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Observational Study

Studying the relationship between clinical features and mental health among late-onset myasthenia gravis patients

Lu Yu, Li Qiu, Hao Ran, Qian Ma, Ya-Ru Lu, Wei-Bin Liu

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Abstract

BACKGROUND

Mental disorders are common comorbidities among individuals with neurological diseases, and the prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high. There have been few studies on the mental health of patients with late-onset myasthenia gravis (MG).

AIM

To examine the relationship between clinical features and the mental health symptoms within late-onset MG patients.

METHODS

A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021. Patients were classified into two groups: early-onset MG (age at onset < 50 years, $n = 63$) and late-onset MG (age at onset ≥ 50 years, $n = 42$). Social demographic data and information about marital status, education level, clinical symptoms, serum antibody levels, and therapies used were collected for all participants. Participants were also evaluated using the Myasthenia Gravis Composite scale, the Myasthenia Gravis Activities of Daily Living scale, the Myasthenia Gravis Quality of Life 15 (MG-QOL-15) questionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A). The relationship between clinical features and mental health in late-onset MG patients was examined using multivariate logistic regression analyses.

RESULTS

Late-onset MG patients were more prone to dyspnea, had higher levels of serum anti-acetylcholine receptor antibodies, and higher total scores on the MG-QOL-15, HAM-D, and HAM-A questionnaires, than early-onset MG patients had ($P < 0.05$). Among those with late-onset MG, female patients had higher total HAM-D and HAM-A scores than male patients had ($P < 0.05$). High scores on the QOL-15 questionnaire were associated with higher incidences of anxiety and depression, and the association was found to be independent after adjusting for confounding risk factors. In the late-onset subgroup, the areas under the receiver operating characteristic curves for the MG-QOL-15 score-based diagnostic accuracy for anxiety and depression state were 0.816 ($P = 0.001$) and 0.983 ($P < 0.001$), respectively.

CONCLUSION

Higher MG-QOL-15 scores were a risk factor for anxiety and depression in late-onset MG, and women with late-onset MG were more likely to have anxiety and depression than men were.

Key Words: Mental health; Late-onset myasthenia gravis; Anxiety; Depression

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Core tip: Mental disorders are the common comorbidities among myasthenia gravis (MG) patients in older age. In this study, we found that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher scores on the Myasthenia Gravis Quality of Life 15 questionnaire were an independent risk factor for anxiety and depression in patients with late-onset MG. This is the first report detailing the relationship between clinical features and mental health in the subgroup of MG patients with late disease onset.

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder that is mainly caused by autoantibodies binding to nicotinic acetylcholine receptors (AChRs) at muscle endplates, and is characterized by skeletal muscle fatigability and weakness[1,2]. MG is also associated with emotional, cognitive, and behavioral symptoms[3].

Mental disorders are the most common comorbidities among individuals with neurological diseases, and the prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high[4]. MG is an autoimmune disease that can lead to disability. The global prevalence of MG is roughly 40-180 cases per 1 million individuals[5]. However, there are limited data on the relationship between mental disorders and MG, especially in patients with late-onset forms of the disease. Furthermore, because myasthenic symptoms of MG may overlap with somatic symptoms of depression and anxiety[6], such as fatigue or shortness of breath, which are also common in mental disorders, and facial weakness and blepharoptosis generally convey an impression of depression and apathy[7], comorbidities accompanied by mental and myasthenic symptoms may be misdiagnosed, thus the need to focus on both mental and physical therapies has been highlighted[8,9].

Mental disorders have often been reported; the incidence is up to 59% of MG patients, with depression being the most common disorder, followed by anxiety and hypochondria[10]. The unpredictable progression, chronic course and long-term treatment for MG can lead to limitations and reductions in quality of life (QOL)[11-13], which were found to predispose to psychological stress[7]. There is a questionnaire specifically aimed at assessing QOL among MG patients (Myasthenia Gravis Quality of Life 15-item (MG-QOL-15) scale, including 15 test items that address MG-specific social functioning and uses five response options, based on which QOL can be effectively rated[14,15]. The measures of MG-QOL-15 try to capture patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal, and higher scores on the MG-QOL-15 questionnaire were indicative of more severe clinical cases to some extent[13].

