Original Report

Spectrum of Type I and Type II Syndromes and Associated Malformations in Chinese Patients with Mayer-Rokitansky-Küster-Hauser Syndrome: A Retrospective Analysis of 274 Cases

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A B S T R A C T

Study Objective: To analyze the spectrum of type I and type II malformations in Chinese patients with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome.

Design, Setting, Participants, Interventions, and Main Outcome Measures: This was a cross-sectional descriptive study that used data from a National Clinical Research Center for Obstetrical and Gynecological Diseases of China, reviewed from January 2009 to July 2017. Data of in- and outpatients with MRKH syndrome were reviewed and analyzed.

Results: A total of 274 cases were included in the analysis: 197/274 (71.9%) with type I MRKH syndrome and the remaining 77/274 (28.1%) with type II MRKH syndrome. The rate of concurrent deformities was 32/244 (13.1%) for renal malformation, and 49/125 (39.2%) for skeletal malformation. Nine patients had renal and skeletal malformations (Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia). Cardiac, neurologic, and other malformations (eg, anal atresia) were sporadic. The percentage of type II MRKH syndrome in our cohort was considerably higher than that reported 43/594 (7.2%) in a previous large-scale study in southern China, but lower than that 489/1259 (46.2%) reported for Caucasian individuals.

Conclusion: The spectrum of type I and type II MRKH syndrome varies across different races and geological locations.

Key Words: Mayer-Rokitansky-Küster-Hauser syndrome, malformations, Müllerian aplasia

Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also known as Müllerian aplasia, refers to congenital absence of the upper two-thirds of the vagina with infertile uterine development or even with no uterus. Clinically, MRKH syndrome is characterized by primary amenorrhea with normal secondary sexual characteristics, normal ovarian functions, and a normal 46, XX karyotype.[1,2] The syndrome might occur as isolated agenesis or hypogenesis of Müllerian ducts (type I), or combine with ovarian and/or renal malformation (type II), or as Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia (MURCS) syndrome.[1,3]

Reports from western countries and China showed a significant difference in ratios of type II syndrome. A meta-analysis of 521 MRKH syndrome cases (not including Chinese patients) suggested concurrent urinary system malformation or ovarian dysfunction in 24% and concurrent renal malformation, skeletal deformity, and cardiac malformation in 12% of the patients.[3] A cross-sectional study of 594 Chinese MRKH syndrome patients published in 2016 showed a much lower rate 43/594 (7.2%) of concurrent malformations.[4] Such a racial difference was of potential significance but requires further validation.[5]

In the current cross-sectional study, we reviewed the clinical data of 274 Chinese patients with MRKH syndrome and analyzed the spectrum of type I and type II malformations and associated syndromes.

Materials and Methods

Patients

The cohort consisted of all patients who presented between January 1, 2009 and July 31, 2017 to the Department of Obstetrics and Gynecology at Peking Union Medical College Hospital with MRKH syndrome. MRKH syndrome was evaluated and diagnosed as described previously.[6] Patients with primary amenorrhea and normal secondary sexual characteristics, normal ovarian functions and a normal 46, XX karyotype were included.[1,2] Major exclusion criteria were 46, XY karyotype and other abnormal karyotypes, secondary amenorrhea, and vaginal atresia with hematometra and hematocolpos.

The study protocol was approved by the ethics committee of Peking Union Medical College Hospital. Patient consent was waived because of the retrospective nature of the study.

Patient Evaluation

Data on genital malformation (encoded with Q51-Q52) were retrieved from the hospital medical record system.

The authors indicate no conflicts of interest.

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Cases with any of the following diagnoses on medical records were included: MRKH syndrome, congenital absence of vagina, and congenital vaginal atresia. We collected patient demographic and baseline data, including age, personal and family history, and laboratory tests (eg, testosterone and follicle-stimulating hormone level, and karyotype). A thorough gynecologic examination was undertaken for each subject. Radiologic evaluation included transabdominal, transvaginal, or transrectal 2-dimensional or 3-dimensional ultrasonography, x-rays, and magnetic resonance imaging (MRI) of the pelvis. Organ malformations were classified according to the Vagina Cervix Uterus Adnex-associated Malformation (VCUAM) classification.[7]

Statistical Analyses

The data were recorded, analyzed, and presented using Microsoft Office Excel.

