Am J Otolaryngol 40 (2019) 292–296

Contents lists available at ScienceDirect

Am J Otolaryngol

journal homepage: www.elsevier.com/locate/amjoto

Clinical features of laryngeal myasthenia gravis: A case series

XiangLi Yang[a], Lin Niu[a], ChunWei Yang[a,*], Lin Wang[a], JiXiang Liu[a], GuoYing He[b]

[a] Department of Otolaryngology Head and Neck Surgery, Tianjin Union Medical Center, Tianjin 300121, China
[b] Department of Neurology, Tianjin Union Medical Center, Tianjin 300121, China

ARTICLE INFO

Keywords:
Myasthenia gravis
Laryngeal
Dysarthria
Dysphagia
Diagnosis

ABSTRACT

Background: Myasthenia gravis (MG) is an autoimmune disease. Dysarthria, dysphagia, and difficulty swallowing as exclusive initial and primary complaints in MG (laryngeal MG) are rare and seldom reported.
Methods: Here we review and analyze the largest series of laryngeal MG patients.
Results: A total of 30 patients with laryngeal MG as primary manifestation were found in 20 case reports/series. Dysarthria was the most frequent primary symptom (14/30), followed by dysphagia (11/30), slurred speech (4/30) and dysphonia (1/30). Sixty-three percent visited the otolaryngology department first. Only 23.33% of patients were diagnosed with MG at the first clinic visit. Forty-five percent laryngeal MG patients were acetylcholine receptor (AChR) antibody positive, 52.9% showed decremental response in the repetitive nerve stimulation (RNS) test, and 92.6% were positive in the neostigmine/edrophonium test. Fluctuating weakness was examined in 16 of 30 patients and observed in 14/16 patients.
Conclusion: Laryngeal MG is a rare and possibly under-diagnosed condition. The patients can present with dysarthria, dysphagia, or difficulty swallowing. Fluctuation in severity of disease by neostigmine/edrophonium test is a typical feature for MG patients. AChR antibody and RNS tests should be included to evaluate the pathologic changes in the neuromuscular junction.

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease in which autoantibodies bind to acetylcholine receptors (AChR) or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction [1]. A wide range of clinical presentations allows classification of MG into subtypes based on distribution of the involved muscle [2]. Walander first described dysphagia and dysarthria in MG patients in 1959 [3]. However, dysarthria, dysphagia, and difficulty swallowing as exclusive initial and primary complaints in MG (laryngeal MG) are rare and seldom reported [4].

Here we report the largest series, to our knowledge, of laryngeal MG patients, and we review and analyze the published reports. Our main purposes are to determine the clinical manifestations of MG, recommend further examination by the otolaryngologist, and discuss aids in diagnosis.

2. Methods

2.1. Search strategy and study screening

A systematic literature search was conducted in February 28, 2018 on PubMed (from January 1966), Embase database (from 1947), the China National Knowledge Infrastructure Database (CNKI, from 1994), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP, from 1989), and Wanfang Database (from 1998). Key search terms used were myasthenia, primary, initial, first, prominent, incipient, dysphonia, dysarthria, dysphagia, swallow, speech, hoarseness, voice, vocal, and laryngeal. All citations and selected articles were read in full and rated on quality by two independent reviewers (X Yang and C Yang).

All case reports and case series about laryngeal myasthenia gravis were included. Patients with the following features were excluded: 1) without sufficient or consistent data, 2) duplicate publications.

2.2. Data extraction

The search flow is presented in Fig. 1. A data extraction sheet was

* Corresponding author at: Department of Otolaryngology Head and Neck Surgery, Tianjin Union Medical Center, No.190 Jieyuan Road, Hongqiao District, Tianjin 300121, China.
E-mail address: yangchunwei1979@163.com (C. Yang).

