

Anxiety symptoms in patients with Mayer-Rokitansky-Küster-Hauser syndrome: a cross-sectional study

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Abstract

Background: As a congenital malformation that results in infertility and an inability to have vaginal intercourse, Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome places a considerable psychological burden on patients, which results in anxiety symptoms. However, only single case studies or a few small to medium-sized cross-sectional studies were identified to focus on anxiety symptoms in MRKH patients. Thus, the aim of this study was to explore the status of anxiety symptoms and the related factors in patients with MRKH syndrome.

Methods: This cross-sectional study involving 141 patients with MRKH syndrome and 178 healthy women was conducted from January 2018 to December 2018. All participants were required to complete a demographic questionnaire and the Generalized Anxiety Disorder 7-item scale (GAD-7), Patient Health Questionnaire-9, Eysenck Personality Questionnaire-Revised, Short Scale for Chinese, and Chinese Version of the Female Sexual Function Index. The main outcome was the anxiety symptoms measured by the GAD-7. Main outcome was compared between the MRKH syndrome group and the healthy control group. Then, we explored the related factors by comparing patients with and without anxiety symptoms.

Results: Of the respondents, 24.1% experienced moderate to severe anxiety symptoms. Patients with MRKH syndrome manifested more severe anxiety symptoms than healthy women. Negative self-evaluation of femininity (odds ratio [OR] 2.706, 95% confidence interval [CI] 1.010–7.247), neurotic personality traits (OR 1.100, 95% CI 1.029–1.175), and coexisting depressive symptoms (OR 4.422, 95% CI 1.498–13.049) were more prevalent in anxious patients.

Conclusion: The findings stress the importance of anxiety symptom screening in MRKH patients and identify patients at risk of anxiety symptoms, providing a possible basis for future intervention.

Keywords: MRKH syndrome; Anxiety; Risk factors

Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare disease with an estimated incidence of 1 per 4000 to 5000 females.^[1] Due to an embryonic developmental aberration of the Mullerian duct, the uterus and the upper two-thirds of the vagina are absent in patients with MRKH syndrome. Patients diagnosed with this condition, therefore, experience sexual intercourse difficulty and infertility because of the malformation. MRKH syndrome is often associated with malformations in renal and skeletal systems. Therefore, this disease is typically classified as type 1, which is characterized by normal development of other systems, and type 2, with abnormal renal and/or skeletal malformations.^[2]

Anxiety is a common but often neglected emotional expression in patients in medical settings,^[3] with patients with MRKH syndrome being no exception. A large body of literature reports that a diagnosis of MRKH syndrome has a variety of psychological effects on patients, including depression, self-esteem and body image disturbances, feelings of incompleteness, and doubts about female identity.^[4–6] However, very little is known about the anxiety status of this population. Only a few case studies have reported the patient's anxious feelings. After diagnosis, patients might feel anxiety about their femininity, physical image, and infertility.^[7,8] A few studies enrolling relatively small samples have taken anxiety symptoms as one of the outcome measures, but without further analysis of the potential risk factors.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000000648

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Chinese Medical Journal 2020;133(4)

Received: 19-09-2019 Edited by: Li-Min Chen

Thus, to fill this gap in the current literature, our study aimed to investigate the incidence of anxiety symptoms and identify factors associated with anxiety symptoms in a large sample of MRKH patients.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee of the Peking Union Medical College Hospital (PUMCH) (No. S-K471). Informed written consent was obtained from all patients before their enrollment in this study.

Study participants

The study was conducted from January 2018 to December 2018 at the Center of Obstetrics and Gynecology of PUMCH. All women with a confirmed diagnosis of MRKH syndrome who had been seen in our clinic within the previous year and were over 16 years old were invited to join the study. Patients reporting pre-existing psychiatric disorders were excluded from our study. The female controls were age-matched women without symptoms of somatic disorders recruited from the Physical Examination Center of this hospital.

Study design

This study was a web-based cross-sectional survey. An estimated sample size of 120 cases was calculated. Eligible patients and female controls were given an introductory letter explaining the purpose and voluntary nature of the survey, attached to which was a link to the online questionnaire. If participants consented to participate in this study, they signed the informed consent form, completed the questionnaire through the attached link and submitted the survey to the webserver.

