Bulbar-Predominant Presentation of Late-Onset Myasthenia Gravis

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BACKGROUND

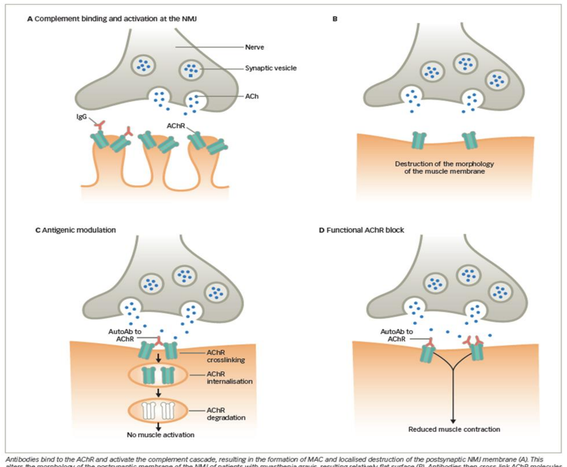
56 y/o Caucasian American male presents at the outpatient clinic to establish primary care.

Chief Complaint: Dysphagia, “muffled voice” for 4 months

INTRODUCTION

- Myasthenia gravis (MG) is an uncommon autoimmune disorder affecting approximately 0.02% (150 - 200 cases per million) of the American population with a similar prevalence globally.[1]
- MG is characterized by the production of antibodies directed against post-synaptic receptors of the neuromuscular junction (NMJ). Muscular nicotinic acetylcholine receptors (AchR) are the most common target.
- Investigation of ‘seronegative’ patients has led to the identification of additional antibodies, muscle-specific kinase (MuSK) and low-density lipoprotein receptor-related protein 4 (LRP-4), which occur in a small subset of MG patients.[2,3,4]
- The generation of the aforementioned antibodies leads to their binding at post-synaptic sites and subsequent inhibition of muscular depolarization.[5]
- Classic presentation: muscular fatigability which worsens with repetition and improves with rest. Most commonly presents with ptosis, double-vision, extremity weakness (often in the hands with diminished grip strength) and reduced dexterity of digits.

Figure 1: Pathogenic mechanism of anti-acetylcholine antibodies in myasthenia gravis



Antibodies bind to the AChR and activate the complement cascade, resulting in the formation of MAC and localised destruction of the postsynaptic NMJ membrane (A). This alters the morphology of the postsynaptic membrane of the NMJ of patients with myasthenia gravis, resulting relatively flat surface (B). Antibodies then cross-link AChR molecules on the NMJ postsynaptic membrane. These cross-linked AChR molecules are internalised and degraded, a process known as antigenic modulation, reducing the number of AChR molecules on the postsynaptic membrane (C). Finally, antibodies bind the ACh-binding sites of the AChR, causing functional block of the AChR by interfering with binding of ACh released at the NMJ (D). This results in failure of neuromuscular transmission and therefore reduced muscle contraction.
AChR = acetylcholine receptor; IgG = immunoglobulin G; MAC = membrane attack complex; NMJ = neuromuscular junction. Figure adapted from Conti-Fine et al.[5]

CASE PRESENTATION

HISTORY OF PRESENT ILLNESS:
- Moved to new area 4 months prior. Previously working at a tire manufacturing plant.
- URI symptoms: fever/chills, fatigue, malaise, rhinosinusitis, cervical LAD
- Influenza/SARS-COV-2 negative
- Antibiotics + Corticosteroids → Symptom resolution
- New symptoms over next month: progressive dysphagia, globus sensation, vocal changes
- Several ‘urgent-care’ visits → Abx + Steroids → transient improvement

PMHx: Childhood asthma, Migraine, Tobacco abuse
FHx: Lung Ca (mother), Diabetes Mellitus
SHx: non-smoker, 30 pack-years dip, occasional EtOH, no recreational drug use, occupational exposures

ED visit: complete dysphagia
- CXR: negative for acute intrathoracic abnormalities
- CT Neck w/ contrast: mild chronic bilateral maxillary and ethmoid paranasal sinus disease w/o evidence of mass, swelling or cerebellar ischemia

Figure 1: Modified Barium Swallow (MBS) revealing dysphagia secondary to oropharyngeal muscular dysfunction evidenced by residual after initial swallow.

LABWORK:
- CBC, CMP, TSH wnl
- Viral panel: negative except Coxsackie A virus IgG
- Inflammatory & Autoimmune markers: negative
- AChR Binding Ab: positive
- AChR Blocking Ab: positive

TREATMENT:
-Symptomatic: Acetylcholinesterase inhibition (Pyridostigmine 30 mg TID)
-Chronic immunomodulatory: glucocorticoids

ALTERNATIVE THERAPIES:
-Rapid immunomodulatory: therapeutic plasma exchange, IVIG
-Surgery: thymectomy

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

DISCUSSION

Myasthenia gravis was confirmed on the basis of an elevated acetylcholine receptor antibody. However, this presentation was atypical as only 15% of MG patients present with bulbar symptoms: dysarthria, dysphagia, or fatigable chewing. Bulbar-predominant presentation is especially uncommon in the ‘late onset’ subtype.[6] Although muscular fatigability is the hallmark of any kind of myasthenia [7], it can be absent or less pronounced in the bulbar forms. Isolated bulbar presentation is rare in MG, and may be confused with diseases of the oropharynx and other neurological conditions. [8-11]

The patient discussed was over 50 years of age and lacked evidence of thymoma on imaging, consistent with Late Onset Myasthenia Gravis (LOMG). The main immunologic difference between early- and late-onset MG is the presence of anti-muscle titin antibodies, which are found in approximately 50% of patients with LOMG. Early-onset MG patients are more often DR3 positive.[12]

This case demonstrates the diagnostic challenge posed by LOMG and the importance of its consideration in patients with bulbar symptoms. Initially this patient was misdiagnosed with velopharyngeal insufficiency based on the predominant symptoms of dysphagia and lack of classic ocular findings. This presumption led to a futile work up for suspected adult acquired VPI including the investigation of infectious/inflammatory etiologies, delaying management of the underlying condition

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FIGURE 1: Jacob S. Myasthenia Gravis – A Review of Current Therapeutic Options. European Neurological Review. 2018;13(2):86-92. doi: https://doi.org/10.17925/ENR.2018.13.2.86

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