Heliyon 10 (2024) e28893

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Clinical characteristics of late-onset myasthenia gravis

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ARTICLE INFO

Keywords:
Myasthenia gravis
Late-onset myasthenia gravis
Comorbidities
Medication
Clinical features

ABSTRACT

Objective: Late-onset myasthenia gravis (LOMG) often has comorbidities, and its initial symptoms may be ignored or misdiagnosed as other diseases. There were few large surveys on LOMG. Our study aimed to summarize clinical characteristics of LOMG to improve the rate of correct MG diagnosis.

Methods: A retrospective cohort study included 240 LOMG patients with onset age ≥65 years old who were treated at PLA General Hospital from January 1, 2003 to January 1, 2023.

Results: The male to female ratio was 1:1.2 ($P = 0.699$). MGFA clinical classification: Class I 31.3%, Class IIa 12.9%, Class IIb 51.3%, Class IIIa 0.8%, Class IIIb 0.8%, Class IV 0.4%, Class V2.5%. The onset symptom was ptosis in 78.8% and diplopia was in 18.8%. Swallowing dysfunction in the stage of LOMG was in 41.7%. The incidence of thymoma in LOMG was 14.2%. 85.4% of patients antibodies against the muscle acetylcholine receptor (AChR) are detected. The overall incidence of supramaximal repetitive nerve stimulation (Jolly test) was 57.1%, among which the highest positive rate (50.7%) was in the facial nerve. Jolly test of Class IIb was tested in the highest positive rate and Class I was in the lowest one ($\chi 2 = 7.023$, $P = 0.030$).

Conclusion: There was no significant difference in the incidence of LOMG between males and females. The clinical manifestations were mainly Class I and Class II, and severe MG was rare. The most common onset symptom was ptosis. The incidence of LOMG with thymoma was low. Supramaximal repetitive nerve stimulation (Jolly test) of the facial nerve was the easiest to detect and Jolly test of Class IIb was tested in the highest positive rate and Class I was in the lowest one.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by autoantibodies in the postsynaptic membrane of the neuromuscular junction. MG occurs in any age groups. The high incidence of MG is in two age groups: the first incidence peak is in the 20-30-year-old population, mainly females, and the second incidence peak is in the 60-80-year-old population, mainly males [1]. The latest

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https://doi.org/10.1016/j.heliyon.2024.e28893
Received 11 November 2023; Received in revised form 26 March 2024; Accepted 26 March 2024
Available online 27 March 2024

epidemiological survey showed that the 70-74-year-old population in China was the high-risk population [2]. MG includes early-onset myasthenia gravis (EOMG) and late-onset MG (LOMG), generally defined by a cut-off age of 65 years [3–6]. It was high sensitive to nondepolarizing neuromuscular blocking agent (NMBA) and multiple medications [7–16]. Due to advancing age, ptosis in MG were often mistaken for the loose and sagging skin around the eyelids caused by aging, while diplopia was thought to be caused by macular degeneration and cataracts. In addition, LOMG patients were often accompanied by cerebrovascular disease, Parkinson's disease, or motor neuron disease, all of which might delay the identification and judgment of the early symptoms of MG in time. Therefore, the prevalence of LOMG was likely to be underestimated. There were few large surveys on LOMG. Our study aimed to analyze the large clinical data of LOMG patients to summarize clinical characteristics of LOMG.

2. Methods

2.1. Demographic data

The retrospective cohort study searched the inpatient clinical database of Neurology Department, PLA General Hospital, from January 1, 2003, to January 1, 2023, for ≥65 years old patients diagnosed with MG. LOMG patients were determined according to Myasthenia Gravis Foundation of American (MGFA) clinical classification when the patient was in most serious condition since the onset of MG. LOMG was defined as MG with onset age ≥65 years old [17]. We collected data on demographics, comorbidities, supramaximal repetitive nerve stimulation (Jolly test), MGFA clinical classification, and thymus abnormalities. All LOMG patients

Table 1
Demographics and clinical variables.

