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Clinical aspects of Mayer–Rokitansky–Kuester–Hauser syndrome: recommendations for clinical diagnosis and staging

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BACKGROUND: The Mayer–Rokitansky–Kuester–Hauser (MRKH) syndrome is a malformation of the female genitals (occurring in one in 4000 female live births) as a result of interrupted embryonic development of the Müllerian (paramesonephric) ducts. This retrospective study examined the issue of associated malformations, subtyping, and the frequency distribution of subtypes in MRKH syndrome. METHODS: Fifty-three MRKH patients were investigated using a newly developed standardized questionnaire. Together with the results of clinical and diagnostic examinations, the patients were classified into the three recognized subtypes [typical, atypical and MURCS (*Mü*llerian duct aplasia, *r*enal aplasia, and *c*ervicothoracic *s*omite dysplasia)]. RESULTS: The typical form was diagnosed in 25 patients (47%), the atypical form in 11 patients (21%), and the most marked form—the MURCS type—in 17 patients (32%). Associated malformations were notably frequent among the patients. Malformations of the renal system were the most frequent type of accompanying malformation, with 23 different malformations in 19 patients, followed by 18 different skeletal changes in 15 patients. CONCLUSIONS: In accordance with the literature, this study shows that associated malformations are present in more than a third of cases. Therefore, new basic guidelines for standard diagnostic classification involving patients with suspected MRKH are presented.

Key words: diagnostic malformations/genital or Müllerian duct malformations/MRKH syndrome/staging malformations/vaginal aplasia

Introduction

The Mayer–Rokitansky–Kuester–Hauser (MRKH) syndrome is regarded as an inhibitory malformation of the Müllerian (paramesonephric) ducts. Clinically, this malformation of the female genital organs presents as a rudimentary solid bipartite uterus with solid vagina (‘uterus bipartitus solidus rudimentarius cum vagina solida’). Avicenna (AD 980–1037) and Albucasis (AD 1013–1100), described successful correctional treatment for vaginal aplasia. However, these reports cannot be clearly connected with today’s MRKH syndrome, since exploration of the internal genital organs did not take place during that period. Exploration was first described by the Bonn anatomist and physiologist Mayer (1829). This was a report of a single case, with the malformation only being inadequately described as ‘uterus bipartitus’. Kussmaul (1859) and also Rokitansky (1938) also reported the same diagnosis of malformation in one case each. Kuester (1910) for the first time summarized and collected individual cases from the literature in a review paper. It was only in 1961 that the ‘rudimentary solid septate uterus with solid vagina’ was first given its current name, ‘Mayer–Rokitansky–Kuester syndrome’ by the gynaecologist Hauser (Hauser and Schreiner, 1961), later being extended to ‘Mayer–Rokitansky–Kuester–Hauser’ syndrome.

The MRKH syndrome develops *in utero* between the fourth and twelfth week of pregnancy. Griffin *et al.* (1976) reported familial clustering. The molecular basis for the condition has not yet been fully explained. Activation of Müllerian inhibiting substance (MIS) or anti-Müllerian hormone might offer one possible explanation, leading to regression of the Müllerian ducts and thus to vaginal atresia or uterine agenesis. A recent molecular investigation did not identify any deletions or polymorphisms in the promoter region, and measurements of MIS in affected patients did not demonstrate any increased serum concentrations, and overexpression of MIS was therefore not present (Oppelt *et al.*, 2004). The molecular basis for the MRKH syndrome is currently unknown. In addition, no other gene variation in MIS, MIS-Receptor (MISR2) and Wilm’s

Table I. Classification of the Mayer–Rokitansky–Kuester–Hauser (MRKH) syndrome according to Schmid-Tannwald and Hauser (1977) and Duncan *et al.* (1979)

MRKH syndrome	Associated malformations
Typical	Tubes, ovaries, and renal system generated and developed
Atypical	Malformations in the ovary or renal system
MURCS	Malformations in the skeleton and/or heart; muscular weakness, renal malformations

MURCS = Müllerian aplasia, renal aplasia, and cervicothoracic somite dysplasia (association).

tumours were found (Van Lingen *et al.*, 1998; Resendes *et al.*, 2001; Zenteno *et al.*, 2004).

MRKH patients have normal development of the female phenotype, with normal thelarche and pubarche, and a female karyotype (46,XX) with primary amenorrhoea. The clinical picture shows a septate, rudimentary uterus, aplasia of the cervix and vagina, and normal or hypoplastic bilateral adnexa. Brown (1959) and Fraser *et al.* (1973) have shown both that ovarian function is intact, as evident in correctly timed pubarche and thelarche and the presence of a biphasic basal temperature curve, and also that hormonal secretion does not differ from that in normal individuals.

