

Lambert–Eaton myasthenic syndrome

Autoimmune presynaptic failure of neuromuscular transmission

Mechanism • clinicopathologic correlation • diagnosis

Lambert–Eaton myasthenic syndrome

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The disease is a presynaptic autoimmune channelopathy

- Autoantibodies interfere with calcium-dependent acetylcholine release at motor terminals.
- The principal defect is impaired neuromuscular transmission—not primary skeletal-muscle destruction.
- A distinctive physiological finding is improved muscle response after brief activation.

Presynaptic Ca²⁺-channel autoimmunity



Less Ca²⁺-dependent ACh release



Reduced end-plate activation



Painless muscle weakness

A localization framework for weakness

- Muscle contraction depends on a motor axon, neuromuscular junction, and intact muscle fiber.
- Failure at the junction can produce weakness despite preserved structural continuity of the nerve and muscle.
- In LEMS, the most informative lesion is presynaptic.

Motor axon

Delivers the
action potential

Synapse

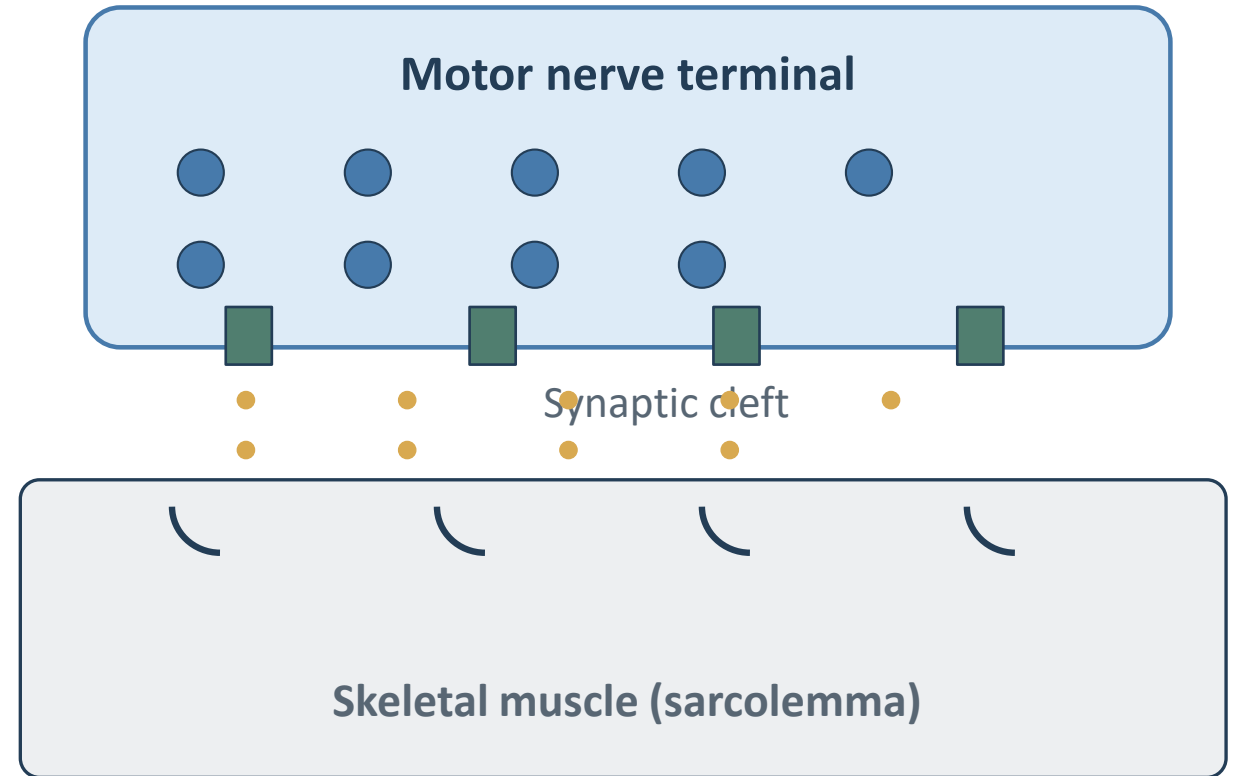
Transmits via ACh

Muscle fiber

Generates force

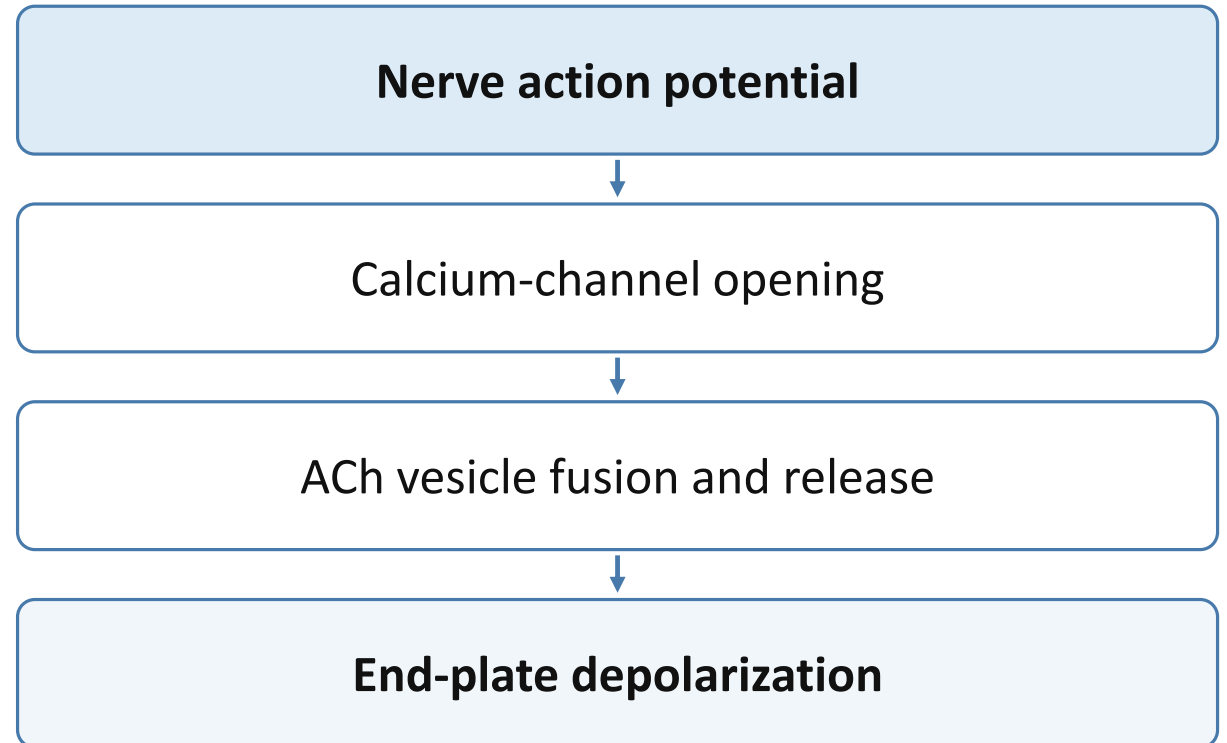
Anatomy: The motor nerve terminal and muscle end plate

- Terminal boutons release acetylcholine into the synaptic cleft.
- The postsynaptic sarcolemma concentrates acetylcholine receptors in specialized folds.
- The distinction between pre- and postsynaptic compartments is diagnostically essential.



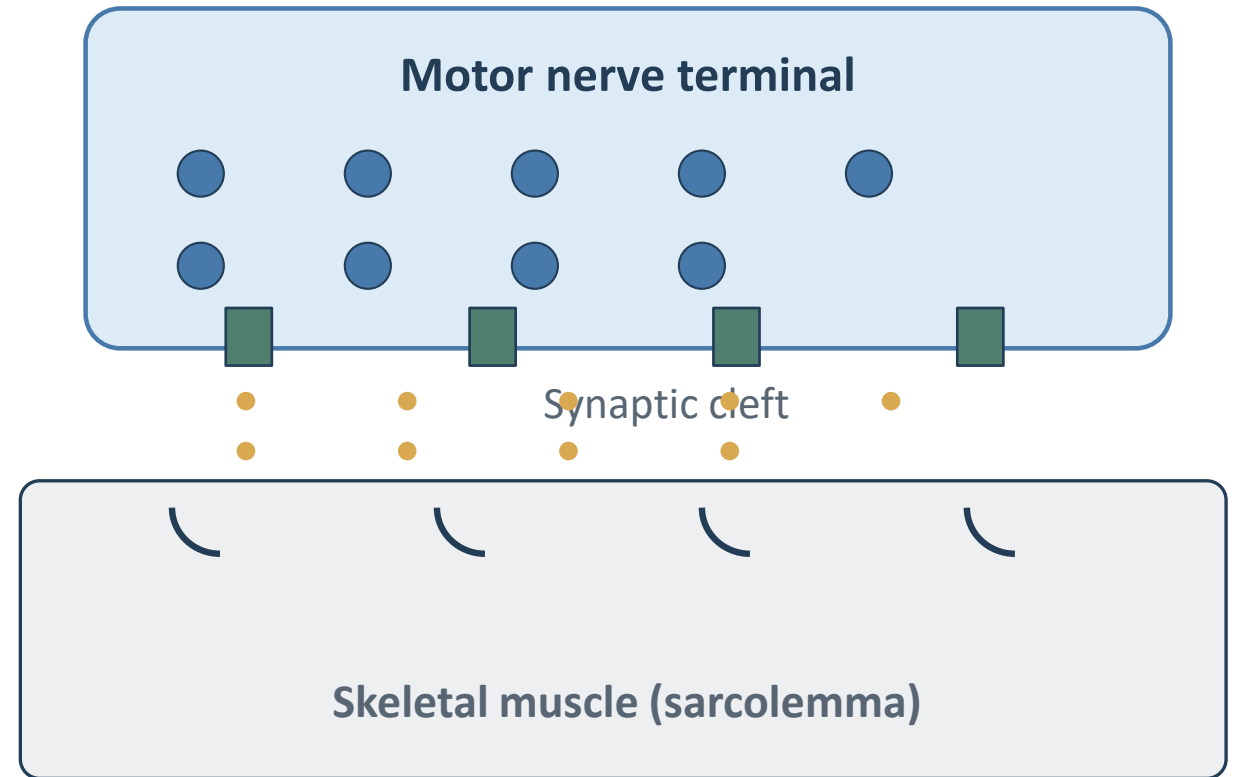
Normal excitation–secretion coupling

- Motor nerve depolarization opens presynaptic voltage-gated calcium channels.
- Entering calcium couples the electrical impulse to synaptic-vesicle fusion.
- Acetylcholine released from vesicles activates muscle end-plate receptors.



Calcium influx is the critical presynaptic trigger

- Electrical arrival at the bouton alone is insufficient for normal quantal transmitter release.
- Presynaptic calcium entry promotes fusion of transmitter-containing vesicles.
- LEMS disrupts this step upstream of the muscle acetylcholine receptor.



ACh released across the cleft

Acetylcholine must reach a receptive sarcolemma

- Release occurs on the neuronal side of the synaptic cleft.
- ACh then interacts with receptors clustered on the muscle membrane.
- The postsynaptic membrane can be structurally intact but receive too little transmitter in LEMS.

