Heliyon 10 (2024) e30015

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Case report

Myasthenia gravis with tongue muscle atrophy: A case series

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ARTICLE INFO

Keywords:
Myasthenia gravis
Tongue muscular atrophy
Myogenic damage
AChR-MG
MuSK-MG

ABSTRACT

Here, we presented 6 patients who were admitted to our institution and diagnosed as myasthenia gravis (MG) with tongue muscle atrophy. All these 6 patients developed symptoms of bulbar muscle weakness in acetylcholine receptor antibodies positive MG (AChR-MG) (3/6), muscle-specific receptor tyrosine kinase antibodies positive MG (MuSK-MG) (1/6), and sero-negative MG (2/6). Most of patients had "triple-furrowed" tongue except for patient 2 with irregular atrophy of tongue muscle. Tongue muscle atrophy occurs in patients with MuSK-MG, AChR-MG, and sero-negative MG. Atrophied tongue muscles of five patients with MG were reversible after immunotherapy.

1. Introduction

Myasthenia gravis (MG) is an acquired autoimmune disease mediated by autoantibodies, where the targets are the proteins of postsynaptic membrane, There are different types of autoantibodies that mainly include acetylcholine receptor (AChR) antibodies, muscle-specific receptor tyrosine kinase (MuSK) antibodies and low-density lipoprotein receptor-related protein 4 (LRP4) antibodies [1]. The disease is characterized by fluctuating skeletal muscle weakness and fatigue. Muscle atrophy is uncommon in MG. However, compared with anti-AChR antibodies positive MG (AChR-MG) patients, muscle atrophy is more common in anti-MuSK antibodies positive MG (MuSK-MG) patients and mainly involves facial muscles and tongue muscle [2]. Here, we present the clinical characteristics of 6 cases of MG with tongue muscle atrophy.

1.1. Cases presentation

Of 6 patients included in this case series (Table 1), 5 (83 %) are female and 5 (83 %) are early-onset MG. Although the initial symptoms were different, all patients developed bulbar muscle weakness in the course of disease, such as dysarthria, chewing and deglutition difficulties, characterized by diurnal variation, exacerbation with fatigue and improvement with rest. Serum antibodies were tested, 3 patients (50 %) had positive anti-AChR antibodies, 1 patient (17 %) had positive anti-MuSK antibodies, and 2 patients

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https://doi.org/10.1016/j.heliyon.2024.e30015
Received 28 September 2023; Received in revised form 7 April 2024; Accepted 18 April 2024
Available online 19 April 2024

(33 %) had negative antibody. Low-frequency (3 Hz) repetitive nerve stimulation (RNS) tests in the bilateral accessory nerve showed a decrement of more than 15 % in the amplitude of the compound muscle action potential (CMAP) in 5 MG patients, while high-frequency (30–50 Hz) RNS tests showed no increment of CMAP in all patients, which met the diagnostic criteria for MG. All patients had a positive response to neostigmine, 2 patients (33 %) had antinuclear antibodies, and 2 patients (33 %) had anti-thyroid antibodies. There were no abnormalities in thymus and the levels of creatine kinase. Myositis and other autoimmune diseases were ruled out in all patients. Cranial MRI had been conducted in all patients and no brainstem lesions were detected.

Quantitative electromyography (EMG) recordings were obtained from tongue muscles of patient 1 and 3. Muscle activity at rest and during slight and maximal voluntary muscle contraction was analyzed. The motor unit activity potentials (MUAPs) duration, amplitude, and polyphasicity were evaluated (Table 2). No spontaneous potentials and no neurogenic damages were recorded. Short duration, low amplitude, polyphasic MUAPs of slight voluntary muscle contraction were recorded in tongue muscles of these two patients. The results indicated myogenic damage in tongue muscles of patient 1 and 3.

The morphology of tongue muscle and ADL scores of 5 patients (except patient 4) were shown in Fig. 1 at the time of initial discovery of tongue muscle atrophy and follow-up. The time interval from the first symptom to the discovery of tongue muscle atrophy ranged from 2 months to 4 years in all patients. Most of patients had a triple furrowed morphology due to central atrophy and lateral thinning of the tongue except for patient 2 with irregular atrophy of tongue muscle. Most patients were not treated or underwent short-term, minimal glucocorticoids (GC) therapy prior to the discovery of tongue atrophy. Azathioprine (AZA) and one round of Rituximab (RTX) therapy were applied in patient 5 and 6 respectively. Subsequently all patients received long-term, regular treatment with cholinesterase inhibitors, GC and other immunosuppressants. All patients were graded according to the state grading criteria after intervention formulated by MG Foundation of America (MGFA), 1 patient (17 %) achieved drug response (PR), 4 patients (66 %) had significant improvement of symptoms, and 1 patient (17 %) died of myasthenia gravis crisis. The symptoms and atrophied tongue muscles of five patients were significantly improved and the ADL scores were significantly decreased during follow-up.