https://doi.org/10.1016/j.amjoto.2018.11.002
Received 9 October 2018

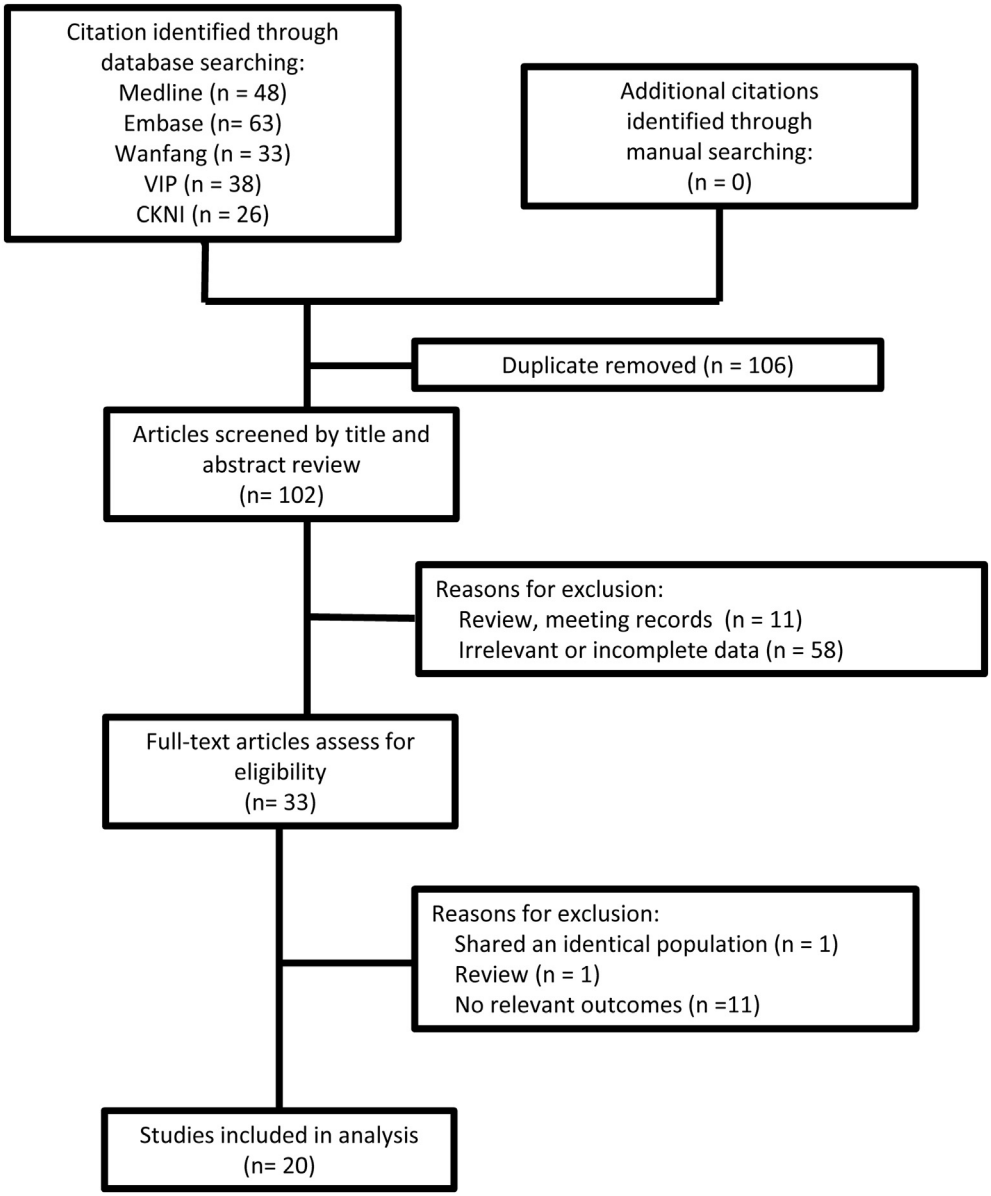

Fig. 1. Flowchart of search strategy and study selection.

used to record study and patient demographic variables, primary symptom, secondary symptom(s), fluctuation, first visited department, duration before definite diagnosis, whether examined with a fibrolaryngoscope, repetitive nerve stimulation (RNS) test, single fiber electromyography (SFEMG), chest computerized tomography (CT) or magnetic resonance imaging (MRI), brain CT or MRI, anticholinesterase test, thymus pathology, acetyl choline receptor (AChR) antibody test, muscle-specific tyrosine kinase (MuSK) test, treatment, and prognosis. Data were extracted and verified by two investigators (L Niu and G He).