Longer disease duration, severity of disease, and MG-induced respiratory failure may contribute to the increased rates of depression[16,17]. Compromised swallowing and communication abilities, unpredictable and fluctuating nature of respiratory dysfunction suggests concerning risk factors for

developing anxiety among MG patients[7,16-18]. Fewer work restrictions could be protective factors for developing mental disorders in the limited observational studies[19]. Late-onset MG occurring in older adults is more difficult to manage mainly because of the multiple comorbidities[20,21] and MG with late disease onset is on the rise in recent years[22]. Due to the frequent occurrence of comorbidities in older people that might be confused with MG symptoms[23], awareness of the occurrence of mental disorders in older age groups of MG is needed for earlier intervention and thus a better outcome. To this end, this cross-sectional study aimed to investigate the relationship between clinical features and mental health in patients with late-onset MG.

MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted in The First Affiliated Hospital of the Sun Yat-sen University, in Guangzhou, China. A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021. Clinical data were collected, and scores on clinical scales were procured through face-to-face evaluations with professional neurologists. This study was approved by the Ethics Committee of The First Affiliated Hospital of the Sun Yat-sen University. We obtained informed consent from all patients prior to the scale-based clinical examinations.

Inclusion and exclusion criteria

All participants were diagnosed with MG according to international consensus-based guidelines[24]. This study included patients who met the following criteria: (1) Diagnosed with MG; (2) aged ≥ 16 years; and (3) ability to fully cooperate during clinical scale-based evaluations. Patients were excluded if they: (1) Were under treatment with antianxiety and/or antidepressant drugs; and (2) had incomplete data.

Clinical data and scales

We collected data on sociodemographic characteristics, inducing factors, comorbidities, specific clinical features (*i.e.*, disease duration, Myasthenia Gravis Foundation of America Classification, symptoms at first evaluation, and mental status), details of serum antibodies levels [*i.e.*, levels of anti-AChR/muscle-specific tyrosine kinase (MuSK) antibodies], and immunotherapy history. Patients were independently examined using the Myasthenia Gravis Composite (MGC) scale, the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, the MG-QOL-15 questionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D), and the Hamilton Anxiety Rating Scale (HAM-A) by two neurologists (both of whom were qualified to perform these evaluations).

The MGC scale[25] is composed of 10 items that measure symptoms and signs of MG, with a maximum score of 50 points, the reliability coefficient of the MGC scale was 98%, indicating excellent test-retest reliability. The MG-ADL scale[26] is composed of eight questions, aims to assess disability of ocular (2 items), bulbar (3 items), respiratory (1 item), and limb (2 items), with each response graded from 0 (normal) to 3 (most severe), and the total score ranges from 0 to 24, reliability coefficient was 93.7%. The MG-QOL-15 consists of 15 items: mobility (9 items), symptoms (3 items), general contentment (1 item), and emotional well-being (2 items)[27], with each response graded from 0 (not at all) to 4 (very much), and total scores of up to 60 points, the Chinese MG-QOL-15 had excellent internal consistency (Cronbach's $\alpha = 0.928$). Higher scores on MGC, MG-ADL, or MG-QOL-15 scales were indicative of more severe clinical cases. The HAM-A and HAM-D scales consist of 14 and 17 items, respectively, and are used to measure mental health symptoms[28,29]. The total scores are 56 (for the HAM-A) and 53 (for the HAM-D), and total HAM-A scores were classified as no (< 7), potential (7-13), assured (14-29), and severe (> 29) anxiety. Total HAM-D scores were classified as no (< 7), potential (7-17), assured (17-24), and severe (> 24) depression, the Cronbach's coefficient of them was > 0.8 , indicating good internal consistency. The above questionnaires and scales were administered in the Chinese language, and are all reliable, valid, and widely used[30-33].

Groups

Participants were categorized into the following subgroups according to their age at disease onset[34]: early-onset MG (age at onset < 50 years, $n = 63$) and late-onset MG (age at onset ≥ 50 years, $n = 42$). HAM-A scores ≥ 7 and HAM-A scores < 7 were considered to be indicative of anxiety and nonanxiety states, while HAM-D scores ≥ 7 and HAM-D scores < 7 were classified to be depressive and nondepressive states, respectively[35,36]. Patients were considered seropositive for anti-AChR antibodies if their titers were > 0.45 nmol/L on ELISA. They were deemed seropositive for anti-MuSK antibodies if their titers were > 0.05 nmol/L on a radioimmunoassay. All test reagents were purchased from RSR Ltd. (Cardiff, United Kingdom).