Variable	
Number of patients, N	240
Age in years, median, quartile	70(65–95)
Gender, n (%)	108 males (45%)
	132 females (55%)
Onset symptoms, n (%)	
Eyelid ptosis	191(79.6%)
Binocular diplopia	45(18.8%)
Limb weakness	12(5%)
Dysarthria	10(4.2%)
Dysphagia	8(3.3%)
MGFA Typologies, n (%)	
I	75(31.3%)
IIa	31(12.9%)
IIb	123(51.3%)
IIIa	2(0.8%)
IIIb	2(0.8%)
IV	1(0.4%)
V	6(2.5%)
Ab, n (%)	
AChR Ab	205(85.4%)
Titin Ab	18(7.5%)
MuSK Ab	2(0.8%)
RyR Ab	1(0.4%)
AChR Ab + Titin Ab	5(2.1%)
AChR + Titin + MuSK Ab	3(1.3%)
No Ab	6(2.5%)
Thymus abnormalities, n (%)	51(21.3%)
Thymoma	34(14.2%)
Thymus hyperplasia	14(5.8%)
Thymus degeneration insufficiency	2(0.8%)
Thymic cysts	1(0.4%)
Comorbidities	
Hypertension, n (%)	100(41.7%)
Diabetes, n (%)	29(12.1%)
Cataract, n (%)	22(9.2%)
Hyperlipemia, n (%)	14(5.8%)
Tumor, n (%)	4(1.7%)
Cerebral infarction, n (%)	3(1.3%)
supramaximal repetitive nerve stimulation (Jolly test) (N = 209)	
Facial nerve,n(%)	106(50.7%)
Axillary nerve, n(%)	76(36.4%)
Accessory nerve,n(%)	54(25.8%)
Median nerve,n(%)	16(7.7%)
Ulnar nerve,n(%)	26(12.4%)
Peroneal nerve,n(%)	3(1.4%)

performed thymoma screening, blood antibodies tests and MGFA clinical classification, which ranged from class I (ocular muscle weakness only) to class V (state of intubation) and the thymus data of patients were obtained from Imaging scan (contrast enhanced computed tomography) and histopathology.

2.2. Inclusion criteria

The diagnosis of MG needed to meet at least three of the following criteria: (1) Clear MG history. (2) Characteristic skeletal muscle fatigue. (3) Positive neostigmine test. (4) Supramaximal repetitive nerve stimulation (Jolly test). The nerves examined by Jolly test were the facial nerve, ulnar nerve, axillary nerve and accessory nerve.

All individuals and/or their parents provided informed consent to participate in this study and approval was provided by the Ethics Committee of PLA General Hospital (HZKY-PJ-2022-22).

2.3. Statistical analysis

Analysis was performed using SPSS version 20 (IBM, Armonk, NY). The measurement data that conformed to normal distribution were expressed as mean ± standard deviation (X ± S), while discrete variables were expressed in median (quartile). And the counting data was expressed by numbers and percentage. The associations between the gender and the age of onset were analyzed through Mann-Whitney *U* test. The associations between MGFA typologies and gender, facial nerve conduction, thymus abnormality and comorbidities were respectively analyzed using Pearson's chi-squared tests or Fisher exact tests. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic data

From January 1, 2003 to January 1, 2023, 240 LOMG patients (including 108 males and 132 females) were hospitalized in PLA General Hospital. Demographics and clinical variables were in Table 1. There was no statistical difference in onset ages between sexes (Mann-Whitney *U* test was used because of no normal distribution in ages, $U = 6922.00$, $P = 0.699$). In 205 patients (~85.4%) antibodies against the muscle acetylcholine receptor (AChR) are detected, while in 7.5% antibodies against titin are detected. In ~2.5% of MG patients no autoantibodies can be found.Onset symptoms of LOMG.

Ptosis was the most common onset symptom in 78.8% and diplopia was in 18.8%. Bulbar palsy with limb weakness as onset symptom was in 27.9%. Swallowing dysfunction in the stage of LOMG was in 41.7%.

