# Neuromuscular Review
# CTU Noon Rounds

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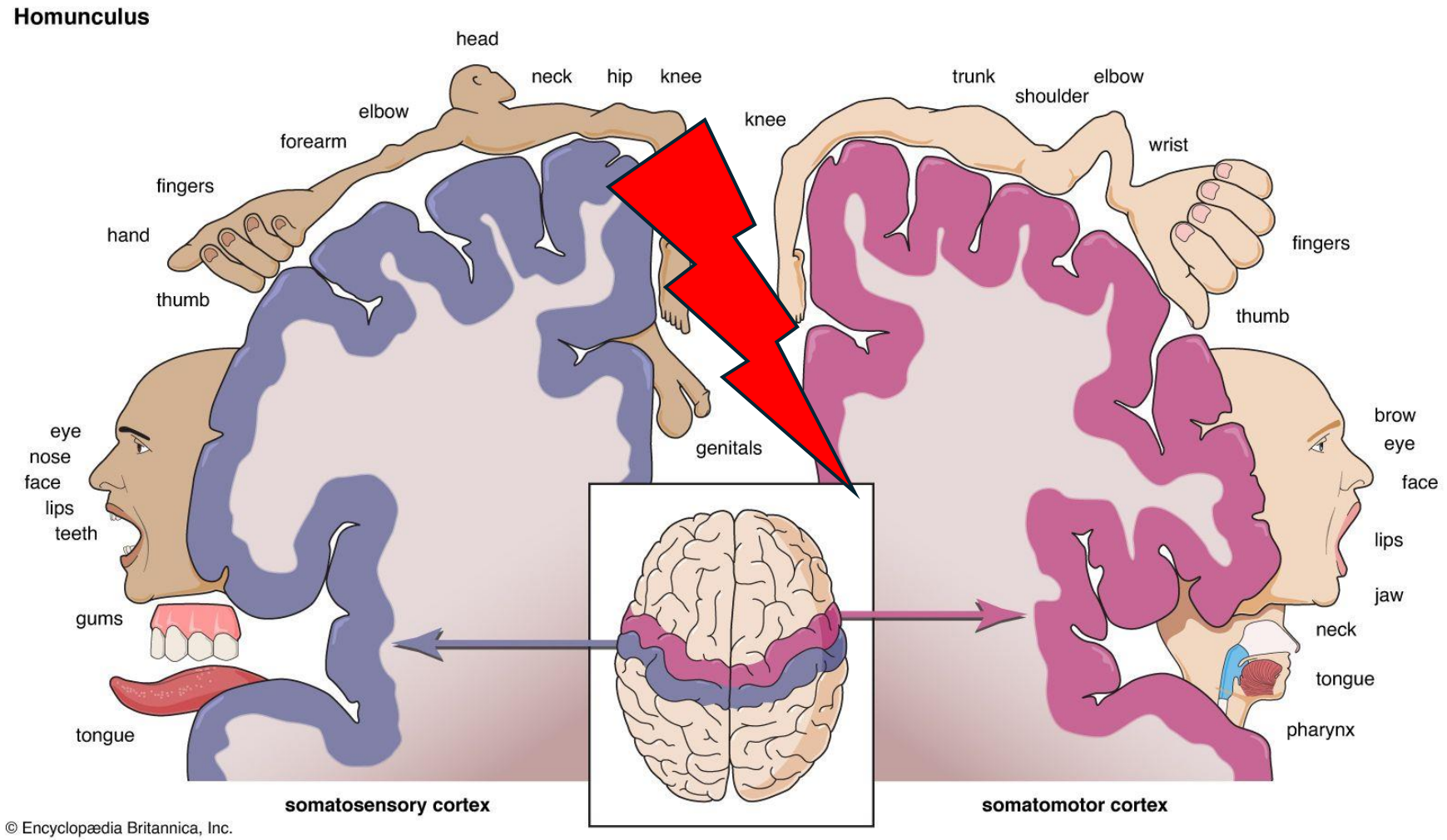
# A stem to get us started…

- 43 yo F with Acute bilateral leg weakness…

Broadly, there are several distinct localizations for this presentation:

1. CNS – Intracranial, spinal cord
2. PNS – anterior horn cell, peripheral nerve (cauda/multifocal), neuromuscular junction, muscle

# Intracranial cause of bilateral leg weakness



# Approach to Weakness Consult

- Where is the weakness?
  - Proximal, distal, or proximal & distal
  - Face involved?
  - Respiratory involvement?
- How long has it been going on for?
- Tempo? (progressive, static, speed of onset, speed of progression, variable/diurnal)
- Sensory loss?
- Pain?
- Bulbar symptoms? (double vision, speaking, swallowing difficulties)
- Shortness of breath?
- Associated features (for every patient)
  - Bowel/bladder dysfunction
  - Infectious symptoms/recent infection.
  - Fever, weight loss, night sweats
  - More as indicated by level of suspicion