Statistical analysis

Statistical analyses were performed using SPSS version 25 software (IBM, Chicago, United States) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA). Categorical data were presented as counts and percentages, and were analyzed using Fisher's exact test or χ^2 test. Numerical data were presented as medians and interquartile ranges (partial distribution), and compared using the Mann-Whitney *U* test. Correlations were estimated with Pearson or Spearman correlation coefficients. Clinical determinants of anxiety and depression were used in multivariate logistic regression analyses, while gender, age at onset, body mass index (BMI), anti-AChR antibody levels, and MG-QOL15 scores were considered confounding risk factors. Receiver operating characteristic (ROC) curves were drawn to evaluate the value of MG-QOL-15 scores for diagnosing anxiety and depression. Significance was accepted if *P* values were < 0.05 , and are denoted as ^a*P* < 0.05 , ^b*P* < 0.01 , and ^c*P* < 0.001 .

RESULTS

Baseline characteristics

Patients with late-onset MG (age at onset ≥ 50 years) accounted for 40.0% (*n* = 42) of the 105 patients, and those with early-onset MG (age < 50 years) accounted for 60.0% (*n* = 63). Among the patients with late-onset MG, 45.24% were women, and 54.76% were men. Among the early-onset MG patients, 58.73% were women, and 41.27% were men.

The medians (interquartile ranges) of HAM-A scores were 5 (5.5) in early-onset patients and 8.5 (7.5) in late-onset patients. These scores were significantly different between the two groups (*P* < 0.001 ; **Figure 1A**). The HAM-D scores were 7 (8) and 10.5 (7.75) in early-onset and late-onset patient groups, respectively, and there was a significant difference between the two groups (*P* = 0.018; **Figure 1B**). There were also significant differences in BMI, disease duration, dyspnea symptoms, anti-AChR antibody levels, and MG-QOL-15 scores between the two groups (*P* < 0.05). HAM-A and HAM-D scores were significantly higher in female patients with late-onset MG than in those with early-onset MG (*P* < 0.001 and *P* = 0.001, respectively), but no significant differences were observed when only male patients were considered in these analyses (*P* = 0.192 and *P* = 0.731, respectively; **Figure 2A** and **B**). Baseline characteristics of the early-onset and late-onset groups are shown in **Table 1**.

Correlation between clinical features and age at onset, assessed using Pearson or Spearman correlation analysis

There was a positive correlation between age at onset and BMI (*r* = 0.41, *P* < 0.001), anti-AChR antibody levels (*r* = 0.31, *P* = 0.001), MG-QOL-15 scores (*r* = 0.32, *P* = 0.001), HAM-A scores (*r* = 0.41, *P* < 0.001), and HAM-D scores (*r* = 0.26, *P* = 0.007). However, there was a negative correlation between age at onset and disease duration (*r* = 0.59, *P* < 0.001). Correlations between all clinical features and age at onset are detailed in **Table 2**.

Clinical determinants of anxiety and depression in MG patients, measured using logistic analysis

Based on results from univariate analyses as well as previous literature[14-19], variables that may be relevant for mental health outcomes (gender, age at onset, BMI, anti-AChR antibody levels, and MG-QOL-15 scores) were included in a logistic regression model. No multicollinearity amongst the variables was found (variance inflation ranged from 1.072 to 1.536; tolerance ranged from 0.651 to 0.933) (**Supplementary Table 1**).

When the incidence of anxiety and depression were included as independent variables in the logistic analysis, they were associated with age at onset and MG-QOL-15 when other confounders were not considered. However, only MG-QOL15 scores were found to be independently associated with an increased risk of anxiety [odds ratio (OR) 1.10, 95%CI 1.04-1.15, *P* < 0.001] after adjusting for possible confounds (including gender, age at onset, BMI, and anti-AChR antibody levels). MG-QOL-15 scores were also significantly associated with the incidence of depression in MG patients (OR 1.20, 95%CI: 1.10-1.30, *P* < 0.001) (**Table 3**).

