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# Bulbar-Predominant Myasthenia Gravis Associated With Muscle-Specific Tyrosine Kinase Antibodies: A Diagnostic Challenge

Shirley Gandhi [1], Maleeha Abedi [2], Brianna Woodbeck [1], Sneh Parekh [1], Win Aung [1]

1. Internal Medicine, University of Florida College of Medicine – Jacksonville, Jacksonville, USA 2. Neurology, University of Florida College of Medicine – Jacksonville, Jacksonville, USA

**Corresponding author:** Shirley Gandhi, shirleygandhi12@gmail.com

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## Abstract

Muscle-specific tyrosine kinase (MuSK) myasthenia gravis (MG) is an uncommon subtype of MG characterized by prominent bulbar and facial weakness with the potential for rapid progression and respiratory compromise. Patients are typically negative for acetylcholine receptor (AChR) antibodies, which may contribute to delayed recognition and diagnosis. We present a 20-year-old postpartum woman who developed a sore throat followed by progressive dysphagia shortly after an uncomplicated vaginal delivery. Persistent and worsening bulbar symptoms prompted further neuromuscular evaluation. AChR antibodies were negative, whereas MuSK antibodies were markedly elevated at 1934 U/mL, supporting the diagnosis of MuSK-positive MG with predominant bulbar involvement. This case highlights the importance of considering MuSK-MG in patients with unexplained progressive bulbar symptoms despite negative AChR antibody testing. Early recognition of this clinical phenotype and appropriate serologic testing are essential to facilitate timely diagnosis and treatment.

**Categories:** Family/General Practice, Neurology, Internal Medicine
**Keywords:** bulbar symptoms, gravis biotype, hypernasal speech, myasthenia, pregnant females

## Introduction

Muscle-specific tyrosine kinase (MuSK) myasthenia gravis (MG) is an uncommon and often severe subtype of MG first identified in 2001 [1,2]. MuSK plays a critical role in neuromuscular transmission by facilitating acetylcholine receptor clustering through agrin and low-density lipoprotein receptor-related protein 4 (LRP4) signaling. Disruption of this pathway impairs neuromuscular transmission and muscle contraction [3,4]. Unlike acetylcholine receptor (AChR) antibody-positive MG, MuSK-MG frequently presents with rapidly progressive facial, oropharyngeal, and masticatory muscle weakness. However, isolated bulbar involvement without ptosis or limb weakness may complicate diagnosis, particularly in the postpartum setting. Given the risk of respiratory compromise, prompt respiratory assessment and close monitoring are essential [1-4].

Diagnosis relies on recognition of characteristic clinical findings and targeted serologic testing. Patients are frequently negative for AChR antibodies, whereas anti-MuSK antibodies provide highly specific diagnostic evidence. Additionally, patients may demonstrate limited responsiveness or intolerance to acetylcholinesterase inhibitors, including pyridostigmine [2,5]. Treatment includes corticosteroids and steroid-sparing immunosuppressive agents, while severe or refractory cases may require plasma exchange, intravenous immunoglobulin (IVIG), or rituximab [5,6].

We present the case of a 20-year-old postpartum woman with bulbar-predominant MuSK-MG without ptosis or limb weakness, highlighting the diagnostic challenges of this presentation and the importance of early recognition, targeted serologic testing, and timely treatment to prevent respiratory complications.

## Case Presentation

A 20-year-old primigravida was admitted at 11 weeks of gestation with hyperemesis and persistent sinus tachycardia. Thyroid function testing revealed markedly suppressed thyroid-stimulating hormone (TSH; <0.005 µIU/mL), elevated free thyroxine (T4; 3.84 ng/dL), and elevated free triiodothyronine (T3; 5.6 pg/mL). Thyrotropin receptor, thyroid peroxidase, and thyroid-stimulating immunoglobulin antibodies were negative. Thyroid ultrasonography demonstrated mildly heterogeneous parenchyma with increased vascularity but no nodules. Propylthiouracil (PTU) 50 mg three times daily was initiated.

At 26 weeks of gestation, while taking PTU, she reported recurrent episodes of "losing her voice" and intermittent dysphagia to solid foods. No otolaryngologic or formal swallowing evaluation was performed. PTU was discontinued several weeks later, after which her symptoms resolved and were attributed to the medication. However, these episodes may have represented early manifestations of previously unrecognized neuromuscular disease.

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She underwent an uncomplicated spontaneous vaginal delivery at 38 weeks of gestation. Thyroid function had normalized before delivery, and endocrinology diagnosed gestational transient thyrotoxicosis mediated by human chorionic gonadotropin (hCG), recommending no further antithyroid therapy.