Presynapse

ACh supply and
release

Cleft

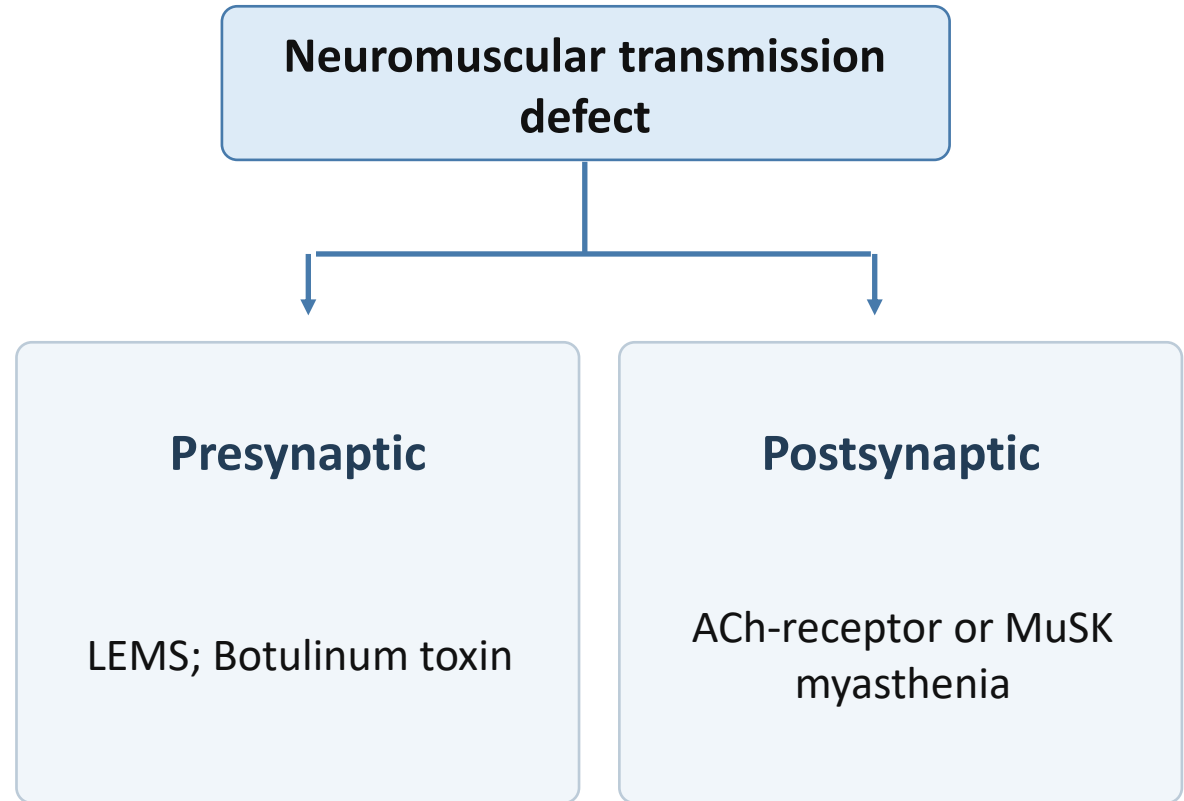
Neurotransmitter
transit

Postsynapse

ACh receptor
activation

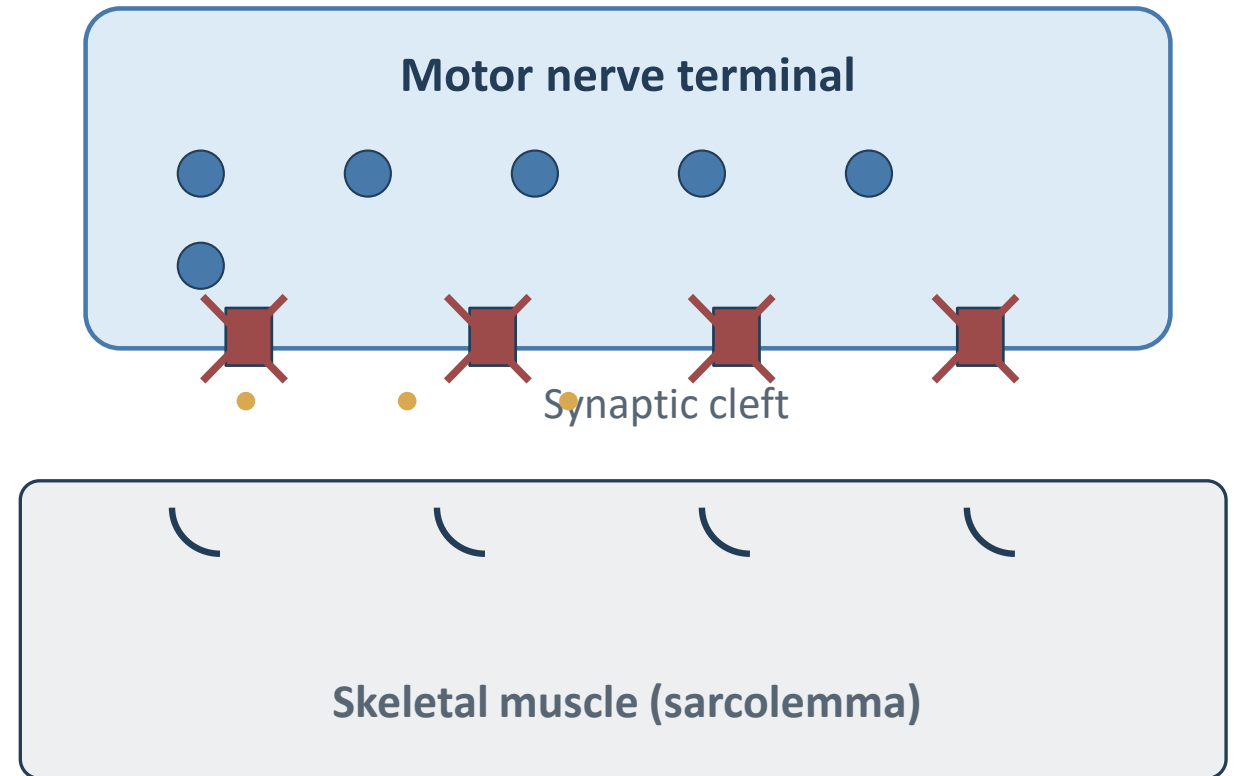
The neuromuscular junction is a common disease target

- Autoantibodies, inherited defects, and toxins can impair neuromuscular transmission.
- The same symptom—painless weakness—may result from lesions at different molecular steps.
- Correct presynaptic versus postsynaptic localization guides interpretation.



LEMS autoantibodies target voltage-gated calcium channels

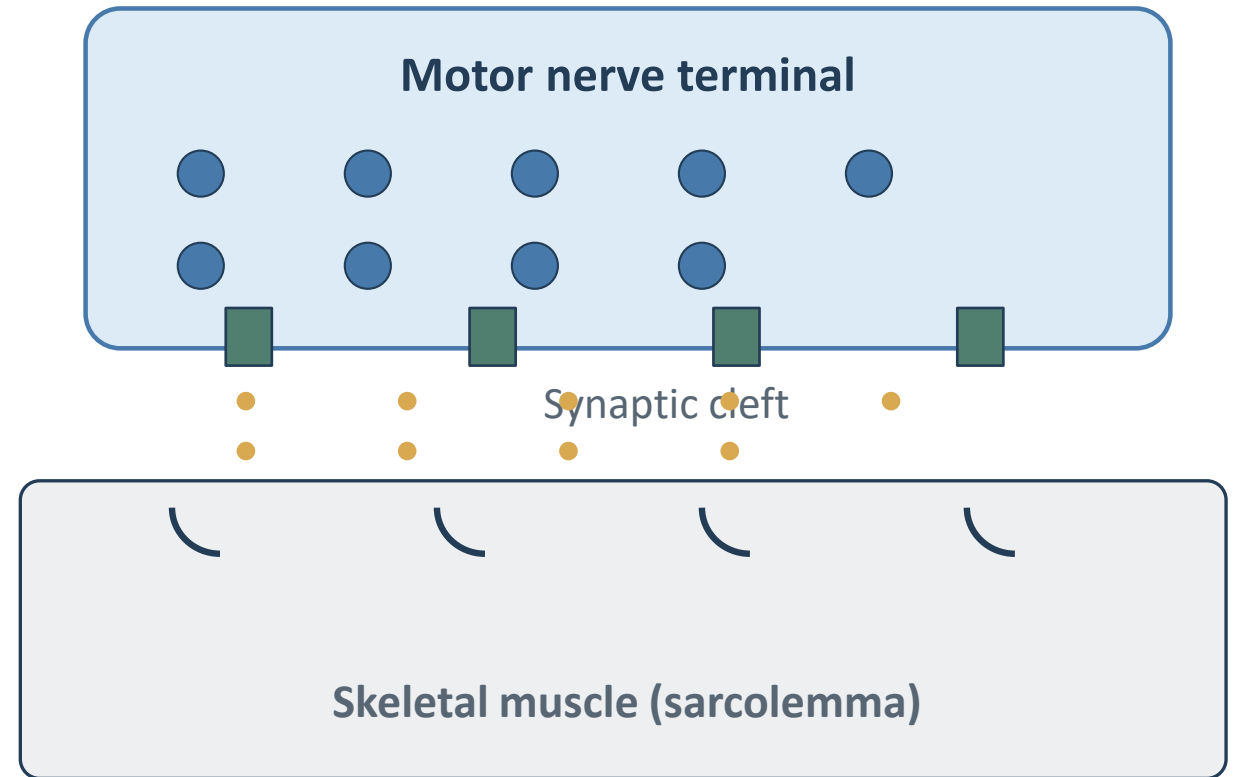
- The relevant antigens are presynaptic calcium channels, principally the P/Q type.
- Channel dysfunction reduces calcium entry during motor nerve activity.
- Consequently, fewer ACh quanta are available to activate muscle fibers.



Fewer ACh quanta released

The P/Q-type channel is a functional antigen

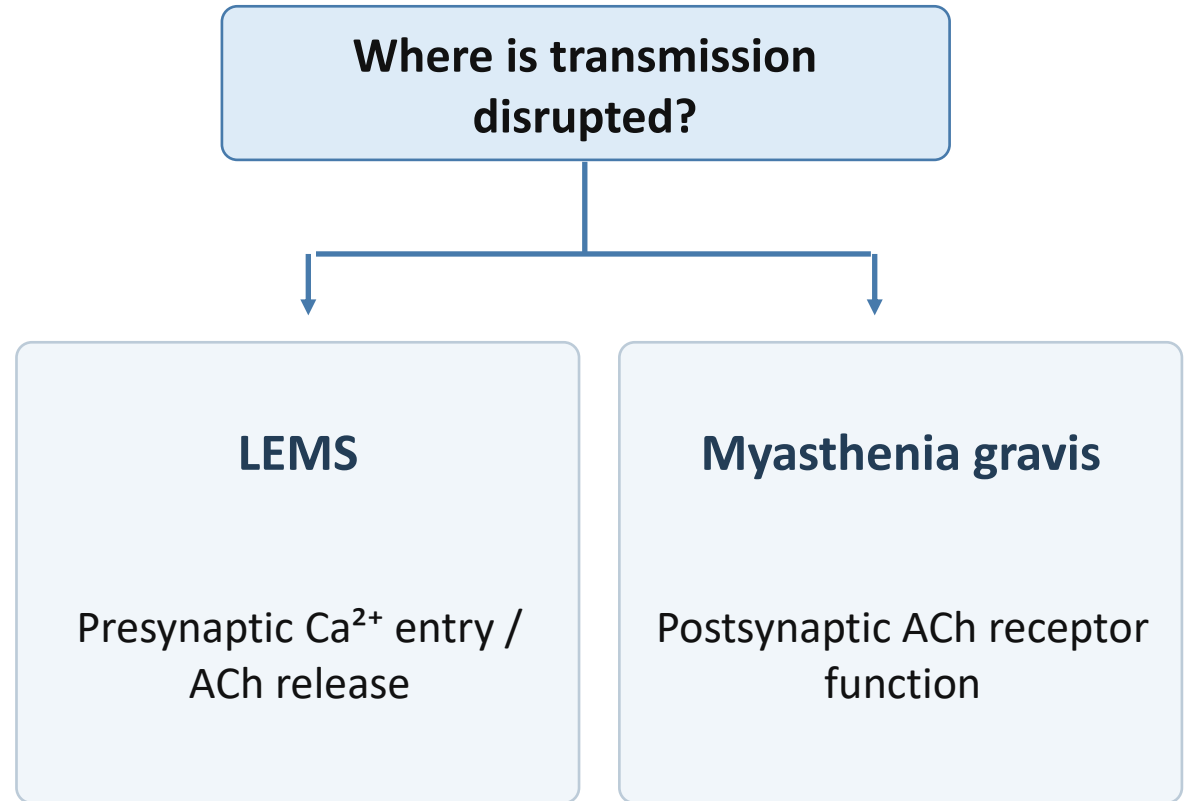
- P/Q-type voltage-gated calcium channels (CaV2.1) are concentrated in motor nerve-terminal active zones.
- Antibodies directed to these channels interfere with efficient transmitter release.
- Channel-directed immunity is the central mechanistic distinction from typical ACh-receptor myasthenia.



ACh released across the cleft

Presynaptic disease: Intact receptors, reduced transmitter

- In LEMS, defective ACh output originates at the nerve terminal.
- In common myasthenia gravis, impaired postsynaptic reception dominates.
- The two disorders can therefore show different behavior during repetitive activation.



Antibody-mediated failure follows a causal sequence

- Presynaptic antigen recognition is upstream of reduced calcium-dependent release.
- Reduced ACh output diminishes end-plate activation.
- Failure to reliably activate muscle fibers manifests as fluctuating strength.

