach, these young girls are rarely invited to a periodic uro-nephrological follow- up. The absence of a comparison with a multidisciplinary team ensures that patients don't have a full knowledge of pathology and they are not sensitized to have future renal problems, susceptibility to urinary infections or to monitor blood pressure. Dispersion in the area is unquestionably a negative factor in the progression of kidney disease, which could be fixed by the establishment of an adequate follow up.

Conclusions

In conclusion, a holistic perspective on Mayer-Rokitansky-Küster-Hauser syndrome, encompassing both gynecological, urological and renal considerations, is essential for accurate diagnosis and comprehensive management. Early detection during pediatric age not only facilitates timely medical intervention but also provides crucial emotional and psychosocial support, laying the foundation for a better quality of life for affected individuals.

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