2. Discussion

MG combined with muscle atrophy has been previously reported, and the involved muscles include the tongue, facial, extraocular, sternocleidomastoid, occlusal, and posterior cervical muscles [3–7]. Muscle atrophy can be found in AChR-MG and MuSK-MG, of which tongue muscle atrophy is mostly common in MuSK-MG [8]. In the present case series, the possibility of neurogenic damage was ruled out by needle EMG. It has been shown that MG can be coupled with myositis [9], however, the clinical characteristics and normal creatine kinase exclude myositis. Moreover, congenital myasthenic syndrome (CMS) was excluded from the two sero-negative patients because of their middle-aged onset of disease, predominantly cranial and facial muscle weakness, and response to immunotherapy, which was inconsistent with the presentation of CMS. Therefore, in our patients, tongue muscle atrophy can be found in AChR-MG, MuSK-MG and sero-negative MG patients. All of them had a “triple-furrowed” tongue except for patient 2 with irregular tongue atrophy. These patients had different onset symptoms, but all of them showed signs of bulbar muscle with comparatively severe clinical symptoms as the disease evolved (MGFA IIa-V, patient 2 developed myasthenia gravis crisis).

MG with muscle atrophy is a rare phenomenon and is currently thought to be linked to the following factors: (1) long-term disease

Table 1
Clinical characteristics of MG patients with tongue muscle atrophy.

Patient no.	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender	F	F	M	F	F	F
Age at onset (years)	43	50	50	34	61	49
Initial symptoms	Weight loss	Dysarthria, dysphagia	Dysarthria	Ptosis, diplopia	Lower limbs weakness, ptosis	Coughing on drinking water
Other symptoms	Dysarthria, dysphagia, limbs weakness	Dysmasesia, limbs weakness, dyspnea	Dysphagia, blurred vision, chewing weakness	Dysphagia, dysarthria, chewing weakness, upper limbs weakness, dyspnea	Lower limbs numbness and muscle atrophy	Diplopia, ptosis, limbs weakness, dysphagia
Antibody type	antibody-negative	antibody-negative	AChR-ab+	AChR-ab+	AChR-ab+	MuSK-ab+
Neostigmine test	positive	positive	positive	positive	positive	positive
RNS	positive	positive	positive	positive	negative	positive
Thymus gland	Normal	Normal	Normal	Normal	Normal	Normal
ANA Titer	Negative	Negative	Negative	1:100	1:100	Negative
Thyroid autoantibodies (IU/ml)	Negative	Negative	Negative	TPOAb 94 TGAb 3928	TPOAb 101	Negative
Creatine kinase	Normal	Normal	Normal	Normal	Normal	Normal
Other autoimmune diseases	NF	NF	NF	NF	NF	NF
MGFA classification	IIIa	V	IIa	IIb	IIIa	IIIa
Myasthenia crisis	No	Yes	No	No	No	No

Footnote: F = female; M = male; SN = seronegative; AChR-ab = acetylcholine receptor antibody; MuSK-ab = muscle-specific receptor tyrosine kinase antibody; RNS = repetitive never stimulation; ANA = antinuclear antibody; TPOAb = thyroid peroxidase antibody; TGAb = thyroglobulin antibody; NF = not found; MGFA = Myasthenia Gravis Foundation of America.

Table 2
Needle EMG findings of tongue muscles.

Patient no.	Patient 1	Patient 3
spontaneous potential	normal	normal
MUAPs	short duration low amplitude polyphasic	short duration polyphasic

Footnote: EMG = electromyography; MUAPs = motor unit activity potentials.