Anti-P/Q-type VGCC response



Less presynaptic Ca^{2+} entry



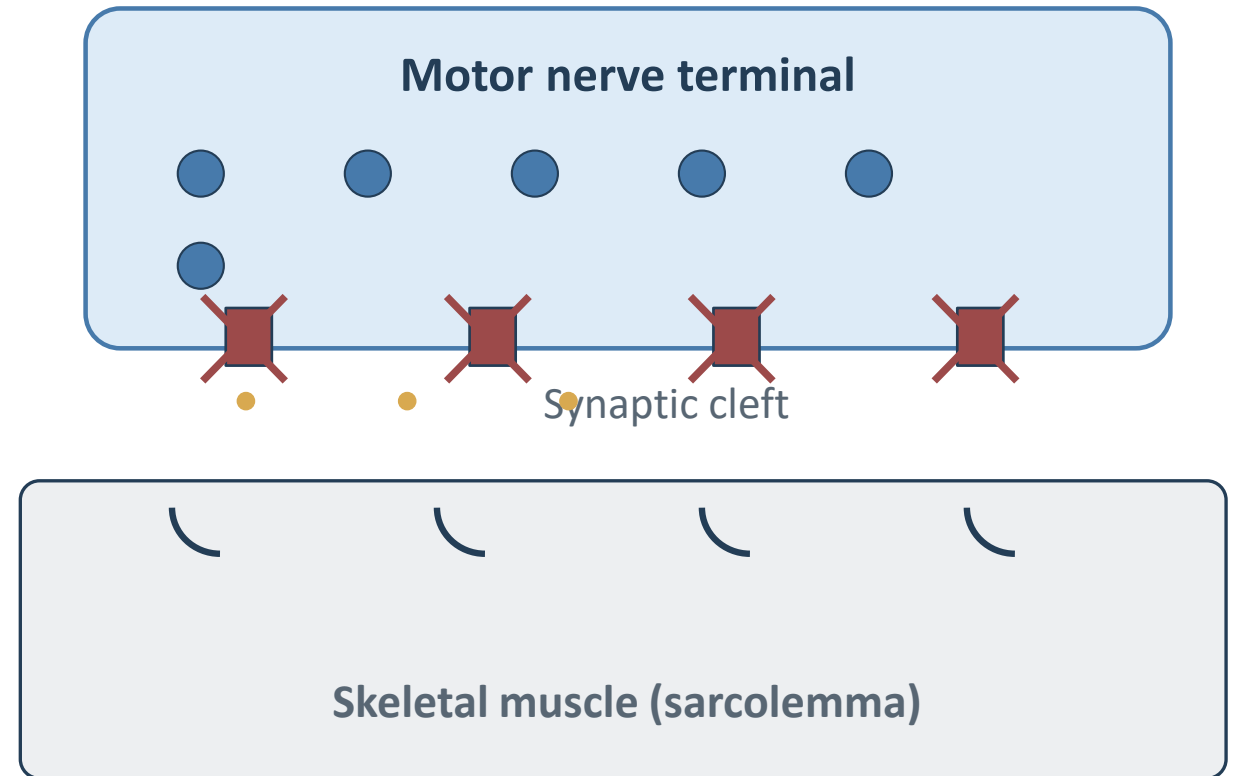
Reduced ACh quantal release



Weakness and fatigability

Why the muscle remains weak despite neural impulses

- A motor impulse may arrive but fail to release enough ACh.
- The postsynaptic response may not consistently reach the threshold for muscle-fiber excitation.
- The clinical deficit reflects transmission failure rather than a primary muscle-fiber lesion.



Fewer ACh quanta released

Reduced quantal content links antibody to weakness

- ACh is released in discrete vesicular packets (quanta).
- Presynaptic calcium-channel inhibition decreases the number released per impulse.
- Electrophysiologic responses provide functional evidence of this reduced transmitter output.

Lower calcium availability



Fewer ACh vesicles released



Smaller end-plate response

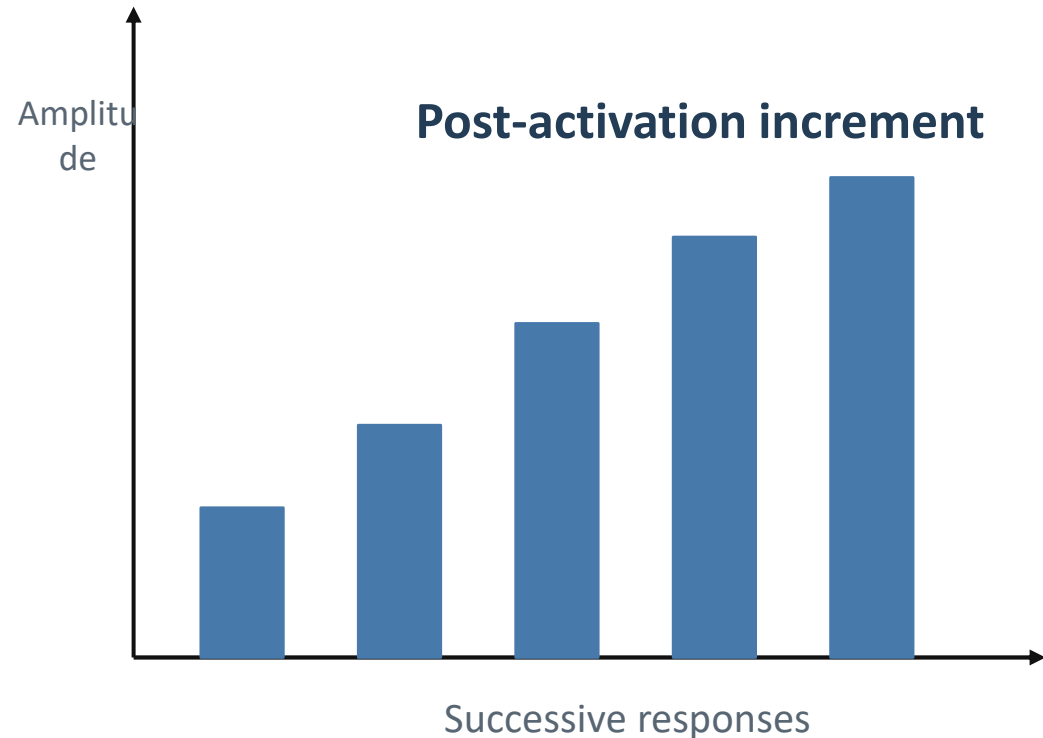


Fewer muscle fibers activated

Brief contraction can transiently improve transmission

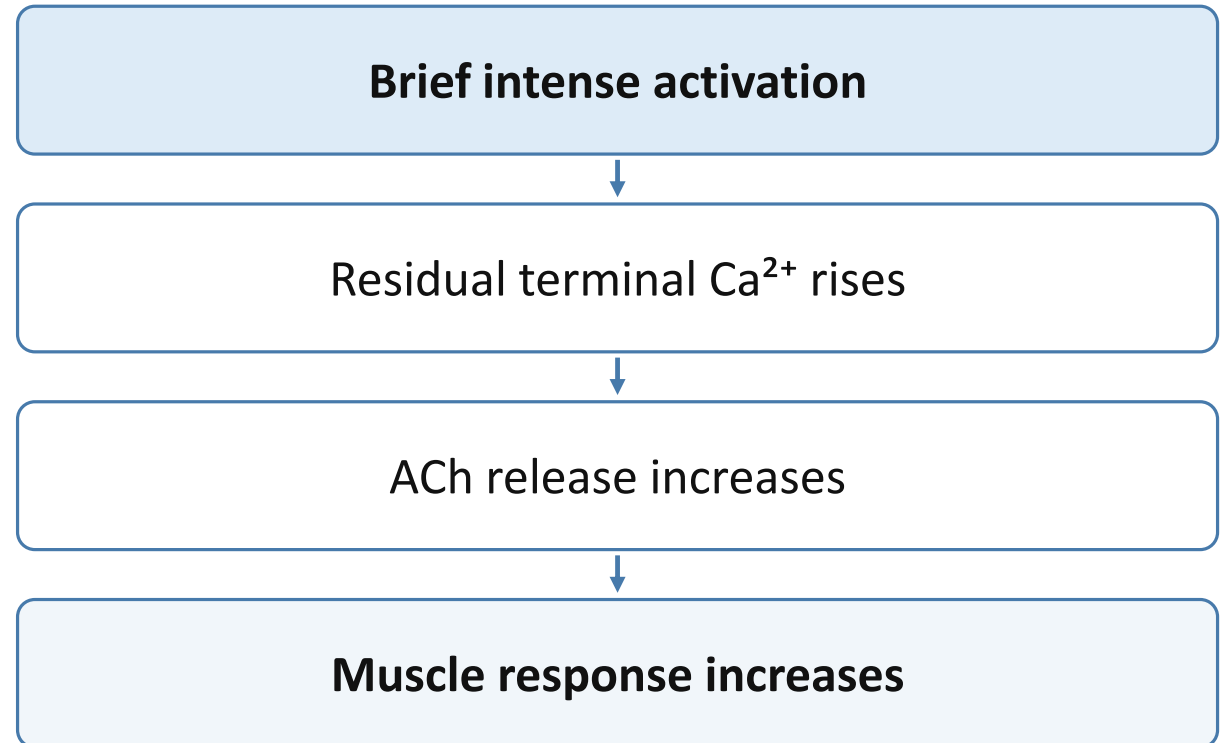
- Muscle strength in LEMS often improves after several seconds of activity.
- Repeated impulses transiently enhance residual calcium availability in the terminal.
- More transmitter release produces post-activation facilitation.

QUALITATIVE SCHEMATIC — NOT A PATIENT TRACE



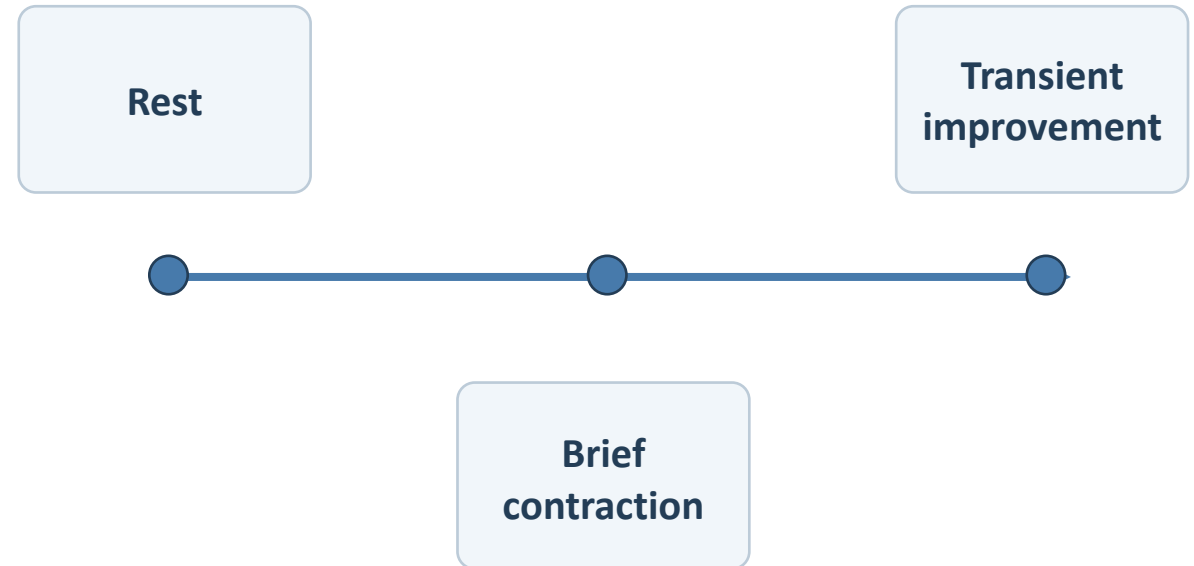
Post-activation facilitation identifies a presynaptic defect

- Baseline calcium-dependent release is impaired in LEMS.
- Short bursts of impulses temporarily improve the probability of ACh release.
- An increased evoked muscle response immediately after activation supports presynaptic localization.



Facilitation is not the same as sustained endurance

- The improvement after brief contraction is transient.
- Prolonged exertion may still cause fatigue and functional limitation.
- Record the timing of examination: Strength and reflexes can vary immediately after activity.



Typical electrophysiology contains both decrement and increment

- A low resting compound muscle action potential (CMAP) suggests low baseline transmitter release.
- Low-frequency repetitive nerve stimulation often produces decrement.
- Brief exercise or high-frequency stimulation elicits an increment—a diagnostic clue.