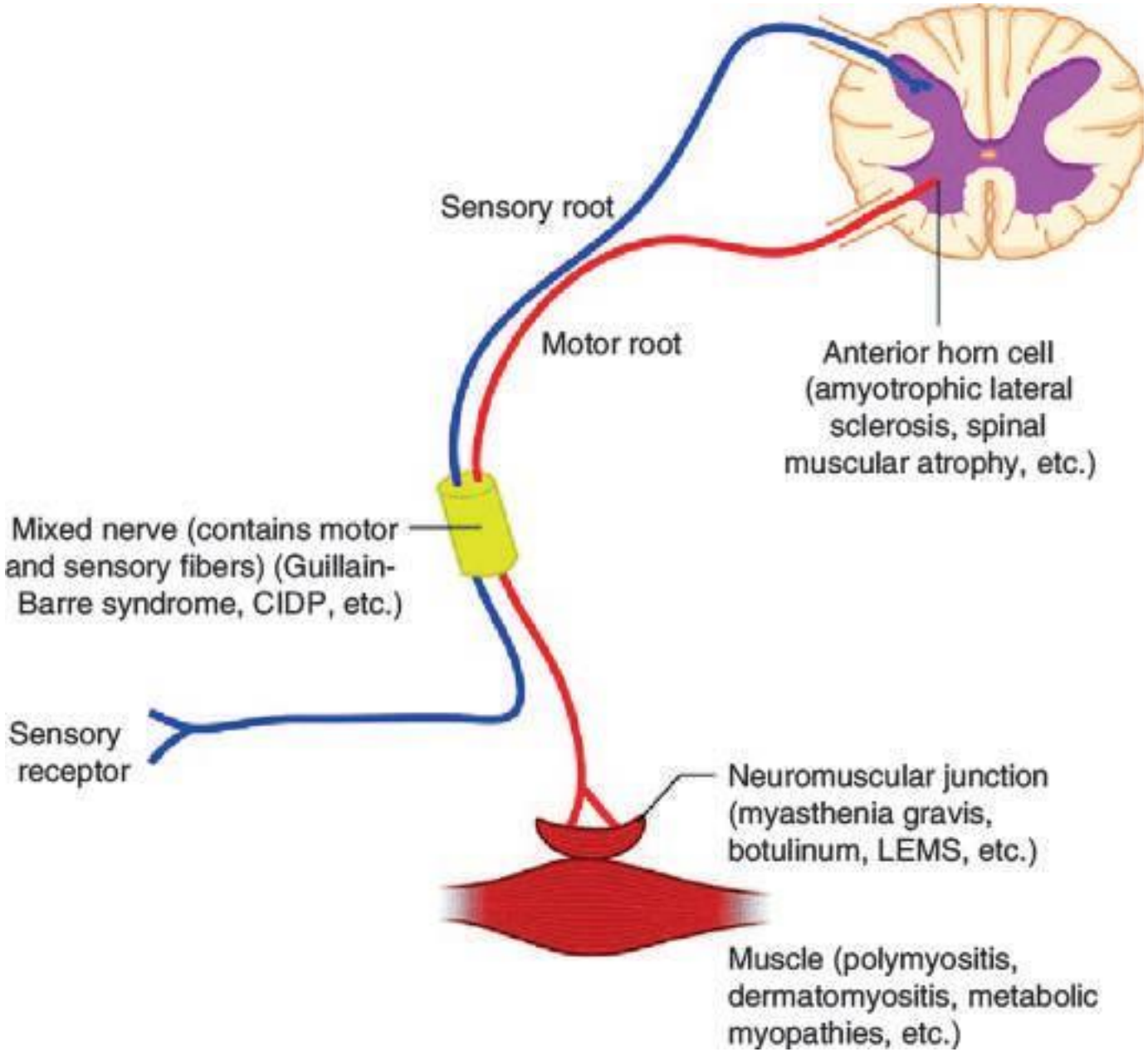
# Localization

| | Upper Motor Neuron | Lower Motor Neuron |
|---|---|---|
| Tone | Increased | Decreased |
| Bulk | Normal | Atrophy/fasciculations |
| Reflexes | Increased<br>Clonus | Decreased/absent |
| Plantar response | Upgoing | Downgoing |

UMN Caveats:

- Pyramidal weakness (UE extensor, LE flexor)
- If UMN signs are present, they shouldn't be ignored (you need an explanation)
- Patients with UMN lesions do not have all signs, or any if presentation is acute/hyperacute

True pathologically brisk reflexes should have spread


Sensory root
Motor root
Anterior horn cell (amyotrophic lateral sclerosis, spinal muscular atrophy, etc.)
Mixed nerve (contains motor and sensory fibers) (Guillain-Barre syndrome, CIDP, etc.)
Sensory receptor
Neuromuscular junction (myasthenia gravis, botulinum, LEMS, etc.)
Muscle (polymyositis, dermatomyositis, metabolic myopathies, etc.)

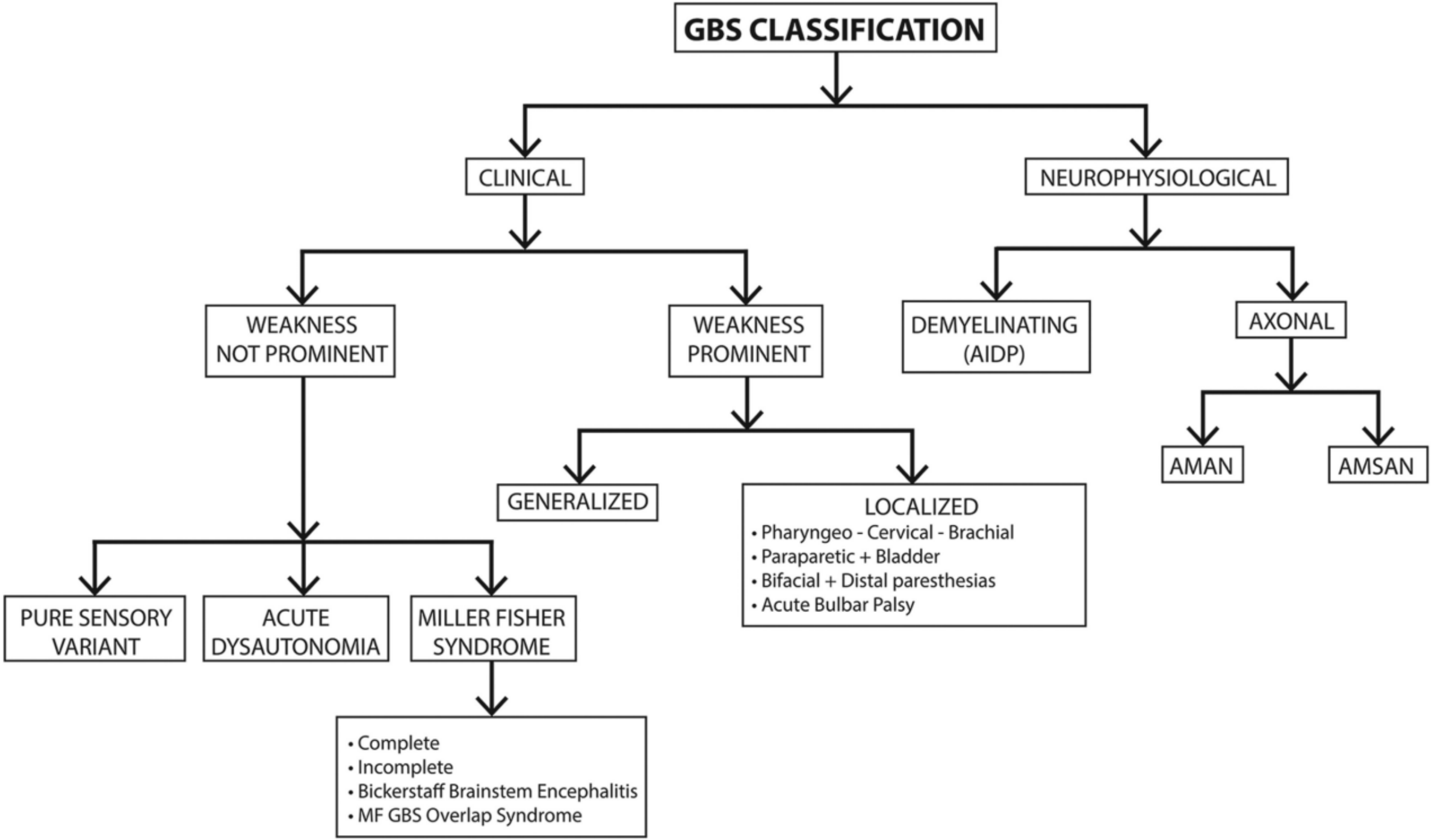
# Guillain–Barré Syndrome

- Immune mediated peripheral nerve disorder, typically triggered by preceding infection