Diagnostic value of MG-QOL15 scores for examining mental health in late-onset MG patients

When multivariate analysis was performed after adjusting for related confounds, MG-QOL-15 scores were found to be independent risk factors for anxiety and depression. In patients with late-onset MG, the median (interquartile ranges) MG-QOL-15 scores in the nonanxiety and anxiety groups were 8 (10.5) and 20 (17), respectively, and there were significant differences between the two groups (*P* < 0.001). Similarly, MG-QOL-15 scores were significantly different between the depression and nondepression groups (*P* < 0.001 ; **Supplementary Figures 1A** and **2A**). We also examined whether MG-QOL-15 scores could help to diagnose or predict anxiety/depression state in late-onset MG patients using ROC curves [the larger the area under the ROC curve (AUC), the higher the diagnostic accuracy], and the smallest point that maximizes the value of (sensitivity + specificity - 1) is calculated as the cut-off value, which would lead to the maximum degree of classification for anxiety/depression state. In our study, the AUC

Table 1 Comparison between early-onset and late-onset groups

	Total patients (n = 105)	Early-onset (n = 63)	Late-onset (n = 42)	P value
Gender (n, %) ¹				
Male	49 (46.67)	26 (41.27)	23 (54.76)	0.231
Female	56 (53.34)	37 (58.73)	19 (45.24)	
Marital status (n, %) ²				
Married	63 (60.0)	33 (52.38)	30 (71.43)	0.067
Single (unmarried/divorced/widowed)	42 (40.0)	30 (47.62)	12 (28.57)	
Education (n, %) ²				
Primary school and below	26 (24.76)	12 (19.05)	14 (33.33)	0.073
Secondary school	44 (41.90)	25 (39.68)	19 (45.24)	
College and above	35 (33.33)	26 (41.27)	9 (21.43)	
Career change due to illness (n, %) ²				0.955
No change	69 (65.71)	41 (65.08)	28 (66.67)	
Leave of absence	24 (22.86)	15 (23.81)	9 (21.43)	
Transfer/unemployment	12 (11.43)	7 (11.11)	5 (11.90)	
BMI (kg/m ²) ³	21.71 (5.77)	20.51 (4.21)	24.36 (4.53)	< 0.001 ^c
Disease duration (mo) ³	5.00(12.21)	7.00(13.34)	4.00(8.50)	0.016 ^a
MGFA classification at evaluating (n, %) ¹				
I	28 (26.67)	21 (33.33)	7 (16.67)	0.255
II	40 (38.10)	22 (34.92)	18 (42.86)	
III	31 (29.52)	16 (25.40)	15 (35.71)	
IV	6 (5.71)	4 (6.35)	2 (4.76)	
Thymectomy (n, %) ²	44 (41.90)	28 (44.44)	16 (38.10)	0.551
Comorbidities (n, %) ²	49 (46.67)	32 (50.79)	17 (40.48)	0.299
Inducing factor (n, %) ¹				
Respiratory infection	12 (11.43)	6 (9.52)	6 (14.29)	0.470
Overfatigue	3 (2.86)	1 (1.59)	2 (4.76)	
No triggers	90 (85.71)	56 (88.89)	34 (80.95)	
Clinical features				
Onset symptom				
Blepharoptosis (n, %) ²	97 (92.38)	59 (93.65)	38 (90.48)	0.711
Dysphagia (n, %) ²	50 (47.62)	29 (46.03)	21 (50.00)	0.842
Limb muscle weakness (n, %) ²	55 (52.38)	31 (49.21)	24 (57.14)	0.550
Dyspnea (n, %) ²	15 (14.29)	5 (7.94)	10 (23.81)	0.043 ^a
Serum antibody (nmol/L) ³				
Anti-AChR Ab	9.54 (25.98)	3.11 (17.98)	17.51 (27.45)	0.002 ^b
Anti-MuSK Ab	0 (1.13)	0.31 (2.17)	0 (0)	0.098
Seronegative (n, %) ²	16 (15.24)	11 (17.46)	5 (11.90)	0.582
Immunotherapy at evaluating				
Glucocorticoids (n, %) ²	76 (72.38)	49 (77.78)	27 (64.29)	0.181
Azathioprine (n, %) ²	31 (29.52)	19 (30.16)	12 (28.57)	0.861
Tacrolimus (n, %) ²	8 (7.62)	3 (4.76)	5 (11.90)	0.262

Leflunomide (<i>n</i> , %) ²	22 (20.95)	13 (20.63)	9 (21.43)	0.922
No immunotherapy (<i>n</i> , %) ²	53 (50.48)	32 (50.79)	21 (50.00)	0.936
Neuropsychological scales				
MGC ³	6.00 (6.50)	6.00 (6.00)	7.00 (7.00)	0.103
ADL ³	3.00 (3.00)	3.00 (4.00)	3.00 (2.00)	0.960
QOL-15 ³	14.00 (15.00)	12.00 (13.50)	16.00 (20.00)	0.027 ^a
HAM-A ³	6.00 (7.00)	5.00 (5.50)	8.50 (7.50)	< 0.001 ^c
HAM-D ³	8.00 (7.00)	7.00 (8.00)	10.50 (7.75)	0.018 ^a

¹*n* (%), Fisher's exact test.²*n* (%), Pearson's χ^2 test.³Median (25%Q, 75%Q), Mann-Whitney *U* test.^a*P* < 0.05.^b*P* < 0.01.^c*P* < 0.001.