Low CMAP

Resting response

Decrement

Low-frequency
trains

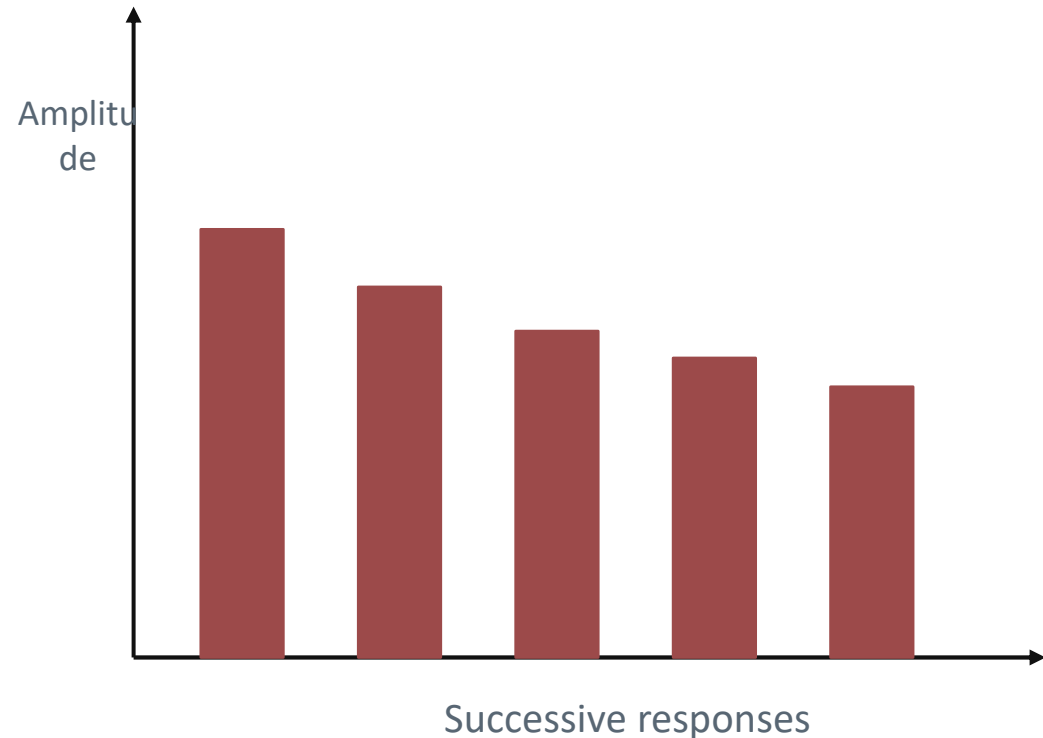
Increment

Post-activation /
rapid trains

Low-frequency stimulation can produce decrement

- Repeated slow stimuli may progressively exhaust an already limited release reserve.
- The evoked muscle response decreases across the stimulus train.
- Decrement alone does not reliably distinguish LEMS from myasthenia gravis.

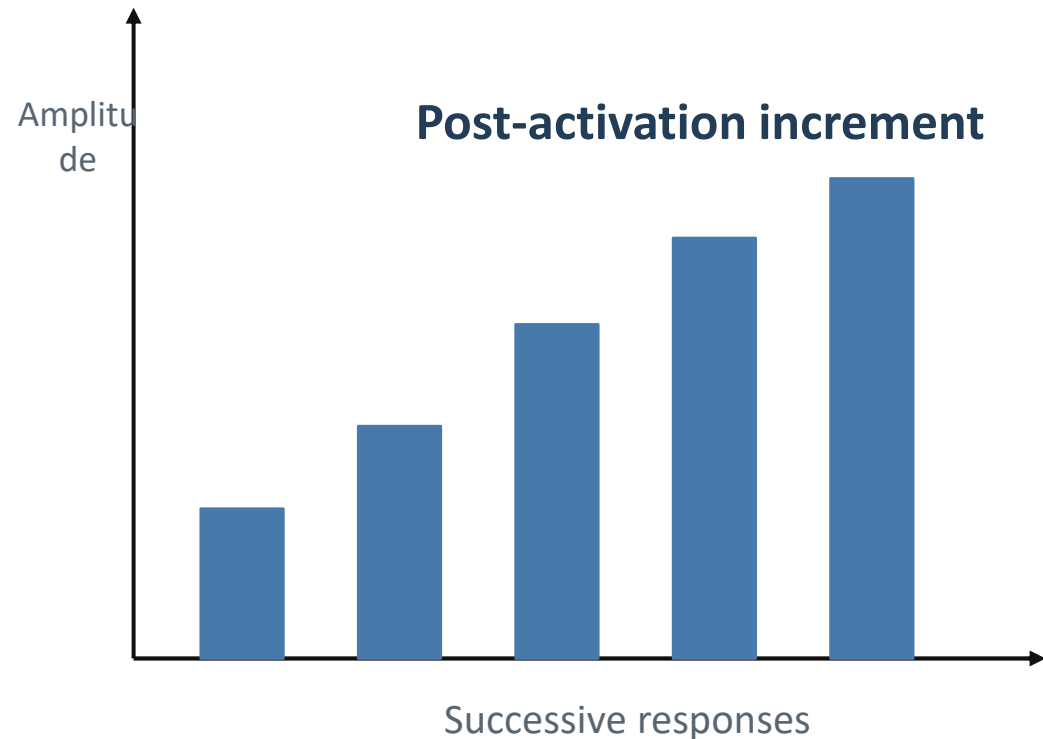
SCHEMATIC — not quantitative data



A post-exercise increment is the discriminating response

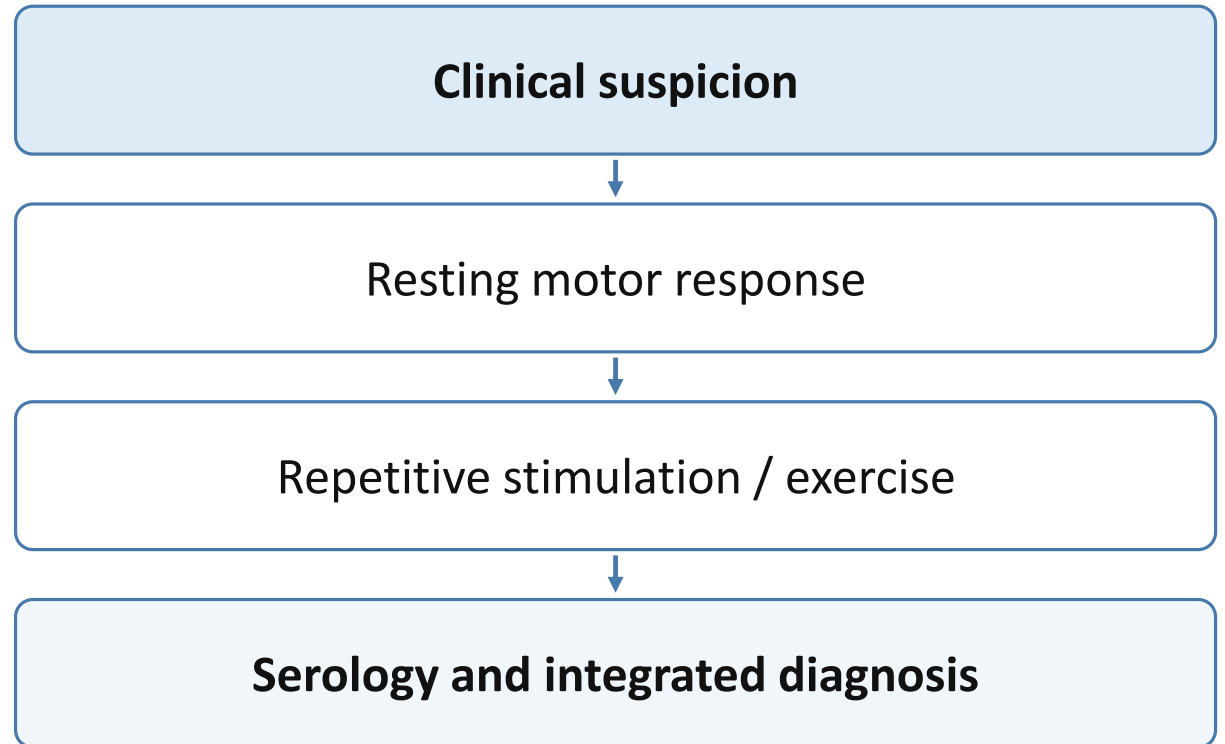
- After brief maximal contraction, the evoked response can markedly increase.
- This facilitation reflects enhanced presynaptic ACh release.
- Interpret the finding with the clinical phenotype and antibody results.

QUALITATIVE SCHEMATIC — NOT A PATIENT TRACE



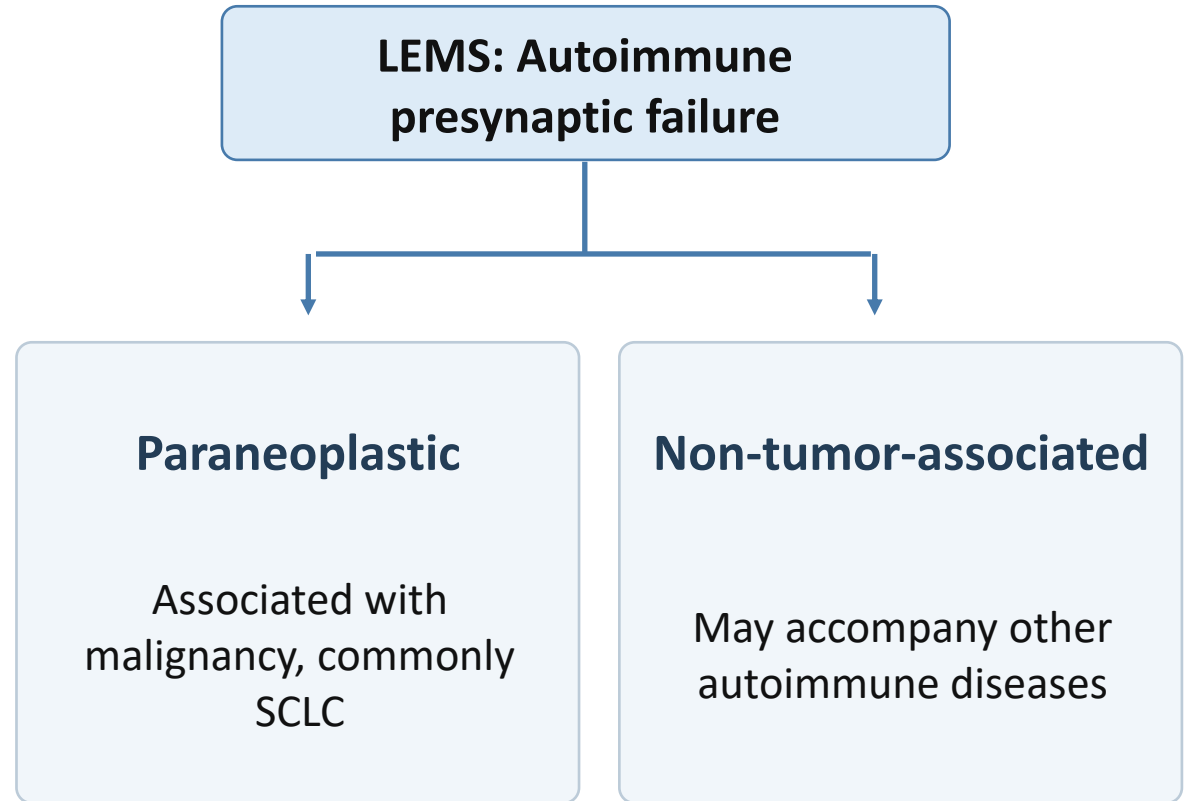
Electrophysiology must be interpreted as a pattern

- No isolated waveform feature should replace careful clinical examination.
- Resting CMAP reduction, low-rate decrement, and post-activation increment are complementary.
- Technical quality, muscle selection, and activation protocol influence interpretation.



Autoimmune LEMS exists with or without malignancy

- One form accompanies an underlying neoplasm (paraneoplastic LEMS).
- Another occurs without a detected tumor and may coexist with autoimmune disease.
- The neuromuscular physiological defect is shared by both forms.



Small-cell lung carcinoma is the dominant tumor association

- Underlying cancer in about half of patients.
- The associated malignancy is most often small-cell carcinoma of the lung.
- Recognizing LEMS may therefore reveal an occult malignancy.