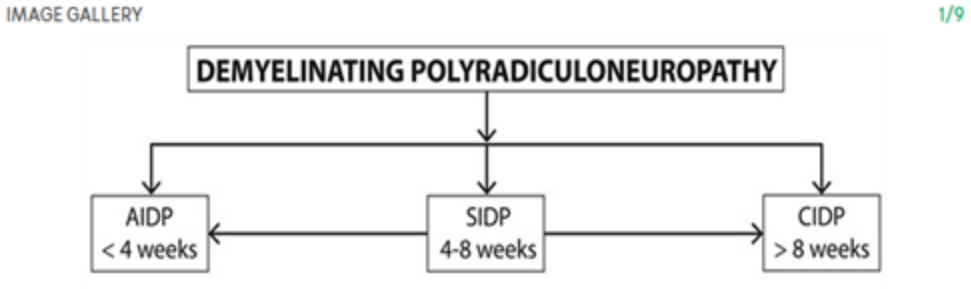
- GBS is an umbrella term, with several important variants

- **Most common** cause of flaccid paralysis, slight male predominance, 8-81 yo, 2/100,000 incidence

- **Pathogenesis -** molecular mimicry from similarities between antigenic structure of pathogens and humans leads to humoral and T-cell mediated response
  - Several neural targets identified: GM1, GQ1b, GT1a


GBS CLASSIFICATION
CLINICAL
NEUROPHYSIOLOGICAL
WEAKNESS NOT PROMINENT
WEAKNESS PROMINENT
DEMYELINATING (AIDP)
AXONAL
AMAN
AMSAN
GENERALIZED
LOCALIZED
• Pharyngeo - Cervical - Brachial
• Paraparetic + Bladder
• Bifacial + Distal paresthesias
• Acute Bulbar Palsy
PURE SENSORY VARIANT
ACUTE DYSAUTONOMIA
MILLER FISHER SYNDROME
• Complete
• Incomplete
• Bickerstaff Brainstem Encephalitis
• MF GBS Overlap Syndrome

# GBS (AIDP) - Clinical Features




**Required features**

- Progressive weakness (proximal and distal muscles)
  - "Ascending" - Legs > arms
- Areflexia or hyporeflexia
- Subacute progression (nadir within 4 weeks)

**Strongly supportive features**

- Symmetric
- Painful paraesthesia, minimal sensory impairment
- Back pain
- Autonomic dysfunction
- Cranial neuropathy (CN 7 most common, can be bilateral)
- Typical CSF findings

**Uncommon presentation:** Elevated ICP from significantly elevated CSF protein

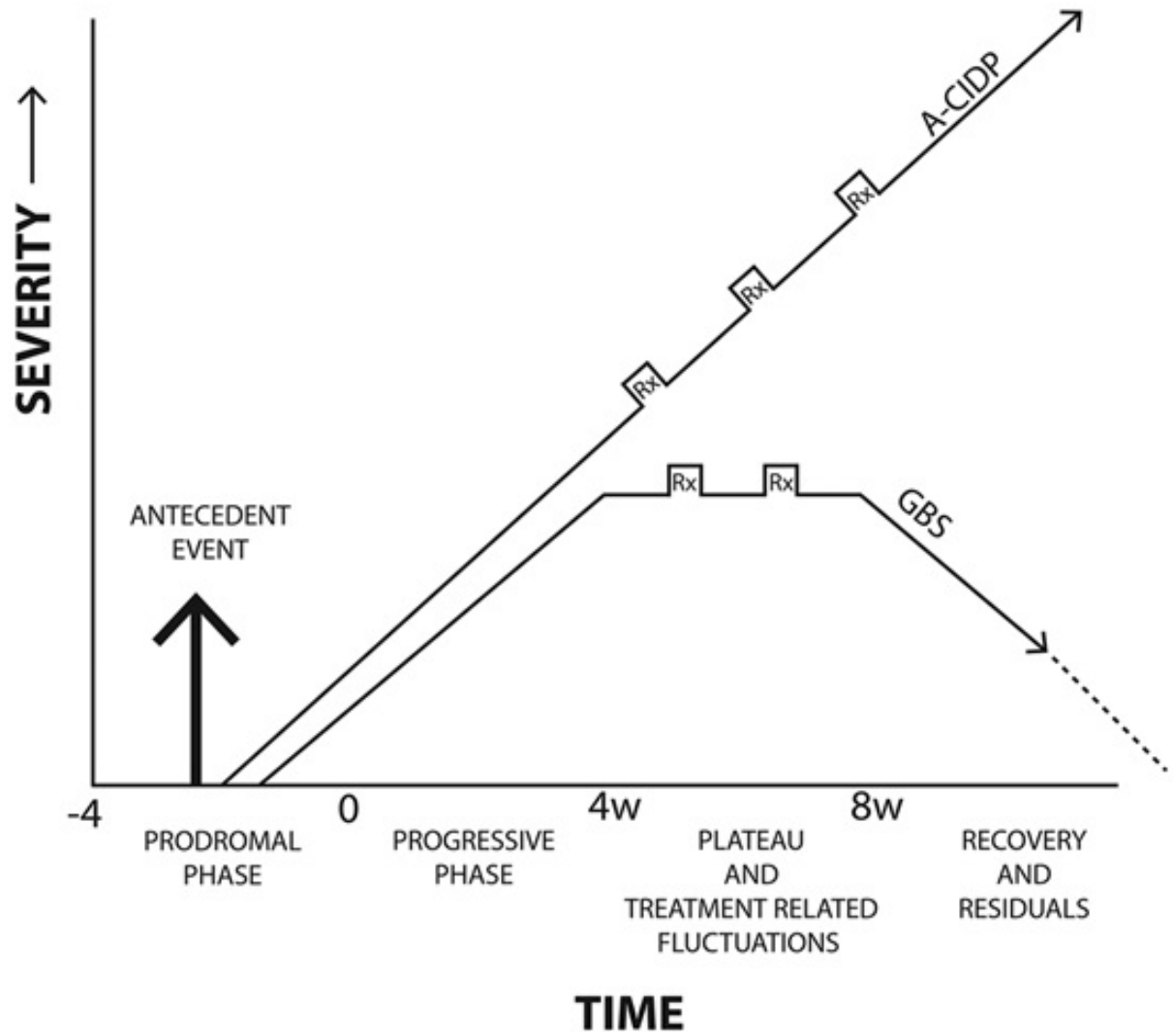
GBS is a clinical diagnosis! No investigations are needed for a clear case