2.3. Statistical analysis

Statistical analysis was performed with SPSS Statistics 13 (SPSS Corporation, Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA). A two-sided comparison with $P < 0.05$ was considered statistically significant. Differences between groups were analyzed by the independent sample *t*-test or the Mann-Whitney *U* test (for nonparametric comparisons) for continuous variables and by the chi-squared test or Fisher exact test for categorical variables.

3. Results

3.1. Clinical characteristics of included studies

A total of 30 patients with MG with laryngeal symptoms as the primary manifestation were found in 20 case reports/series published between 1999 and 2017 [4–23], including 14 women and 16 men. General information from published reports of laryngeal myasthenia gravis are shown in Table 1. The age ranged from 4 years to 84 years, mean 44.40 ± 4.34 years. Patients were stratified by gender, age, first symptom, second symptom, AChR antibody, MuSK antibody, thymus test, and first department visited.

Distribution of primary symptoms and first department visited are shown in Fig. 2. Dysarthria was the most frequent primary symptom (14/30, 46.7%), followed by dysphagia (11/30, 36.7%), slurred speech (4/30, 13.3%) and dysphonia (1/30, 3.3%). Nineteen patients (63.3%) visited the otolaryngology department first, 6 patients (20%) the department of neurology, 2 patients (6.67%) the emergency department, and the other three patients visited the department of internal medicine (3.33%), oral department (3.33%) and respiratory department (3.33%),

Table 1
General information of published reports of laryngeal myasthenia gravis.

No. of patients	Publication year	Language	Age of onset	Gender	Primary symptom	Subsequent symptoms	3rd symptom	Fluctuation	First visit department	Duration before diagnosis (months)	Ref.
1	2006	Chinese	68	M	Dysarthria	Dysphagia	Limb weakness	Yes	ENT	2	5
2	2004	Chinese	47	F	Dysarthria	Dysphagia	Limb weakness	Yes	ENT	4	6
3	2013	Chinese	73	M	Dysphagia	Ptosis	Limb weakness	Yes	ENT	3	7
4	2013	Chinese	71	F	Dysarthria	Weakness	NA	Yes	ENT	24	7
5	2016	Chinese	9	F	Slurred speech	Cough	Dysphagia	Yes	Respiratory	13	8
6	2016	Chinese	52	F	Dysarthria	Dysphagia	NA	Yes	Neurology	1	9
7	2009	Chinese	37	M	Dysarthria	Cough	Chest distress	Yes	ENT	1	10
8	2002	Chinese	32	M	Dysarthria	Ptosis	NA	Yes	ENT	120	11
9	1999	Chinese	35	M	Dysphagia	NA	NA	NA	ENT	0.5	12
10	2004	Chinese	15	F	Dysarthria	Dysphagia	NA	No	ENT	9	13
11	2002	English	16	F	Dysarthria	Dysphagia	Facial weakness	Yes	Neurology	3	14
12	2002	English	56	M	Dysphagia	Dysphonia	NA	NA	ENT	2	14
13	2002	English	53	F	Dysphagia	Nasal regurgitation	Ocular weakness	NA	ENT	12	14
14	2004	English	77	M	Dysphagia	NA	NA	NA	Neurology	1	15
15	2006	English	77	M	Slurred speech	Dysphonia	Dysphagia	Yes	Neurology	2	16
16	2005	English	5	M	Slurred speech	Swallowing difficulties	Eyelid weakness	NA	Emergency Department	1	17
17	2005	English	4	M	Slurred speech	Facial weakness	Eyelid weakness	Yes	Emergency Department	1	17
18	2007	English	50	M	Dysarthria	na	NA	NA	ENT	NA	4
19	2007	English	65	M	Dysarthria	Dysphagia	NA	NA	ENT	NA	4
20	2007	English	28	F	Dysarthria	Dysphagia	Diplopia	NA	ENT	NA	4
21	2007	English	25	M	Dysarthria	Dysphagia	NA	NA	ENT	NA	4
22	2007	English	24	F	Dysarthria	Diplopia	Ptosis	NA	ENT	NA	4
23	2007	English	25	F	Dysarthria	Dysphagia	Ptosis	NA	ENT	NA	4
24	2007	English	31	F	Dysarthria	Diplopia	Ptosis	NA	ENT	NA	4
25	2008	English	66	M	Dysphagia	Loss of chewing power	Slurred speech	Yes	Oral Department	3	18
26	2013	English	84	M	Dysarthria	Vocal fatigue	NA	NA	ENT	2	19
27	2015	English	62	F	Dysphagia	Dysarthria	Dyspnea	No	Neurology	6	20
28	2015	English	58	F	Dysphonia	No	No	Yes	ENT	312	21
29	2016	English	22	M	Dysarthria	Facial weakness	Diplopia	No	Neurology	0.5	22
30	2017	English	65	F	Dysphagia	Diplopia	Limb weakness	Yes	Internal Medicine	4	23