LEMS

Immune
channelopathy

About half

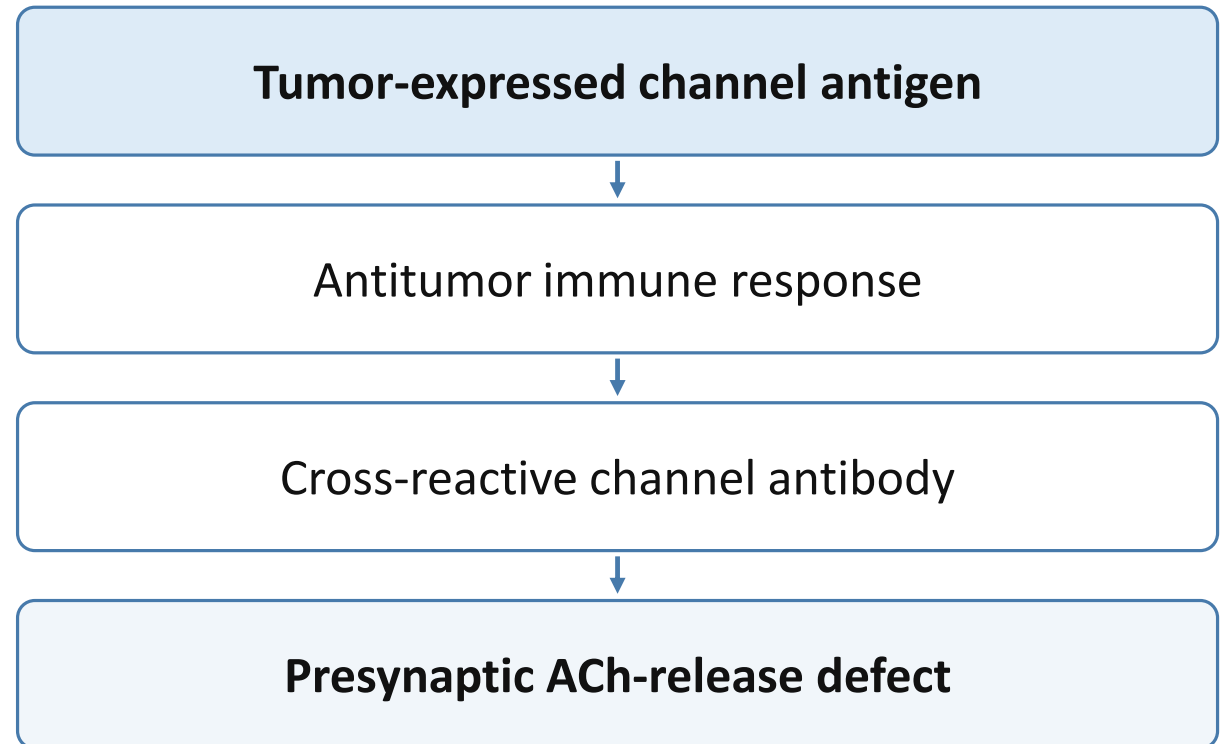
Underlying
malignancy

SCLC

Most frequent
tumor type

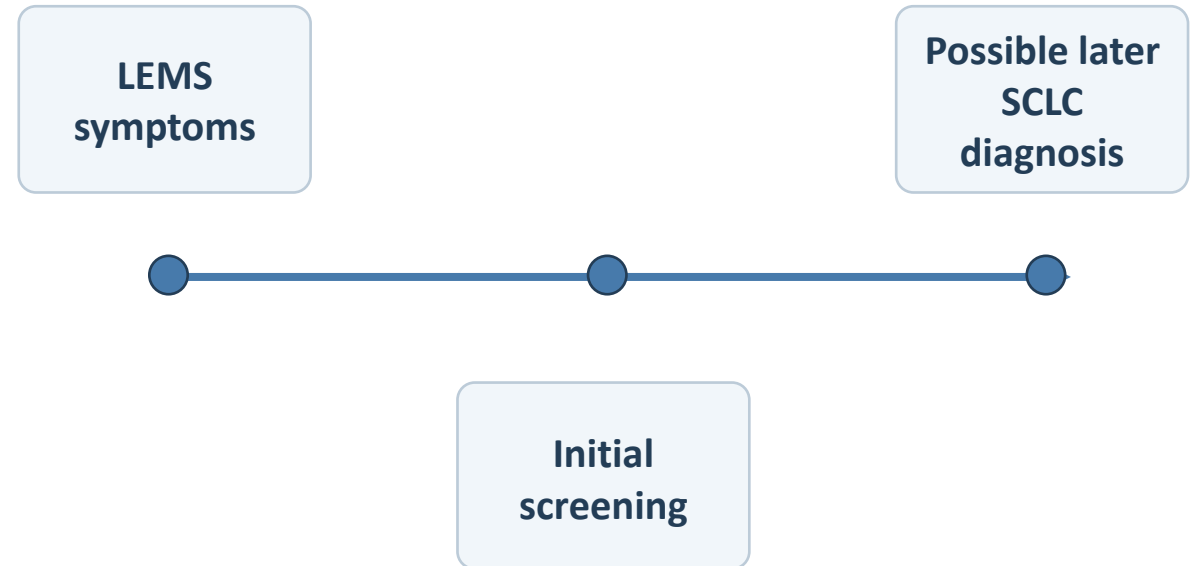
Paraneoplastic immune recognition is a proposed mechanism

- Small-cell lung cancer may express calcium-channel antigens also found at motor terminals.
- A tumor-induced immune response is thought to cross-react with neuronal channels.
- This explanation is biologically plausible but is presented by Robbins as a hypothesis.



Neurologic symptoms can precede cancer detection

- Lambert–Eaton weakness can arise before a tumor has been diagnosed.
- The interval may extend for years in some patients,.
- An initially negative malignancy evaluation does not eliminate future cancer risk.



Cancer surveillance is part of syndrome evaluation

- Confirming the neuromuscular syndrome should trigger assessment for an occult malignancy.
- Chest imaging is central because of the SCLC association.
- Follow-up screening strategy should be individualized using specialist protocols and risk factors.

Clinical + physiological LEMS



Evaluate for underlying SCLC



Address a detected malignancy



Continue follow-up when appropriate

Non-tumor-associated LEMS may cluster with autoimmunity

- A substantial fraction of patients have no identified neoplasm.
- Vitiligo and thyroid disease as examples of associated autoimmunity.
- These associations reinforce an immune mechanism but are not themselves diagnostic of LEMS.

LEMS

Autoimmune
presynaptic
dysfunction

Thyroid disease

Possible
autoimmune
association

Vitiligo

Another
described
association

Clinical triad: Proximal weakness, hyporeflexia, dysautonomia

- The characteristic pattern combines proximal limb weakness with depressed tendon reflexes.
- Autonomic dysfunction—often dry mouth—provides an important localizing clue.
- The full triad need not be simultaneously prominent in every patient.

Limb weakness

Usually proximal;
Legs early

Tendon reflexes

Reduced or
absent

Autonomic features

Dry mouth and
other symptoms

Weakness commonly begins in the proximal legs

- Hip-girdle and thigh muscles are often most affected early.
- Patients may struggle to climb stairs or rise from a chair.
- The distribution can resemble other causes of proximal weakness unless reflexes and autonomic signs are assessed.

Hip flexion

Proximal motor
task

Chair rise

Functional
limitation

Stairs

Common patient
complaint

Upper-limb and cranial weakness may emerge later

- Proximal weakness can extend beyond the lower limbs.
- Oculobulbar symptoms may develop; They are generally less dominant initially than in classic myasthenia gravis.
- Severe cases can involve respiratory muscles, requiring careful clinical assessment.

Proximal leg weakness



Additional limb involvement



Possible ocular / bulbar symptoms



Severe: Respiratory involvement

Autonomic dysfunction reflects channel involvement beyond motor terminals

- Presynaptic calcium channels also participate in autonomic neurotransmission.
- Reduced transmitter release can produce non-motor manifestations.
- These findings help differentiate LEMS from many primary myopathies.

Autonomic neuronal channels affected



Reduced neurotransmitter output



Abnormal autonomic function



Dry mouth and related symptoms

Dry mouth is a valuable diagnostic clue

- Xerostomia is a commonly reported autonomic symptom.
- Constipation, altered sweating, and erectile dysfunction may also occur.
- A targeted autonomic review can change the localization of otherwise nonspecific proximal weakness.

Dry mouth

Commonly reported

Gastrointestinal

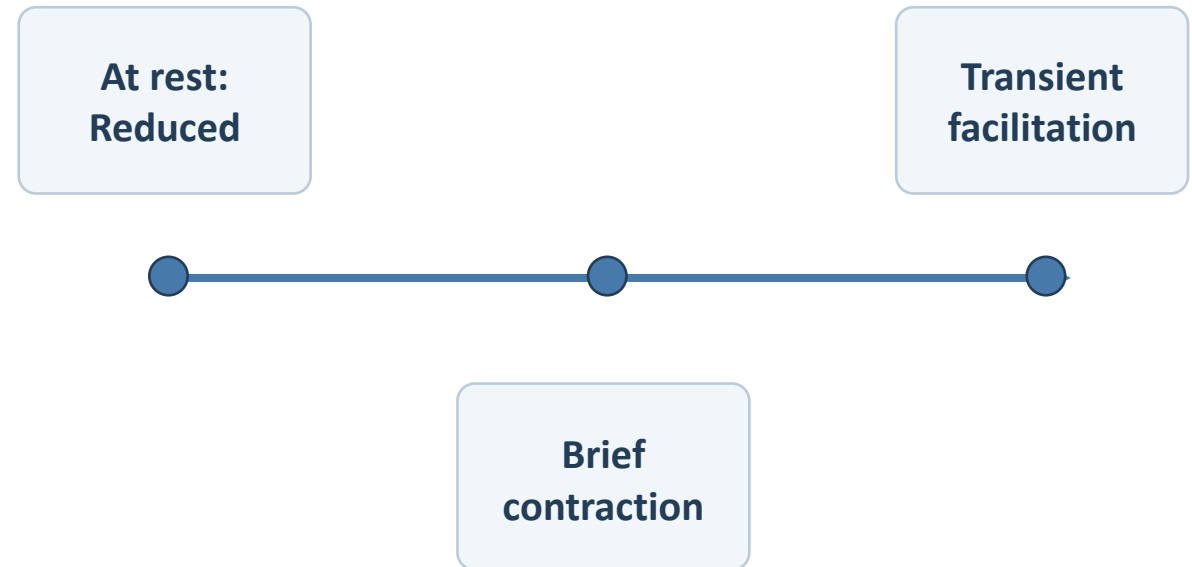
Constipation

Other

Sweating / sexual function

Tendon reflexes may increase after activation

- Hyporeflexia or areflexia is characteristic at rest.
- A brief voluntary contraction may transiently make a reflex more readily elicited.
- Compare reflex assessment before and immediately after activation when clinically appropriate.



Bedside examination should test for reversibility

- Assess baseline power in affected proximal muscle groups.
- Repeat selected maneuvers after several seconds of maximal activation.
- A transient rise in strength or reflex amplitude supports—but does not independently confirm—LEMS.

Establish baseline



Brief maximal activation



Reassess strength / reflexes



Integrate with electrophysiology

Painless fatigue localizes poorly without further clues

- Disorders at the neuromuscular junction commonly produce painless weakness.
- Proximal distribution alone also occurs in myopathies and some neuropathies.
- LEMS-specific clues are post-activation facilitation, autonomic features, and depressed reflexes.

Weakness

Common to
multiple
disorders

Facilitation

Presynaptic clue

Autonomic + reflex

Strengthen LEMS
suspicion

A focused history can raise suspicion for LEMS

- Ask about progressive leg weakness and difficulty with stairs or chair rise.
- Elicit dry mouth, bowel symptoms, and other autonomic complaints.
- Review prior malignancy, smoking exposure, and the time course of neurological symptoms.

Motor

Function and progression

Autonomic

Dry mouth / constipation

Cancer risk

History and risk factors

Serum channel antibodies support an autoimmune diagnosis

- Most patients have detectable antibodies to P/Q-type VGCC.
- A positive result supports the diagnosis in a compatible clinical and neurophysiological setting.
- Antibody testing should be interpreted alongside the full syndrome—not in isolation.