The extent of MRKH syndrome is variable, and it is associated with various additional malformations. This is reflected in the classification, which is subdivided into typical and atypical depending on each additional malformation that is present (Table I). When additional associated malformations of the renal system and skeleton are present, Duncan *et al.* (1979) proposed the term MURCS (*Mü*llerian duct aplasia, *r*enal aplasia, and *c*ervicothoracic *s*omite dysplasia). In order to verify hints of specific associated malformations with MRKH, this study analysed all symptoms of 53 patients.

Materials and methods

Between January 2002 and September 2004, 53 MRKH patients from Austria, Switzerland, and Germany were included in the study. The patients presented either to the Department of Gynecology at the University of Erlangen, in contact with the Erlangen MRKH Forum website (www.mrkh-syndrom.de), or were identified in collaboration with the following hospitals: the Department of Gynecology at the University of Tübingen; the Department of Gynecology at the University of Hamburg at Eppendorf; and the Department of Gynecology at the Bürgerhospital, Frankfurt am Main.

All patients received the questionnaire and there were no non-responders. The patients were questioned using a newly developed standardized questionnaire (including 77 questions) with regard to general details, personal data, and symptoms. The syndrome was confirmed and classified using surgical reports and letters from the patients' physicians. The patients were classified using the Schmid-Tannwald classification (Schmid-Tannwald and Hauser, 1977) and/or the Duncan classification (Duncan *et al.*, 1979) (typical, atypical, MURCS).

A diagnosis of MRKH syndrome was made with laparoscopy in 53 women included in the study. At the time of data collection, the youngest of the patients was aged 13 and the oldest was 53 (median 26 years). Approval for the study was obtained from the ethics committee at the University of Erlangen (ethics vote no. 3074).

Results

In the group of 53 patients, 25 women (47%) had the typical form of MRKH syndrome, 11 women (21%) had the atypical form, and 17 patients (32%) had the marked form known as MURCS (Table II).

The rudimentary uterus was present as a horn or bud in symmetrical form in 39 women (74%); in two patients (4%), it was formed asymmetrically, with the agenesis located on the right side in one case and on the left in the other. Bilateral agenesis was diagnosed in 12 patients (23%). Unilateral agenesis of the tubes was seen in three patients (6%), and bilateral agenesis in only one patient. One woman had unilateral agenesis of the ovary, and two had bilateral gonadal streaks. Other benign changes observed included unilateral ovarian fibroma in one case and a myoma in the uterine horn in another patient.

The group of patients included 19 women with MRKH (36%) who also had anomalies in the renal system. These included 12 cases of unilateral agenesis (five left-sided, seven right-sided; 23%), nine cases of unilateral pelvic kidney (one left-sided, eight right-sided; 17%), and two left-sided sclerotic kidneys (4%).

Fifteen patients were suffering from skeletal malformations in the wider sense (28%). The most frequent changes involved the spine. Six patients with these conditions had scoliosis (11%), and vertebral arch disturbances at C4–5 were diagnosed in one patient. In one case spinal malformations were also reported, each in association with Scheuermann's disease and Klippel–Feil syndrome. One patient had radial aplasia–thrombocytopenia syndrome with bilateral club hand, and two had hypoplasia of the wrist. Hip deformities were observed in four patients. Other skeletal malformations noted in the group were: one deformed elbow, an absence of one-third of the lower arm, a jaw anomaly, absence of wisdom teeth, and one case of talipes varus. When all of the skeletal malformations are taken together, it is notable that the extremities were affected in 47% of the cases.

Isolated malformations were observed in the study in the form of three cases of ventricular septal foramen and two of unilateral hearing impairment. There were also seven cases of inguinal hernia. Other changes noted included one naevocytic naevus, one case of hypothyroidism, one of high blood pressure, and one cataract.

Forty of the women underwent vaginal reconstruction surgery, two decided in favour of Frank's dilation method, and 14 women in the group have not yet received a neovagina to date.