ENT: ears, nose, and throat; NA: not available.

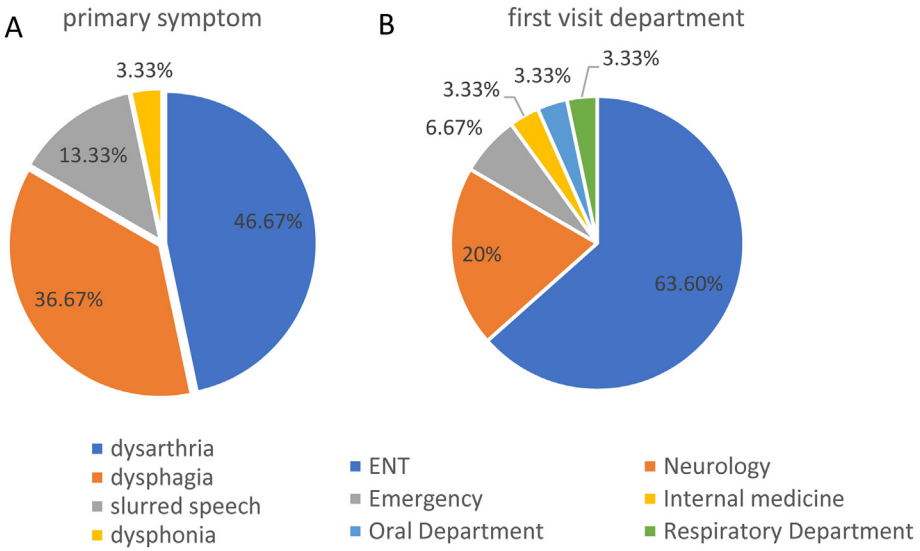

Fig. 2. Distribution of primary symptom (A) and first department visited (B) in laryngeal myasthenia gravis.

Table 2
Clinical features of patients with laryngeal MG.

Feature	N (F/M)	*P*	OR (95%CI)
Total number	30 (14/16)		
Age		0.73	1.33(0.32–5.64)
15–50 years	16 (8/8)		
> 50 years	14 (6/8)		
AChR antibody		1.00	1.5(0.26–8.82)
Positive MG	9 (5/4)		
Negative MG	11 (5/6)		
RNS test		0.35	3.33(0.45–24.45)
Normal	8 (5/3)		
Decremental response	9 (3/6)		
Thymus CT scan		0.58	2.57(0.19–34.50)
Thymoma	3 (2/1)		
Non-thymoma	16 (7/9)		
Neostigmine/edrophonium test		1.00	0.92(0.05–16.47)
Negative	2 (1/1)		
Positive	25 (13/12)		

N: number of patients; MG: myasthenia gravis; AChR: acetylcholine receptor; RNS: Repetitive Nerve Stimulation.

respectively (Fig. 2). The disease duration prior to definite diagnosis of MG ranged from 0.5 to 312 months (median 3 months, interquartile range from 1 to 9 months).

The main clinical features of patients with laryngeal MG are shown in Table 2. Forty-five percent (9/20) of laryngeal MG patients were AChR antibody positive, 52.9% (9/17) showed decremental response in the RNS test, 15.8% (3/19) showed thymoma by thymus CT scanning, and 92.6% (25/27) were positive in the neostigmine/edrophonium test. There was no difference in age, AChR antibody, RNS, thymus CT scan, or neostigmine/edrophonium test results between female and male laryngeal MG patients (Table 2). Fluctuating weakness was assessed in 16 of 30 patients (53.3%) and determined to be present in 14/16 (87.5%) patients. The presence of the MuSK antibody was measured in ten laryngeal MG patients, with 20% (2/10) positive [20,22]. MRI or CT scanning of brain was performed in ten patients, for exclusion of brain lesions. Fibrolaryngoscopic examination was performed on 23 patients, and 13 patients (56.5%) were found to have a deficit in vocal fold mobility.