Clinical phenotype

Proximal weakness ± autonomic signs

Electrophysiology

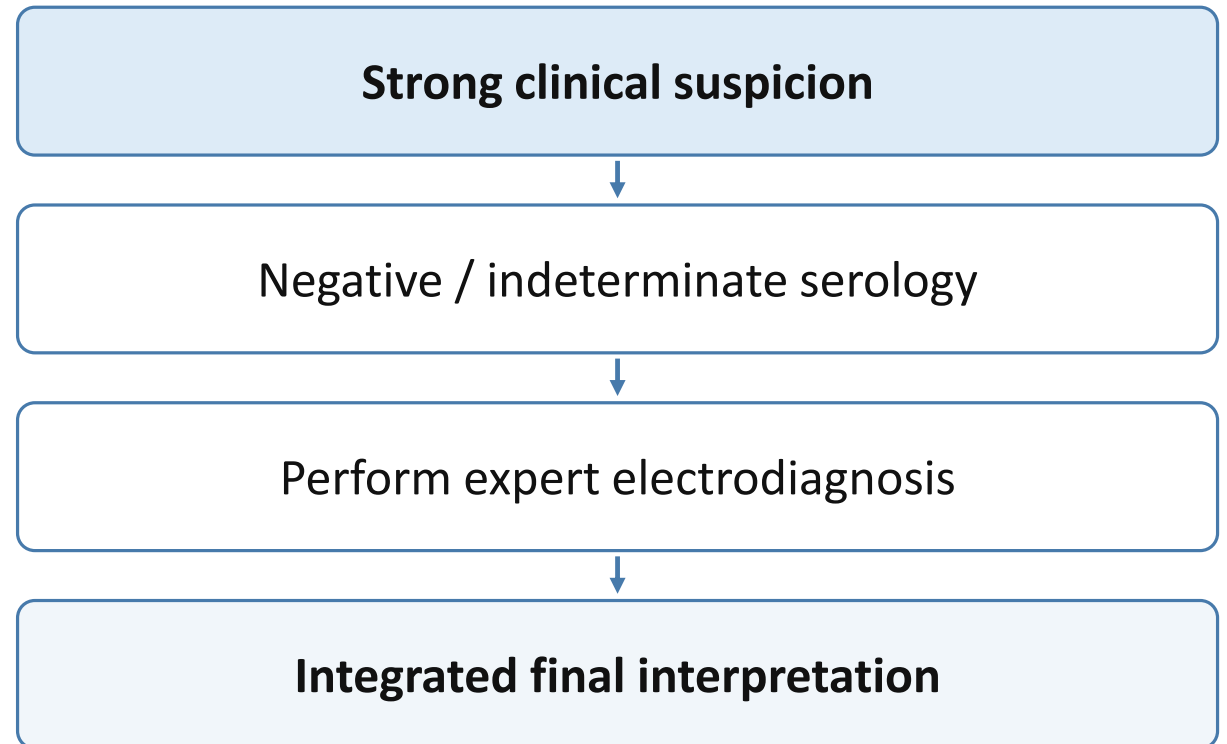
Presynaptic response pattern

Anti-P/Q VGCC

Supportive serology

A negative channel-antibody result does not exclude LEMS

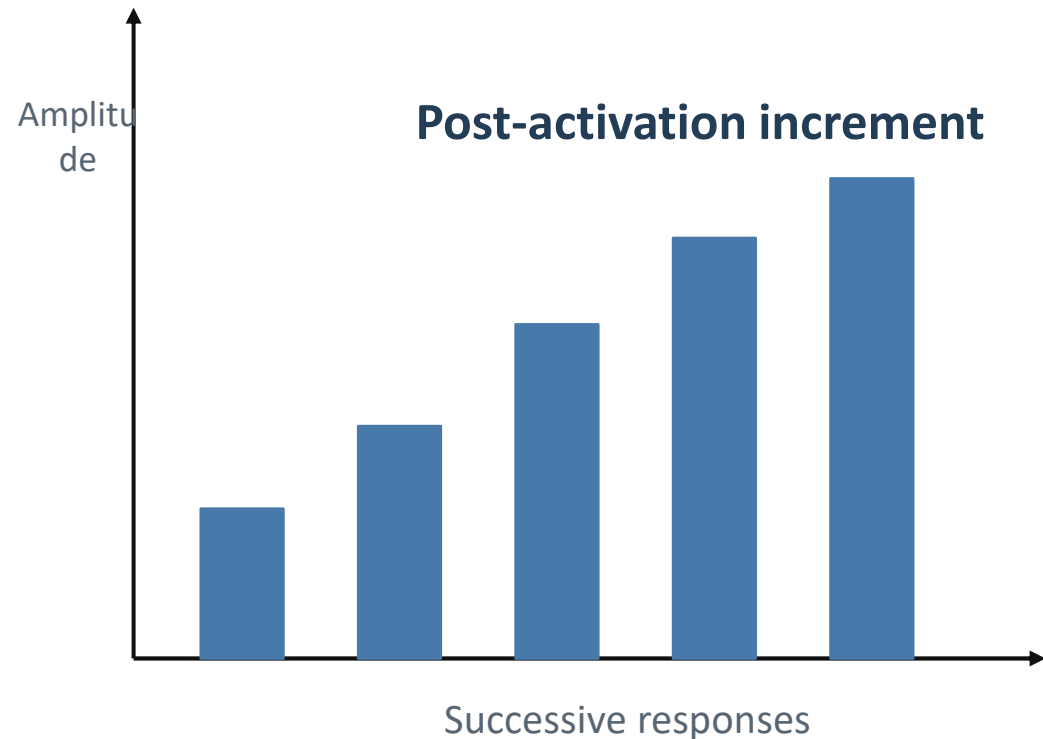
- Reviews report antibodies in approximately 90% of affected patients—not all patients.
- Seronegativity therefore cannot replace careful electrodiagnostic evaluation.
- The probability of disease depends on the entire presentation and objective physiological findings.



Resting CMAP amplitude provides a baseline

- Compound muscle action potentials reflect the summed electrical response of activated muscle fibers.
- LEMS often has low initial CMAP amplitudes before exercise.
- The response may become larger after activation when transmitter output transiently increases.

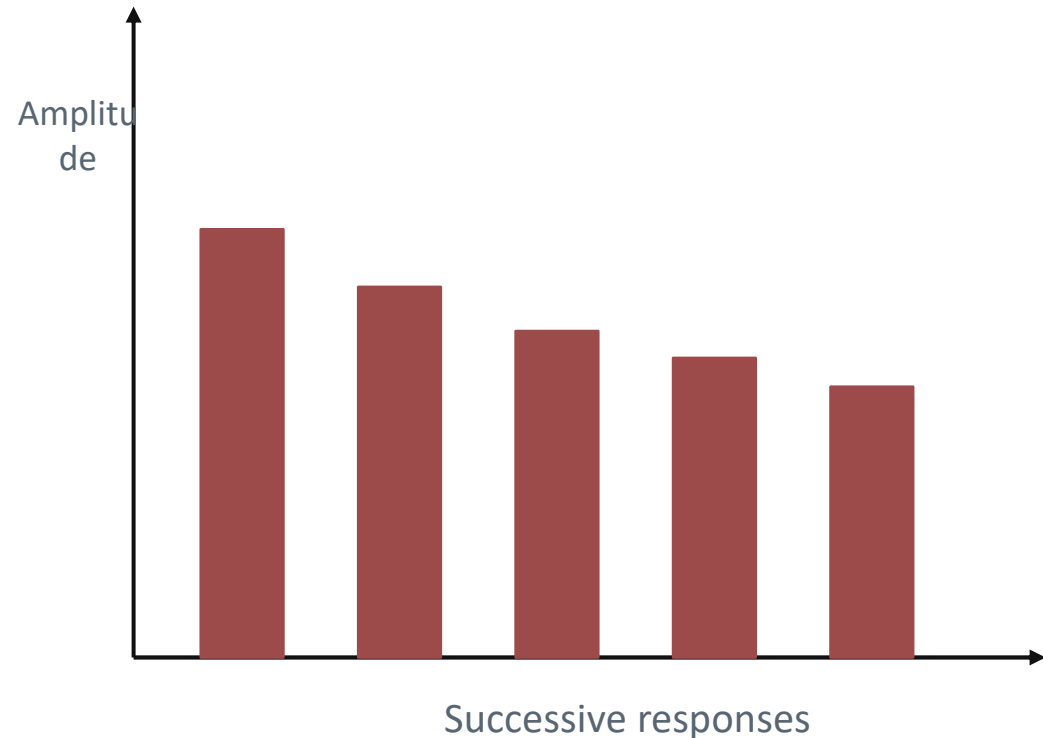
QUALITATIVE SCHEMATIC — NOT A PATIENT TRACE



Low-rate repetitive stimulation is not pathognomonic

- A decremental response can occur in LEMS during low-frequency stimulation.
- Myasthenia gravis also produces decremental responses.
- The decisive distinction often requires testing the response to brief exercise or rapid stimulation.

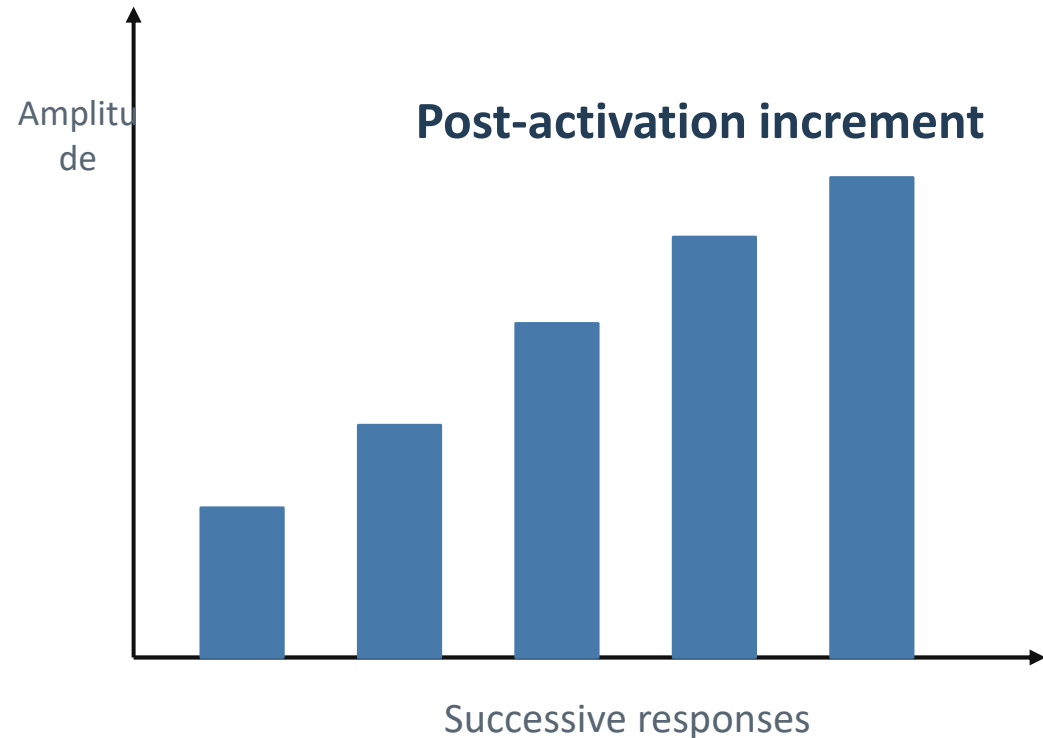
SCHEMATIC — not quantitative data



Post-activation increment reflects physiologic reserve

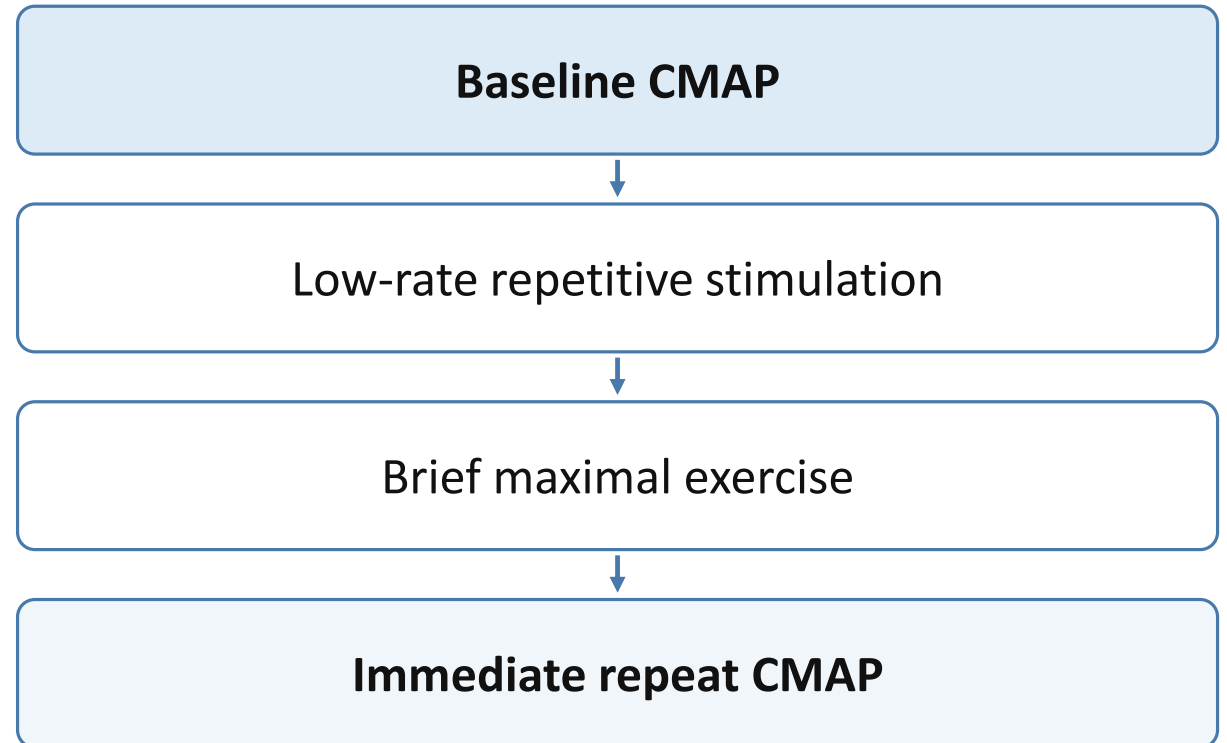
- Transient accumulation of calcium can partially bypass reduced resting entry.
- The resulting increased ACh release recruits additional muscle fibers.
- An increment is expected immediately after activation; Timing matters.