Discussion

Various malformations associated with MRKH syndrome have been described in the literature. They originate in the interaction between the Wolffian and Müllerian ducts during the first few weeks of embryonic growth. The most frequent associated malformations reported are changes in the area of the urogenital tract. Nation (1944) drew attention to disturbances of the urogenital tract in connection with genital malformations. Unilateral renal aplasia was present in 44% of the cases he reported. In 1957, in a study reporting experience in vaginal reconstructions, Barrows (1957) also reported on ectopic locations of the

Table II. Classification and associated malformations in Mayer–Rokitansky–Kuester–Hauser (MRKH) patients

Patient no. (lab. no.)	Vagina	Uterus		Ovary		Tube		Kidney		Skeleton	Inguinal hernia	Heart	Classification	Associated malformations
		Left	Right	Left	Right	Left	Right	Left	Right					
1. (205)	a	b	b										Typical	
2. (288)	a	b	b										Typical	
3. (376)	a	c	c										Typical	
4. (384)	a	b	b										Typical	
5. (752)	a	b	b										Typical	
6. (1104)	a	b	b	ND	ND	ND	ND	ND	ND			ND	Typical	Myoma
7. (1138)	a	b	b										Typical	
8. (1193)	a	b	b										Typical	
9. (1231)	a	c	c										Typical	
10. (1337)	a	b	b	ND	ND	ND	ND						Typical	
11. (1740)	a	b	b										Typical	
12. (1899)	a	b	b	ND	ND	ND	ND						Typical	
13. (2454)	a	c	c										Typical	
14. (2585)	a	b	b					ND	ND			ND	Typical	
15. (2703)	a	b	b										Typical	
16. (2899)	a	b	b	ND	ND	ND	ND						Typical	
17. (3116)	a	b	b										Typical	
18. (3147)	a	b	b										Typical	
19. (3231)	a	b	b								Yes		Typical	Naevocytic naevus
20. (3294)	a	b	b										Typical	
21. (3350)	a	b	b										Typical	
22. (3434)	a	b	b										Typical	
23. (3477)	a	b	b										Typical	
24. (3478)	a	c	c										Typical	
25. (3481)	a	c	c										Typical	
26. (331)	a	b	b				c		c				ATypical	
27. (368)	a	c	c						c				ATypical	
28. (1239)	a	c	c		c		c						ATypical	
29. (1617)	a	c	c						d				ATypical	
30. (2179)	a	b	b					e					ATypical	
31. (2285)	a	b	b										ATypical	
32. (2885)	a	b	b	ND	ND	ND	ND		c				ATypical	Hypothyroidism
33. (2910)	a	b	b	ND	ND	ND	ND		c				ATypical	
34. (3258)	a	b	b					d	d			ND	ATypical	Merged
35. (3394)	a	c	c			ND	ND		c		Yes		ATypical	
36. (3417)	a	c	c					c	d		Yes		ATypical	Dwarfism, fibroma
37. (390)	a	b	b					ND	ND	Yes			MURCS	Scoliosis
38. (448)	a	b	b					c		Yes	Yes		MURCS	Corticopulmonary septal defect
39. (751)	a	c	b	c		c		c	d	Yes			MURCS	Scoliosis
40. (1832)	a	c	c	Streak	Streak				c	Yes			MURCS	
41. (1891)	a	b	b					e		Yes			MURCS	Scheuermann's disease, scoliosis
42. (2097)	a	b	b	ND	ND	ND	ND		d			c	MURCS	Aorticopulmonary septal defect
43. (1094)	a	b	b	ND	ND	ND	ND		d	Yes			MURCS	Talipes varus, congenital dysplasia of the hip
44. (1232)	a	b	b	ND	ND	ND	ND			Yes			MURCS	Hearing problems, hypoplasia of the wrist
45. (1402)	a	b	b			c	c		d	Yes		c	MURCS	Open duct and jaw anomaly
46. (1504)	a	b	b	ND	ND	ND	ND			Yes			MURCS	Absence of 1/3 of the left arm
47. (1664)	a	b	b					c	d	Yes	Yes		MURCS	High blood pressure, hypoplasia of the wrist, Scoliosis
48. (1665)	a	c	b	Streak	Streak			c		Yes			MURCS	Deformed elbow, scoliosis, congenital dysplasia of the hip
49. (2599)	a	c	c							Yes			MURCS	Radial aplasia–thrombocytopenia syndrome with bilateral club hand, Congenital dysplasia of the hip
50. (2969)	a	b	b							Yes	Yes		MURCS	Vertebral arch disturbances at C4/5, inner ear hearing loss
51. (3021)	a	b	b							Yes			MURCS	Cataract, scoliosis
52. (3103)	a	b	b								Yes	c	MURCS	Aorticopulmonary septal defect
53. (3521)	a	b	b				c		c	Yes			MURCS	Klippel–Feil syndrome

