Myasthenia Gravis (MG): Clinical Overview & Management Approaches

A Resource for Clinicians

Background

- Myasthenia gravis (MG) is often misdiagnosed, with substantial delay in appropriate therapy initiation
- Numerous treatments have been approved for MG
- This document captures highlights from an MDA webinar with two MG experts.
- View the companion webinar here.

Overview

Age of onset and prognosis

Bimodal age distribution, but can develop at any age

- **Incidence peaks**: 30-40 and 60-70 years; slow incidence rise thereafter
- **Female preponderance**: <40 years
- **Male preponderance**: >50 years
- **Juvenile MG:** onset <18 years ~10% of cases; slightly higher in females

Better outcomes observed among patients with later-onset MG

Classifications

Clinical status

- **Ocular MG**: weakness restricted to ocular muscles: ~20%
- **Generalized MG**: weakness in other muscles
  - Bulbar, Axial, Limb
  - Respiratory

Antibody types

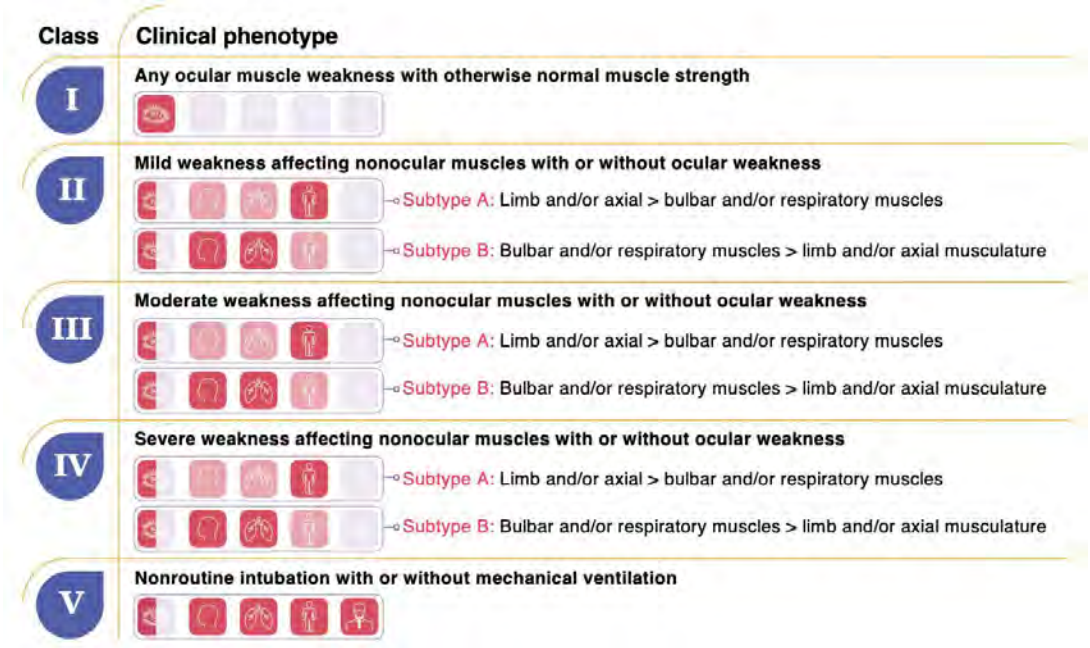
- Anti-AChR: ~50%- 85%
- Anti-MuSK: <10%

Thymoma

- Occurs in ~10% to 15% of patients with MG
- Patients with thymoma **tend to be AChR+** with moderate-to-severe course of generalized symptoms
- **Thymic follicular hyperplasia** with large germinal centers of B cells tends to be a more common finding than thymoma in MG

AChR, acetylcholine receptor; MuSK, muscle-specific kinase. 1. Hehir MK. *Neurol Clin*. 2018;36(2):253-260. 2. Gilhus NE. *Lancet Neurol*. 2015;14(10):1023-1036. 3. Hehir MK.. *Continuum (Minneap Minn)*. 2022;28(6):1615-1642. 4. Punga AR. *Lancet Neurol*. 2022;21(2):176-188. 5. Morren JA. *Cleve Clin J Med*. 2023;90(2):103-113. 6. Gwathmey KG. *Semin Neurol*. 2015;35(4):327-339. 7. Dresser L. *J Clin Med*. 2021;10(11):2235.