3.2. Treatment and prognosis

Seven of 30 (23.3%) patients were diagnosed with MG at the first clinic visit. The other patients were diagnosed with chronic pharyngitis, psychoneurosis, ischemic cerebral disease or amyotrophic lateral sclerosis.

Ninety-one percent (21/23) of laryngeal MG patients were given glucocorticoids or other immunosuppressants, 94.5% (21/22) were given a cholinesterase inhibitor, and 70% (7/10) received thymectomy. Eight percent (2/25) had an unsatisfactory prognosis and were regarded as having refractory MG (Fig. 3) [5,8].

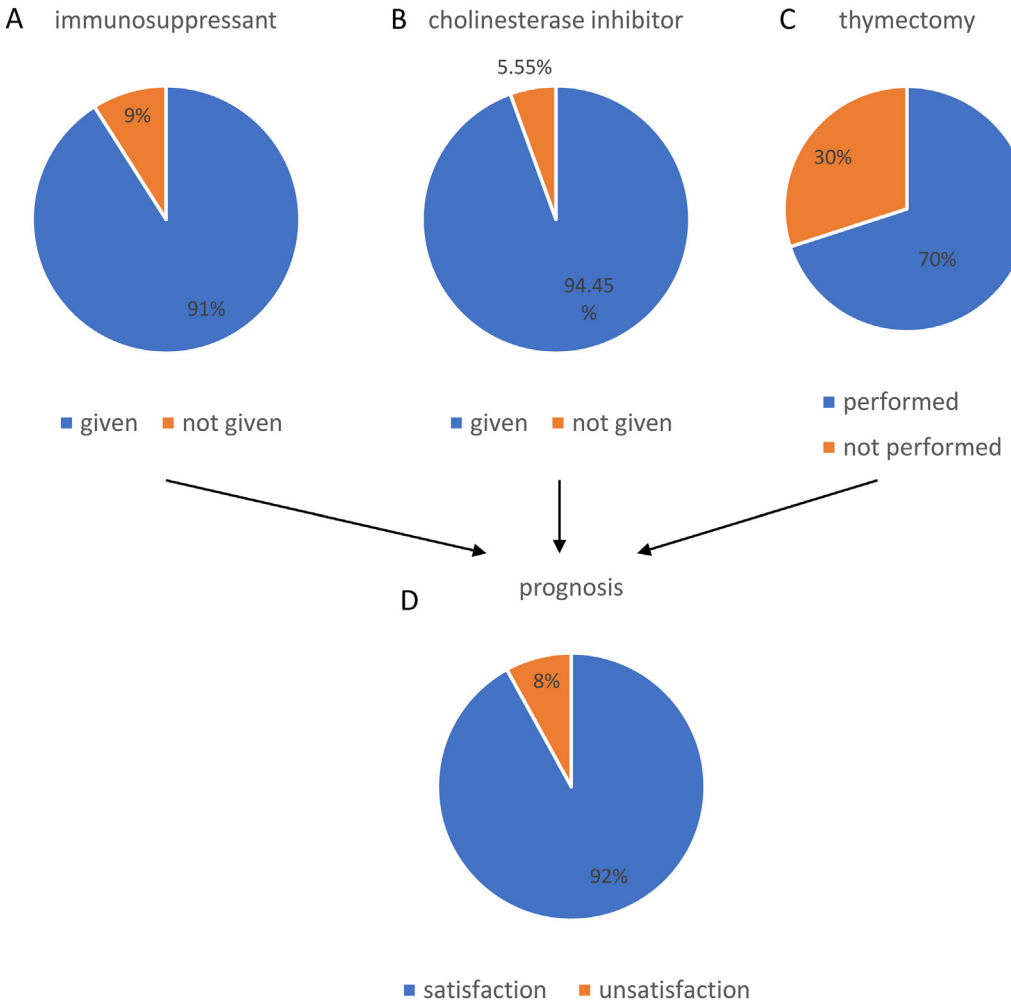

Fig. 3. Treatment and prognosis of laryngeal myasthenia gravis. (A) immunosuppressant usage; (B) cholinesterase inhibitor usage; (C) thymectomy performance; (D) prognosis.