Questionnaire

The initial questionnaire gathered data pertaining to the patient's demographic background and medical history. The demographic background consisted of age, religious belief, education level, family income level, marital status, and the state of sexual partner and offspring. Moreover, self-evaluation of patient's family relationship and supports got from family were also collected in the questionnaire. Medical history part inquired about the type of disease, post-diagnosis period, and treatment received. Then, the Chinese version of the Generalized Anxiety Disorder 7-item scale (GAD-7) was used to assess the anxiety states of the participants. Though initially designed for detecting generalized anxiety disorder, the GAD-7 has also performed well in detecting other common anxiety disorders, such as panic disorder, social anxiety disorders, and post-traumatic stress disorder.^[9] It is used in primary care and has been validated in a general population sample.^[10] Therefore, growing evidence supports that the GAD-7 can be used as a self-report anxiety measure for initial screening. The Chinese version has been

validated on outpatients in Chinese general hospitals.^[11] It comprises seven items, with each item scored from 0 to 3. Anxiety symptoms can be grouped as minimal (0–4), mild (5–9), moderate (10–14), or severe (15–21) based on the GAD-7 total score. Using a score of 10 as a cut-off, the sensitivity and specificity of the GAD-7 for diagnosing anxiety disorder are 0.86 and 0.95, respectively.^[11] Hence, the participants were divided into anxiety and non-anxiety groups based on a cut-off score of 10.

In addition to the GAD-7 to evaluate anxiety symptoms, other validated measurements and questions related to the participants' psychological states were used: (1) the Patient Health Questionnaire-9 is a widely used depression screening instrument validated in the general population.^[12] It is a nine-item self-administered questionnaire whose questions reflect all nine criteria upon which the diagnosis of Diagnostic and Statistical Manual of Mental Disorders, 4th edition depressive disorder is based.^[13] Using the summed-item scoring method, it was determined that a cut-off point of ≥ 10 had a pooled sensitivity of 0.77 and a specificity of 0.85 for screening depression symptoms, representing satisfactory diagnostic performance for screening purposes.^[14] (2) The Eysenck Personality Questionnaire-Revised, Short Scale for Chinese is a personality-measuring tool with satisfactory reliability and validity in the general population over 16 years old.^[15] Extraversion (E), neuroticism (N), psychoticism (P), and lie inventory (L) were the four sub-scales administered. (3) The Chinese Version of the Female Sexual Function Index was used to assess sexual function in patients who had received non-surgical or surgical intervention for the construction of a neovagina and had been sexually active in the past 4 weeks. Based on epidemiological research with Chinese women, patients with FSFI total scores less than 23.45 were defined as having sexual dysfunction.^[16,17] (4) Related questions such as "Do you think you possess good femininity?" and "What's your plan for generating offspring?" were also added to the questionnaire. These questions aimed to evaluate patients' attitudes towards their female identity and parenthood, which are reported to be affected after a diagnosis of MRKH syndrome.^[4]

Statistical analysis

The differences with respect to the results of GAD-7 between the MRKH patients and healthy women were analyzed based on one-way analysis of covariance, with the demographic variables of age, educational level and family income as covariates. Then, patients were divided into anxiety and non-anxiety groups based on the GAD-7 score. Univariable analysis was used to assess variables associated with the outcomes. Factors with a $P < 0.1$ in the univariable analysis were then used in the stepwise multiple logistic regression analysis to identify the potential risk factors for anxiety symptoms in patients with MRKH syndrome. The descriptive statistics are presented as the mean values \pm standard deviations (SD) or medians and interquartile ranges for continuous variables and frequencies for categorical variables. Pearson χ^2 and Fisher's exact tests were used to analyze categorical variables, while independent samples t tests or Mann-

Whitney *U* tests were performed to analyze continuous variables. $P < 0.05$ was considered statistically significant. For pairwise comparisons, the Bonferroni-adjusted P value was calculated. All statistical analyses were performed with the IBM® SPSS® 21.0 statistical package (SPSS Inc., Chicago, IL).