BMI: Body mass index; ADL: Activities of daily living scale; MGC: Myasthenia Gravis Composite scale; MG-QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale.

Table 2 Correlation between clinical features and age at onset

Clinical features	Correlation	95%CI	<i>t</i>	<i>P</i> value
Disease duration	-0.59	-0.70, -0.446	-7.370	< 0.001 ^c
BMI	0.41	0.233, 0.555	4.520	< 0.001 ^c
Anti-AChR Ab	0.31	0.128, 0.475	3.335	0.001 ^b
QOL-15	0.32	0.133, 0.479	3.383	0.001 ^b
HAM-A	0.41	0.236, 0.557	4.548	< 0.001 ^c
HAM-D	0.26	0.074, 0.432	2.759	0.007 ^b

^a*P* < 0.05.^b*P* < 0.01.^c*P* < 0.001.

BMI: Body mass index; MG-QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale.

for MG-QOL-15 scores at a cut-off value of 14.5 in the anxiety group was 0.816 (*P* = 0.001), and the sensitivity-specificity was 75.86% and 84.62%, respectively (Supplementary Figure 1B). The AUC for MG-QOL-15 scores at a cut-off value of 14.5 in the depression group was 0.983 (*P* < 0.001), and the sensitivity-specificity were 70.59% and 100%, respectively (Supplementary Figure 2B).

DISCUSSION

In the current study, late-onset MG patients had higher total scores on the MG-QOL-15, HAM-A, and HAM-D scales compared with early-onset group MG patients, and there was a positive linear correlation between age at onset and MG-QOL-15 scores, HAM-A scores, and HAM-D scores. These results support the idea that late-onset MG is correlated with more severe impairments to patients' QOL and mental state. MG has previously been demonstrated to affect QOL, as well as mental and physical health[37]. Factors that influence QOL in MG include trouble with eyesight, skeletal muscle weakness, activity limitations, and unhealthy mental state[38,39]. MG-QOL-15 scales have also previously been applied to assess MG-related dysfunction[40]. Several studies reported that MG-QOL-15 scores in MG patients are highly and positively correlated with scores on the HAM-A and HAM-D scales[38,41,42]. These findings supported the notion that low QOL correlates with poor mental health in MG patients.

We also found that female patients with late-onset MG were more susceptible to anxiety and depression. It is important to examine what factors are related to the mental health of patients with late-onset MG and why there are sex-related differences. The prevalence of depression and anxiety is higher among women than men. This difference in mental disorders is the result of a complex interplay

Table 3 Multivariate logistic model of the clinical determinants of anxiety/depression in myasthenia gravis patients

Variables	Model 1		Model 2	
	OR (95%CI)	P value	OR (95%CI)	P value
Anxiety				
Gender	0.96 (0.45-2.07)	0.917	0.65 (0.25-1.68)	0.372
Age at onset	1.04 (1.02-1.07)	0.002 ^b	1.02 (0.99-1.05)	0.305
Disease duration	0.93 (0.88-0.98)	0.070	0.97 (0.90-1.04)	0.414
BMI	1.10 (0.99-1.23)	0.075	1.05 (0.92-1.21)	0.485
Anti-AChR Ab	1.02 (1.00-1.05)	0.092	1.02 (0.99-1.05)	0.274
QOL-15	1.10 (1.05-1.16)	< 0.001 ^c	1.10 (1.04-1.15)	< 0.001 ^c
Depression				
Gender	0.82 (0.36-1.82)	0.636	0.56 (0.19-1.64)	0.293
Age at onset	1.03 (1.00-1.06)	0.022 ^a	1.03 (0.99-1.06)	0.162
Disease duration	0.98 (0.93-1.03)	0.418	1.06 (0.98-1.15)	0.172
BMI	1.05 (0.93-1.17)	0.440	0.97 (0.83-1.13)	0.678
Anti-AChR Ab	1.10 (0.99-1.04)	0.387	1.01 (0.97-1.05)	0.582
QOL-15	1.19 (1.10-1.28)	< 0.001 ^c	1.20 (1.10-1.30)	< 0.001 ^c

^a $P < 0.05$.^b $P < 0.01$.^c $P < 0.001$.

