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Unusual presentations of myasthenia gravis and misdiagnosis

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Myasthenia gravis (MG) poses diagnostic challenges due to its diverse clinical presentations. Diagnosing MG remains complex despite advancements, necessitating further understanding of its diverse clinical profiles. We conducted a retrospective analysis of 290 MG cases. Patient demographics, symptomatology, and diagnostic outcomes were reviewed. Patients were categorized into two groups: those displaying classical presentations and those manifesting unusual presentations. The patients with unusual presentations were comprehensively evaluated and the demographic and clinical characteristics of the two groups were compared. In our study of 290 patients with MG, 20 presented with unusual manifestations (6.9%). These included isolated dropped head, bilateral facial weakness, distal limb weakness (e.g., foot and hand drop), weakness of limb-girdle muscles, and isolated ocular findings without ptosis. When patients were categorized into two groups based on their initial symptoms, no significant differences in demographic and clinical features were observed between the classical and unusual groups, except for a higher prevalence of anti-MuSK antibodies and more frequent administration of rituximab in patients with unusual presentations. Recognizing unusual MG presentations is crucial for timely management. Our study underscores the diverse clinical spectrum of MG, emphasizing the need for nuanced diagnostic approaches and prompt intervention.

Keywords Myasthenia gravis, Unusual presentations, Muscle-specific kinase antibody

Diagnosing myasthenia gravis (MG) typically involves assessing the clinical profile, specific autoantibodies, and electrodiagnostic tests (repetitive nerve stimulation and single-fiber electromyography). Fatigable muscle weakness, exacerbated by activity and partly relieved by rest, constitutes the primary clinical feature of MG. Predominantly, initial symptoms manifest in the ocular region, often presenting as double vision and ptosis.

Despite significant advancements in understanding both clinical and pathophysiological aspects of MG, diagnosing MG can still pose challenges due to its often unusual clinical presentations. Unusual clinical features can include isolated weakness in facial muscles, limbs, or the neck, mimicking other neurological or myopathic conditions[1–8]. MG can also manifest with respiratory difficulties or unusual ocular findings, further complicating diagnosis[9,10].

While accumulating knowledge about these clinical characteristics has significantly improved the diagnosis of MG, there is still insufficient data on the prevalence and characteristics of these unusual presentations. The literature consists mostly of case reports or brief descriptions within series focused on MG[1,2,5,7,9–19]. We aimed to systematically define the clinical and laboratory characteristics of MG patients with unusual presentations in a large single-center series of deeply phenotyped patients.

Methods

We retrospectively analyzed patient records from our tertiary neuromuscular center, focusing on individuals diagnosed with myasthenia gravis between 2010 and 2023. The diagnosis of MG relied on a combination of clinical and laboratory criteria. Inclusion criteria included fluctuating muscle weakness along with the following findings:

(1) Positive results on the acetylcholine receptor (AChR) or muscle-specific kinase (MuSK) antibody assay;
(2) More than a 10% decrease in the compound muscle action potential amplitude during repetitive nerve stimulation;

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(3) Finding increased jitter on single-fiber electromyography (SFEMG);
(4) Exclusion of alternative diagnosis.

Definite MG is diagnosed if two of the criteria 1, 2, or 3 and criterion 4 are fulfilled. Patients with onset before 18 years of age were excluded from the study. Additionally, we excluded patients who were lost to follow-up or for whom relevant information was missing.

Demographic and historical data were extracted from institutional electronic records, encompassing details such as age at the initial visit and symptom onset, gender, the specialty of the diagnosing physician, symptoms and signs suggestive of MG, antibody, and electrophysiological testing results.

Patients were categorized into two groups: those displaying classical presentations and those manifesting unusual presentations. Patients displaying classical presentations, such as ocular muscle involvement characterized by eyelid ptosis, fluctuating diplopia, or a combination of both, as well as those manifesting classical bulbar symptoms like dysarthria, dysphagia, and dysphonia, were categorized as exhibiting classical presentations. Conversely, unusual presentations at onset, such as isolated dropped head, bilateral facial weakness, distal limb weakness (e.g., foot and hand drop), and weakness of limb girdle muscles, isolated ocular findings without ptosis were classified as having unusual onset symptoms. We conducted a comprehensive analysis of these patients to delve deeper into factors such as diagnostic delays, the initial healthcare providers consulted, the number of healthcare professionals seen before the diagnosis of myasthenia gravis.

