Original Study

Typical and Atypical Associated Findings in a Group of 346 Patients with Mayer-Rokitansky-Kuester-Hauser Syndrome

Katharina Rall MD [1,*], Simone Eisenbeis PhD [1], Verena Henninger MD [1], Melanie Henes MD [1], Diethelm Wallwiener MD [1], Michael Bonin PhD [2], Sara Brucker MD [1]

[1] University Hospital Tuebingen, Department of Obstetrics and Gynecology, Tuebingen, Germany
[2] University Hospital Tuebingen, Department of Medical Genetics, Microarray Facility, Tuebingen, Germany

A B S T R A C T

Study Objective: The Mayer-Rokitansky-Kuester-Hauser (MRKH) syndrome is characterized by vaginal and uterine aplasia in a 46,XX individual. Multiple abnormalities may be associated with MRKH syndrome, and it appears to overlap other syndromes. The aim of this study was to describe the spectrum of associated malformations and syndromes as well as abnormal karyotypic findings in a large cohort of 346 patients.

Design, Setting, and Participants: The study is a retrospective analysis of 346 MRKH patients treated in the University Hospital in Tuebingen between 1998 and 2013.

Main Outcome Measures: The dataset was screened for typical associated malformations as well as atypical malformations and abnormal karyotypes. A complete review of the literature was included.

Results: Among our cohort of 346 patients, we found that 53.2% had MRKH type 1, 41.3% had MRKH type 2, and 5.5% had MURCS syndrome. The group with associated malformations included 57.6% renal, 44.4% skeletal, and 30.8% other malformations. Additionally, we found 2 cases of absent radius syndrome, 3 cases of anal atresia, and 1 patient with oculodentodigital dysplasia, and other atypical malformations. Abnormal karyotypes were found in 5 cases, and 39 siblings and 11 parents had known malformations.

Conclusions: This study supports the hypothesis that the syndrome has a multifactorial pathogenesis. With the high numbers of associated malformations reported in this study, patients with MRKH syndrome should be regarded as having a complex syndrome. Molecular–genetic analyses in larger numbers of children after surrogacy, twin pregnancies, and familial cases may make it possible to obtain further information about the etiology of the syndrome.

Key Words: MRKH syndrome, Uterovaginal aplasia, Associated malformations, Associated syndromes, Abnormal karyotype, Klippel-Feil syndrome, VACTERL association, DiGeorge syndrome

Introduction

The Mayer-Rokitansky-Kuester-Hauser (MRKH) syndrome (OMIM 277000) is the second most common cause of primary amenorrhea. The frequency of the syndrome is reported to be 1:4000 to 5000 female live births. It is characterized by congenital absence of the uterus and the upper two-thirds of the vagina in women with a normal female karyotype and normally developed, hormonally functioning ovaries.[1–3] Primary amenorrhea with or without coital problems is the main reason for consulting a gynecologist. The MRKH syndrome may occur isolated (type I), as well as associated malformations that mainly affect the renal and skeletal system, including, to a lesser extent, other defects (type II and Müllerian-renal-cervicothoracic-somite abnormalities [MURCS] association).[4] MURCS syndrome is not clearly defined in the literature. For example, Oppelt et al[5] included patients with inguinal hernia and a cardiac defect in the MURCS group.[5] Malformative combinations (including Müllerian anomalies) often affect different organs derived from the mesoderm, such as heart, lungs, and the urogenital system.[6] In their review of the literature that included 521 cases, Oppelt et al[5] found 64% of patients with MRKH type 1, 24% with type 2, and 12% with MURCS syndrome. They did not consider atypical associated malformations, associated syndromes, or abnormal karyotypes. Atypical findings, like the VACTERL (vertebral anomalies, anal atresia, cardiovascular anomalies, esophageal atresia, renal anomalies, limb anomalies) association or thrombocytopenia-absent radius (TAR) syndrome have been reported in single cases in combination with MRKH syndrome.[7,8]

Familial cases have been explained with incomplete penetrance and variable expressivity or by small chromosomal aberrations undetectable in standard karyotypes.[9] The association of abnormalities in Müllerian duct development with other organ systems suggests that crucial genes of fetal development and sex differentiation are potential candidates.[2,10] So far, most of the genetic investigations have been unproductive. Only the *WNT4* gene has been clearly implicated in MRKH syndrome, and it found to be associated with signs of hyperandrogenism in at

The authors indicate no conflicts of interest.
The authors thank all patients who participated in this study. Dr Rall was the recipient of a temporary research fellowship within the PATE, fortüne and TÜFF programs (Nos. 1835-0-0, 2047-0-0, and 2159-0-0) of the University of Tuebingen. The authors acknowledge support by the Open Access Publishing Fund of the University of Tuebingen.

* *Address correspondence to:* Dr Katharina Rall, MD, Department of Obstetrics and Gynecology, University Center for Rare Female Genital Malformations, University Hospital Tuebingen, Calwerstrasse 7, 72076 Tuebingen, Germany; Phone: +49-7071-2980791; fax: +49-7071-294663
E-mail address: Katharina.Rall@med.uni-tuebingen.de (K. Rall).