Model 1: Unadjusted; Model 2: Adjusted for possible confounders including gender, age at onset, body mass index, and anti-acetylcholine receptor antibody. BMI: Body mass index; QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; OR = exp (β).

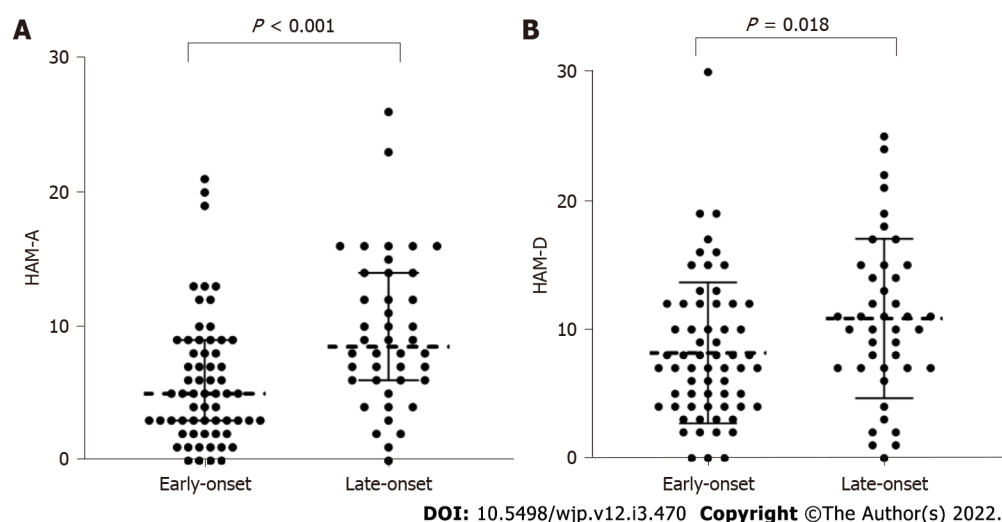


Figure 1 Hamilton anxiety rating and the Hamilton depression rating scores according to age of onset. A: The median (interquartile range) of Hamilton anxiety rating (HAM-A scale scores in early-onset and late-onset groups were 5 (5.5) and 8.5 (7.5), respectively. The HAM-A scale score was significantly higher in the late-onset group than early-onset group ($P < 0.001$); B: The Hamilton depression rating (HAM-D) score levels in early-onset and late-onset groups were 7 (8) and 10.5 (7.75), respectively. The HAM-D scale score was significantly higher in the late-onset group than early-onset group ($P = 0.018$). P value was calculated using Mann-Whitney U test.

between genetic, hormonal and psychosocial factors[43-45]. Some studies have shown that women rather than men carrying the SS genotype of serotonin transporter gene-linked promoter region (5-HTTLPR) more easily develop depressive symptoms under a negative environment[46,47]. Female patients with MG tend to have more severe cases of the disease, and may also be affected by hormonal changes associated with menstruation, pregnancy, and/or postpartum fluctuations in hormone levels [48-50]. Previous studies have reported that the use of glucocorticoids is associated with changes in