Results

We distributed questionnaires to 218 eligible patients and received 141 valid responses, resulting in a response rate of 64.7%. By advertisement-based recruitment, we received 178 valid questionnaires from healthy women. Table 1 displays the demographic characteristics of the patients. The mean age of the patients was 25.8 ± 4.6 years, and the

average post-diagnosis period was 7.7 ± 4.5 years. 92 patients (65.2%) were diagnosed with type 1 MRKH syndrome while 49 patients (34.8%) were diagnosed with type 2 MRKH syndrome. Nearly half of the patients (67/141, 47.5%) had received non-surgical dilation, and nearly one-third of the participants (41/141, 29.1%) had received vaginoplasty surgery, 37 by the biomaterial graft method, and four by the peritoneal method. The remaining 33 patients (33/141, 23.4%) had not received any treatment because of emotional immaturity or a lack of desire to proceed with therapy at the moment. Among the 141 patients, 14 women (9.9%) had religious beliefs, 103 women (73.0%) had achieved a bachelor's degree or above, 89 women (63.1%) had a medium to low family income, 111 women (78.7%) were single, and 70 women (49.6%) had sexual partners. Only three (2.1%) had offspring by adoption or surrogacy. In addition, 91 women (64.5%) had a positive self-evaluation of their femininity. A total of 112 patients (79.4%) had plans regarding offspring, of which 53.9% were willing to choose surrogacy.

Analyses of the demographic features showed the age of patients and female controls were comparable while the education level and the family income level were significantly higher in female controls. Thus, the GAD-7 results were compared with age, education level and family income controlled. GAD-7 score was 6.0 (3.5, 9.0) in women with MRKH syndrome while 5.0 (1.0, 7.0) in female controls, which was significantly higher in patient group ($F = 10.005$, $P = 0.002$).

Incidence and factors associated with anxiety symptoms

Figure 1 displays the incidence of different levels of anxiety symptoms in both groups. Of the patients, 32.6% (46/141) had minimal anxiety symptoms, 43.3% (61/141) had mild symptoms, 16.3% (23/141) had moderate symptoms, and 7.8% (11/141) had severe anxiety symptoms. However, in the healthy group, 49.4% (88/178) had minimal symptoms, 38.8% (69/178) had mild symptoms, only 9.0% (16/178) had moderate symptoms, and 2.8% (5/178) had severe symptoms.

To further explore the factors related to the onset of anxiety symptoms, based on the widely used cut-off score of 10 for the GAD-7, 34 participants (24.1%) were assigned to the anxiety group. Table 2 displays the results of the univariable analysis. In terms of sociodemographic features, married patients were more likely to present anxiety symptoms ($\chi^2 = 5.256$, $P = 0.022$). Regarding the psychological aspects, negative self-evaluation of femininity ($\chi^2 = 10.685$, $P = 0.001$), depressive symptoms ($\chi^2 = 35.920$, $P < 0.001$), introversion ($t = 3.086$, $P = 0.004$), and neurotic ($t = 8.134$, $P < 0.001$) personality traits were more prevalent in the anxiety group. In addition, anxiety status was significantly different among patients with different states of sexual function ($\chi^2 = 12.826$, $P = 0.002$). Compared to patients with normal sexual function and sexually inactive patients, patients with sexual dysfunction were more likely to display anxiety symptoms (Bonferroni-adjusted $P = 0.015$, Bonferroni-adjusted $P = 0.003$).

Table 1: Demographic features of the MRKH patient group (N= 141).

