NOTES
NEUROMUSCULAR JUNCTION DISEASES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Disorders impairing neuromuscular transmission lead to muscle fatigability, weakness

CAUSES

- Autoantibody production
  - Targeted against neuromuscular transmission pathway proteins
- Myasthenia gravis (MG)
- Lambert–Eaton myasthenic syndrome (LEMS)
- Transient acquired neonatal myasthenia
- Genetic mutation
  - Affecting pathway components (e.g., congenital myasthenia)

COMPLICATIONS

- Respiratory muscles involved → potentially fatal respiratory failure

SIGNS & SYMPTOMS

- Primary clinical manifestation
  - Painless muscle weakness without significant muscle atrophy
  - Ocular, extraocular, oropharyngeal, bulbar, neck, limb, respiratory muscles

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Thymoma (MG)
- Small-cell lung carcinoma (LEMS)

LAB RESULTS

- Serologic test for specific antibodies

OTHER DIAGNOSTICS

Electrophysiologic study

- Repetitive nerve stimulation
  - Decremental response/improvement
- Electromyogram
  - ↓ muscle action potential

Pulmonary function test (PFT)

- Periodically
  - Detect respiratory muscle involvement in forced vital capacity (FVC) ↓

TREATMENT

- Treat underlying cause (e.g. LEMS malignancy)

MEDICATIONS

- Acetylcholinesterase inhibitors
  - Inhibit acetylcholine degradation → ↑ acetylcholine concentration in neuromuscular junction (symptomatic therapy)
- Immunomodulating agents
  - ↓ autoantibody production
  - Individuals with poor acetylcholinesterase inhibitor response
  - Corticosteroids/other immunosuppressive agents
- If above fails/emergency (e.g., myasthenic crisis)
  - Plasmapheresis/intravenous immunoglobulin (IVIG)

LAMBERT–EATON MYASTHENIC SYNDROME (LEMS)

osms.it/lambert-eaton-myasthenic

PATHOLOGY & CAUSES

- Rare autoimmune disorder
  - Autoantibodies inhibit presynaptic calcium channels on motor neurons → reduced acetylcholine release in neuromuscular junction
- Muscle weakness
  - Improves temporarily after repeated muscle use (no significant muscle atrophy)
- Mostly affects somatic nervous system, can also affect autonomic nervous system's parasympathetic part
- Middle-aged adults (most cases)

CAUSES

Type II hypersensitivity reaction

- B cells produce antibodies that target, block voltage-gated calcium channels located presynaptically on motor neurons → only few unbound channels available to open, allow calcium in → ↓ calcium within neuron (insufficient to trigger acetylcholine release) → ↓ acetylcholine release in neuromuscular junction → attached muscle fiber does not contract
- Repeated stimulation by brain's electrical impulses → enough calcium might get through remaining unbound calcium channels → acetylcholine release → muscle contraction

RISK FACTORS

- Malignancy
  - Strong small-cell lung cancer association; stimulus for antibody production is same calcium channel expression in neoplastic cells
  - Other associated malignancies include lymphoproliferative disorders (e.g., Hodgkin's lymphoma)
- Autoimmune diseases
  - Hashimoto's thyroiditis, diabetes mellitus type 1, vitiligo

COMPLICATIONS

- Respiratory muscle involvement → respiratory failure
- Underlying malignancy → can lead to death

SIGNS & SYMPTOMS

- Progressive, symmetrical proximal muscle weakness (e.g., shoulders, hips, thighs) → difficulty climbing stairs/standing when seated
  - *Paraneoplastic LEMS:* more rapidly progressive course
- Warming-up phenomenon
  - Repeated muscle use → weakness temporarily relieved
- Reflex strength ↓
  - Muscle activation → reflex recovery/improvement
- Small minority
  - Ocular, oropharyngeal muscle involvement
- Advanced stages
  - Possible respiratory muscles involvement → respiratory failure (myasthenic crisis)
- Autonomic symptoms
  - Dry mouth (most common), constipation, blurry vision, erectile dysfunction, urinary problems, syncope

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Chest
  - Detect underlying small-cell lung cancer
- Abdomen, pelvis also recommended
- Negative initial malignancy evaluation
  - Periodical screening recommended

LAB RESULTS

- Serological tests
  - Detect antibodies against the voltage-gated calcium channels

OTHER DIAGNOSTICS

- Electrophysiologic studies
  - *Repetitive nerve stimulation:* ↑ muscle action potential amplitude
  - *Electromyogram:* ↑ muscle action potential amplitude after exercise
- PFT
  - ↓ FVC → respiratory muscle involvement