MGFA Clinical Classification



MGFA, Myasthenia Gravis Foundation of America. 1. Gwathmey KG, Burns TM. Semin Neurol. 2015;35(4):327-339.

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Clinical Manifestations

Motor Weakness

- Subacute onset of fatiguing and fluctuating motor weakness
- Variable severity over the course of a day
- Slowly progressive course with relapsing/remitting symptoms
- Excess heat, sustained exertion, provocative medications, or systemic illness may incite worsening
- Distribution of weakness

Ocular Manifestations

- Ocular symptoms tend to be among the earliest manifestations of disease[1]
- Asymmetric, fluctuating, and fatiguing eyelid ptosis
- Dysconjugate gaze with symptomatic binocular diplopia
- Ocular examination features include:
  - Eye closure weakness
  - Cogan lid twitch
  - Curtain sign
  - Ice pack test

Bulbar and Respiratory Weaknesses

Cranial/bulbar weakness is common in patients with generalized disease

Manifestations:

- Jaw closure weakness and fatigue with sustained activation
- Flattened/blunted facial expressivity/excursion
- Dysphagia predominantly to liquids
- Nasal regurgitation (due to prominent soft palate weakness)
- Dysarthria and dysphonia (characterized by nasal, breathy, or hoarse tone)

Respiratory weakness is observed in up to 40% of patients

Limb Manifestations

Approximately 75% of patients will eventually develop limb weakness

- Asymmetric and proximal-predominant pattern
- Neck flexors >> extensors
- Only 10% to 15% will manifest limb weakness at initial presentation

Generalization of disease occurs within 2 to 3 years of initial onset

- More prevalent in seropositive patients

1. Hehir MK. *Neurol Clin.* 2018;36(2):253-260. 2. Gwathmey KG. *Semin Neurol.* 2015;35(4):327-339. 3. Gilhus NE. *Lancet Neurol.* 2015;14(10):1023-1036. 4. Punga AR. *Lancet Neurol.* 2022;21(2):176-188. 5. Gilhus NE. *J Neurol.* 2023;270(7):3329-3340. 6. Juel VC. *Orphanet J Rare Dis.* 2007;2:44.