QUALITATIVE SCHEMATIC — NOT A PATIENT TRACE



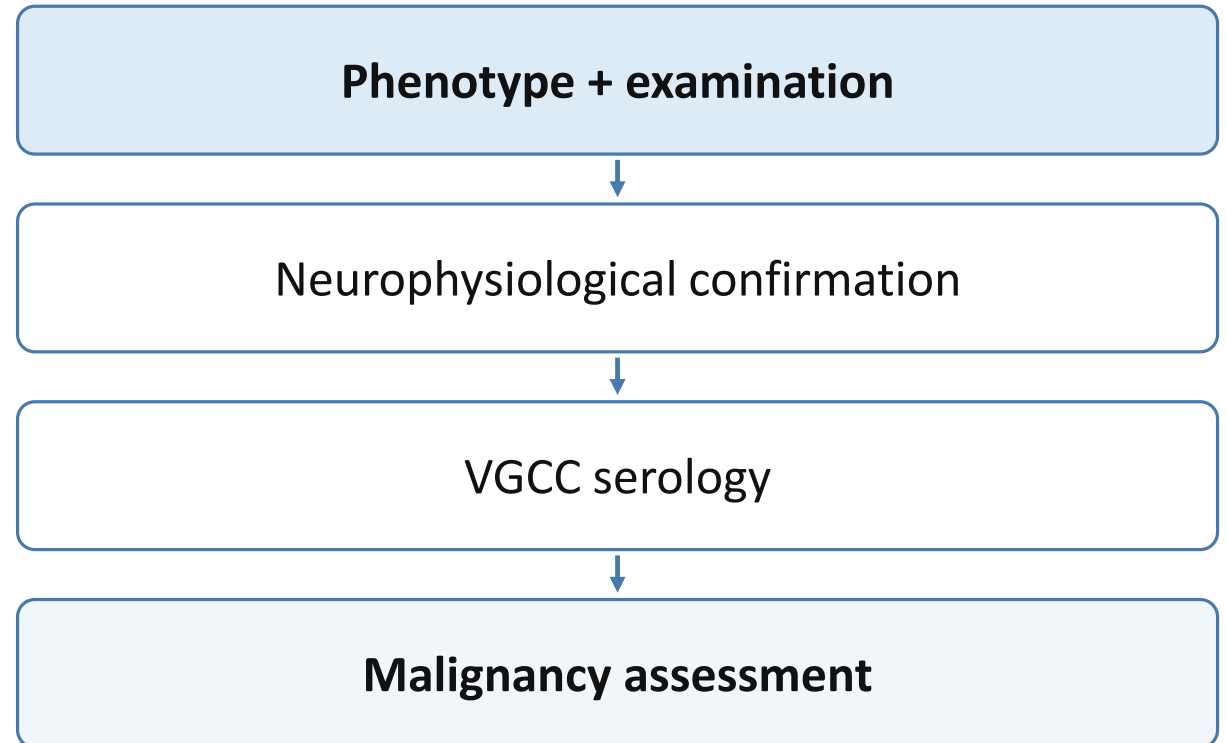
Electrodiagnosis requires correct timing and technique

- Obtain baseline recordings before facilitating the muscle.
- Compare low-frequency responses with those after brief activation.
- Poor activation, temperature effects, and technical artifacts can mislead interpretation.



An integrated diagnostic sequence limits false conclusions

- Clinical localization leads to targeted neurophysiology and serology.
- A coherent triad is more persuasive than one isolated abnormality.
- Tumor evaluation follows LEMS recognition rather than substituting for neurologic confirmation.



LEMS and myasthenia gravis affect opposite sides of the synapse

Feature	Lambert–Eaton syndrome	Myasthenia gravis
Dominant site	Presynaptic calcium channels	Postsynaptic AChR or MuSK
Transmission defect	Reduced ACh release	Reduced ACh receptor function
Brief activity	Strength may improve	Weakness commonly worsens
Typical context	SCLC association	Thymic abnormalities often associated

Clinical discrimination: LEMS versus myasthenia gravis

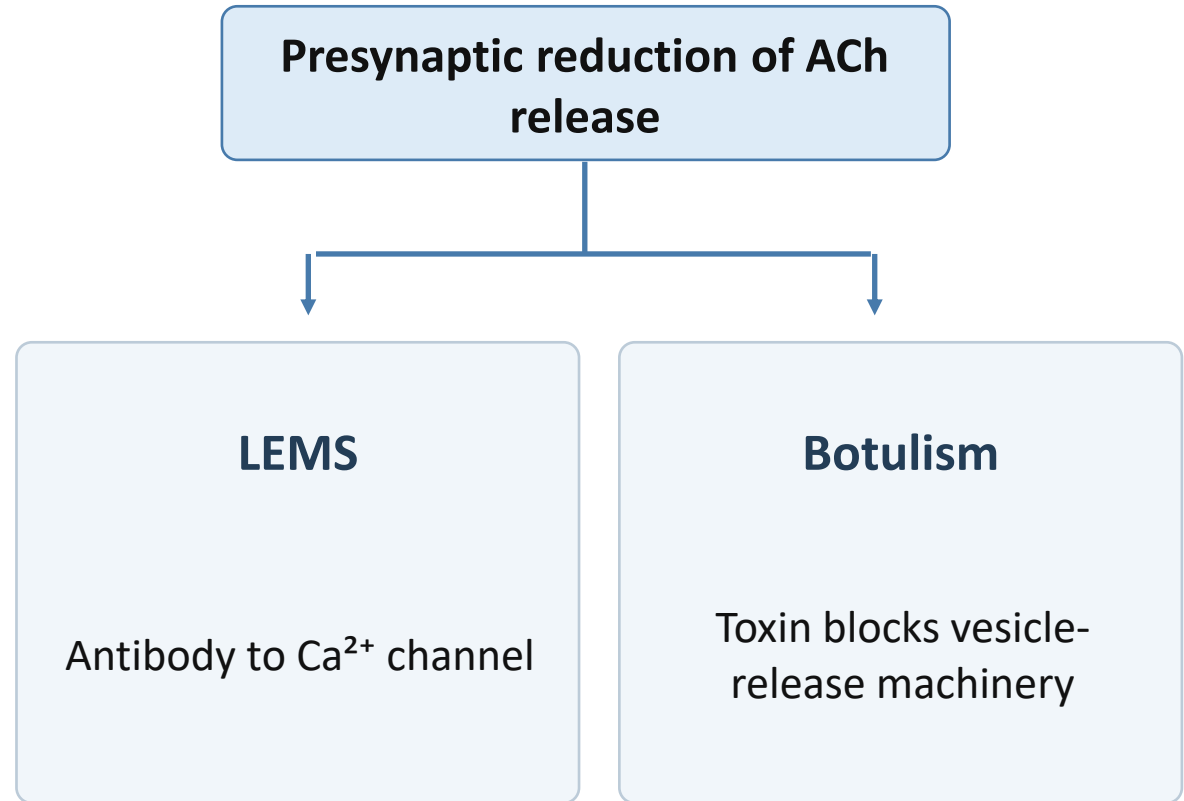
Clinical clue	LEMS	Typical AChR myasthenia
Early emphasis	Proximal legs	Ocular weakness often prominent
Reflexes	Often reduced / absent	Usually maintained
Autonomic features	Common	Not a defining feature
Activation	Brief facilitation	Exertional fatigability
Cancer link	Small-cell lung cancer	Thymoma in a subset

Electrophysiologic discrimination requires increment testing

Test feature	LEMS	Myasthenia gravis
Resting CMAP	Often reduced	Often preserved
Low-rate repetitive train	Decrement may occur	Decrement may occur
After brief contraction	Marked facilitation possible	No characteristic marked increment
Diagnostic principle	Presynaptic release failure	Postsynaptic receptor dysfunction

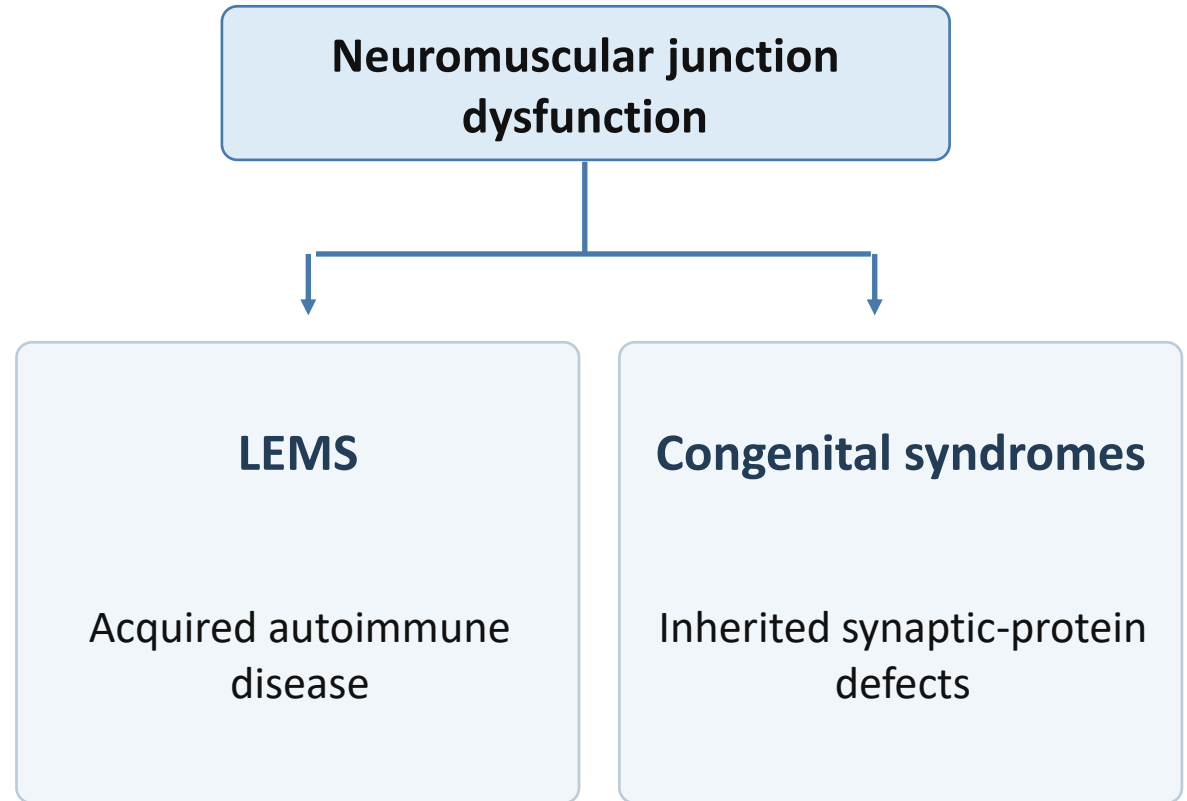
Botulism is another presynaptic disorder—but by a different mechanism

- Botulinum neurotoxin blocks vesicular ACh release from presynaptic terminals.
- LEMS instead involves antibodies to presynaptic calcium channels.
- Exposure history, clinical tempo, autonomic findings, and electrodiagnosis distinguish the mechanisms.



Congenital myasthenic syndromes require a different framework

- Congenital syndromes result from inherited defects in synaptic proteins.
- Clinical onset can be perinatal or later depending on the affected gene.
- Genetic disease differs from the acquired autoimmune pathogenesis of LEMS.



Primary myopathy can resemble proximal LEMS weakness

- Proximal weakness and impaired chair rise are not unique to the neuromuscular junction.
- Autonomic symptoms and exercise-related reflex facilitation favor LEMS localization.
- Serological and electrodiagnostic studies can distinguish junctional dysfunction from primary muscle disease.

Phenotype

Similar proximal weakness

Distinguish

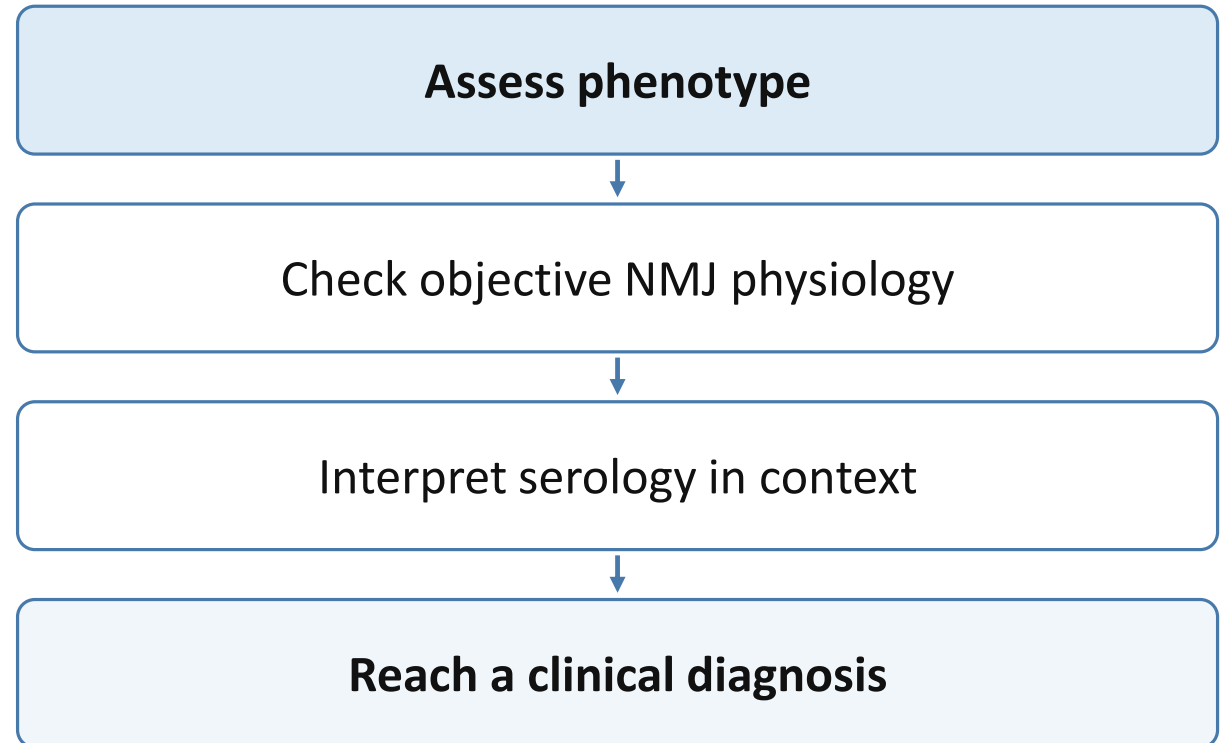
Reflexes and autonomic signs

Confirm

Neurophysiology + serology

A positive VGCC antibody without the syndrome is insufficient

- A laboratory result must be interpreted against pre-test probability.
- Compatible clinical and electrophysiological findings increase diagnostic confidence.
- Do not diagnose or exclude LEMS using serology as the sole criterion.