The local ethics committee approved the study (Bursa Uludag University, Uludag Faculty of Medicine, number 2023-27/34). Informed consent was obtained from all subjects and/or their legal guardian(s), and all methods were performed in accordance with the relevant guidelines and regulations.

Statistical Package for the Social Sciences (IBM SPSS Statistics, New York, USA) 28.0 software was used for statistical evaluations, and $p < 0.05$ was accepted as the limit of significance. The chi-square test was performed for categorical variables. For group comparisons, Mann–Whitney U Test and Fisher's exact tests were used where appropriate.

Results

A total of 16 patients were excluded from the initial cohort of 339 patients due to failure to meet inclusion criteria. Additionally, 33 patients were excluded due to the irrelevance of their data. Consequently, the study enrolled a total of 290 patients, consisting of 270 with classical presentations and 20 with unusual onset, as depicted in Fig. 1. Table 1 provides a comprehensive overview of the clinical characteristics of the enrolled patients.

Serum antibody assays revealed anti-AChR antibody seropositivity in 223 patients, anti- MuSK antibodies in 15 patients, and double seronegativity in the remaining 52 patients. Among the 290 patients, 20 presented with unusual presentations (Fig. 2). Specifically, five patients exhibited dropped head, with one reporting concurrent hiccups. No other bulbar symptoms were observed aside from dropped head. Moreover, four patients presented with a dropped hand, while one presented with dropped foot. Notably, five patients demonstrated proximal weakness coupled with respiratory difficulty, devoid of any associated ocular manifestations. Furthermore, two patients initially diagnosed with Bell's palsy were later identified to have facial diplegia. Additionally, two patients presented with pseudo 6th nerve palsy without ptosis, and one patient presented with pseudo internuclear ophthalmoplegia (INO) without ptosis. The details of these 20 patients are presented in Table 2.

MG patients were divided into two cohorts according to the presence or absence of unusual findings, and a comparative analysis of their features is shown in Table 3. There were no significant intergroup differences in sex, age at diagnosis, anti-AChR antibody seropositivity, comorbid disease, presence of thymoma, thymectomy, hospitalization in intensive care unit, and previous treatment. Anti-MuSK antibody seropositivity was statistically more frequently reported in patients with unusual presentations than in those with classical presentations ($p = 0.014$). Our study revealed a higher frequency of rituximab use in patients with unusual presentations of myasthenia gravis compared to those with classical presentations ($p = 0.008$).

Misdiagnosis

Among the 20 patients with unusual presentations, various misdiagnoses were encountered. For instance, patients were initially misdiagnosed with conditions such as diabetic cranial nerve palsy, myalgia, myopathy, radiculopathy, rheumatic disease, entrapment neuropathy, Amyotrophic Lateral Sclerosis, demyelinating disease, depressive disorder, and pulmonary embolism. These misdiagnoses were predominantly made in primary and secondary care hospitals or during consultations with non-neurology specialists, rather than in specialized neuromuscular centers. The limited access to advanced diagnostic expertise and tools in these settings likely contributed to the diagnostic challenges.

Discussion

In this study, we systematically evaluated the clinical and laboratory features of MG patients with unusual presentations in a large single-center series. Our findings highlight the diverse clinical spectrum of MG and emphasize the importance of considering unusual presentations in the differential diagnosis of muscle weakness.

Table 4 presents the typical and unusual presentations of myasthenia gravis, as outlined in the current literature[1,2,5,7,9–19]. Typical manifestations of MG include ptosis, diplopia, and bulbar symptoms such as dysarthria, dysphagia, and dysphonia[20,21]. However, it is important to note that there is no universally agreed-upon consensus for unusual presentations of MG. The classification used in this study is based on expert consensus, clinical observations, and insights from previous case reports and studies, reflecting the variability in MG presentations observed across different clinical settings. Our study contributes to the ongoing discussion by highlighting the diverse presentations of MG, including several unusual manifestations that can be easily misdiagnosed as other conditions.