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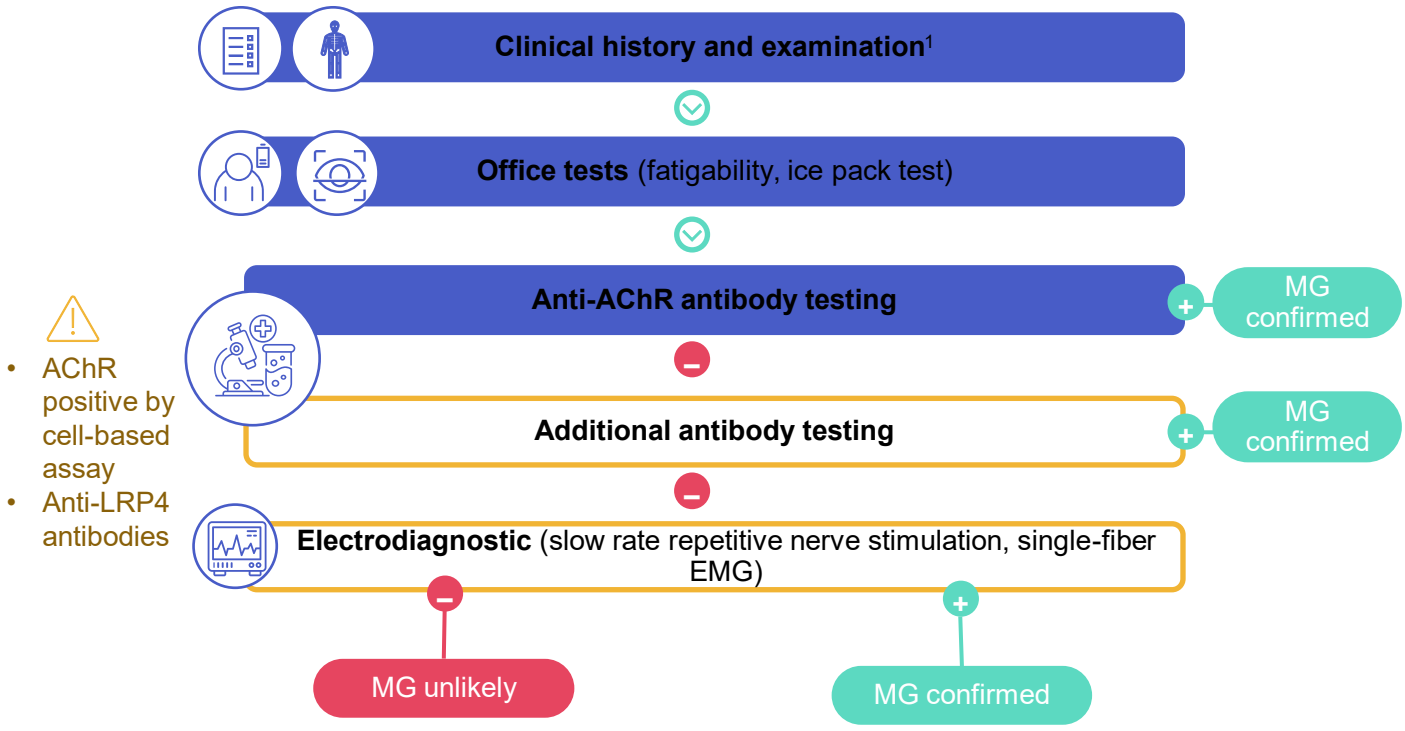
Key Steps in Diagnostic Algorithm



- AChR positive by cell-based assay
- Anti-LRP4 antibodies

AChR, acetylcholine receptor; EMG, electromyography; LRP4, lipoprotein-related protein 4; MG, myasthenia gravis.

1. Hehir MK 2nd. *Continuum (Minneap Minn).* 2022;28(6):1615-1642.

Considerations for Differential Diagnosis[1-3]

Disease mimics	Ptosis	Ophthalmoparesis	Diplopia	Asymmetry	Clinical feature(s)
Myasthenia gravis	Yes	Yes	Yes	Yes	
Congenital myasthenic syndromes	Yes	Variable	Rarely	No	• Congenital
Mitochondrial disease	Yes	Yes	No	Rare	• Systemic manifestations
Muscular dystrophy	Yes	Variable	Variable	No	• Congenital • Minimal fluctuation
Orbital myositis	Rare	Yes	Yes	Yes	• Orbital pain
Thyroid orbitopathy	No	Yes	Yes	Yes	• Proptosis
Brainstem lesion	Yes	Yes	Yes	Yes	• Localized/fixed deficit • Long-tract signs
Cranial neuropathy	Yes	Yes	Yes	Yes	• Localized/fixed deficit
Lambert-Eaton syndrome	Yes	Yes	Yes	Yes	• Areflexia + facilitation • Dysautonomia

Table adapted from Punga et al, 2022.[1] Used with permission from Elsevier.

1. Punga AR. Lancet Neurol. 2022;21(2):176-188. 2. Gwathmey KG. Semin Neurol. 2015;35(4):327-339. 3. Juel VC. Orphanet J Rare Dis. 2007;2:44.

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MG Management

Treatment goal: Complete disease remission or minimal manifestations of disease, defined as presence of mild and nonimpairing motor weakness[1,2]

Therapeutic approaches[1]:

- Phenotype/weakness distribution
- Serum antibody status
- Association with thymoma
- Medical comorbidities

Pharmacologic interventions[1]:

- Symptomatic and transiently improve weakness, or
- Disease-modifying/immunosuppressive

Surgical intervention limited to thymectomy[3]

1. Hehir MK 2nd. *Continuum (Minneap Minn).* 2022;28(6):1615-1642. 2. Sanders DB. *Neurology*. 2016;87(4):419-425. 3. Iorio R. *Nat Rev Neurol.* 2024;20(2):84-98.

