CME ACTIVITY

Beyond AChR:

Recognizing and Treating MuSK Ab+, LRP4 Ab+, and Triple Seronegative Myasthenia Gravis

Case-based perspectives on diagnosis, targeted therapy selection, and quality-of-life considerations in non-AChR Ab+ myasthenia gravis

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Learning Objectives:

- Describe the current hypotheses regarding disease mechanisms in MuSK Ab+, LRP4 Ab+, and triple seronegative MG and apply this mechanistic understanding to diagnostic reasoning and treatment planning.
- Recognize the subtype-specific clinical features of MuSK Ab+, LRP4 Ab+, and triple seronegative MG and apply an appropriate diagnostic workup.
- Identify patients with MuSK Ab+, LRP4 Ab+, or triple seronegative MG who are suboptimally controlled on traditional therapies and apply subtype-specific evidence to guide timely transition to newer therapies.
- Articulate the distinct treatment burden and disease progression patterns in MuSK+, LRP4+, and triple seronegative MG and apply treatment goals that reflect the potential benefits of targeted over traditional therapy.

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Why Non-AChR MG Subtypes Are Underrecognized

- Most MG education — and most clinical trial data — is built around AChR antibody–positive disease (AchR Ab+), which represents the majority of generalized cases
- Rarer forms of MG, such as MuSK Ab+, LRP4 AB+, and seronegative MG each carry distinct clinical courses, diagnostic pitfalls, and treatment responses that don't map neatly onto AChR-based algorithms
- Delayed or incorrect diagnosis is common: atypical antibody profiles are frequently misread as "mild" disease, misattributed to other conditions, or left unexplored once initial serology is negative
- **This activity uses three real-world cases to build a practical, subtype-specific approach to diagnosis and treatment selection**

Gilhus NE, et al. N Engl J Med. 2016;375:2570–2581.
MuSK = muscle=specific kinase. LRP4 = lipoprotein receptor-related protein 4

MG Serostatus Classification at a Glance

Subtype	Approx. Prevalence (Generalized MG)	Key Mechanistic Feature	Complement Fixing?
AChR Ab+	~85%	Functional AChR blockade, crosslinking/internalization, complement activation	Yes (IgG1/3)
MuSK Ab+	~5-7%	Disrupts MuSK–LRP4 interaction, impairing AChR clustering via Dok-7	No (IgG4)
LRP4 Ab+	~1–2% (~10% of AChR/MuSK-negative)	Disrupts AChR clustering via the Dok-7 pathway	Variable
Triple Seronegative	~10%; more common in ocular MG	No detectable AChR/MuSK/LRP4 Ab by standard assay; ~20% AChR+ on cell-based assay	Variable

Gilhus NE, et al. N Engl J Med. 2016;375:2570–2581.

PART 1

MuSK Ab+ Myasthenia Gravis

A more severe, treatment-distinct phenotype that often demands earlier consideration of targeted therapy

CASE 1 · PART 1

MuSK Ab+ MG — Initial Presentation

- 36-year-old female with several months of fluctuating diplopia, ptosis, proximal arm and leg weakness, and occasional dysphagia.
- Nerve conduction studies with repetitive stimulation show a decrement consistent with a neuromuscular junction disorder.
- AChR antibodies are negative; MuSK antibodies are positive.
- Pyridostigmine is started with minimal effect; prednisone is started at 20 mg daily and gradually increased to 60 mg daily.

Tips: *A pattern of prominent bulbar and respiratory involvement, fluctuating course, and a lukewarm response to acetylcholinesterase is characteristic of MuSK Ab+ MG and should raise early suspicion for a more treatment-resistant course (Expert opinion).*

KNOWLEDGE CHECK

Given this patient's fluctuating bulbar symptoms and MuSK antibody positivity, which statement best reflects current practice for targeted therapy selection?

A. IVIG is generally more effective than plasma exchange in MuSK Ab+ MG.

B. Complement inhibitors are an appropriate first targeted therapy given IgG-mediated pathology.

C. Rituximab should be considered as an early therapeutic option given consensus guidance and clinical experience in MuSK Ab+ MG.

D. Thymectomy offers clear benefit regardless of MuSK serostatus.

Correct Answer:

Narayanaswami P et al Neurol. 2021; 96: 114–122

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D. Thymectomy offers clear benefit regardless of MuSK serostatus.

Correct Answer: C

MuSK antibodies are predominantly IgG4 and do not fix complement, so C5 inhibitors e.g., eculizumab, ravulizumab, zilucoplan) are not expected to work. Patients often respond better to plasma exchange than IVIG, and thymectomy has no clear benefit in MuSK Ab+ disease. International consensus guidance supports considering rituximab early in the MuSK Ab+ course.