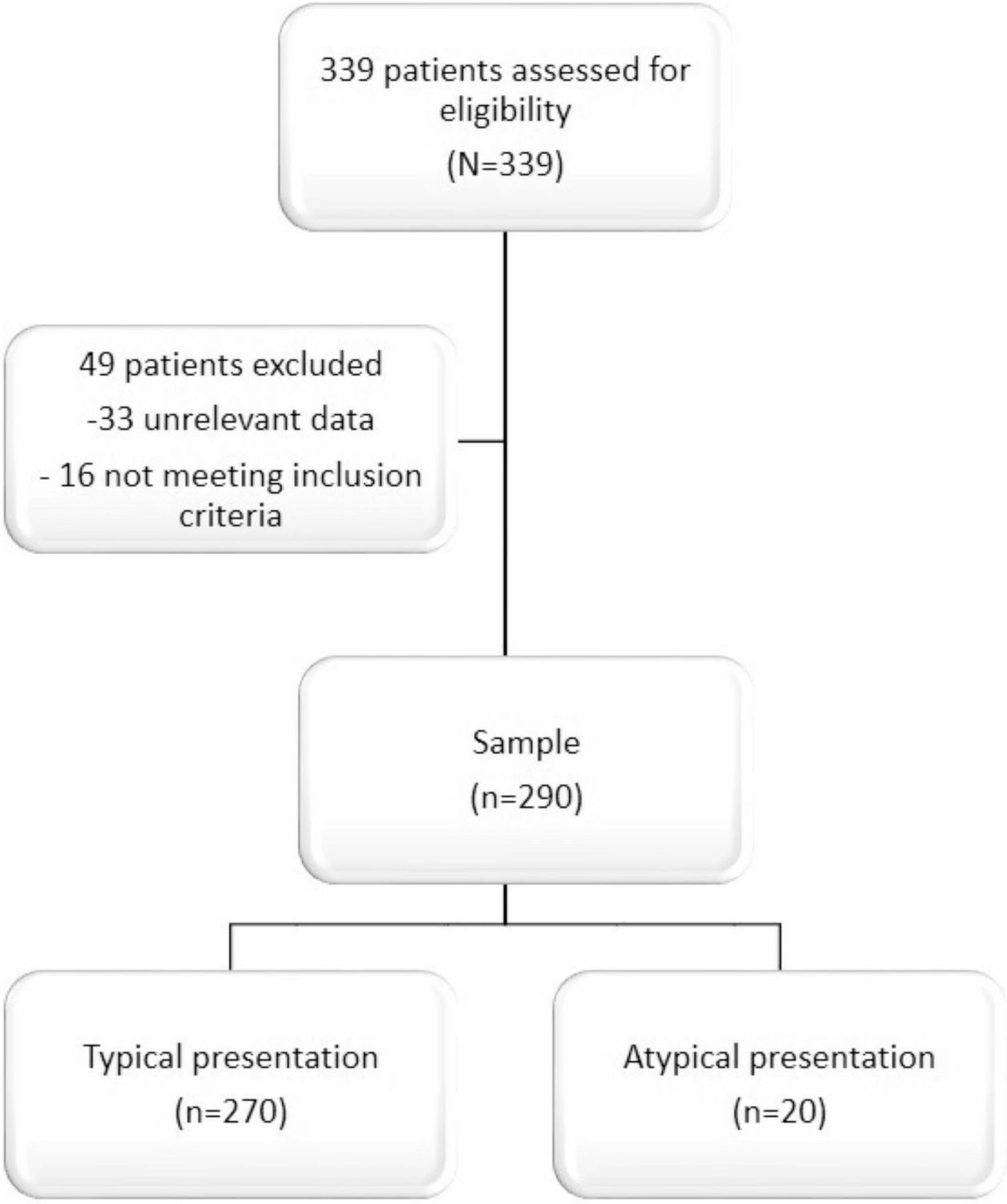

Fig. 1. Flowchart shows MG patients included in the study.

According to our analysis, unusual manifestations of MG account for approximately 6.9% of all MG cases. Our study found no significant differences in various factors between classical and unusual MG cases, including sex, age at diagnosis, anti-AChR antibody seropositivity, comorbidities, thymoma, thymectomy, and intensive care unit admissions. However, the prevalence of anti-MuSK antibody positivity was found to be higher in unusual MG cases, suggesting its potential utility in aiding diagnosis in such presentations. Additionally, rituximab use was more frequent in patients with unusual myasthenia gravis presentations than in typical cases. This could be related to the higher prevalence of anti-MuSK antibody positivity observed in these patients.