Pharmacological Interventions

Symptomatic treatments[1,2]

AChEi

- Pyridostigmine

Alternative agents

- Albuterol, 3,4-diaminopyridine
- Ephedrine

Disease modifying/immunosuppressive treatments[1,3-5]

Corticosteroids

T- and/or B-cell activation/ proliferation blockers
Azathioprine
Mycophenolate mofetil
Methotrexate
Cyclosporine
Tacrolimus
Satralizumab*
Telitacicept*

B-cell cytotoxic agents
Rituximab
Inebilizumab*

Complement pathway inhibitors
Eculizumab, ravulizumab, and zilucoplan
Pozelimab + cemdisiran,* gefurulimab,* vemircopan,* and iptacopan*

Neonatal Fc receptor antagonists
Efgartigimod
Rozanolixizumab
Nipocalimab* and batoclimab*

*Investigational for MG.
AChEi, acetylcholinesterase inhibitor; MG, myasthenia gravis.

1. Hehir MK 2nd. *Continuum (Minneap Minn).* 2022;28(6):1615-1642. 2. Gilhus NE. *Lancet Neurol.* 2015;14(10):1023-1036. 3. Morren JA. *Cleve Clin J Med*. 2023;90(2):103-113. 4. Vanoli F. *Curr Opin Neurol.* 2023;36(5):410-415. 5. Nair SS. *Immunotargets Ther.* 2023;12:25-45.

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Myasthenia Gravis (MG): Clinical Overview & Management Approaches (cont)

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Therapeutic Management Strategies

1

Pyridostigmine[1,2] (180-240 mg daily) + / - **Early thymectomy**[1,2] for patients AChR+

If no clinical remission

2 Immunosuppression

Corticosteroid[1-3]

- Prednisone: 20-60 mg daily with slow tapers thereafter
- Efficacy onset: 2-6 weeks*

Azathioprine +/-

- Azathioprine: 50 mg daily and titrated to 150 mg daily (2-3 mg/kg/d)
- Efficacy onset: >6 months

Mycophenolate mofetil +/-

- 500 mg daily and titrated to 500-1500 mg BID
- Efficacy onset: >6 months

3 Acute, adjunct, bridging therapies[1]

IVIG infusion

- Loading dose 2 g/kg and maintenance between 0.4-1 g/kg with variable dosing interval

Plasma exchange

4 Novel therapies

(Approved for use in AChR+, generalized MG patients)

Complement pathway inhibitors[1,4-6]

- Meningococcus inoculation required
- Efficacy onset within 2 weeks

FcRn inhibitors[1,4-6]

- Efficacy onset: 1-5 weeks
- Redosing frequency not established

*Transient worsening of weakness may occur within the first 3 weeks. AChR, acetylcholine receptor; BID, twice daily; FcRn, neonatal fragment crystallizable receptor; IVIG, intravenous immunoglobulin; MG, myasthenia gravis. 1. Hehir MK 2nd. *Continuum (Minneap Minn).* 2022;28(6):1615-1642. 2. Gilhus NE. *Lancet Neurol.* 2015;14(10):1023-1036. 3. Morren JJ. *Cleve Clin J Med*. 2023;90(2):103-113. 4. Iorio R. *Nat Rev Neurol*. 2024;20(2):84-98. 5. Narayanaswami P. *Neurology*. 2021;96(3):114-122. 6. Vanoli F. *Curr Opin Neurol.* 2023;36(5):410-415

Clinician Resources

Key Publications

- Sanders DB, et al. Neurology. 2016;87(4):419-425.
- Narayanaswami P, et al. *Neurology.* 2021;96(3):114-122.
- Beloor Suresh A, et al. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559331/
- Morren JA, Li Y. *Cleve Clin J Med.* 2023;90(2):103-113.

Access companion MDA webinar here

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