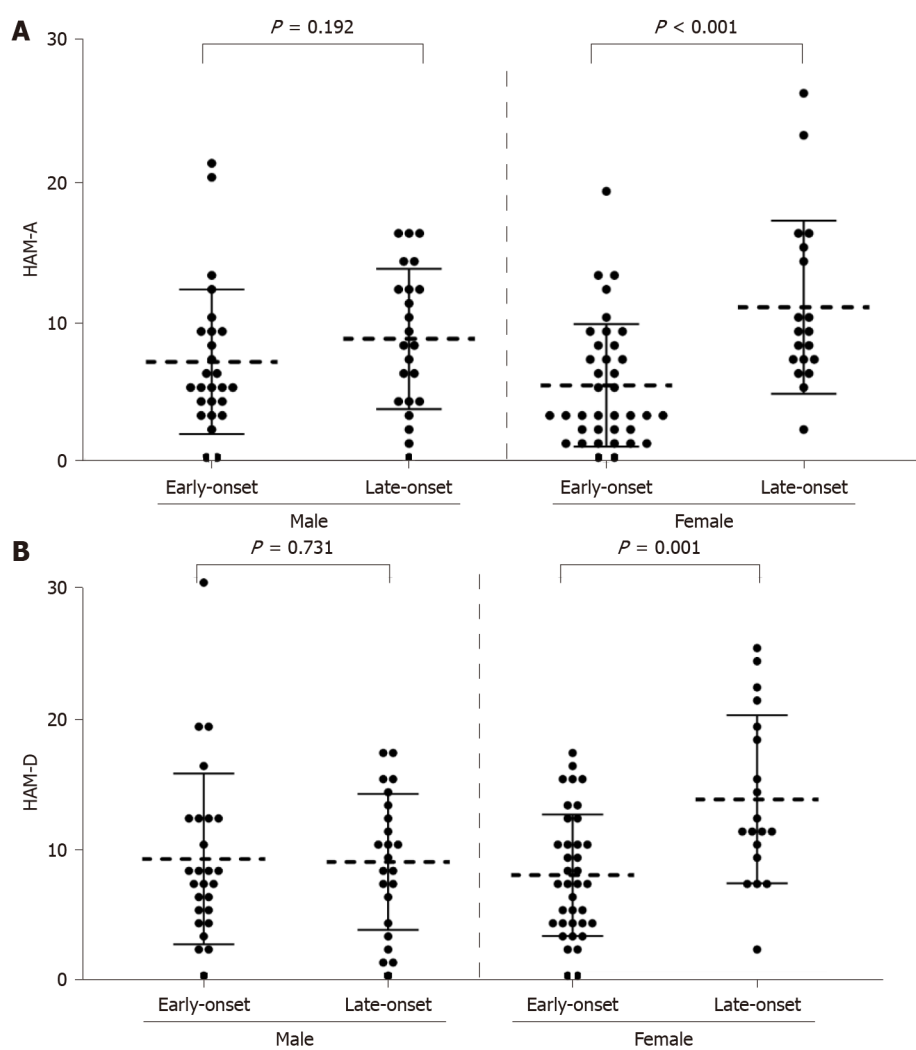


Figure 2 Hamilton anxiety rating and the Hamilton depression rating scores according to age of onset and sex. A: The median (interquartile range) of Hamilton anxiety rating (HAM-A scale levels in late-onset groups were 3 (6), and 9 (8), respectively, and HAM-A scale scores were significantly higher in late-onset group than early-onset group in women ($P < 0.001$); B: The Hamilton depression rating (HAM-D) score levels in early-onset and late-onset groups were 7 (7) and 11 (10), respectively, and HAM-D scale score was significantly higher in late-onset group than early-onset group in women ($P = 0.001$). There were no significant differences in men for both HAM-A and HAM-D scale scores. P value was calculated using Mann-Whitney U test.

physical appearances, leading to conditions such as moon face and/or central obesity, which may have greater negative sociopsychological effects on women with MG than men. Moreover, some patients with late-onset MG do not have positive responses to medication, and some are intolerant to treatment, which can result in refractory conditions[51]. Female patients with late-onset MG may endure the adverse effects of comorbidities longer than their male counterparts, which would contribute to poorer QOL[52]. These factors could explain why female MG patients had higher susceptibility to anxiety and depression than male patients.

Our study showed that MG-QOL-15 scores were independently associated with an increased risk of anxiety and depression when gender, age at onset, BMI, and anti-AChR antibody levels were adjusted for in a multivariate analysis. We found that the ORs (95% CIs) of MG-QOL-15 scores for the anxiety and depression groups were 1.10 (1.04-1.15, $P < 0.001$) and 1.20 (1.10-1.30, $P < 0.001$), respectively, indicating that under the same conditions of gender, age at onset, and other factors, the odds of anxiety state increased by 10% and depression state increased by 20% for each increase in MG-QOL-15 scores, and high MG-QOL-15 scores were indeed a risk factor for anxiety/depression state. Previous studies have demonstrated that lower perceived QOL is highly correlated with mental impairment in MG patients[9, 53,54]. In late-onset groups, the areas under the ROC curves for MG-QOL-15 scores at a cutoff value of 14.5 in the anxiety and depression groups were 0.816 and 0.983, respectively, which suggested that MG-QOL-15 scores had good diagnostic accuracy for the mental disorders, at least among late-onset MG patients. Our data revealed that MG-QOL-15 score cutoff of 14.5 could be a good indicator for poor mental health in need of attention among late-onset MG patients. Further research is needed for fine-tuning this threshold.