	Full cohort ($n = 290$)
Age at onset	49.40 ± 18.11 (18–88)
Sex	
Male	139 (47.9%)
Female	151 (52.1%)
Antibody profile	
Ach	223 (76.9%)
Musc	14 (4.8%)
Double seronegative	53 (18.3%)
Phenotype	
Ocular onset	163 (56.2%)
Generalized onset	127 (43.8%)
Comorbidity	194 (66.9%)

Table 1. Demographic and clinical characteristics of included MG cases.

Previous studies suggest that 90% of MG patients experience ptosis, and within two years, around 50% of those with this ocular symptom progress to generalized MG[11]. It has been observed that ocular MG can present with unusual manifestations such as pseudo internuclear ophthalmoplegia, pseudo-6th nerve palsy, vertical deviation, esotropia, and vergence anomalies[9,10]. In our series, pseudo-sixth nerve palsy was identified in two patients, while one patient presented with pseudo-INO. Although some patients had accompanying eye movement abnormalities, those with ptosis were not considered unusual presentations, as the ptosis helped in the diagnostic process. Pure and isolated ocular phenotypes of anti-MuSK MG are rarely reported[22]. Nevertheless, the identification of Anti-MuSK antibody seropositivity in an MG patient with pseudo-6 nerve palsy in our cohort provides additional support to previous research, suggesting the potential presence of Anti-MuSK seropositivity in cases of ocular MG.

Facial paralysis is another rare finding in MG patients[1,2,12–14]. There are case reports and case series of patients presenting with facial paralysis associated with MG[1,2,12–14]. While facial paralysis may be bilateral in some MG cases and unilateral in others, our study identified two patients presenting with isolated facial diplegia, without exhibiting symptoms of ptosis and initially followed up for a period due to bilateral Bell's palsy.

Isolated presentations of drop head, dysphagia, dysphonia, and dyspnea in MG warrant thorough investigation due to their rarity and potential diagnostic challenges[2–4,15,23,24]. Drop head can result from various etiologies, encompassing both neuromuscular and non-neuromuscular conditions[5]. MG contributes to approximately 12.3% of cases of drop head cases[6]. A study demonstrated that head drop occurred in approximately 10% of MG cases over the course of the disease, with a significantly higher prevalence observed in elderly individuals compared to younger cohorts[16]. The majority of these cases tested positive for AChR antibodies, although there was one case of positivity for MuSK antibodies. It is worth mentioning that isolated head drop as an initial symptom in MG is uncommon, with only three cases identified among 508 MG patients in a retrospective study[2]. Isolated presentations of dysphagia, dysphonia, and dyspnea in MG are rarely documented in literature. They typically emerge as isolated case reports, highlighting their unique clinical significance and the need for further investigation[3,4,15]. In our study, we observed five patients presenting with drop head. Among these five patients, three tested positive for MuSK antibodies, while two tested positive for AChR antibodies. None of the patients in our cohort exhibited isolated dysphagia, dysarthria, or isolated dyspnea. Notably, one patient demonstrated hiccups alongside head drop. The pathophysiology of hiccups remains unclear in MG. Hiccups involve complex neurological mechanisms, including both central and peripheral components. In MG, impaired neuromuscular transmission in the diaphragm may potentially trigger hiccups. Furthermore, in cases with bulbar involvement, dysfunction in respiratory rhythm regulation and swallowing may contribute to the onset of hiccups[25].

In our study, a subset of MG patients (1.72%) presented with limb-girdle weakness without involvement of the ocular muscles. A previous study found that 3.8% of MG patients had persistent limb-girdle weakness without oculobulbar involvement[19]. This manifestation often complicates diagnosis as MG may not be considered initially due to the absence of oculobulbar weakness. Furthermore, the predominant proximal muscle weakness, adult onset, and myogenic changes observed in needle electromyography contribute to misdiagnoses, with some patients being incorrectly labeled as having polymyositis despite normal creatine kinase (CK) levels. Genetic myopathies, such as muscular dystrophies, can also complicate the diagnostic process, as they may present with similar symptoms and, in some cases, co-occur with MG, further complicating the diagnosis[26]. The diagnosis of MG was confirmed through antibody tests and neurophysiological studies. Neurophysiological techniques, including repetitive nerve stimulation and single-fiber electromyography, provide definitive evidence of neuromuscular transmission deficits, especially in seronegative cases[27]. In cases where proximal weakness is prominent in the lower extremities, Lambert–Eaton myasthenic syndrome (LEMS) becomes a notable differential diagnosis[23]. However, ruling out LEMS is facilitated by the absence of a compound muscle action potential (CMAP) amplitude increase exceeding 100% during high-frequency repetitive nerve stimulation, in addition to antibody tests[28].