# GBS - Red Flags

- Severe respiratory dysfunction with limited limb weakness at onset
- Slow progression over 4 weeks without cranial nerve, autonomic, or respiratory involvement
- Severe sensory signs with limited weakness at onset
- Bladder or bowel dysfunction at onset
- Sharp sensory level on torso
- Marked persistent asymmetric weakness
- Fever at onset
- CSF pleocytosis (greater than 50 × 10/L), particularly if polymorphonuclear cells are prominent

- **Guillain-Barre Syndrome (GBS)**
  - Inflammatory polyradiculoneuropathy
  - Clinical features
    - Progressive bilateral leg/arm weakness + mild sensory loss
    - Cranial neuropathies (bifacial weakness)
    - Pain + paraesthesias
    - Respiratory/autonomic dysfunction common but atypical to be severe without severe weakness
    - **Preceding infection, surgery, vaccination**
    - **Decreased/absent reflexes*****

No imaging needed if typical




95% monophasic course

# GBS - Helpful Investigations

**CSF**

- Albumino-cytologic dissociation
  - Elevated protein (above lab normal), WBC normal
- Auto-antibody positivity
  - GQ1B for Miller-Fisher, anti-GM1/GD1 for AMAN/ASMAN

**Imaging**

- MRI with contrast showing nerve root thickening and enhancement

**NCS/EMG**

- Demyelinating, sensory > motor polyneuropathy
- **Not helpful if performed too early, typically needs at least two weeks after onset for Wallerian degeneration to set in**

CSF protein can be normal in the first week
LP is to rule-out infection, not to rule-in GBS

# GBS - Subtypes

**Miller-Fisher syndrome**

- Clinical triad of ophthalmoplegia, areflexia, ataxia
- GQ1b mediated
- On the same spectrum of disease as Bickerstaff brainstem encephalitis

**Axonal variants (AMAN, ASMAN)**

- More common in Asia. Typically diarrheal illness. More common in children
- Prognosis
  - Quick recovery within days, similar to AIDP
  - Prolonged recovery, high morbidity, severe weakness/respiratory failure

**Focal variants**

- Pharyngeal-cervical-brachial
- Pure sensory
- Acute pandysautonomia

IMAGE GALLERY

| Guillain-Barré syndrome subtype | Target antigen |
|---|---|
| Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) | LM1, Gal-C |
| Acute motor axonal neuropathy (AMAN) | GM1, GM2, GD1b, GT1b, GM3, GD1a, GalNac-GD1a |
| Acute motor-sensory axonal neuropathy (AMSAN) | GM1, GM1b, GD1a |
| Bickerstaff brainstem encephalitis | GQ1b |
| Miller Fisher syndrome | GQ1b, GM1b, GT1a, GD3, GD1c |
| Pharyngeal-cervical-brachial variant | GT1a, GQ1b, GD1b |
| Sensory ataxic variant | GD1b |

[a] Gangliosides nomenclature: Gangliosides are composed of a glycosphingolipid (ceramide and oligosaccharide) with one or more sialic acids (eg, *N*-acetylneuraminic acid) linked on the sugar chain. In their nomenclature, G stands for ganglioside, the second letter represents the number of sialic acid residues (M = 1, D = 2, T = 3, Q = 4), the numeral represents the number of neutral carbohydrates, and the lowercase letter (a/b) represents the isomeric position of sialic acid residue.

# GBS - Treatment

**When to start?** Patient unable to walk 10m, rapid progression of weakness, autonomic features, swallowing difficulties, shortness of breath

## Immunotherapy

- Goals of therapy: speeds recovery by 40-50%
  - **Does not stop progression of disease**
  - **Does not change degree of nerve damage**
- Only effective within the first 2-4 weeks (before natural nadir)
- IVIg and plasma exchange have equal efficacy
- No role for corticosteroids; some evidence of harm

Recall that IVIg and PLEX do not work immediately. Peak effect is within a few days

# IVIG vs PLEX

| IVIG | PLEX |
| --- | --- |
| 0.4mg/kg over 5 days | 5 sessions over 10 days |
| Time to effect 1-2 days, peak 1-2 weeks | Time to effect 1-2 days, peak 10-14 days |
| Transfusion reaction, headache, rash, aseptic meningitis, hemolytic anemia, thromboembolism | Hypotension, sepsis, impaired clotting, HypoCa<br><br>** higher discontinuation rates |
| Typically first line treatment due to logistics and access | Reserved for patients with contraindications/refractory to IVIG, severe, presentations. |

# GBS - Supportive Care

** 30% of GBS will progress to respiratory failure if not treated

Mortality from GBS is either due to **respiratory failure** or **severe autonomic dysfunction (hypertensive crises, symptomatic tachycardia/bradycardia)**

**Markers of respiratory dysfunction**

- Neck flexion weakness
- Dysarthria, nasal speech, weak cough, facial weakness
- Single-breath count < 15
- Bedside spirometry measures
  - FVC < 20mL/kg or < 1L (IBW)
  - MIP < 30
  - MEP < 40
  - 30% worsening on any of the above in 24h

Oxygenation, $pCO_2$, pH are not good markers of when to intubate for GBS!

# GBS - Supportive Care

**All patients with GBS need to be on telemetry**

- Relevant at SPH; no dedicated NICU beds

**Elective intubation is much preferred for GBS**

- Emergency intubation can provoke blood pressure shifts/bradycardia when already prone to dysautonomia