Narayanaswami P et al. Neurol. 2021; 96: 114–122

Recognizing and Confirming MuSK Ab+ MG

Signs & Symptoms

- Prominent bulbar, facial, and neck-extensor weakness
- Frequent respiratory involvement and crisis risk
- Often more severe than AChR Ab+ disease at presentation

Diagnostic Testing

- AChR antibodies typically negative
- MuSK antibody assay confirms diagnosis
- RNS or single-fiber EMG supports NMJ dysfunction when serology is pending

First-Line Efficacy

- Pyridostigmine: often poorly tolerated or minimally effective
- Plasma exchange (PLEX): generally effective
- IVIG: appears less effective than PLEX in this subtype
- FcRn Inhibitors effective
- Early B cell inhibition should be considered

Hehir MK et al. Neurol. 2017;89:1069–1077. | *Narayanaswami P, et al. Neurol. 2021;96:114–122.*

CASE 1 · PART 2

MuSK Ab+ MG — Crisis and the Need for Targeted Therapy

- On follow-up two months later, the patient is visibly dyspneic and unable to tolerate oral intake for several days due to dysphagia.
- A recently diagnosed UTI was treated with ciprofloxacin — a known risk factor for NMJ decompensation.
- She is admitted directly from clinic for impending myasthenic crisis, requires intubation, and is treated with 5 sessions of PLEX over 10 days.
- After extubation, generalized and ocular symptoms improve, but she remains significantly symptomatic on high-dose prednisone.
- After confirming hepatitis B serostatus, she is treated with rituximab 1000 mg IV x2 over 2 weeks; over the following 4–6 months, symptoms improve markedly and prednisone is weaned to under 20 mg daily.

Tips: *Fluoroquinolones and other NMJ-blocking exposures are a recurring, modifiable precipitant of crisis in MG — medication reconciliation belongs in every visit, not just the first. [Expert opinion]*

Safety and Efficacy of Targeted Therapies in MuSK Ab+ MG

Therapy Class	Role in MuSK Ab+ MG	Key Consideration
Anti-CD20 (rituximab)	Consider early; blinded prospective review supports benefit specifically in MuSK Ab+ MG	Time to effect ~3–6 months; screen hepatitis B before infusion
Complement inhibitors (eculizumab, ravulizumab, zilucoplan)	Not expected to work	MuSK antibodies are IgG4 and not directly involved in the complement system
FcRn inhibitors (efgartigimod, rozanolixizumab, nipocalimab)	FDA-approved for MuSK Ab+ MG	Antibody-independent mechanism — reduces circulating IgG regardless of target. Various formulations (subcutaneous injections, intravenous infusions).
CD19 Ab (inebilizumab)	FDA-approved for MuSK Ab+ MG	Reduces B cells. Intravenous infusions.
Clinical trial enrollment	Reasonable option for refractory or treatment-limited patients	Discuss access and eligibility early, particularly when standard options plateau

Howard JF Jr, et al. Lancet Neurol. 2017;16:976–986. | Howard JF Jr, et al. Lancet Neurol. 2021;20: 526–536. | Hehir MK, et al. Neurol. 2017;89:1069–1077. | Nowak RJ, et al. N Engl J Med. 2025;392:2309–2320.

Quality of Life & Patient Expectations: MuSK vs. AChR Ab+ MG

- Patients with MuSK Ab+ MG often experience a more severe initial course, including higher rates of respiratory crisis and bulbar involvement, which shapes expectations differently than a typical AChR Ab+ trajectory.
- Prolonged steroid dependence — even alongside steroid-sparing agents — is common and drives much of the treatment-related burden patients report.
- MuSK Ab+ patients often respond well to off label use of rituximab, setting expectations around a multi-month time-to-effect helps patients tolerate the interval before symptomatic benefit.
- Discuss the crisis risk and modifiable precipitants (infection, certain antibiotics) explicitly — patients living with this subtype benefit from an action plan, not just a medication list.

Hehir MK, et al. Neurol. 2017:89;1069–1077. | *Narayanaswami P, et al. Neurology. 2021; 96:114–122.*

Clinical Pearls: MuSK Ab+ MG

- ✓ **Suspect early:** prominent bulbar/respiratory symptoms and a lukewarm response to pyridostigmine should raise suspicion for MuSK Ab+ disease before serology returns.
- ✓ **Choose PLEX over IVIG** for rescue therapy when possible — IVIG appears less effective in this subtype.
- ✓ **Skip complement inhibitors** — MuSK antibodies are IgG4 and do not fix complement, so C5 inhibition is not expected to help.
- ✓ **Move to rituximab early** rather than cycling through additional oral steroid-sparing agents when steroid dependence persists.
- ✓ **CD19 Ab and FcRn Antagonists are FDA-approved for MuSK Ab+ MG,** offering a targeted option independent of the complement pathway.
- ✓ **Counsel on precipitants:** infection and certain antibiotics (e.g., fluoroquinolones) are common, modifiable triggers of crisis.