1083-3188/$ - see front matter
http://dx.doi.org/10.1016/j.jpag.2014.07.019

least 4 cases.[10–13] Recently, several recurrent copy number variants have been described, but none of them were confirmed in a larger group of patients.[2,14] Cases of discordant monozygotic twins make the involvement of epigenetic factors more likely.

The aims of this study were to describe the spectrum of typical and atypical malformations and associated syndromes, as well as abnormal karyotypic findings, in a large cohort of 346 women with MRKH syndrome and then compare these with those in the literature.

Patients and Methods

Patients

The study is a retrospective analysis of 346 women who were treated for MRKH syndrome between January 1998 and November 2013 in the Department of Obstetrics and Gynecology at the University Hospital of Tuebingen (Germany). From 2008 on, the majority of the patients had received a standardized questionnaire that included questions regarding relatives with malformations. During routine workup, all of the patients received renal ultrasonography and magnetic resonance imaging of the pelvis, including the renal system. The vast majority of the patients underwent laparoscopy during laparoscopy-assisted creation of a neovagina.[15] All of the patients were informed that the data were to be analyzed in the context of research studies, and they provided written consent. Approval for the study was obtained from the Ethics Committee at the University of Tuebingen.

Statistical Methods

All data are presented as frequencies and percentages using Microsoft Office Excel 2009. Where necessary, patients with incomplete data were excluded from the total numbers in order to provide correct percentages.

Results

Typical Associated Malformations

Among our cohort of 346 patients, we found 184 patients (53.2%) with MRKH type 1, 143 (41.3%) with MRKH type 2, and 19 (5.5%) with MURCS syndrome. Within the group with known associated malformations, we found 92 with renal (57.6%, unknown in 2 cases), 71 with skeletal (44.4%, unknown in 2 cases), and 48 with other associated malformations (30.8%, unknown in 6 cases) (Table 1). Twenty -five patients had renal and skeletal malformations, and 15 had renal and other malformations. Among the renal malformations were 44 (47.8%) unilateral renal ageneses; 27 (29.3%) pelvic kidneys; 4 (4.3%) cirrhotic kidneys; 12 (13.0%) duplicated renal systems, 2 of which were also malrotated; 8 (8.7%) malrotated kidneys; 1 horseshoe kidney, and others (Table 1). Several patients had combined renal and other urological anomalies (e.g., duplicated systems). Within the group with skeletal malformations, we found 38 cases (54.9%) of scoliosis, 11 (15.5%) hip dysplasias, 3 (4.2%) caudal congenital fusions of the vertebral bodies, and several others. This group included 5 cases with associated Klippel-Feil syndrome (KFS) (Table 1). The first case had an associated malrotated pelvic kidney and congenital strabismus. The second case had renal agenesis and a right-sided heart. The third case had a pelvic kidney on one side and a cirrhotic kidney on the opposite side as well as astigmatism. The fourth case had an associated pelvic kidney, and the fifth had a malrotated pelvic kidney, hip dysplasia, and hearing impairment.

Table 1
Typical Associated malformations (N = 162)

Associated Malformations	No. (%)
Renal malformations*	92 (57.6)
Unilateral agenesis	44 (47.8)
Pelvic kidney	27 (29.3)
Double kidney	12 (123)
Malrotation	8 (8.7)
Cirrhotic kidney	4 (4.3)
Horseshoe kidney	1 (1,1)
Skeletal malformations*	71 (44.4)
Scoliosis	38 (54.9)
Hip dysplasia	11 (15.5)
Caudal fusion of vertebrae	3 (4.2)
Klippel-Feil syndrome	5 (3.1)
Typical other malformations*	48 (30.8)
Ears	14 (29.2)
Eyes	12 (25)
Heart	7 (14.6)
Ears and heart	2 (4.2)
Ears and eyes	1 (2.1)
Inguinal hernia	54 (15.6)

* More than 1 malformation per patient is possible.

Among the other malformations, 14 (29.2%) affected the ears, 12 (25%) affected the eyes, and 7 (14.6%) affected the heart; in 1 patient, both the ears and eyes were affected, and in 2 patients, both the ears and heart were affected.

Fifty-four (15.6%) of the MRKH patients underwent inguinal hernia repair in early childhood.

Malformations in Siblings and Parents

A total of 39 patients reported siblings with malformations; 42 patients had no siblings; and in 58, there were no data with respect to siblings. Of the patients with affected siblings, 10 of the siblings had MRKH type 1, 25 had MRKH type 2, and 4 showed MURCS association. Two sisters also had MRKH syndrome, 4 had other uterine malformations, 9 sisters had renal malformations (1 was an otherwise healthy monozygotic twin), 8 sisters and 6 brothers had skeletal malformations, and 19 siblings had other malformations. Our cohort includes 5 pairs of discordant monozygotic twins; 4 of the MRKH patients had at least an associated renal abnormality, whereas 4 of the healthy twins were not affected by any kind of malformation. Of the 3 dizygotic twins in our cohort, 1 brother died from associated malformations.

Among the parents of the patients, 1 mother had a uterine malformation, 4 mothers and 2 fathers had renal malformations, 2 mothers had skeletal malformations, and 1 mother and 1 father had a cardiac malformation.