**If a patient is worsening/early in disease, we do not have treatment that prevents worsening**

# GBS - Prognosis

**Prognostic tool - EGRIS, Erasmus GBS outcome score**

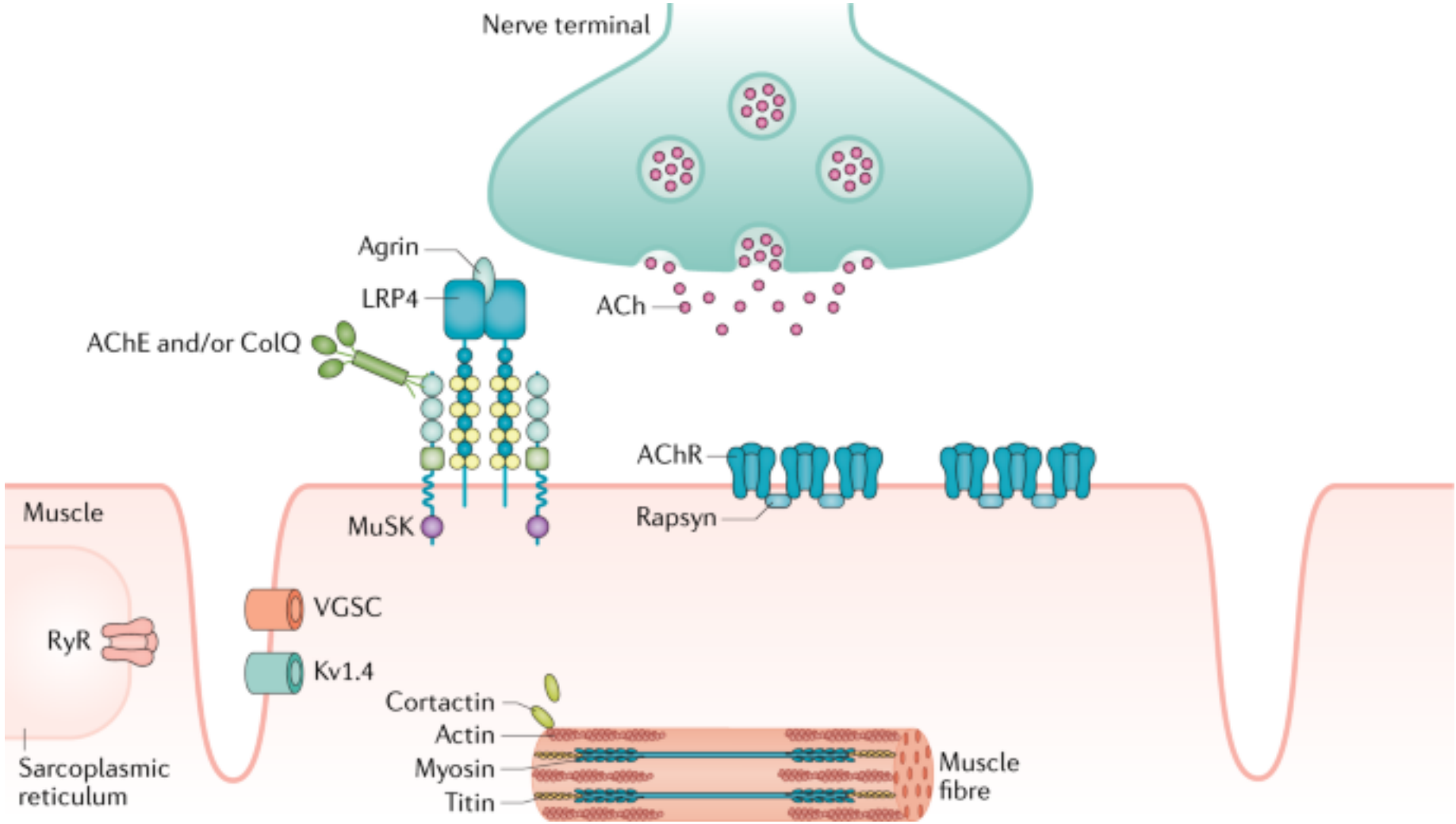
- Predicts need for mechanical ventilation, functional outcome at 6mo
  - Time from onset to hospitalization
  - Facial/bulbar weakness at admission
  - Sum score of how severe weakness is
  - Preceding diarrhea is higher risk

**Overall prognosis is good**

- 80% walk independently at 6mo
- Over 50% fully recover after 1 year
- 10-15% severe disability
- Common residual symptoms
  - Weakness, paraesthesias, pain

**Predictors of poor prognosis:** age >60, rapid progression, bed bound, ventilation, preceding campylobacter illness

# Myasthenia Gravis



# MG - Introduction

**Pathophysiology**

- Antibody-mediated, autoimmune attack on the **postsynaptic acetylcholine receptor**
- Localization: **Neuromuscular junction**

**Epidemiology**

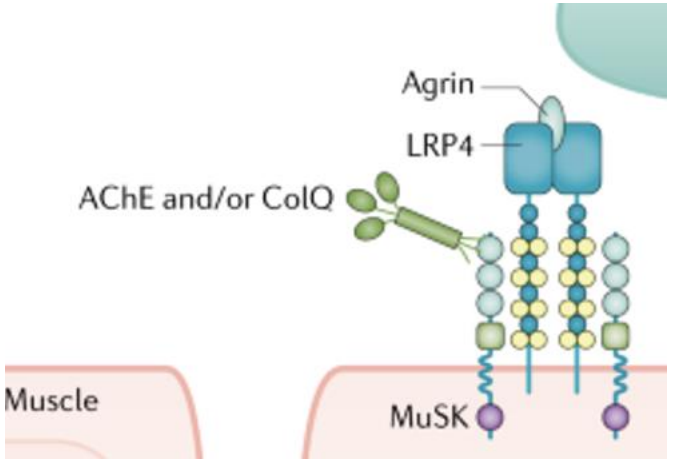
- 10 - 20 cases per 100k people
- Bimodal distribution
  - F > M in young cohort (peak around age 30)
  - F = M in older cohort (peak around age 50)
- **Ocular myasthenia -** symptoms isolated to the eyes; typically generalize within 2 years of onset

# MG - Clinical Features

**Clinical Features**

- Pure motor
- Distribution: symmetric, proximal > distal, + bulbar, + resp involvement
- Fatigability of weakness
  - Diurnal variation of symptoms
- Pathognomonic hallmark
  - Bilateral, asymmetric ptosis without pupillary involvement.
  - Worse at the end of the day

# MG - Diagnosis




**Primarily a clinical diagnosis**

**Investigations**

- EMG: Decrement on repetitive stimulation. Jitter on single fibre. No myopathic features
- Antibody testing: anti-AChR, anti-MuSK, LRP-4 if others are negative, 5-10% are seronegative
- CT chest w/contrast: rule-out thymoma
  - Thymoma in 15% of MG