Narayanaswami P, et al. Neurol. 2021;96:114–122. | Howard JF Jr, et al. Lancet Neurol. 2021;20:526–536. | Brauner S, et al. JAMA Neurol. 2020; 77:974–981.

PART 2

LRP4 Ab+ Myasthenia Gravis

A rare and frequently misunderstood serostatus — where diagnostic reassessment can be as important as treatment selection

CASE 2 · PART 1

LRP4 Ab+ MG — Initial Presentation

- 65-year-old female presents with decades of intermittent neck and bilateral limb weakness, beginning with a 'heavy' feeling of the head and neck that spreads to the extremities.
- Two more severe episodes (2022, 2024) included difficulty chewing, swallowing, and slurred speech; she also reports diplopia with prolonged eye use.
- During her 2024 admission, LRP4 antibodies were positive; anti-MuSK and AChR (blocking/binding/modulating) antibodies were negative.
- She is started on pyridostigmine 180 mg ER daily with a robust response, and subsequently trials IVIG without significant benefit.

Tips: *An LRP4-positive result is often treated as diagnostically definitive — but a poor response to standard first-line MG therapy should prompt reassessment rather than escalation for escalation's sake. [Expert opinion]*

KNOWLEDGE CHECK

This LRP4 antibody–positive patient has a poor response to pyridostigmine and IVIG, and a sibling with a similar, unexplained syndrome. What is the most appropriate next step?

A Increase the 180 mg pyridostigmine dose and reassess in three months

B Initiate a complement inhibitor

C Pursue genetic testing for a congenital myasthenic syndrome

D Repeat LRP4 antibody testing to confirm the original result

Correct Answer:

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D. Repeat LRP4 antibody testing to confirm the original result

Correct Answer: C

A family history of similar symptoms plus a poor response to standard immunotherapy is a red flag for a genetic neuromuscular junction disorder. LRP4 positivity does not rule out congenital myasthenic syndrome (CMS), and CMS does not respond to immunosuppression — genetic testing changes management.

LRP4 Ab+ MG: Myth or Reality?

Signs & Diagnostic Testing

- Clinical phenotype often resembles AChR Ab+ MG more closely than MuSK Ab+ disease.
- LRP4 antibody assays vary in sensitivity/specificity across laboratories.
- Slow repetitive nerve stimulation and single-fiber EMG support an NMJ diagnosis when serology is ambiguous.

"Myth or Reality"

- A positive LRP4 result is not always the whole story — LRP4 positivity has been described in genetically confirmed congenital myasthenic syndromes.
- A poor treatment response, family history, or atypical course should prompt genetic evaluation, not just dose escalation.

1st/2nd-Line Efficacy

- When autoimmune LRP4 Ab+ MG is confirmed, patients are generally treated much like AChR Ab+ MG.
- Pyridostigmine, corticosteroids, and standard steroid-sparing agents remain reasonable first steps.
- Efgartigimod's FDA approval is not restricted by serostatus, so it remains an option for confirmed LRP4 Ab+ MG.

Narayanaswami P, et al. Neurology. 2021;96:114–122. | Howard JF Jr, et al. Lancet Neurol. 2021;20:526–536.

CASE 2 · PART 2

LRP4 Ab+ MG — Diagnostic Reframe and Targeted Management

- EMG/NCS ultimately shows an abnormal decrement on slow repetitive nerve stimulation; a periodic paralysis panel is unrevealing.
- Given a sibling also being treated for seronegative MG, a hereditary arthrogryposis panel is sent and reveals homozygous pathogenic RAPSN mutations — confirming congenital myasthenic syndrome (CMS), not autoimmune LRP4 Ab+ MG.
- A trial of amifampridine is stopped due to intolerable orthostatic dizziness with syncope.
- She ultimately does best on pyridostigmine ER 180 mg BID; targeted, mechanism-specific management rather than immunosuppression.