Treatment targets transmitter release, immunity, and cancer

- Symptomatic treatment improves effective presynaptic ACh release.
- Immune-directed treatment addresses antibody-mediated dysfunction when indicated.
- If SCLC is present, tumor-directed treatment is a core component of care.

Symptomatic

Enhance ACh
release

Immunologic

Reduce immune-
mediated effects

Oncologic

Treat associated
tumor

Amifampridine enhances presynaptic transmitter release

- Amifampridine (3,4-diaminopyridine) blocks presynaptic potassium channels.
- Prolonged depolarization allows more calcium entry through remaining functional channels.
- The resulting increase in ACh release can improve strength and function.

Presynaptic K⁺-channel block



Prolonged nerve-terminal action potential



Enhanced Ca²⁺ entry



Increased ACh release

Symptomatic therapy has important safety considerations

- Amifampridine is a treatment for LEMS, not a cure for autoimmune channel dysfunction.
- The FDA label includes seizure-related precautions and contraindications.
- Prescription choice, dosing, and monitoring require patient-specific specialist evaluation.

Benefit

More effective
ACh release

Risk

Seizure
precautions

Oversight

Specialist
prescribing /
monitoring

Immunotherapy addresses the autoimmune component

- Immunosuppressive approaches analogous to those used in myasthenia gravis.
- Selected patients may receive immunomodulation when symptomatic measures are insufficient.
- Choice depends on severity, clinical context, and concurrent tumor management.

Persistent autoimmune dysfunction



Consider immune-directed treatment



Reduce pathogenic antibody effect



Reassess function and adverse effects

The associated malignancy changes management priorities

- LEMS can be a presenting clue to small-cell lung carcinoma.
- Cancer assessment should not be delayed by partial neurologic improvement.
- Treatment of the detected tumor may be relevant to the neurologic syndrome as well as oncologic prognosis.

Recognize LEMS



Detect associated malignancy



Tumor-directed care



Longitudinal neurologic review

Follow-up should track both neurologic and oncologic outcomes

- Document limb function, bulbar/respiratory symptoms, and autonomic complaints.
- Assess treatment tolerability and the durability of improvement.
- For patients without detected cancer, surveillance decisions follow specialist cancer-risk assessment.

Function

Strength and
daily activities

Therapy

Response /
adverse effects

Cancer

Assessment and
surveillance

Case: An older adult with progressive proximal leg weakness

- Several months of difficulty climbing stairs and rising from a chair.
- Examination shows reduced tendon reflexes and dry mouth.
- Strength improves immediately after several seconds of maximal contraction.

Motor

Proximal leg weakness

Reflex

Reduced at rest

Autonomic

Xerostomia

Case interpretation: Localize before naming the tumor

- The combined pattern strongly suggests presynaptic neuromuscular-junction dysfunction.
- Obtain electrodiagnostic testing and anti-P/Q-type VGCC serology.
- If LEMS is confirmed, assess for occult small-cell lung cancer.

Clinical LEMS phenotype



Neurophysiology + channel serology



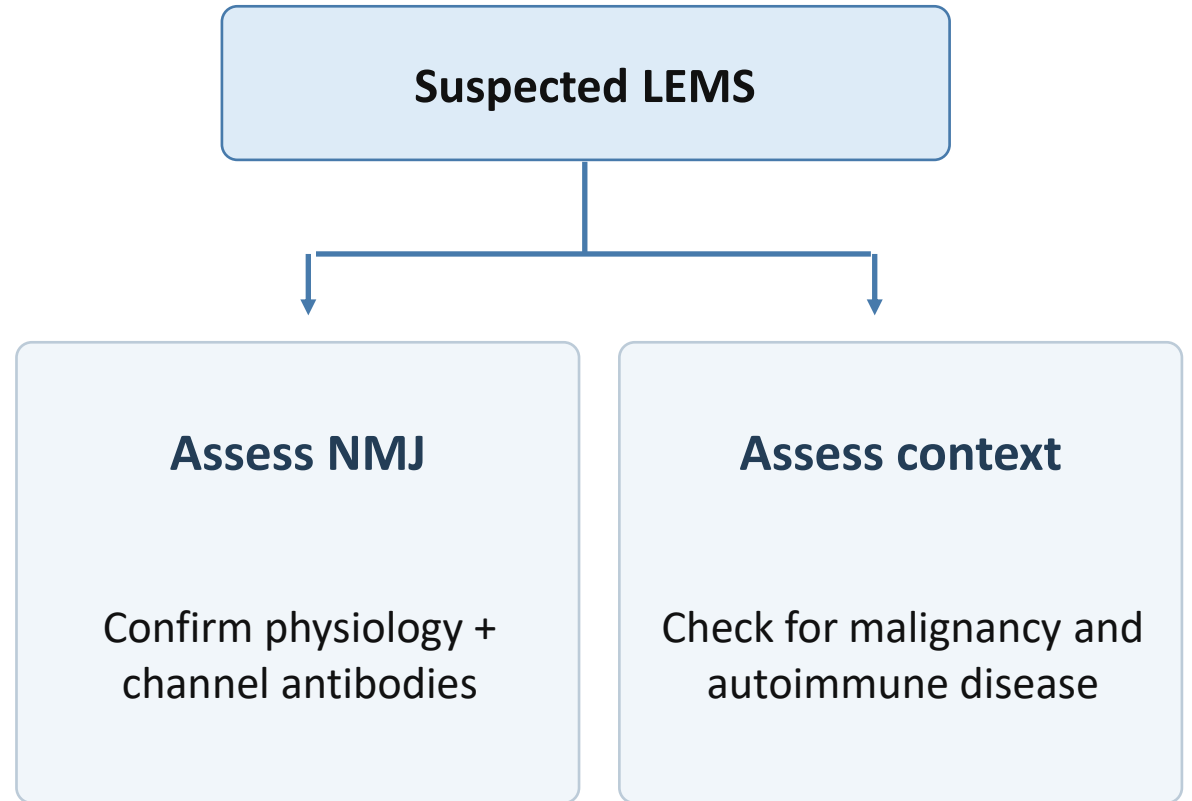
Cancer evaluation



Individualized treatment

Case: An autoimmune background without known malignancy

- A patient with thyroid autoimmune disease develops proximal weakness.
- Resting reflexes are diminished; An increment appears after brief activation.
- Absence of a known tumor does not rule out the LEMS diagnosis.



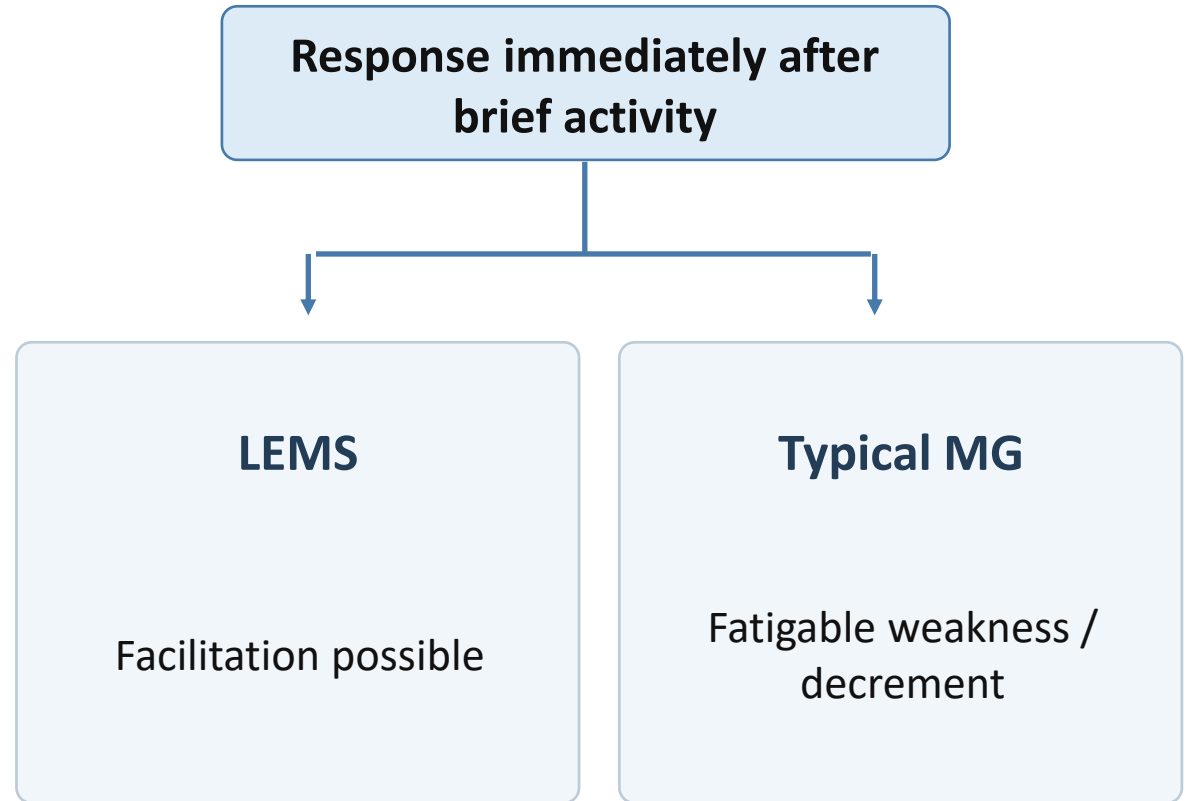
Case interpretation: Negative initial imaging is not the endpoint

- A compatible clinical/electrophysiologic syndrome remains diagnostically meaningful.
- Negative initial chest imaging should be interpreted in light of evolving cancer risk.
- Clinical follow-up is needed regardless of whether an associated cancer is identified.



Misconception: All myasthenic weakness worsens with brief effort

- Typical myasthenia gravis can worsen with repeated use.
- In LEMS, a short burst of activity can improve strength and electrical response.
- This contrast follows directly from the location of the transmission defect.



Misconception: LEMS can be dismissed without a visible tumor

- Non-neoplastic LEMS and autoimmune comorbidities.
- Neurologic symptoms may predate discovery of SCLC.
- Clinical assessment must treat the neurologic diagnosis and the malignancy search as related but distinct tasks.

Confirm presynaptic disorder



Evaluate tumor association



Do not equate negative scan with no LEMS



Reassess risk over time

Synthesis: Three mechanisms explain the disease

- Anti-P/Q-type VGCC antibodies reduce presynaptic calcium-dependent ACh release.
- Short bursts of activation transiently enhance release and muscle response.
- Paraneoplastic recognition of channel antigens is a proposed route to immune initiation.

Autoimmunity

Presynaptic
channel target

Facilitation

Activity raises
ACh release

Paraneoplasia

Frequently linked
to SCLC

Synthesis: A clinically recognizable phenotype

- Proximal weakness, diminished reflexes, and autonomic complaints suggest LEMS.
- Electrophysiologic facilitation and channel antibodies provide confirmatory evidence.
- The possibility of small-cell lung carcinoma changes clinical evaluation.

Recognize

Proximal
weakness +
autonomic signs

Confirm

RNS / exercise +
VGCC serology

Investigate

Associated SCLC

Selected scientific references

Source	Contribution
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Lipka AF, Verschuuren JJG. Handb Clin Neurol. 2024;200:307–325.	Clinical phenotype, antibodies, screening, electrodiagnosis
Ivanovski T, Miralles F. Degener Neurol Neuromuscul Dis. 2019;9:27–37.	Diagnostic physiology and clinical differentiation
FDA. FIRDAPSE (amifampridine) prescribing information. 2025.	Drug mechanism, indications and safety