On postpartum day 7, she developed a sore throat and progressive dysphagia to both solids and liquids. Over the following days, her symptoms progressed to dysphonia and hypernasal speech, accompanied by decreased oral intake, reported weight loss, and concern for aspiration. She was admitted on postpartum day 10, approximately 3 days after symptom onset. Neurological examination revealed predominantly facial and bulbar involvement without ptosis, diplopia, or significant proximal limb weakness. Cranial nerve examination demonstrated an intact gag reflex and symmetric palatal elevation. Facial muscle testing revealed reduced eyebrow elevation and forehead wrinkling, along with bilateral weakness of eyelid closure, while lower facial strength remained preserved. Although dysphagia, dysphonia, and hypernasal speech were clinically evident, quantitative assessments of lingual and neck muscle strength were not documented. Detailed findings regarding the remaining cranial nerves, distal limb strength, deep tendon reflexes, sensation, and coordination were not available in the initial examination documentation. Formal assessment of bulbar fatigability and respiratory muscle strength was not performed or documented during the initial evaluation, as her symptoms were initially suspected to be secondary to laryngeal pathology.

Flexible laryngoscopy demonstrated mild supraglottic squeeze and pooling of secretions in the piriform sinuses, with preserved bilateral vocal fold mobility. Given the preceding sore throat and dysphonia, laryngeal inflammation was initially suspected. Repeat thyroid studies showed mildly suppressed TSH with normal free T4, while ultrasonography demonstrated homogeneous thyroid parenchyma with resolution of the previously observed hypervascularity. Endocrinology considered the dysphagia unlikely to be related to thyroid dysfunction. A videofluoroscopic swallow study demonstrated laryngeal penetration with thin liquids and pureed consistencies without documented aspiration. Despite significant dysphagia and concern for aspiration, enteral feeding was not required.

On hospital day 4 (postpartum day 13), reassessment identified her speech as predominantly hypernasal rather than hoarse, raising clinical suspicion for neuromuscular junction dysfunction. Acetylcholine receptor (AChR) and muscle-specific tyrosine kinase (MuSK) antibody testing was ordered that day, with blood samples collected on postpartum day 14. Given the high clinical suspicion for myasthenia gravis (MG), empiric treatment was initiated before serologic confirmation. Pyridostigmine was started at 30 mg and titrated to 60 mg every six hours. The patient reported subjective improvement in swallowing and speech; however, objective reassessment of her bulbar weakness could not be completed before she left against medical advice on hospital day 6 (postpartum day 15) to care for her newborn.

Serologic results returned approximately 3 weeks after collection, around postpartum day 35, revealing negative AChR and striational antibodies and markedly elevated MuSK antibodies (1,934 U/mL; reference <1.0 U/mL), confirmed by dilution. Testing was performed through Labcorp (Burlington, North Carolina, US), whose corresponding assay uses radioimmunoprecipitation (RIPA), although the specific method was not independently verified. LRP4 antibody testing was not performed. Electrodiagnostic studies were not performed; the diagnosis was established serologically in the setting of a characteristic phenotype. Chest computed tomography (CT) was performed to evaluate for thymic pathology and demonstrated no evidence of thymic enlargement, thymoma, or other anterior mediastinal masses.

Following discharge, her symptoms recurred after she ran out of pyridostigmine. At approximately six weeks postpartum, nearly four weeks after her initial discharge, she was readmitted with worsening dysphagia, pooling of oropharyngeal secretions, and episodic dyspnea. Her single-breath count was 16, while negative inspiratory force could not be reliably measured because of an inadequate lip seal associated with significant orofacial weakness. Formal vital capacity measurements and neck muscle strength assessments were not documented in the available records. She received intravenous immunoglobulin (IVIG) at a total dose of 2 g/kg over four days, with subsequent clinical improvement.

At outpatient neuromuscular follow-up eight weeks postpartum, she continued to demonstrate prominent facial and bulbar weakness despite the absence of ptosis, including with sustained upward gaze. Examination revealed bilateral lid lag with blinking and moderate-to-severe weakness of eyelid closure. She also demonstrated severe cheek puff weakness with air escaping through her lips, along with marked bilateral tongue weakness on protrusion and lateral movement. Limb strength was preserved except for mild weakness of the left biceps and right triceps (4+/5). Her Myasthenia Gravis Activities of Daily Living (MG-ADL) score was 6, with 2 points each for talking, chewing, and breathing, while her 15-item Myasthenia Gravis Quality of Life (MG-QOL15) score was 13 [7,8].