3.2. Comorbidities

Hypertension was the most common comorbidity (41.7%) and cerebral infarction was the lest comorbidity (1.3%). The incidence of thymoma in LOMG was 14.2% (Table 1). By Fisher exact tests, there was no statistically significant difference among different MGFA typologies in comorbidities ($F = 5.424$, $P = 0.488$) (Table 2)

3.3. Jolly test

The overall incidence of supramaximal repetitive nerve stimulation (Jolly test) was 57.1%. Among positive Jolly test, facial nerve was easily to test positive rate (50.7%). There was axillary nerve positive rate 36.4%, accessory nerve positive rate 25.8%, median nerve positive rate 7.7%, ulnar nerve positive rate 12.4% and peroneal nerve positive rate 12.4% (Table 1).

Table 2
Variable of LOMG in MGFA typologies.

Variable		MGFA Typologies							*F*	*P*-Value
		I	IIa	IIb	IIIa	IIIb	IV	V		
Gender	Male	35	14	54	0	1	1	3	3.008	0.907
	Female	40	17	69	2	1	0	3		
Thymus abnormality	Yes	16	4	28	2	1	0	0	9.676	0.099
	No	59	27	95	0	1	1	6		
Comorbidities	Yes	38	14	67	0	0	1	3	5.424	0.488
	No	37	17	56	2	2	0	3		

The associations between MGFA typologies and gender, facial nerve conduction, thymus abnormality and underlying diseases were respectively analyzed using Fisher exact tests. *$P < 0.05$.

3.4. MGFA typologies

MGFA typologies of LOMG were mainly Class I and Class II (Fig. 1). By Fisher exact tests, there was no statistically significant difference among different MGFA typologies in gender ($F = 3.008$, $P = 0.907$) (Table 2).

According to the analysis of Pearson's chi-squared tests, there was a significant difference among Class I, Class IIa, and Class IIb in supramaximal repetitive nerve stimulation (Jolly test) of facial nerve ($\chi 2 = 7.023$, $P = 0.030$) (Table 3), among which Class IIb had the highest positive rate (59.6%) and Class I had the lowest positive rate (39.1%).

4. Discussion

The incidences of males and females in LOMG were similar, and there were no significant different incidences of males and females in different classes of MGFA. MGFA typologies of LOMG were mainly Class I and Class II, especially Class IIb. Supramaximal repetitive nerve stimulation of facial nerve was the highest positive. A study found that MGFA Class I was more common in LOMG compared with EOMG (41.3%) [18]. But in our study, MGFA Class IIb was the most common (51.3%) in LOMG. Ptosis was the most common onset symptom in 78.8% and diplopia was in 18.8%. Bulbar palsy with limb weakness as onset symptom was in 27.9%. Swallowing dysfunction in the stage of LOMG was in 41.7%. The onset symptom of ptosis was often mistaken for the loose and sagging skin around the eyelids caused by aging, while diplopia was thought to be caused by macular degeneration and cataracts.

Due to onset age ≥65 years old of LOMG patients, LOMG often associated with hypertension, hyperlipidemia, diabetes, cataract, cerebrovascular disease and tumors and other factors, among which hypertension is the most common (41.7%). Some LOMG patients were initially diagnosed as ischemic stroke or transient ischemic attack due to imaging examinations. But the mendelian randomization analyses indicated no causal effects of general MG on ischemic stroke of all causes [19]. Swallowing dysfunction in the stage of LOMG was in 41.7%. Therefore, the possibility of MG should also be considered first in elderly patients with sudden isolated swallowing dysfunction. Especially after the use of neuromuscular junction blocking antibiotics or other drugs, MG-like symptoms were triggered in elderly patients, the possibility of MG was higher [14]. This difference in the incidence of thymoma might be attributed to the fluctuation of incidence in different age groups [17]. And no difference in the incidence of thymoma was found among MGFA typologies in our study. A national survey in Asia showed that the incidence of thymoma increased among people aged 50–65, but decreased among people over 65 [20]. In our study, only 14.2% of LOMG with thymoma were present.