Variables	Values
Age (years)	25.8 ± 4.6
Post-diagnosis period (years)	7.7 ± 4.5
Type of disease	
Type 1	92 (65.2)
Type 2	49 (34.8)
Therapy received	
Non-surgical dilation	67 (47.5)
Vaginoplasty surgery	41 (29.1)
None	33 (23.4)
Religious belief	
Yes	14 (9.9)
No	127 (90.1)
Education level	
≤Secondary school	38 (27.0)
≥Bachelor	103 (73.0)
Family income	
Medium to low	89 (63.1)
High	52 (36.9)
Marital status	
Single	111 (78.7)
Married	30 (21.3)
Sexual partner	
Yes	70 (49.6)
No	71 (50.4)
Offspring	
Yes	3 (2.1)
No	138 (98.1)
Family relationship	
Good	114 (80.9)
Average	27 (19.1)
Support from family after diagnosis	
Yes	127 (90.1)
No	14 (9.9)
Plan regarding offspring	
Adoption	36 (25.5)
Surrogacy	76 (53.9)
No	29 (20.6)
Good femininity	
Yes	91 (64.5)
No	50 (35.5)

All data were shown as mean ± standard deviation or *n* (%). MRKH: Mayer-Rokitansky-Küster-Hauser syndrome.

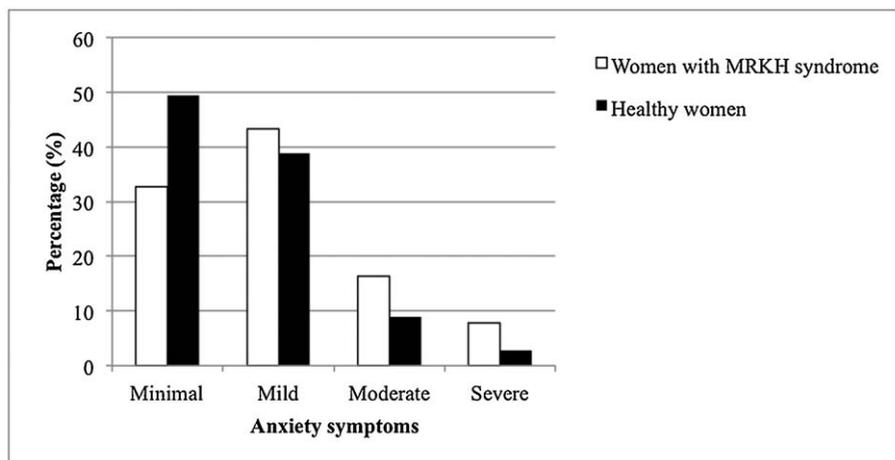


Figure 1: Incidence of different levels of anxiety symptoms in patients with MRKH syndrome and healthy women. The white column indicates women with MRKH syndrome, and the black column indicates healthy women. MRKH: Mayer-Rokitansky-Küster-Hauser syndrome.

Then, multiple stepwise logistic regression was conducted to screen potential risk factors for anxiety symptoms. We found that women with negative self-evaluations of their femininity (odds ratio [OR] 2.706, 95% confidence interval [CI] 1.010–7.247), coexisting depressive symptoms (OR 4.422, 95% CI 1.498–13.049), and neurotic personality traits (OR 1.100, 95% CI 1.029–1.175) were more likely to exhibit anxiety symptoms [Table 3].

Discussion

As a congenital malformation that results in infertility and an inability to have vaginal intercourse, MRKH syndrome creates a substantial psychological burden that includes anxiety symptoms. Our study found that 24.1% of patients experienced moderate to severe anxiety symptoms, while the figure for healthy women was only 11.8%. Moreover, the GAD-7 scale score was significantly higher in the patient group.

To date, only a few studies have evaluated anxiety symptoms in MRKH patients, and the results have been inconclusive. Liao found that the Hospital Anxiety and Depression Scale scores for anxiety were higher in 58 women with MRKH syndrome than in the reference sample.^[18] Another study including only five MRKH patients reached a similar conclusion using the State-Trait Anxiety Inventory.^[5] However, another two studies enrolling 66 and 54 MRKH cases, respectively both claimed that the anxiety scores showed no significant difference between the MRKH group and the control group.^[19,20] Relatively small sample sizes and the use of various measurement instruments may explain the discrepancy in these results. Based on our findings and a review of previous studies, we note that the severity of anxiety symptoms is increased in patients with MRKH syndrome. With more severe anxiety symptoms, patients with MRKH syndrome are at a higher risk of anxiety disorders. Therefore, for this group of women, anxiety evaluation is of great importance. However, in the busy and complex clinical setting, it is difficult to conduct

diagnostic evaluations for anxiety disorders for every patient. Therefore, evaluating anxiety symptoms using a simple measuring tool and referring high-risk patients to psychology professionals is a feasible solution.