Given her persistent bulbar weakness and recurrent hospitalization, rituximab was initiated approximately eight weeks postpartum for long-term disease control. She received 4 infusions of rituximab 600 mg each between postpartum weeks 8 and 12. At the time of manuscript preparation, her clinical response to rituximab remained under evaluation, with ongoing monitoring of bulbar symptoms, disease exacerbations, hospitalizations, and functional status.

Table *1* lists the clinical timeline for this patient.

| Timepoint | Clinical events and findings | Management |
|---|---|---|
| 11 weeks' gestation | Hyperemesis, persistent sinus tachycardia, suppressed TSH, and elevated free T4 and T3. Thyroid antibodies were negative. | Propylthiouracil (PTU) 50 mg three times daily initiated. |
| 26 weeks' gestation | Intermittent dysphonia and dysphagia to solids. | PTU discontinued several weeks later, followed by symptom resolution. |
| 38 weeks' gestation | Uncomplicated spontaneous vaginal delivery with normalization of thyroid function. | Diagnosed with gestational transient thyrotoxicosis; no further antithyroid therapy. |
| Postpartum day 7 | Progressive dysphagia to solids and liquids, dysphonia, and hypernasal speech. | Initial symptom onset. |
| Postpartum day 10 (hospital day 1) | Admitted for worsening bulbar symptoms. Facial weakness was present without ptosis or significant limb weakness. | Initial evaluation focused on suspected laryngeal pathology. |
| Hospital days 1–3 | Flexible laryngoscopy demonstrated mild supraglottic squeeze and pooling of secretions with preserved vocal fold mobility. Swallow study demonstrated laryngeal penetration without documented aspiration. | — |
| Postpartum day 13 (hospital day 4) | Hypernasal speech, rather than isolated hoarseness, raised suspicion for neuromuscular junction dysfunction. | AChR and MuSK antibody testing ordered; empiric pyridostigmine initiated. |
| Postpartum day 14 (hospital day 5) | Subjective improvement in swallowing and speech. | Pyridostigmine titrated from 30 mg to 60 mg every 6 hours. Blood samples collected for antibody testing. |
| Postpartum day 15 (hospital day 6) | Patient left the hospital before objective reassessment of bulbar weakness. | Discharged against medical advice. |
| Approximately 5 weeks postpartum | AChR and striational antibodies were negative; MuSK antibody was markedly elevated at 1,934 U/mL. Chest CT showed no thymic pathology. | MuSK-positive myasthenia gravis diagnosed. |
| Approximately 6 weeks postpartum | Readmitted with recurrent dysphagia, secretion pooling, and episodic dyspnea after running out of pyridostigmine. Single-breath count was 16. | IVIG 2 g/kg total dose administered over 4 days, with clinical improvement. |
| 8 weeks postpartum | Persistent facial and bulbar weakness, including impaired eyelid closure, cheek puff, and tongue strength. MG-ADL score 6; MG-QOL15 score 13. | Rituximab initiated for long-term disease control. |
| Postpartum weeks 8–12 | Continued outpatient management. | Four rituximab infusions of 600 mg each. |
| Current follow-up | Long-term clinical response to rituximab remains under evaluation. | Ongoing monitoring of bulbar symptoms, exacerbations, hospitalizations, corticosteroid requirements, and functional status. |

**TABLE 1: Clinical timeline of pregnancy and postpartum-onset MuSK-positive myasthenia gravis**

Chronological summary of clinical presentation, diagnostic evaluation, and therapeutic management from early pregnancy through postpartum follow-up. The timeline highlights gestational transient thyrotoxicosis, early bulbar symptoms, progressive postpartum facial and bulbar weakness, confirmation of muscle-specific kinase (MuSK)-positive myasthenia gravis, and subsequent treatment with pyridostigmine, intravenous immunoglobulin (IVIG), and rituximab. Long-term clinical response to rituximab remains under evaluation.

AChR, acetylcholine receptor; CT, computed tomography; IVIG, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; MG-QOL15, 15-item Myasthenia Gravis Quality of Life questionnaire; MuSK, muscle-specific kinase; PTU, propylthiouracil; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone

## Discussion

Serologic testing plays an important role in the diagnosis of MG, particularly in patients with atypical clinical presentations. Although AChR antibodies are the most common serologic marker, a negative result does not exclude autoimmune MG. MuSK and low-density lipoprotein receptor-related protein 4 (LRP4) antibody testing should be considered alongside AChR antibody testing in patients with a predominantly bulbar phenotype. In our patient, the markedly elevated MuSK antibody level of 1,934 U/mL (reference range: <1.0 U/mL; ⩾1.0 U/mL considered positive) supported the diagnosis of MuSK-positive MG and had important therapeutic implications.