4. Discussion

Clinical presentation of MG has been well known and described for years, but only a few case reports or series address laryngeal MG specifically. In this study, we found that dysarthria and dysphagia were the most frequent primary symptoms for laryngeal MG. Most laryngeal MG patients went to the otolaryngology department. Immunosuppressive treatments were needed for most laryngeal patients.

Only 23% of patients were diagnosed correctly during the first clinic visit. Although ocular weakness occurs in approximately 85% of patients with MG [24], a prototypical disease of the neuromuscular junction [2], bulbar weakness, presenting with dysarthria, dysphagia, or swallowing difficulties is the initial symptom in up to 15% of patients [2]. Laryngeal weakness as the only primary symptom is a great challenge for doctors, and misdiagnosis may be a problem, even though most patients described here received fibrolaryngoscopic examination for diagnosis and more than half had a deficit in vocal fold mobility.

Fluctuation in severity of disease in the involved muscle is a typical symptom of MG patients [25,26], and fluctuating muscular weakness that increases with effort is a characteristic manifestation of MG. Only half the patients described here were assessed for fluctuating weakness, with 87.5% being positive. Thus, fluctuating weakness should be assessed for patients with laryngeal weakness. Neostigmine/edrophonium testing was positive for most laryngeal MG patients, suggesting that it is should be standard for the diagnosis. About half of the laryngeal MG patients were AChR antibody positive and showed a decremental response in the RNS test, so these also could lead to earlier diagnosis of laryngeal MG.

Two laryngeal MG patients who were MuSK-antibody positive were reported recently [20,22]. MG with MuSK antibodies account for 6% of all MG cases [26]. The MG patients with MuSK antibodies, sometimes with muscle atrophy, have more severe weakness and have marked symptoms from bulbar and facial muscles [23,27–29]. Furuta et al. reported that MG with MuSK antibody was initially diagnosed as amyotrophic lateral sclerosis [20]. More studies are needed for the relationship of laryngeal weakness and MuSK antibody in MG.

All subgroups of MG responded to an acetylcholine inhibitor. Ninety-two percent were positive in the neostigmine/edrophonium test in the study. And most patients with laryngeal MG needed immunosuppressive therapy to attain full physical function and high quality of life. Two patients were reported to have unchanged or increased weakness after using adequate doses of corticosteroids for an adequate duration. The factors that determine response to corticosteroids need be investigated in the future [28].

5. Conclusions

Laryngeal MG is a rare and possibly under-diagnosed condition, particularly when patients first visit a department other than neurology, as was the case in our group where only 23.33% of laryngeal MG patients had a correct initial diagnosis. The patients can present with dysarthria, dysphagia or difficulty swallowing. Fluctuation in severity of involved muscle disease and in the neostigmine/edrophonium test results are typical features of laryngeal MG patients. AChR antibody and RNS testing should be included to evaluate the pathologic changes in the neuromuscular junction. MuSK antibody testing is needed for patients with negative AChR antibody.

Ethics statement

Not available.

Author contributions

XY and CY designed the study, collected the literature, analyzed and interpreted the data and drafted the manuscript. LN, LW, JL and GH collected and interpreted the data. All authors read and approved the final revision.

Competing interests

None.

Funding

None.