MG is one of the most common paraneoplastic syndromes

# MG - Special Testing

**Ice pack sign** - reversal of ptosis with application of cold

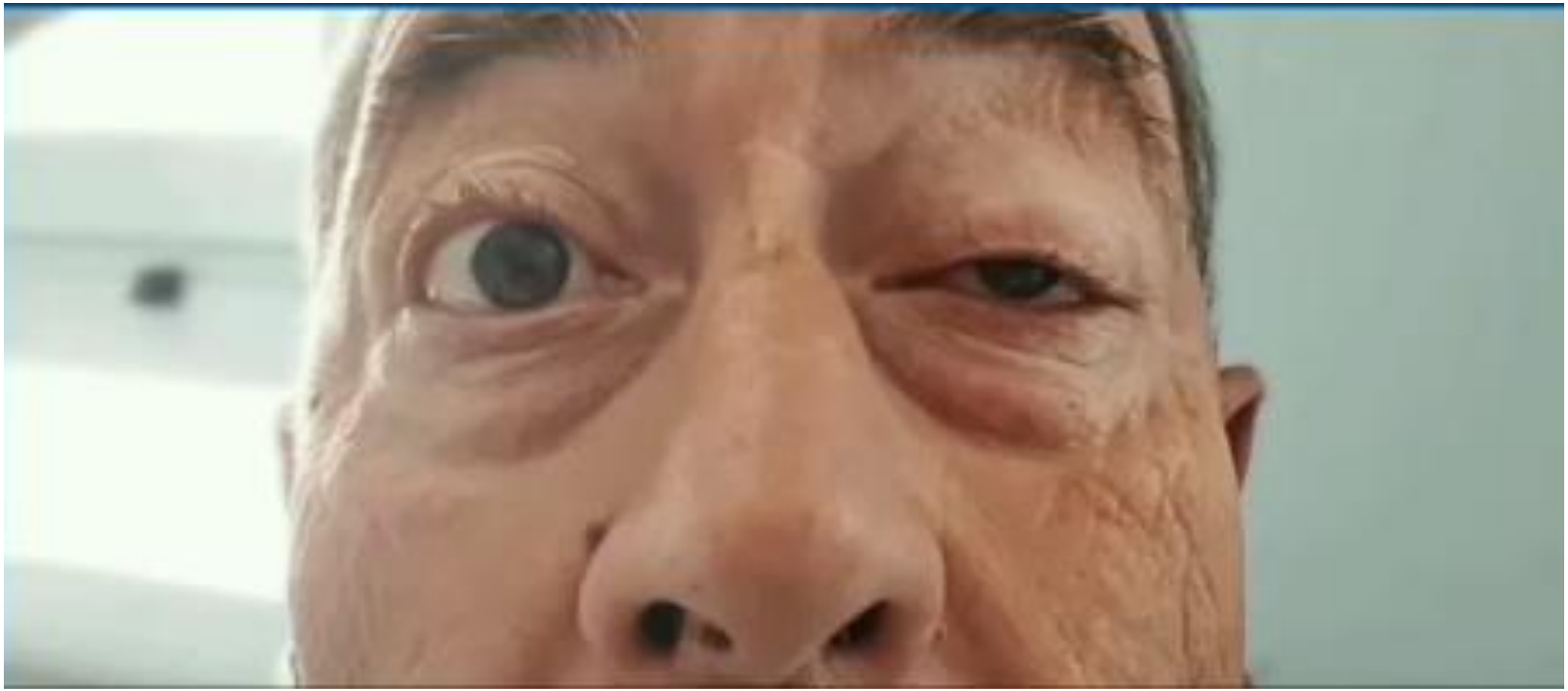
**Curtain sign** - when the ptotic lid is passively elevated, the contralateral lid drops

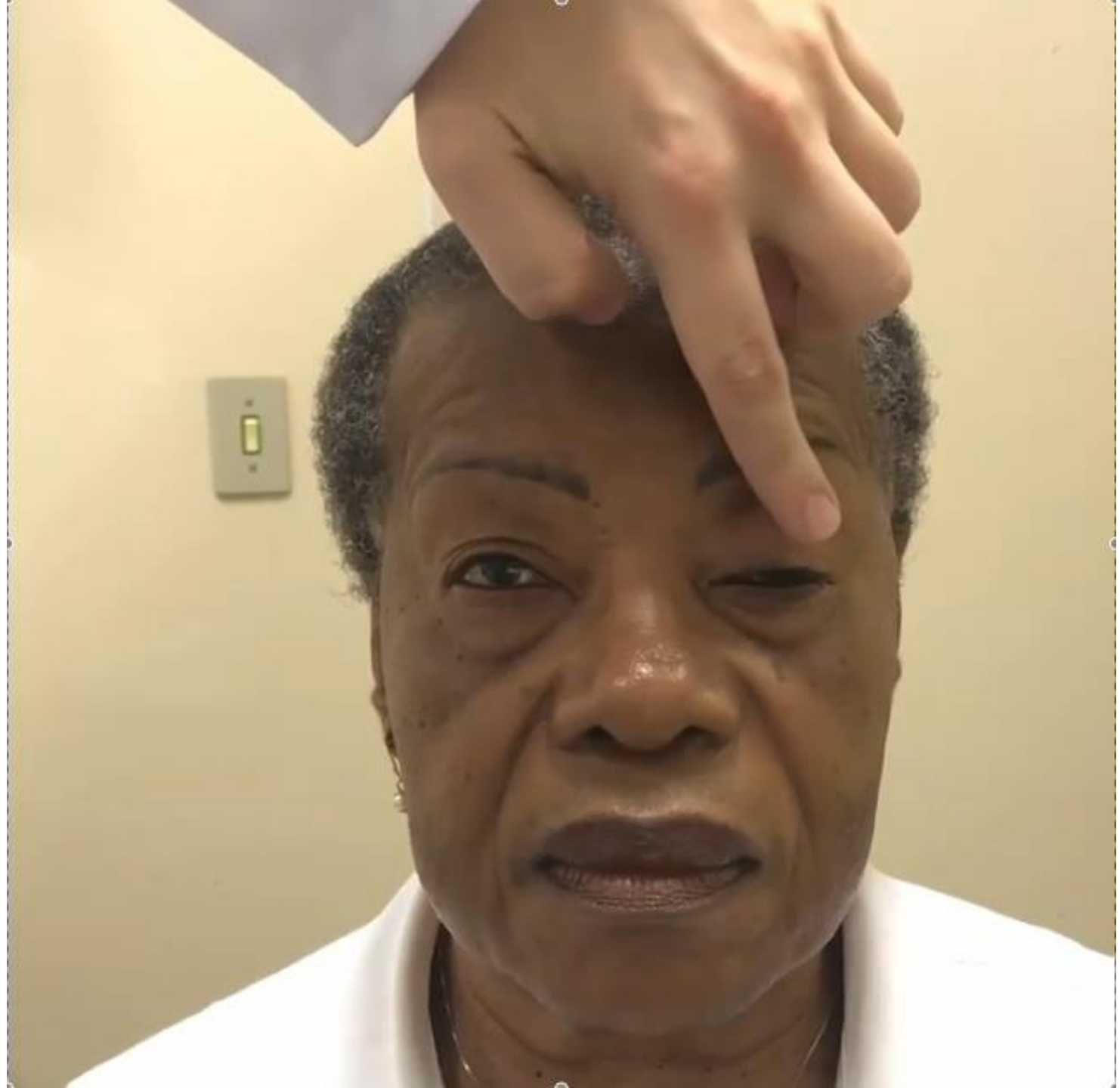
**Cogan's lid twitch –** downgaze followed by quick up-gaze results in ptotic lid twitch