MuSK-positive MG differs from AChR-positive MG in both clinical phenotype and response to treatment. MuSK MG is characterized by prominent bulbar, facial, and respiratory involvement, whereas ocular and generalized limb weakness may be less prominent [5,6,9]. Acetylcholinesterase inhibitors, including pyridostigmine, are often less effective in MuSK MG and may cause more prominent cholinergic adverse effects [5,6,9]. Corticosteroids remain a cornerstone of immunotherapy, although additional immunosuppressive therapy is often required to achieve adequate disease control [9]. Because corticosteroid initiation can occasionally be associated with transient worsening of myasthenic weakness, patients with substantial bulbar or respiratory involvement warrant close clinical and respiratory monitoring during treatment escalation [10,11].

Our patient's subsequent recurrence of dysphagia, excessive secretions, poor oral intake, and episodic dyspnea demonstrated the potential for rapid clinical deterioration in bulbar-predominant MuSK MG. However, given her treatment with pyridostigmine, cholinergic adverse effects may have contributed to her second presentation, particularly the excessive secretions. Although her worsening bulbar symptoms raised concern for a myasthenic exacerbation, a cholinergic contribution could not be definitively excluded. These findings should prompt early assessment for respiratory muscle involvement and a low threshold for rescue therapy when clinically indicated. Intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) are established treatment options for severe exacerbations and impending myasthenic crisis [10,12]. PLEX may be considered for severe MuSK MG exacerbations, although comparative evidence versus IVIG in this subtype remains limited [6,12]. IVIG remains an accepted treatment option and was administered during our patient's exacerbation.

Long-term disease control in MuSK MG often requires steroid-sparing immunotherapy. Rituximab has demonstrated substantial clinical benefit in observational studies of MuSK-positive MG, including improvements in disease severity, reductions in corticosteroid requirements, and sustained remission in some patients [13-15]. These findings have led to consensus recommendations to support early consideration of rituximab in patients with MuSK MG who have an inadequate response to initial immunotherapy. In our patient, recurrent severe bulbar symptoms and the need for prolonged immunosuppression prompted escalation to rituximab, which she subsequently initiated as an outpatient.

This case highlights the diagnostic complexity of MuSK-positive MG and the importance of recognizing its distinctive clinical phenotype. MG has been described as a "snowflake disease" due to its considerable variability in clinical presentation, disease severity, and treatment response, emphasizing that patients may exhibit markedly different clinical manifestations and disease courses [3]. Our patient presented with severe dysphagia, dysphonia, hypernasal speech, and progressive facial and bulbar weakness, yet lacked the more familiar manifestations of MG, including ptosis, diplopia, and significant limb weakness. The absence of these classic findings initially directed the evaluation toward structural and laryngeal causes, delaying recognition of the underlying neuromuscular disorder. Importantly, subtle abnormalities in eyelid closure, cheek puffing, tongue strength, and speech provided critical diagnostic clues that were identified only through a focused neurologic examination.

## Conclusions

This case demonstrates that the absence of ptosis or generalized weakness should not dissuade clinicians from considering myasthenia gravis (MG) in patients with unexplained bulbar dysfunction. Disproportionate facial and bulbar weakness should raise suspicion for MuSK-positive MG, particularly when initial acetylcholine receptor (AChR) antibody testing is negative. Early recognition is important given the potential for respiratory compromise and recurrent exacerbations. A focused physical examination can provide important diagnostic clues and prompt appropriate antibody testing and neuromuscular evaluation, facilitating timely diagnosis and management.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Shirley Gandhi, Brianna Woodbeck, Maleeha Abedi, Sneh Parekh, Win Aung

**Acquisition, analysis, or interpretation of data:** Shirley Gandhi, Brianna Woodbeck, Maleeha Abedi, Sneh Parekh, Win Aung

**Drafting of the manuscript:** Shirley Gandhi, Brianna Woodbeck, Maleeha Abedi, Sneh Parekh, Win Aung

**Critical review of the manuscript for important intellectual content:** Shirley Gandhi, Brianna Woodbeck, Maleeha Abedi, Sneh Parekh, Win Aung

**Supervision:** Win Aung

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