MURCS = Müllerian aplasia, renal aplasia, and cervicothoracic somite dysplasia (association).
[a]Atresia.
[b]Hypoplastic horn.
[c]Agenesis.
[d]Pelvic kidney.
[e]Nephrosclerosis.
ND = not described.

kidney such as pelvic kidney, horseshoe kidney, and double ureter. Hauser and Schreiner (1961) described renal aplasia and duplication of the renal pelvis in MRKH syndrome. Griffin (1976) added descriptions of functional disturbances, malrotations, and solitary kidneys. The renal system is the organ group that shows associated changes most frequently, with 23 different malformations of the renal system in 19 patients (36%) in the present study. This demonstrates the need for diagnostic clarification of the renal system at the first diagnosis of MRKH syndrome (Table III).

Changes in the ovary and tubes can vary in their severity. For example, Gradenwitz (1903), Glimm (1956), and Hauser and Schreiner (1961) reported a tendency toward polycystic degeneration of the ovaries. Rokitansky (1838) and Bompiani and Rigat (1958) described hypoplastic ovaries. In the present study, the group included two patients with bilateral gonadal streaks and one with unilateral ovarian aplasia. Particularly in connection with disturbance of the ovarian primordium, a reduced estrogen level can occur, with effects on the development of secondary sexual characteristics and bone metabolism; age-related hormone measurements are therefore a useful and advisable component of the diagnostic work-up.

As the fundamental embryonic structure involved in the process, the mesoderm establishes the connection between the differentiation of the uterus from the Wolffian and Müllerian ducts, with the development of the urogenital system, and the skeletal system. As was also observed in the present study, Griffin *et al.* (1976) thus noted an increased frequency of skeletal anomalies in addition to renal malformations.

The skeletal malformations observed include spina bifida, sacralization of L5, lumbarization of the sacral bone (S1), and malformations of the cervical vertebrae. This leads to difficulty in distinguishing between Klippel–Feil syndrome (Strubbe *et al.*, 1992) (with the formation of block vertebrae in the cervical region) and MURCS. Since a triggering genetic factor has not yet been described in either case, and both are purely descriptive classifications, these may represent one and the same syndrome in some patterns. Similarly, anomalies of the extremities, particularly in the hands and fingers (syndactyly), rib deformities, cleft palate, shoulder blade and pelvic deformities, as well as vertebral abnormalities, particularly in the cervical and thoracic vertebrae, have also been reported.

Cardiac malformations and neurological disturbances appear to play a minor role (Hauser and Schreiner, 1961; Leduc *et al.*, 1968; Reindollar *et al.*, 1981). For example, three patients in the present study had ventricular septal defects, and two had unilateral hearing problems. It is notable that in both of the latter cases, no other unilateral associated malformations were described (Table II).

Other individually occurring malformations reported have included cheilognathouranoschisis, bowel rotation, and situs inversus (Hauser and Schreiner, 1961; Leduc *et al.*, 1968). However, none of these was observed in the group described here.

The present analysis shows that 53% of the patients were affected by secondary malformations. Malformations may be present (e.g. the teeth) that are at first sight unconnected with the MRKH syndrome. Since no genetic causality has yet been identified with regard to the malformation, it is difficult to confirm any connection between the typical genital malformation and accompanying changes (Oppelt *et al.*, 2004). However, the clinical findings are conspicuous, with associated malformations being reported in the literature in up to 64% of patients with MRKH syndrome (Griffin *et al.*, 1976). For this reason, it is important that patients with MRKH syndrome should be regarded as having not only a genital malformation syndrome, but rather as having a complex syndrome with possible accompanying malformations in other organ groups.

When the associated malformations in a further 16 MRKH groups described in the published literature are added together, the syndrome is seen to be limited to vaginal aplasia and uterine hypoplasia or aplasia in only 64% of the cases (333 of 521 patients; Table IV), representing the typical case of MRKH. In this overall group, the high proportion of associated malformations is again evident, with changes in the renal system representing the largest proportion of the organs affected, in 32% of the patients (n = 166).

Since it is not sensible to conduct a search for every possible malformation, a primary basic diagnostic clarification with additional symptom-oriented diagnoses may be recommended. Table IIIa attempts to provide an overview of essential and supplementary examinations. Magnetic resonance imaging is considered an essential diagnostic tool but laparoscopy is still a recommended analysis to diagnose MRKH. For guidance, Table IIIb lists all of the points that should be discussed with patients in the context of basic diagnostic clarification. An exact documentation, with photographic and/or video documentation during laparoscopy, will contribute greatly to the understanding of each MRKH case.