References

[1] Gilhus NE. Myasthenia gravis. N Engl J Med 2016;375:2570–81.
[2] Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol 2009;8:475–90.
[3] Walander A. Dysphagia and dysarthria in myasthenia gravis. Acta Otolaryngol 1959;50:361–4.
[4] Liu WB, Xia Q, Men LN, et al. Dysphonia as a primary manifestation in myasthenia gravis (MG): a retrospective review of 7cases among 1520 MG patients. J Neurol Sci 2007;260:16–22.
[5] Yin P, Ruan X, Jiang Z, Sima G. Hoarseness as first symptom of late-onset myasthenia gravis: a case report. Chin Arch Otolaryngol Head Neck Surg 2006;13:628.
[6] Chen J, Tian Y, Zhang X. Hoarseness as first symptom of myasthenia gravis, thymoma and coronary disease: a case report. J Clin Otorhinolaryngol (China) 2004;18:742.
[7] Liu Y, Ji Y. Laryngeal symptom as first symptom of myasthenia gravis: 2 case reports. Hebei Medicine. 19. 2013. p. 638–9.
[8] Du Z, Zhang Y, Peng B, et al. Dysarthria as the first symptom of myasthenia gravis patients and treated with Praat software: a case report. Clin J Pediatr 2016;54:466–7.
[9] Wen Y. Recurrent dysarthria as the first symptom of myasthenia gravis: a case report. Women's Health Research. 11. 2016. p. 162.
[10] Zhou H. Dysarthria as the primary symptom of myasthenia gravis: a case report. Sichuan Med J 2009;30:1835–6.
[11] Xie H. Hoarseness as the primary symptom of myasthenia gravis: a case report. Clin J Otorhinolaryngol 2002;37:102.
[12] Zheng T, Zheng E. Swallowing difficulty as the first symptom of myasthenia gravis: a case report. J Clin Otorhinolaryngol (China) 1999;13:396.
[13] Yan W, Li H. Laryngeal paralysis as the first symptom of myasthenia gravis: a case report. JMEP 2004;11:154–5.
[14] Salazar Cabrera C, de Saa Alvarez Md Mdel R, Aparicio Pérez MS, et al. Myasthenia gravis: the otolaryngologist's perspective. Am J Otolaryngol 2002;23:169–72.
[15] McCann P, Pramanik A. Dysphagia and unexpected myasthenia gravis associated with primary biliary cirrhosis, ulcerative colitis and vitiligo. J Am Geriatr Soc 2004;52:1407–8.
[16] Montero-Odasso M. Dysphonia as first symptom of late-onset myasthenia gravis. J Gen Intern Med 2006;21:C4–6.
[17] Felice KJ, DiMario FJ, Conway SR. Postinfectious myasthenia gravis: report of two children. J Child Neurol 2005;20:441–4.
[18] Cook RJ, McParland H, Escudier M. An unusual primary presentation of myasthenia gravis. Br J Oral Maxillofac Surg 2008;46:494–6.
[19] Nemr NK, Simões-Zenari M, Ferreira TS, et al. Dysphonia as the primary complaint in a case of myasthenia gravis: diagnosis and speechtherapy. Codas. 25. 2013. p. 297–300.
[20] Furuta N, Ishizawa K, Shibata M, et al. Anti-MuSK antibody-positive myasthenia gravis mimicking amyotrophic lateral sclerosis. Intern Med 2015;54:2497–501.
[21] Renard D, Hedayat A, Gagnard C. Isolated laryngeal myasthenia gravis for 26 years. Neuromuscul Disord 2015;25:153–4.
[22] Bouwyn JP, Magnier P, Bédat-Millet AL, et al. Anti-MuSK myasthenia gravis with prolonged remission. Neuromuscul Disord 2016;26:453–4.
[23] Khan MS, Tiwari A, Khan Z, et al. Pyridostigmine induced prolonged asystole in a patient with myasthenia gravis successfully treated with hyoscyamine. Case Rep Cardiol 2017;6956298. https://doi.org/10.1155/2017/6956298.
[24] Grob D, Brunner N, Namba T, et al. Lifetime course of myasthenia gravis. Muscle Nerve 2008;37:141–9.
[25] Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 2015;14:1023–36.
[26] Morren J, Li Y. Myasthenia gravis with muscle-specific tyrosine kinase (MuSK) antibodies- a narrative review. Muscle Nerve 2018. https://doi.org/10.1002/mus.26107.
[27] Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology 2016;87:419–25.
[28] Xie Y, Meng Y, Li HF, et al. GR gene polymorphism is associated with inter-subject variability in response to glucocorticoidsin patients with myasthenia gravis. Eur J Neurol 2016;23:1372–9.
[29] Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. Ther Adv Neurol Disord 2018;11:1756285617749134https://doi.org/10.1177/1756285617749134.