Another rare presentation of MG is distal MG[8]. Consistent with previous studies, our study revealed that the upper extremity extensor muscles are the most frequently affected muscles in distal MG. Distal muscle weakness may occur not only throughout the course of the disease but also as an initial presentation of MG[2,29]. While the

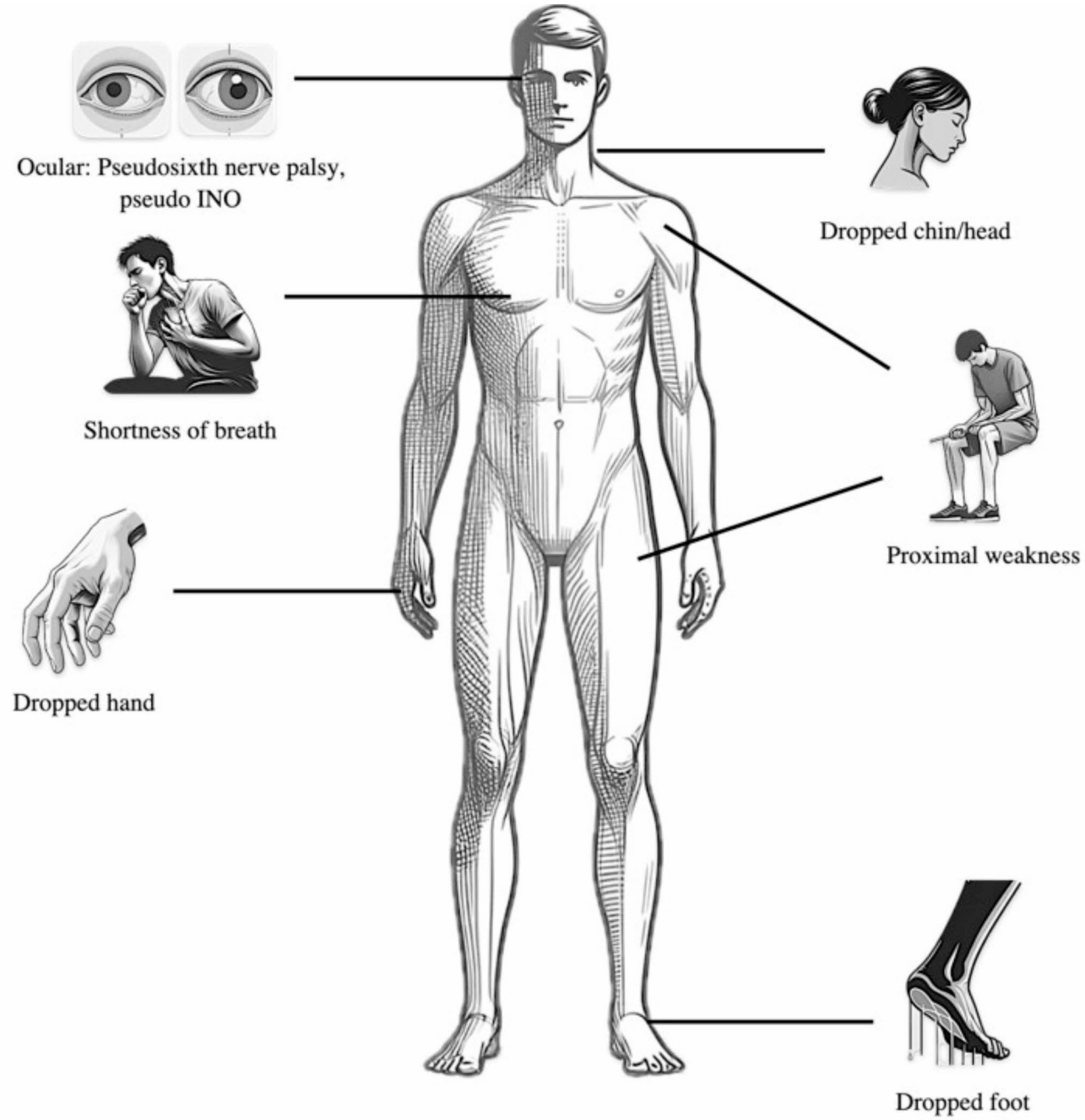

Fig. 2. Unusual presentations of MG.

exact mechanisms for distal muscle involvement remain unclear, it may be hypothesized that certain muscle groups in some patients exhibit differential susceptibility to autoimmune attack. Additionally, antibody subtype and epitope heterogeneity may contribute to the increased susceptibility of extremity muscles in distal MG. This hypothesis requires further investigation in future studies. Another consideration is the potential association of myositis with MG[30]. However, the normal CK levels observed in our patients do not support this association.