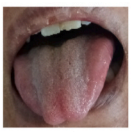
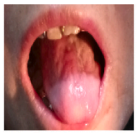
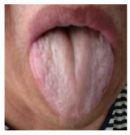
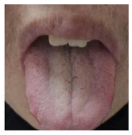
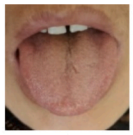
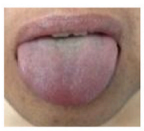
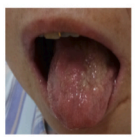
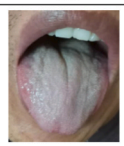
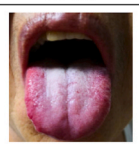
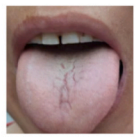
Patient no.		Patient 1	Patient 2	Patient 3	Patient 5	Patient 6
Initial discovery of tongue muscle atrophy	Morphology of the tongue muscle					
	ADL scores	12	NA	6	6	7
	Time interval（months）	12	5	3	48	30
	GC	2 weeks (80 to 40 mg)	0	0	0	6 months (20 mg)
	Immunosuppressant	No	No	No	AZA	RTX (1 cycle)
Follow-up	Morphology of the tongue muscle					
	ADL scores	2	NA	3	1	0
	Time interval (months)	36	5.5	54	54	36
	Therapy	AChEI GC AZA	AChEI AZA/CTX IVIG	AChEI GC IVIG	GC AZA	GC RTX (2 cycle)
	Prognosis	Improved	Dead	Improved	Improved	PR

Fig. 1. Tongue muscle atrophy at different periods Morphology of tongue muscle, ADL scores, treatment, and prognosis were recorded in five MG patients at different periods. Time interval: The time from initial symptoms to the discovery of tongue muscle atrophy. NA: not available. AchEI: acetylcholinesterase inhibitors; GC: glucocorticoids; AZA: azathioprine; CTX: cyclophosphamide; IVIG: intravenous immunoglobulin; RTX: rituximab; PR: pharmacologic remission.

duration of MG: myogenic damage secondary to dysfunction of neuromuscular junction transmission [10]; (2) myopathy induced by long-term medium to high dose of GC application: GC can inhibit muscle protein synthesis through two pathways: suppressing insulin-like Growth Factor (IGF)-I and promoting myostatin, which results in muscle atrophy [11]; (3) MuSK-MG: In MuSK-MG patients, the Atrogin-1 gene is overexpressed and involved in muscle atrophy by inhibiting muscle cell proliferation through signaling pathways [12]. In addition, MuSK antibodies can upregulate the expression of transverse muscle ring finger protein-1 (MuRF-1), a protein associated with muscle atrophy [13]. In this study, patient 2, patient 3, and patient 5 showed tongue muscle atrophy before immunotherapy and patient 1 showed tongue muscle atrophy after short-term GC treatment, which suggested these tongue atrophy were not associated with GC therapy. It was reported that muscle biopsies in MG patients combined with muscle atrophy showed significantly atrophy of type II fiber [14]. Due to the limitations of the invasiveness of this test, tongue biopsy was not performed in our patients. Among these 6 patients, except for one MuSK-MG, tongue muscle atrophy was considered to be associated with a possible secondary myogenic damage arising from impaired neuromuscular junction transmission. MuSK-MG combined with tongue muscle atrophy has been reported to be reversible even if it lasts for several years [15]. Atrophied tongue muscles were significantly improved in four of our patients, with a mean recovery time of 20.38 ± 22.75 months.

In conclusion, MG in combination with tongue muscle atrophy occurs relatively uncommon. The “triple-furrowed” tongue is not only observed in MuSK-MG, but also in AChR-MG and sero-negative MG patients. Most of atrophied tongue muscles were reversible after immunotherapy, accompanied with improvement of clinical symptoms. Notably, MG accompanied by tongue muscle atrophy may herald bulbar syndrome. The mechanisms of MG associated with tongue muscle atrophy need further to be explored.

Ethics and consent

All patients provided informed consent for the publication of their anonymised case details and images.

Data availability statement

Data associated with this study has not been deposited into a publicly available repository and will be made available from the corresponding author on reasonable request.

Funding

This work was supported by grants from Academic promotion programme of Shandong First Medical University (2019QL013), Cultivation Fund for the First Affiliated Hospital of Shandong First Medical University (QYPY2020NSFC0610).

CRediT authorship contribution statement

Xue-Lu Zhao: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Yue-Liang Zheng:** Formal analysis. **Chun-Lin Yang:** Formal analysis. **Jun-Yan Wang:** Formal analysis. **Ying Liu:** Formal analysis, Data curation. **Tong Du:** Formal analysis. **Ze-Yu Zhao:** Formal analysis. **Rui-Sheng Duan:** Formal analysis. **Xiao-Li Li:** Writing – review & editing, Writing – original draft, Formal analysis, 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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