Our study showed that negative self-evaluation of femininity, neurotic personality traits and coexisting depressive symptoms are potential risk factors for anxiety symptoms in MRKH patients.

In terms of self-evaluation of femininity, due to the cross-sectional study design, we cannot determine the causal connection between anxiety symptoms and negative evaluation of femininity in MRKH patients. One possible explanation is that the negative evaluation of female identity is anxiety-arousing. Supporting this, a randomized controlled trial of a cognitive-behavioral therapy (CBT) intervention was based on the premise that the core issue of MRKH syndrome was the threat to the patient's female role; the trial obtained satisfactory improvements in psychological outcomes, including anxiety symptoms, in the CBT intervention group.^[19] This psychotherapy targeting the negative evaluation of femininity improved anxiety outcomes, supporting our hypothesis that doubts about female identity are anxiety-arousing and potential treatment targets for MRKH syndrome.

In addition, neurotic personality traits might contribute to anxiety symptoms in MRKH patients. Similar results were also reported previously.^[21] It has been hypothesized that the diagnosis of MRKH syndrome in adolescence has an impact on the development of personality traits, which may explain the higher neuroticism level in MRKH patients.^[21] Moreover, according to Eysenck's theory, neurotic people are more prone to emotional instability and negative emotions under the stress of life events. This could partly account for the increased anxiety symptoms in MRKH patients. Therefore, when a woman receives a diagnosis of MRKH syndrome, it is of great importance that she receives a thorough psychological state evaluation, and extra attention should be given to neurotic patients.

Table 2: Factors associated with anxiety symptoms in 141 women with Mayer-Rokitansky-Küster-Hauser syndrome.

Variables	Anxiety symptoms		t/χ^2	P
	Anxiety (n = 34)	Non-anxiety (n = 107)		
Age (years)	26.2 ± 3.1	25.7 ± 5.0	0.637*	0.503
Years since diagnosis	8.6 ± 3.6	7.5 ± 4.7	1.433*	0.153
Type of disease			0.240 [†]	0.624
Type 1	21	71		
Type 2	13	36		
Religious belief			0.548 [†]	0.459
Yes	5	9		
No	29	98		
Education level			0.664 [†]	0.415
≤Secondary school	11	27		
≥Bachelor	23	80		
Family income			0.048 [†]	0.826
Medium to low	22	67		
High	12	40		
Marital status			5.256 [†]	0.022
Single	22	89		
Married	12	18		
Sexual partner			2.632 [†]	0.105
Yes	21	49		
No	13	58		
Offspring			1.676 [†]	0.195
Yes (adoption or surrogacy)	0	3		
No	34	104		
Family relationship			1.255 [†]	0.479
Good	26	88		
Average	8	19		
Support from family after diagnosis			1.115 [†]	0.573
Yes	31	96		
No	3	11		
Treatment			0.000 [†]	0.984
Yes	26	82		
No	8	25		
Good femininity			10.685 [†]	0.001
Yes	14	77		
No	20	30		
Plan regarding offspring			0.023 [†]	0.997
Yes	27	85		
No	7	22		
Female sexual dysfunction			12.826 [†]	0.002
Yes	13	14		
No	8	35		
Not sexually active	13	58		
Depressive symptoms			35.920 [†]	<0.001
Yes	26	22		
No	8	85		
EPQ-RSC				
EPQ-P	51.5 ± 8.9	48.6 ± 8.8	1.722*	0.113
EPQ-E	44.5 ± 10.9	51.2 ± 10.9	3.086*	0.004
EPQ-N	68.7 ± 6.1	56.4 ± 11.4	8.134*	<0.001
EPQ-L	50.6 ± 10.0	50.5 ± 9.1	0.103*	0.959

Data were shown as mean ± standard deviation or *n*. **t* values; [†] χ^2 values. EPQ-RSC: The Eysenck Personality Questionnaire-Revised, Short Scale for Chinese; EPQ-P: Psychoticism sub-scale of EPQ-RSC; EPQ-E: Extraversion sub-scale of EPQ-RSC; EPQ-N: Neuroticism sub-scale of EPQ-RSC; EPQ-L: Lie inventory of EPQ-RSC.