Fluctuations were noted in both unusual and classical presentations of MG patients, and this variability was evident when examined within each group. Some individuals in both categories displayed less prominent fluctuations. However, a thorough analysis of fluctuations was not undertaken.

Additionally, compared to healthy individuals, comorbidities are more prevalent in MG patients, which can complicate the diagnostic process[31]. In typical MG presentations, comorbidities may mask or mimic the clinical symptoms of MG, thereby increasing diagnostic difficulty. Moreover, in atypical presentations, where symptoms deviate from the classical pattern, the presence of comorbidities exacerbates the challenges in establishing an accurate diagnosis.

N of patients	Age of onset	Sex	Antibody results	Atypical presentation	Months from onset to diagnosis	First clinic visited (Clinics visited until the diagnosis)	Mis-diagnosis
P1	21	F	MuSK	Pseudo 6 th nerve palsy	36 m	Dep of Ophthalmology (5)	No misdiagnosis
P2	29	F	AChR	Pseudo-6th nerve palsy	1 m	Dep. of Ophthalmology (2)	No misdiagnosis
P3	60	E	AChR	Right internuclear ophtalmopgia	12 m	Dep of Ophthalmology (2)	Diabetic cranial nerve palsy
P4	43	F	MuSK	Dropped-head	24 m	Dep. of Physical therapy (4)	Myalgia, radiculopathy
P5	72	M	AChR	Dropped-head	2 m	Dep. of Neurology (3)	No misdiagnosis
P6	69	F	AChR	Dropped-head	2 m	Dep. of Neurology (2)	No misdiagnosis
P7	53	M	MuSK	Dropped-head, hiccup	2 m	Dep. of Gastroenterology (4)	Normal
P8	26	F	MuSK	Dropped-head	6 m	Dep. of Internal medicine (6)	Rheumatic disease
P9	61	F	AChR	Dropped hand	2 m	Dep. of Physical therapy (8)	Radiculopathy, entrapment neuropathy
P10	61	F	AChR	Dropped hand	24 m	Dep. of Neurology (2)	Amyotrophic lateral sclerosis
P11	36	M	AChR	Dropped hand	5 m	Dep. of Physical therapy (3)	Fibromyalgia
P12	19	M	AChR	Dropped hand finger	1 m	Dep. of Neurology (2)	Demyelinating disease
P13	34	F	AChR	Dropped foot	6 m	Dep. of Neurology (3)	Simulation
P14	31	F	AChR	Postpartum proximal weakness	18 m	Dep. of Psychiatry (6)	Depressive disorder, polymyositis
P15	21	F	AChR	Breathing difficulty, proximal weakness	12 m	Dep. of Internal medicine (5)	Pneumonia
P16	66	F	AChR	Breathing difficulty, proximal weakness	3 m	Dep. of Pulmonary Medicine (7)	Pulmonary embolism, amyotrophic lateral sclerosis
P17	52	F	Seronegative	Proximal weakness	12 m	Dep. of Neurology (2)	Myopathy
P18	57	F	Seronegative	Proximal weakness	1 m	Dep. of Neurology (1)	No misdiagnosis
P19	66	M	AChR	Facial Diplegia	1/3 m	Dep. of Neurology (2)	Bell's palsy
P20	20	F	AChR	Facial Diplegia	2 m	Dep. of Neurology (2)	Bell's palsy

Table 2. The clinical characteristics of MG patients with unusual presentations. *AChR* anti-acetylcholine receptor antibody, *F* female, *M* male, *m* month, *MuSK* anti muscle-specific kinase antibodies