There were reports of aggravation of symptoms in many MG patients after taking statin [15] and 11 cases of MG were aggravated after taking statins in our study. Statins might induce or exacerbate MG symptoms, but not through affecting neuromuscular junction transmission. Studies on pharmacological mechanisms [10,21] found that statins could inhibit the activation of T cells, induce the transformation of helper T cells (Th) cells into Th2 cells, or make the immune abnormality mediated by B cells, thus aggravating the autoimmune response of MG patients.

The use of corticosteroids was limited due to the prevalence of comorbidities such as diabetes mellitus, autogenous cataracts, and osteoporosis in the elderly, as well as the possible impact of comorbid medications on the function of neuromuscular junctions in LOMG patients. There were complex drug interactions and pharmacokinetic changes in immunosuppressants. Elderly patients had poor tolerance to the side effects of MG therapeutic drugs, and their treatment were full of risks. Conventional treatments such as thymectomy, corticosteroids, intravenous immunoglobulin, plasmapheresis and non-specific immunosuppressants have significantly reduced mortality, but many patients still suffer from disease symptoms or adverse drug reactions. New targets and therapies (FcRn antagonists and C5 inhibitors) have emerged around different aspects of MG autoantibody pathogenesis. Therefore, it was necessary to carefully formulate the treatment plan during LOMG clinical treatment. However, LOMG patients had relatively mild clinical symptoms, and the prognosis of long-term follow-up was relatively good.

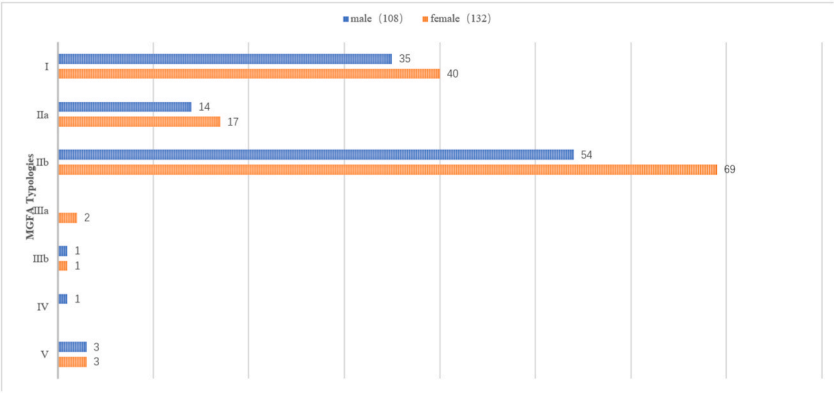

Figure 1. MGFA typologies of LOMG.

Table 3
Jolly test of the facial nerve in Class I and Class II MGFA typologies.

Variable		MGFA Typologies			χ^2	*P*-Value
		I	IIa	IIb		
Jolly test of the facial nerve	Positive	42	12	42	7.023	0.030*
	Negative	27	14	62		

Jolly test of the facial nerve in Class I and Class II MGFA typologies were respectively analyzed using Pearson's chi-squared tests. *$P < 0.05$.

5. Conclusion

In conclusion, our study summarized the clinical characteristics of LOMG patients, which had potential guiding significance for fully understanding LOMG clinical characteristics.

Limitation

The study limitation is the single-center design. For the next step, we will take multi-center study to analysis EOMG and LOMG.

Data availability statement

Data included in article/supplementary material/referenced in article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Chenjing Sun: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zhuangzhuang Ren:** Project administration, Investigation, Formal analysis, Data curation. **Xiuling Miao:** Writing – review & editing, Formal analysis, Data curation. **Yanxu Zheng:** Supervision, Software. **Jun Zhang:** Investigation. **Xiaokun Qi:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation. **Jianguo Liu:** Software, Methodology, Formal analysis. **Feng Qiu:** Writing – review & editing, Software, Methodology, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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