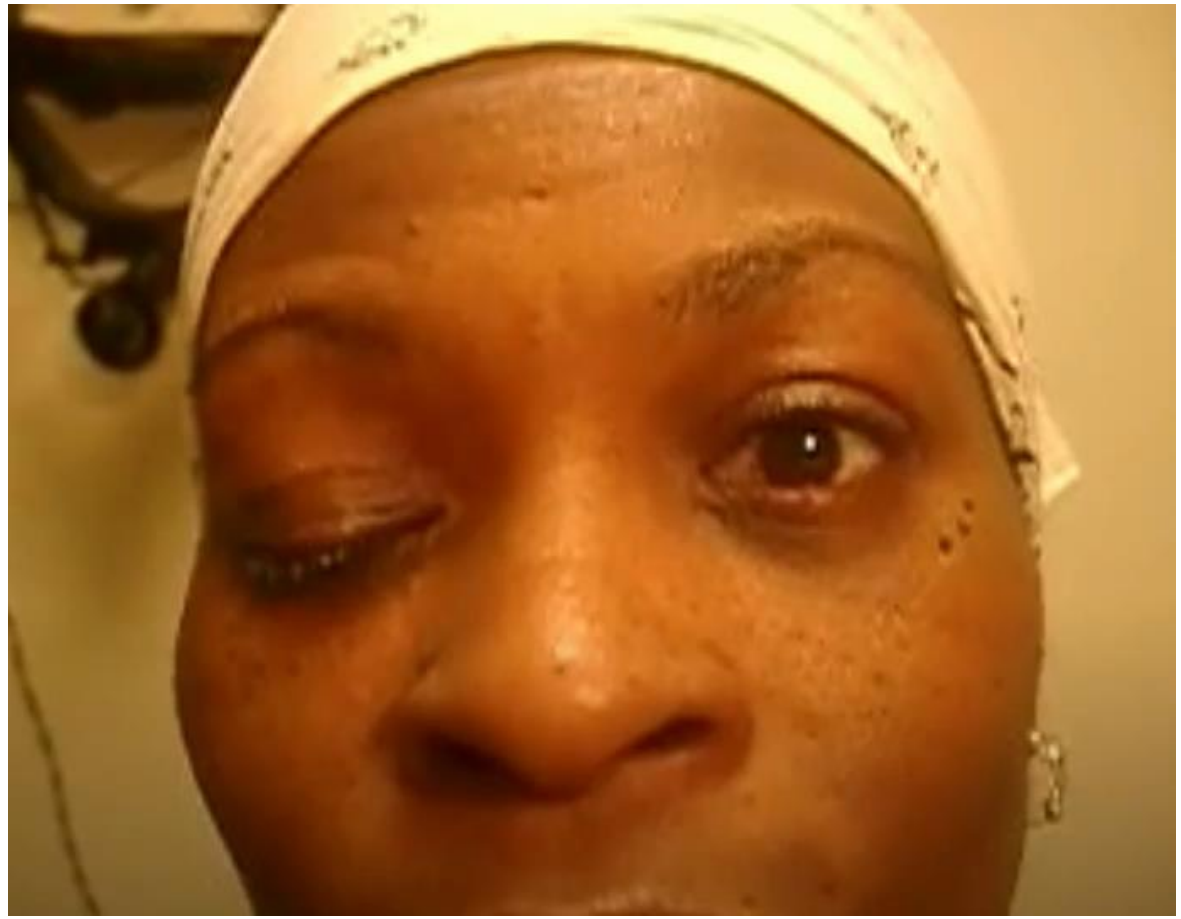
**Fatigable diplopia/ptosis with sustained up-gaze**

***Tensilon test** - edrophonium (AChE inhibitor) is applied to see if ptosis reverses.

- Carries risk of symptomatic bradycardia







# Myasthenic Crisis

**Uncontrolled autoimmunity leading to progressive fatigable weakness in the muscles that control breathing and swallowing**

**20% of patients' first presentation**

**Common triggers**

- Infection
- Post-partum state/pregnancy
- Recent surgery
- Change in immunosuppressive medications
- MG-exacerbating drugs

# Myasthenic Crisis

**Markers of respiratory dysfunction**

- Neck flexion weakness
- Dysarthria, nasal speech, weak cough, facial weakness
- Single-breath count < 15
- Bedside spirometry measures
  - FVC < 20mL/kg or < 1L (IBW)
  - MIP < 30
  - MEP < 40
  - 30% worsening on any of the above in 24h

Oxygenation, $pCO_2$ are not good markers for MG crisis!

# Myasthenic Crisis

**Bottom line**

- When an MG patient is demonstrating fatigable weakness, the underlying pathophysiology requires several days at a minimum for treatment to reach peak effect
- If there are indicators that respiratory status is tenuous and/or worsening, it is almost impossible to avoid intubation
- **If an MG patient is hypoxemic and/or hypercarbic we are already catching them late**

- **Immediate Management if in crisis:**
  - IVIG/PLEX
  - In sever flare, Pyridostigmine can be harmful – can worsen secretion
  - In an acute flare, steroids can worsen

- **Outpatient/Non-Flare Management:**
  - Pyridostigmine - 60mg TID. max dose 120mg Q4h (onset 15-30min, peak at 2 hrs)
    - **SE:** cramps, bloating, diarrhea, urinary frequency, hypotension, bradycardia, salivation, increased sections
  - Neostigmine – SC version if PO not an option
  - Prednisone (3—60mg) if no IVIG/PLEX
  - Steroid sparing agents – AZA, MMF, MTX, Tac, Ritux, Cyclo

# Drugs that worsen MG

**Absolutely avoid**

- Paralytics (rocuronium, succinylcholine)
- Magnesium
- Botox

**All others**

- Antibiotics (aminoglycosides, fluoroquinolones, macrolides)
- B-blocker, CCB
- Amiodarone, Procainamide, quinidine
- Immune checkpoint inhibitors