	Unusual presentation (*N* = 20)	Classical presentation (*N* = 270)	*p*
Age at diagnosis, years (mean, SD)	44.60 ± 18.44	49.76 ± 18.07	0.259
Late-onset MG (> 50), n (%)	9 (45%)	151 (55.9%)	0.475
Sex (M/F), n (%)	6/14 (30%/70%)	133/137 (49.3%/50.7%)	0.152
Ocular Onset, n (%)	3 (15%)	160 (59.3%)	< **0.001**
Anti-AChR-Ab seropositivity	14 (70%)	209 (77.4%)	0.303
Anti- Musc-Ab seropositivity	4 (20%)	11 (4.1%)	**0.014**
Double seronegativity	2 (10%)	51 (18.9%)	0.255
Hospitalization in ICU, n (%)	4 (20%)	35 (13%)	0.274
Myasthenic exacerbations, n(%)	12 (60%)	105 (38.9%)	0.105
Comorbid disease, n(%)	12 (60%)	182 (67.4%)	0.665
Presence of thymoma, n (%)	1 (5%)	33 (12.2%)	0.292
Tymectomy	6(30%)	77 (28.5%)	1.00
Previous treatments, n (%)			
Pyridostigmine	20 (100%)	269(99.6%)	0.931
Steroids	16 (80%)	204 (75.6%)	0.446
Azathioprine	13(65%)	163(60.4%)	0.438
Mycofenolat mofetyl	4(20%)	32(11.9%)	0.226
Rituximab	7 (35%)	31 (11.5%)	0.008
Methotexate	4 (20%)	39(14.4%)	0.342
Eculizumab	0 (0%)	3 (1.1%)	0.806

Table 3. Comparison of the patients with classical and unusual presentations of myasthenia gravis. Significant values are in (bold). [a]Sufficient clinical information was not available for all patients.

Presentation type	Symptoms	Notes
Typical presentations		
Ocular	Ptosis, diplopia[20,21]	Often the first symptoms to appear; key indicators for diagnosis
Bulbar symptoms	Muscle weakness that may escalate to a myasthenic crisis requiring respiratory support[20,21]	Critical to recognize early to prevent life-threatening complications
		Differential diagnosis
Atypical presentations		
Limb-Girdle Weakness	Symmetrical, Proximal arm and leg weakness[7,19,28]	Can mimic other neuromuscular disorders, such as muscular dystrophy, polymyositis, Lambert–Eaton myasthenic syndrome, ALS leading to potential misdiagnosis
Isolated Symptoms	Dropped head[2–6,15,23,24]	May be misdiagnosed as cervical spondylosis, inflammatory myopathy, or motor neuron disease
	Dropped hand[2,8,29]	Misdiagnoses include cervical radiculopathy, peripheral nerve entrapment, or myopathy
	Dropped foot[2]	May be confused with peripheral neuropathy, lumbar radiculopathy, or motor neuron disease
	Isolated Lateral Gaze Palsy (Paralysis of outward gaze in one or both eyes)[10]	May be misdiagnosed as abducens nerve palsy or a structural lesion in the pons
	Internuclear Ophthalmoplegia[9]	Can be confused with multiple sclerosis, brainstem stroke, or Wernicke encephalopathy
	Bilateral facial weakness[1,2,12–14]	May mimic Guillain-Barré syndrome, Bell's palsy, or sarcoidosis
Respiratory and Bulbar Symptoms[2–4]		May be misdiagnosed as angioedema, chronic obstructive pulmonary disease and motor neuron disease

Table 4. Typical and atypical manifestations of MG.

Our study has several limitations. First, it was a retrospective study, which may introduce bias into the findings. Additionally, the data was collected from a single tertiary center, which may restrict the generalizability of the results. Diagnostic delay was not systematically assessed in all patients. Despite these limitations, the study provides valuable information about the unusual clinical features and outcomes of patients with MG. Future studies with larger sample sizes are needed to confirm these findings.

In conclusion, our study provides valuable insights into the clinical features of MG patients with unusual presentations. We emphasize the importance of considering unusual presentations in the differential diagnosis of muscle weakness and the need for early diagnosis and treatment to improve patient outcomes.

Data availability

The datasets analysed during the current study are not publicly available due general data protection policy, but are available from the corresponding author on reasonable request.

Received: 5 December 2024; Accepted: 20 February 2025
Published online: 04 March 2025

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Acknowledgements
none.

Author contributions
EOA-SEL—GG Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing–review and editing. YD-FD Formal analysis, Data curation. Necdet Karli: Writing–review and editing.

Funding
No external funding was received for this research.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Additional information
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