Results

Patient Demographic and Baseline Characteristics

The study flow chart is shown in Figure 1. A diagnosis of MRKH syndrome was noted in a total of 290 patients. Nine cases were excluded because of incomplete clinical data, and 7 cases were excluded because of apparent misdiagnosis. The final analysis included 274 cases: 197/274 (71.9%) with type I MRKH syndrome and 77/274 (28.1%) with type II MRKH syndrome. All patients were ethnically Han Chinese and all cases were sporadic. The age was 23 ± 5.1 (range, 12-59) years.

Concurrent Deformities

Single deformities of the study sample are shown in Table 1. Renal malformation was present in 32/244 cases (13.1%), skeletal malformation in 51/125 cases (40.8%). Unilateral renal agenesis was the most common renal malformation (17/32; 53.1%). Scoliosis was the most frequent skeletal malformation (43/51; 84.3%). Cardiac malformation was noted in 4 cases. Abnormality of the nervous system (congenital deafness) was noted in 1 case. Anal atresia was observed in 5 patients.

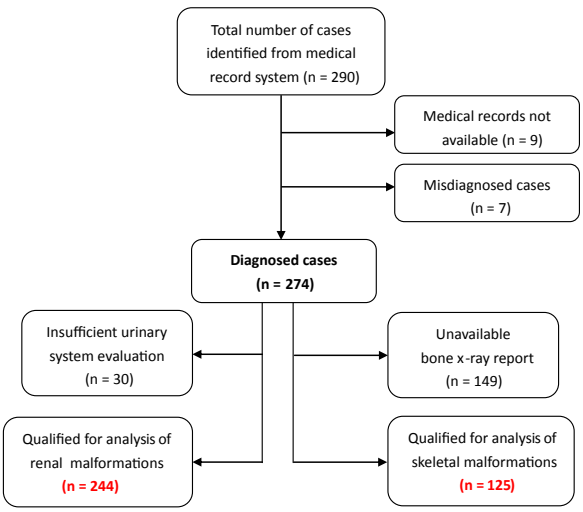

Fig. 1. Study flow chart.

Table 1
Concurrent Single Deformities in the Study Patients

Concurrent malformation	n
Renal	32
Unilateral renal agenesis	17
Right	11
Left	6
Pelvic ectopic kidney	10
Bilateral	6 (including fused kidney in 3 cases)
Unilateral (left)	4 (including polycystic kidney in 1 case)
Bilateral duplex kidney	2
Unilateral renal dysplasia	3
Right	2
Left	1
Hydronephrosis*	4
Right	3
Left	1
Skeletal	51
Scoliosis	43
Vertebral body anomalies†	8
Rib deformity	6
12th rib deletant	4
Others	2
Thoracocyllosis	1
S1 subfissure	1
Cardiac	4
ASD	1
VSD	1
Dextrocardia	2
Neurologic	1 (deaf-mute)
Others	6
Anal atresia	4
Anal stenosis	1
Congenital diaphragmatic hernia	1

ASD, atrial septal defect; VSD, ventricular septal defect
* Combined with other renal malformations.
† Combined with scoliosis.

Combined deformities of the study sample are shown in Table 2. Nine patients had renal and skeletal malformations (MURCS), among whom 2 also had anal atresia. Two patients had skeletal and cardiac malformations. Anal atresia was also present in 1 patient with renal malformation and 1 patient with skeletal malformation, respectively. Congenital diaphragmatic hernia was present in 1 patient with renal malformation.

Table 2
Phenotype Profiles and Number of Combined Deformities

R	S	C	N	O	n	Subtype
+					21	II
	+				38	MURCS?
		+			1	?
			Deaf-mute		1	?
				Anal atresia	1	?
+	+				7	MURCS
+	+			Anal atresia	2	MURCS
+				Anal atresia	1	II?
+				Congenital diaphragmatic hernia	1	II?
	+	+			2	MURCS?
	+			Anal atresia	1	MURCS?
	+	+		Anal atresia	1	MURCS?
32	51	4	1	5	77	

C, cardiac; O, others; MURCS, Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia; N, neurologic; R, renal; S, skeletal.
"+"means having the specific deformity.