** If worried, look at **MG society of America web page**

PNA is more likely to trigger crisis than the antibiotics used to treat it

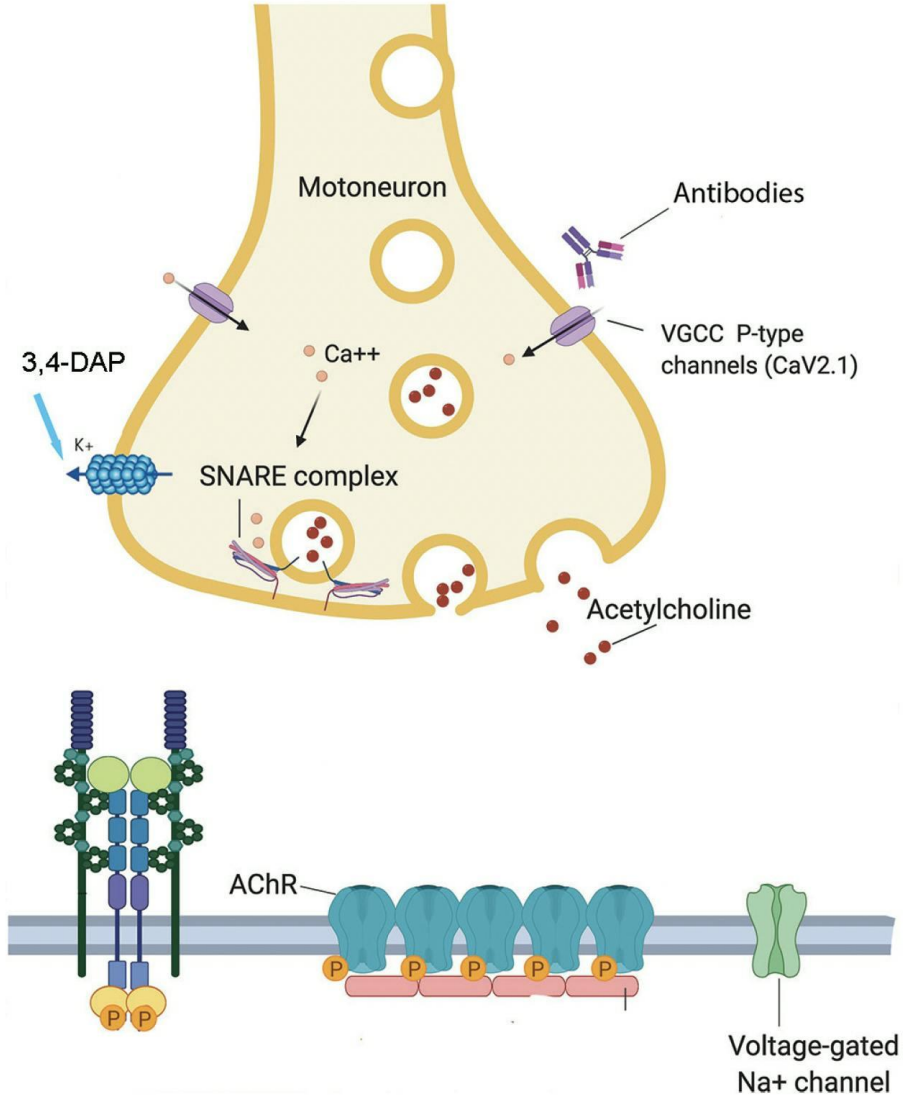
# Lambert-Eaton Myasthenic Syndrome

- **Pathophysiology:**
  - Antibodies against pre-synaptic voltage-gated P/Q voltage gated calcium channels, preventing release of ACh vesicles into the synaptic membrane
  - results in variable ACh release and failure of transmission
  - Can be cancer-associated (paraneoplastic 50%) - most common with SCLC

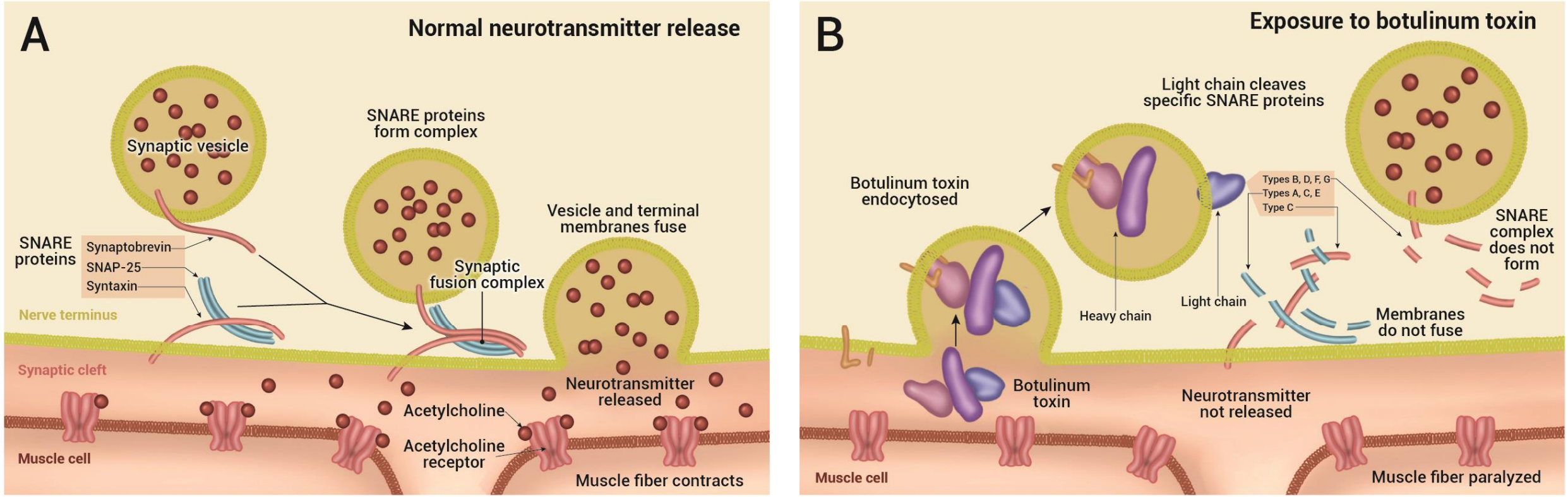
- **Clinical Hallmark:** weakness that improves with strength testing

- **w/u** includes EMG/NCS and CT Chest

- **Treatment:**
  - Amifampiridine phosphate (3,4-DAP) - K channel blockade prolongs depolarization and increases Ach release.
  - Rarely IVIG/PLEX **caution with IVIG and cancer given risk of thromboembolic events



# Botulism




Toxin binds to pre-synaptic neurons and cleaves SNARE proteins (specifically SNAP-25) to prevent formation of synaptic fusion complex and release of Ach

**Clinical Features -** acute, febrile, descending weakness and autonomic dysfunction

- manifests 12-36 hrs after exposure, Can have preceding diarrhea then ileus
- cranial nerves involved first - blurred vision (fixed, dilated pupils), opthalmoparesis, facial droop, dysarthria, dysphagia.
- descending flaccid paralysis, variable reflexes autonomic dysfunction and resp involvement common
- intact mental status, no sensory involvement

**Treatment**

- tx should be initiated within 3 days of admission, intubate if needed.
- Two options:
    - Human Botulism Ig for infants (covers serotypes A/B)
    - Equine heptavalent antitoxin (covers subtypes A-G)
        - highly immunogenic, lots of infusion rxns, monitor closely.
        - HA, fever, rash, urticaria, chills, nausea

**Recovery** can take months, timely treatment can reduce mortality from 60% to 3%

Thank you!