Moreover, coexisting depressive symptoms are also associated with increased onset of anxiety symptoms in patients with MRKH syndrome. Many studies have reported that the comorbidity of anxiety and depression

is prevalent,^[22] which could explain our results to some extent. However, it has also been reported that comorbidity results in more severe psychiatric symptoms, poorer psychosocial functioning, and higher suicide risk.^[23]

Table 3: Factors associated with anxiety symptoms based on a logistic regression analysis.

Variables	OR	OR (95% CI)		P
		Lower	Upper	
Femininity	2.706	1.010	7.247	0.048
Depressive symptoms	4.422	1.498	13.049	0.007
EPQ-N	1.100	1.029	1.175	0.005

CI: Confidence interval; OR: Odds ratio; EPQ-N: Neuroticism sub-scale of the Eysenck personality questionnaire.

Therefore, coexisting depressive symptoms not only provide clues about anxiety symptoms but also remind practitioners to comprehensively evaluate patients' psychological states.

Although we did not arrive at this result due to the limited number of patients with children, several studies have proven that infertility is a risk factor for anxiety disorders.^[24,25] Having been born with infertility, MRKH patients are generally eager to have offspring. In our study, 79.4% of the patients had plans regarding offspring. Providing these patients with fertility opportunities might help alleviate their anxiety. Currently, uterine transplantation and in vitro fertilization (IVF) using a gestational surrogate are two reproductive options for MRKH patients. As uterine transplantation is still considered an experimental procedure, gestational surrogacy is currently a viable treatment option for MRKH patients in countries where it is legally permitted. A systematic review including 14 studies published between 1988 and 2011 reported that 125 MRKH patients underwent 369 cycles of IVF with gestational surrogacy and delivered 71 newborns. No case report was identified regarding the birth of a girl with MRKH syndrome to a mother with MRKH.^[26] In our study, 53.9% of patients were willing to choose surrogacy to have offspring. Surrogacy remains illegal in China; therefore, we are far from solving the problem of infertility in Chinese MRKH patients through surrogacy.

Though both American and Chinese expert consensus on MRKH syndrome recommended offering psychological counseling to patients,^[27,28] there is not enough evidence of the actual psychological status of MRKH patients. That is exactly what this study added to this field. To the best of our knowledge, this study included the largest sample size to date and provided detailed data on anxiety symptoms and related factors in patients with MRKH syndrome. However, our study had the following limitations. First, the diagnostic evaluation of anxiety disorder was not included in the study design. Thus, only conclusions related to anxiety symptoms in MRKH patients can be drawn through our study. We call for further evaluation, including the diagnosis of anxiety disorders, in future studies. In addition, due to strict legal restrictions on surrogacy and adoption, only three patients with children were enrolled in our study. This led to difficulties in analyzing whether having offspring, which is an important potential source of anxiety, was associated with anxiety symptoms in MRKH patients.

In conclusions, two-thirds of patients with MRKH syndrome experience anxiety symptoms, and nearly a quarter have moderate to severe symptoms. Moreover, neurotic personality traits, negative self-evaluation of femininity, and coexisting depressive symptoms are potential risk factors of anxiety symptoms in MRKH patients. Hence, anxiety symptom screening is necessary for patients with MRKH syndrome, and psychological counseling and intervention should be considered independent of other treatments intended to correct anatomical abnormalities in these patients.

Conflicts of interest

None.

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How to cite this article: Song S, Chen N, Duan YP, Kang J, Deng S, Pan HX, Zhu L. Anxiety symptoms in patients with Mayer-Rokitansky-Küster-Hauser syndrome: a cross-sectional study. *Chin Med J* 2020;133:388–394. doi: 10.1097/CM9.0000000000000648