Some research has also reported that patients with MG who received thymectomy or proper immunosuppressive therapy had improved physical health and decreased disability symptoms, which indirectly improved mental health[55,56]. However, our study found that the rate of thymectomy and immunosuppressive treatment was comparable between early-onset and late-onset groups, but that late-onset MG patients had significantly higher levels of serum anti-AChR antibodies and were more prone to dyspnea. The proportion of overweight patients in the late-onset group was greater than that in the early-onset group. This pattern could be related to older age, which contributes to reductions in physical activity and possibly susceptibility to the adverse effects of glucocorticoids[57]. Compared to early-onset MG patients, higher anti-AChR antibody titers were reported in late-onset MG patients[57, 58], which may partly be due to immune dysregulation, including age-related decreases in immunocompetence and increases in the production of autoantibodies[59,60]. Bulbar[23] and ocular symptoms [61] have been previously reported to be more common in late-onset MG patients. However, we found no differences in extraocular or limb muscle involvement between the two groups. Genetic factors may influence these results, since a similar study that reported a higher occurrence of ocular symptoms in late-onset patients also reported a higher proportion of women in the late-onset group[62].

There were some limitations to our study. First, limits in our sampling method make it difficult to draw firm conclusions. Second, our study had a prospective design, so further follow-up and particularly studies that include healthy control groups are needed to validate the results. However, our study had some advantages. For example, all included patients were enrolled from the same neuromuscular outpatient clinic. Thus, they received prompt and high-quality clinical scale evaluations that were performed by well-qualified and trained professionals, which ensured the integrity and authenticity of the data.

CONCLUSION

Our research showed that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher MG-QOL-15 scores were an independent risk factor for anxiety and depression in patients with late-onset MG. To our knowledge, this is the first report detailing the relationship between MG-QOL-15 scores and mental health in the subgroup of MG patients with late disease onset. Thus, this association warrants further exploration in future research.

ARTICLE HIGHLIGHTS

Research background

The prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high, and mental state of myasthenia gravis (MG) patients were seldom assessed by mental scales routinely, so little is known about the exact relationship between MG and mental disorders that often accompany it.

Research motivation

Due to the frequent occurrence of comorbidities in older people that might be confused with MG symptoms, awareness of mental disorders in older age groups of MG is needed for earlier intervention and thus a better outcome. In the present, there have been few studies on the mental health of patients with late-onset MG, so we conducted this study to assess the related factors for developing mental disorders in the subgroup of MG patients.

Research objectives

This study aimed to investigate the relationship between clinical features and mental health in patients with late-onset MG, in addition to treating physical symptoms, attention should also be paid to mental disorders in late-onset MG patients.

Research methods

A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021 in our hospital. Clinical data including sociodemographic, neurological and mental information were collected, and scores on clinical scales were procured through face-to-face evaluations with professional neurologists. The relationship between clinical features and mental health in late-onset MG patients was examined using multivariate logistic regression analyses.

Research results

Late-onset MG patients had higher total scores on the MG Quality of Life 15 (MG-QOL-15) quest-

ionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) compared with early-onset group MG patients. Female patients had higher total HAM-D and HAM-A scores than male patients among late-onset MG ($P < 0.05$), and high scores on the MG-QOL-15 questionnaire were independently associated with higher incidences of anxiety and depression. In late-onset groups, the areas under the receiver operating characteristic curves for MG-QOL-15 scores at a cutoff value of 14.5 in the anxiety and depression groups were 0.816 and 0.983, respectively.

Research conclusions

We found that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher MG-QOL-15 scores were an independent risk factor for anxiety and depression in patients with late-onset MG. An MG-QOL-15 score cutoff of 14.5 could be a good indicator for poor mental health in need of attention among late-onset MG patients.

Research perspectives

In the future, we will seek to determine protective factors against developing mental disorders among late-onset MG. Further follow-up and particularly studies that include healthy control groups are needed to validate the results.

FOOTNOTES

Author contributions: Liu WB was the guarantor and contributed to the conception of the study; Yu L and Qiu L participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Ran H, Ma Q, Lu YR revised the article critically for important intellectual content.

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