Tips: *Once a genetic NMJ disorder is confirmed, the therapeutic conversation shifts entirely. [Expert opinion]*

Quality of Life & Patient Expectations: LRP4 Ab+ MG

- For confirmed autoimmune LRP4 Ab+ MG, quality-of-life expectations and treatment goals are similar to AChR Ab+ disease — most patients do reasonably well with standard first- and second-line therapy.
- When the diagnosis is instead a congenital myasthenic syndrome, patient expectations must be reset: this is a lifelong, non-immune condition, and repeated escalation of immunotherapy carries risk without benefit.
- **A family history of similar, treatment-refractory symptoms is one of the most useful — and most often overlooked — pieces of diagnostic information in this subtype.**

Narayanaswami P, et al. Neurology. 2021;96:114–122.

Clinical Pearls

- ✓ **Treat confirmed LRP4 Ab+ MG** much like AChR Ab+ disease using standard first- and second-line therapy — efgartigimod is FDA-approved without a serostatus restriction, so it remains available here too.
- ✓ **Don't stop at a positive antibody:** a poor response to standard therapy warrants diagnostic reassessment, not automatic escalation.
- ✓ **Ask about family history** — a sibling or relative with a similar unexplained syndrome should prompt consideration of a genetic NMJ disorder.
- ✓ **Reserve genetic testing** for atypical courses, refractory symptoms, or a suggestive family history rather than routine use.
- ✓ **Once CMS is confirmed,** shift away from immunotherapy entirely — management is mechanism-specific (e.g., pyridostigmine, amifampridine, potassium), not immunosuppressive.

Narayanaswami P et al. Neurol. 2021; 96: 114–122. | *Howard JF Jr, et al. Lancet Neurol, 2021; 20: 526–536.*

PART 3

Triple Seronegative Myasthenia Gravis

When standard antibody testing is negative, diagnostic persistence — and therapy sequencing — define the path forward

CASE 3 · PART 1

Triple Seronegative MG — Initial Presentation

- 61-year-old female presents with a history of hypothyroidism, celiac disease, and a prior (now-resolved) antiphospholipid antibody profile presents with fluctuating diagonal diplopia and eyelid lag, worse by day's end.
- She reports running out of air mid-sentence, difficulty with tough foods, and a globus sensation with esophageal dysfunction on swallow study.
- Neuro-ophthalmology attributes her diplopia to a refractive error and does not initially favor an NMJ disorder.
- AChR (including cell-based assay), MuSK, and LRP4 antibodies are all negative; initial EMG/NCS with repetitive stimulation is also negative.
- A trial of pyrodostigmine improves diplopia, swallowing, and fatigue — prompting further neuromuscular workup.

Tips: *A normal standard EMG/NCS does not exclude a neuromuscular junction disorder — when the clinical story and treatment response point toward MG, single-fiber EMG is the next diagnostic step, not a dead end. (Expert opinion]*

KNOWLEDGE CHECK

This patient has a suggestive clinical history, symptomatic improvement with pyridostigmine, but normal AChR/MuSK/LRP4 antibodies and a normal standard EMG/NCS. What is the most appropriate next step before excluding an neuromuscular junction disorder?

A Conclude that MG is unlikely and pursue alternative diagnoses only

B Proceed to single-fiber EMG (SFEMG)

C Start empiric high-dose corticosteroids without further testing

D Repeat standard EMG/NCS in six months

Correct Answer:

Sanders DB, et al. Neurology. 2016;87:419–425.

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B. Proceed to single-fiber EMG (SFEMG)

C. Start empiric high-dose corticosteroids without further testing

D. Repeat standard EMG/NCS in six months

Correct Answer: B

Standard repetitive nerve stimulation has limited sensitivity, especially early or in mild disease. SFEMG is substantially more sensitive for detecting subtle NMJ transmission defects and is the appropriate next step when clinical suspicion remains, as it was here, ultimately showing a moderate transmission defect.

Sanders DB, et al. Neurology. 2016;87:419–425.

Seronegative MG: Diagnostic Delay and Misdiagnosis

Diagnostic Delay Is Common

- Symptoms are frequently attributed to refractive error, TMJ dysfunction, or general fatigue before an NMJ disorder is considered
- Comorbid autoimmune conditions can further obscure the picture

Misdiagnosis & Mimics

- Structural eye disease, esophageal dysmotility, and connective tissue disease can each mimic isolated features of seronegative MG
- A unifying NMJ diagnosis is easy to miss when symptoms are managed by multiple specialists in isolation

Diagnostic Testing

- Cell-based AChR assay can uncover antibodies missed by standard assays in up to ~20% of seemingly seronegative patients
- SFEMG offers the highest sensitivity for confirming an NMJ transmission defect

Mirian A, et al. J Neurol Sci. 2022; 432.