Table 3
Review of the Literature on Associated Malformations in MRKH Syndrome

Data Source or References	Cases, n	Country	Type II, n (%)	Renal, %	Skeletal, %	Cardiac, %	Neurologic, %	MURCS, %	Other
Europe	1259		489 (46.2%)	32.2	21.8	–	–	–	–
Creatsas et al[9]	200	Greece	-	44.5	9	–	4.5	–	–
Oppelt et al[10]	284	Germany	127 (44.7%)	29.6	38	3.5	4.9	13.4	–
Rall et al[8]	346	Germany	162 (46.8%)	26.6	20.5	2.6	–	5.5	–
Kapczuk et al[11]	125	Poland	68 (54.4%)	28.8	32	–	–	41.6	–
Herlin et al[12]	304	Denmark	132 (43.5%)	34.2	12.5	3.6	1.8	–	Anal atresia (1.8%)
China	868		120 (13.8%)	7.1	7.0	–	–	–	–
Pan and Luo[4]	594	China	43 (7.2%)	5.1	1.7	0.5	0	0.2	
Current report	274	China	77 (28.1%)	13.1	40.8	4 cases	1 case	–	Anal atresia (1.8%)

MRKH, Mayer-Rokitansky-Küster-Hauser

Discussion

The current study showed that most Chinese patients (72%) with MRKH syndrome had type I syndrome. Skeletal malformation was the most common abnormality (51/125; 40.8%), followed by renal malformation (32/244; 13.1%).

A total of 6 epidemiological studies of MRKH syndrome have been published: 5 (1259 patients) in European countries[8–12] and 1 in China.[4] Type II MRKH syndrome in European patients accounted for slightly less than half (489/1259; 46.2%) of the entire population (Table 3). This is noticeably higher than the rate of type II MRKH syndrome in Chinese patients (13.8%). The rate of renal malformations in our cohort was higher than in the previous Chinese cohort (13.1% vs 5.1%), but much lower than in European populations (32.2%). The percentage of skeletal malformations in our cohort (40.8%) was much higher than previously reported in China (1.7%), as well as in European cohorts (approximately 9%-38%). Factors that contributed to the observed differences between and within the Chinese and European patients remain unknown, although epigenetic variance has been speculated.[5]

The VCUAM system is the only classification approach to distinguish and categorize the associated malformations in MRKH syndrome.[7] The American Fertility Society and European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy classification system focus on Müllerian anomalies in the uterus, cervix, and vagina.[13] In our experience, the “M” category in the VCUAM system is convenient to use in clinical settings, and can be used to describe the malformations of the criteria for type II MRKH or MURCS syndrome. Using the current definitions, that is “The isolated agenesis or hypogenesis of Müllerian ducts with normal ovaries and kidneys is defined as ‘typical or type I’ MRKH syndrome, ovarian and/or renal malformation together with anomalies of Müllerian system is defined as ‘atypical or type II’ MRKH syndrome, and MURCS refers to ‘Müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia syndrome,’” [1,3] quite a few of combination types could not be classified properly (see the far right column in Table 2). An itemized description is much more clear in our opinion.

With regard to adnexa classification, we believe the VCUAM system is too complicated to use, with limited value in guiding the treatment and prognosis prediction. MRKH syndrome patients are prone to have heterotopic ovaries and Fallopian tube malformations, but these conditions do not need surgery. To classify the Fallopian tubes using the VCUAM system, laparoscopy is the only accurate method, but laparoscopy is not recommended as a routine procedure.[14] As for our current study, only 10% of the patients received laparoscopy, mainly because of symptoms of abdominal pain and pelvic cystic-solid mass, which were actually the obstructive rudimentary uterus or in response to the need for the peritoneal method of vaginoplasty. The evaluation of the adnexa was inadequate to assess patient status using the VCUAM system, however, it does not affect the outcome of treatment.

A major limitation of the current study was its retrospective design. Also, the study spanned a period of 9 years, during which there have been many advances in diagnosis and treatment. The imaging methods were not selected using uniform criteria in the past. Most patients received transabdominal ultrasound imaging because of being virgin or having no vagina. Transrectal ultrasound has been available in our center in recent years. MRI is relatively expensive and generally used for research purposes. With the accumulation of clinical experience, we gradually formed the current auxiliary examination package: (1) karyotype analysis; (2) sex hormone spectrum; (3) transrectal pelvic sonography; (4) renal-ureter sonography; (5) spine radiograph; (6) chest radiograph; and (7) if the ultrasound images were not consistent with the clinical symptoms, for example, the patient had intermittent abdominal pain, but ultrasound did not detect a uterine cavity configuration, supplementary pelvic MRI was implemented.

In conclusion, the current study suggests that the percentage of type II syndrome in Chinese patients with MRKH syndrome is higher than previously reported in China, but somewhat lower than reported in European cohorts. The findings suggest substantial difference across and within races.

Acknowledgments

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