Since MRKH syndrome is purely a diagnosis of exclusion, chromosome analysis is essential to differentiate it from other malformations, such as testicular feminization. Assessment of sex hormones must be regarded as a component of the basic diagnostic clarification, since estrogen production can be

Table IIIa. New basic examinations for diagnostic clarification of Mayer–Rokitansky–Küster–Hauser syndrome

Essential examinations
Chromosome analysis
MRI of the kidneys and small pelvis
Hormone status (LH, FSH, estradiol)
Recommended additional examinations
Ultrasound of the vaginal vestibule, rectum
Diagnostic laparoscopy
Ovarian biopsy

MRI: magnetic resonance imaging.

Table IIIb. Principal symptoms for supplementary examinations to clarify associated malformations

Symptoms	Diagnostic clarification
Urinary incontinence	Urodynamics
Quick exhaustion	Myography, echocardiography
Skeletal malformations	Radiography, computed tomography if appropriate
Hearing loss	Audiography

Table IV. Distribution of the associated malformations in the Mayer–Rokitansky–Kuester–Hauser (MRKH) groups reported in the published literature (multiple descriptors per organ group were possible)

Study	Patients (*n*)	Malformation of the ovary	Malformation of the Fallopian tube	Changes in the renal system	Changes in the skeletal system	Changes in the nervous system	Inguinal hernia	Heart	Classification		
									Typical	Ttypical	MURCS
Plevraki *et al.* (2004)	6	3	4	3	6	ND	ND	ND	0 (0)	1 (17)	5 (83)
Griffin *et al.* (1976)	14	0	0	7	10	ND	ND	1	5 (36)	2 (14)	7 (50)
Chervenak *et al.* (1982)	7	1	2	7	3	ND	ND	ND	3 (43)	1 (14)	3 (43)
Hauser and Schreiner (1961)	21	0	0	3	2	0	4	1	15 (72)	3 (14)	3 (14)
Schmid-Tannwald and Hauser (1977)	33	1	12	7	ND	ND	ND	ND	26 (79)	7 (21)	0 (0)
Seifert *et al.* (1974)	34	ND	ND	7	4	ND	5	ND	25 (74)	5 (15)	4 (11)
Wabrek *et al.* (1971)	10	0	0	3	ND	ND	ND	ND	7 (70)	3 (30)	0 (0)
Yenen (1957)	18	ND	ND	ND	ND	ND	1	ND	18 (100)	0 (0)	0 (0)
Reindollar *et al.* (1981)	37	ND	ND	12	3	ND	2	1	23 (62)	10 (27)	4 (11)
Smith (1983)	22	ND	ND	11	3	ND	8	ND	10 (45)	9 (41)	3 (14)
Darai *et al.* (2003)	7	ND	ND	3	ND	ND	ND	ND	4 (57)	3 (43)	0 (0)
Brun *et al.* (2002)	25	0	0	7	1	0	ND	ND	18 (72)	6 (24)	1 (4)
Fedele *et al.* (2000)	52	0	ND	16	5	ND	ND	ND	34 (65)	13 (25)	5 (10)
Creatsas *et al.* (2001)	111	1	ND	43	9	5	ND	ND	63 (57)	39 (35)	9 (8)
Gauwerky *et al.* (1997)	47	ND	ND	11	ND	ND	ND	ND	36 (77)	11 (23)	0 (0)
Palatynski (1986)	24	3	9	3	ND	ND	ND	ND	21 (87)	3 (13)	0 (0)
Oppelt *et al.* (this report)	53	6	6	23	19	2	7	3	25 (47)	11 (21)	17 (32)
Total	521	15 (3)	33 (6)	166 (32)	65 (12)	7 (1)	27 (5)	6 (1)	333 (64)	127 (24)	61 (12)

Values in parentheses are percentages.
ND = not described.

completely absent in non-functional ovaries, with a consequent negative effect on bone metabolism. In addition, a differential diagnosis from the adrenogenital syndrome (Bryan *et al.*, 1988) should also be performed (e.g. with chromosomal analyses).

Ovarian biopsy is recommended because of the possibility of detecting 'streak gonads' in MRKH patients.

In conclusion, it should be pointed out once again that MRKH syndrome must not be regarded as being exclusively a genital malformation, and that associated malformations are frequently present. Due to their frequency, it is absolutely necessary to clarify these as well during the differential diagnosis of malformations.

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