CASE 3 · PART 2

Triple Seronegative MG — Sequencing Toward Targeted Therapy

- SFEMG confirms a moderate NMJ transmission defect; thymoma and genetic/mitochondrial causes are excluded.
- Prednisone produces sustained improvement, but mycophenolate and azathioprine are each limited by inadequate steroid-sparing effect or intolerance.
- IVIG 2 g/kg produces marked benefit; over time, however, she experiences symptom 'wearing off' between infusions despite interval adjustments.
- Efgartigimod is initiated with marked benefit (MG-ADL improves from 5 to 2), but symptoms recur 2–3 weeks after each cycle; shortening the off-cycle interval (2 weeks on/2 weeks off) restores control.

Tips: *Even without a detectable antibody, this patient responds meaningfully to an FcRn inhibitor. Efgartigimod is FDA-approved regardless of antibody status, including seronegative MG — a reminder that antibody-negative status does not equal 'no autoimmune pathology,' and that dosing interval, not just drug selection, is often the lever that restores control.*

Quality of Life & Patient Expectations: Seronegative MG

- Patients often carry the emotional burden of a delayed or dismissed diagnosis — validating the diagnostic journey is itself part of care.
- 'Wearing off' between infusion-based therapies is a common, under-discussed source of functional decline; ask about the days before the next dose, not just the days after.
- **Efgartigimod is FDA-approved regardless of antibody status, including seronegative MG — this is a relatively recent label expansion, and antibody-negative testing should not by itself limit access to targeted therapy.**

Howard JF Jr, et al. Lancet Neurol. 2021;20:526–536.

Clinical Pearls: Triple Seronegative gMG

- ✓ **Don't stop at a negative panel:** consider a cell-based AChR assay, which identifies antibodies in up to ~20% of apparently seronegative patients.
- ✓ **A normal standard EMG/NCS** does not exclude MG — proceed to single-fiber EMG when clinical suspicion remains high.
- ✓ **Treat much like AChR Ab+ MG** for first- and second-line therapy, while remaining alert for comorbid mimics.
- ✓ **Watch for 'wearing off'** between IVIG or FcRn-inhibitor cycles — adjusting dosing interval can restore benefit before switching therapy classes.
- ✓ **Seronegative status** does not exclude patients from FcRn-inhibitor therapy — efgartigimod is FDA-approved regardless of antibody status, including seronegative gMG.

Mirian A, et al. J Neurol Sci. 2022; 432. | *Howard JF Jr, et al. Lancet Neurol. 2021;20:526–536.*

Faculty Reflections & Potential Practice Changes

MuSK Ab+ MG

Move to rituximab earlier, favor PLEX over IVIG for rescue, and skip complement inhibitors entirely. FcRn-inhibitor therapy also a good option.

LRP4 Ab+ MG

Treat a poor response to standard therapy as a prompt to reconsider the diagnosis — not just to escalate immunotherapy. FcRn-inhibitor therapy also a good option.

Triple seronegative MG

Pursue cell-based antibody assays and SFEMG before abandoning the NMJ hypothesis, and don't withhold FcRn-inhibitor therapy based on serostatus alone.

Hehir MK, et al. Neurol. 2017;89:1069–1077. | *Mirian A, et al. J Neurol Sci. 2022;432.* | *Howard JF Jr, et al. Lancet Neurol. 2021;20:526–536.*

Consolidated Diagnostic & Treatment Framework

Subtype	Diagnostic Priority	Preferred Rescue	Preferred Targeted Therapy
AChR Ab+	Standard serology; CT chest for thymoma	PLEX or IVIG	Complement inhibitors; FcRn inhibitors; anti-CD20 (refractory)
MuSK Ab+	MuSK antibody; RNS/SFEMG if pending	PLEX preferred over IVIG	Rituximab (early); FcRn inhibitors; anti-CD19; not complement inhibitors
LRP4 Ab+	LRP4 antibody; reassess with genetic testing if refractory or family history+	PLEX or IVIG	Standard AChR-like approach once confirmed; efgartigimod (FDA-approved regardless of serostatus)
Triple Seronegative	Cell-based AChR assay; SFEMG	PLEX or IVIG	Efgartigimod (FDA-approved regardless of serostatus); otherwise AChR-like approach

Narayanaswami P, et al. Neurol. 2021;96:114–122. | Wolfe GI, et al. N Engl J Med. 2016;375:511–522. | Howard JF Jr, et al. Lancet Neurol. 2021;20:526–536. | Howard JF Jr, et al. Lancet Neurol. 2021;20:526–536. | Nowak RJ, et al. New Engl J Med. 2025;392:2309–2320.