TREATMENT

MEDICATIONS

- Symptomatic therapy
  - *Acetylcholinesterase inhibitors:* minimal effect
  - *Aminopyridines:* block potassium channels → prolonged nerve membrane depolarization → ↑ calcium entry → ↑ acetylcholine release in neuromuscular junction
- If above methods fail
  - Immunomodulating agents can be used (corticosteroids, other immunosuppressive agents)

OTHER INTERVENTIONS

- Occasionally treated with IVIG/ plasmapheresis
  - More severe cases

MYASTHENIA GRAVIS

osms.it/myasthenia-gravis

PATHOLOGY & CAUSES

- Autoimmune disorder; significant skeletal muscle weakness
  - Decreased acetylcholine receptor function → worsens with muscle use
  - Most common neuromuscular junction disorder
- Type II hypersensitivity reaction
  - B cells produce antibodies against postsynaptic nicotinic acetylcholine receptors of neuromuscular junction/ receptor-associated proteins
  - Autoantibodies targeted against muscle-specific receptor tyrosine kinase (MuSK) → ↓ in acetylcholine receptor function
- Acetylcholine cannot bind → normal action potentials cannot be generated (adjacent muscle
- Complement activated → inflammatory response initiation → postsynaptic membrane damage → acetylcholine receptor destruction
- Bimodal onset age
  - 20–30 years old (biologically-female predominance)
  - 60–70 years old (biologically-male predominance)
- Associated with thymic abnormality; thymus considered antigen source

promoting autoantibody production (most cases)
- Neonatal myasthenia gravis
  - Transient myasthenia form (newborn from individual with myasthenia gravis)
  - Maternal antibodies → transplacental passage → neuromuscular junction function interference
- Rare non-immune mediated forms
  - E.g. congenital myasthenia gravis
  - Mutations affecting neuromuscular transmission

COMPLICATIONS

- Myasthenic crisis
  - Decreased respiratory muscle function → life-threatening respiratory failure (requires mechanical ventilation)
  - Occurs spontaneously/precipitated (e.g. surgery, infection, medication, immunosuppressive-agent withdrawal)

SIGNS & SYMPTOMS

- Fluctuating muscle weakness
  - Exacerbated by repetitive muscle use throughout day/after exertion/repetitive movement
- Improves with rest
- Progression
  - Symptoms continuously present, fluctuate from mild–severe
- Sensation, reflexes preserved

Clinical MG forms

- Ocular myasthenia
  - Limited (eyelid, extraocular muscle); individuals (50%) with ocular myasthenia will → generalized myasthenia (< two years)
- Generalized myasthenia
  - Ocular, bulbar, facial, limb, respiratory muscle
- Ocular muscles
  - Eyelid (ptosis), extraocular (binocular diplopia)
- Bulbar muscle
  - Jaw closure (prolonged chewing → weakness), oropharyngeal (dysarthria, dysphagia), palatal (nasal tone, prolonged speech → hypophonia)
- Facial muscle
  - Facial weakness, facial expression loss
- Neck muscle
  - Cannot keep head up ("drooped head syndrome")
- Limb muscle
  - Proximal, asymmetric muscle weakness
- Respiratory muscle
  - Respiratory failure (myasthenic crisis)

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Chest scan to detect associated thymic abnormalities
  - Abnormal thymus (most cases)
  - Thymoma

LAB RESULTS

- Serologic test
  - Acetylcholine receptor antibodies (AChR-Abs)/muscle-specific receptor tyrosine kinase antibodies (MuSK-Abs)
  - Most specific tests
  - Seronegative for AChR-Abs, MuSK-Abs

OTHER DIAGNOSTICS

- Electrophysiologic studies
  - *Repetitive nerve stimulation studies:* progressive decline in muscle action potential amplitude (decremental response)
  - *Single-fiber electromyography:* increased jitter
- Tensilon test
  - *Edrophonium:* acetylcholinesterase inhibitor with rapid onset, short acting duration
  - Prolongs acetylcholine presence in neuromuscular junction → marked improvement
  - Easy to perform/limited utility; high false-positive rate, possible complications from muscarinic effects

(especially older adults, e.g. bradycardia, bronchospasm)
- PFTs
  - Periodical FVC monitoring; FVC ↓ reveals respiratory muscle involvement
- Ice pack test
  - Ice pack application (2–5 minutes) → MG-affected muscles
  - Neuromuscular transmission improvement in low temperature

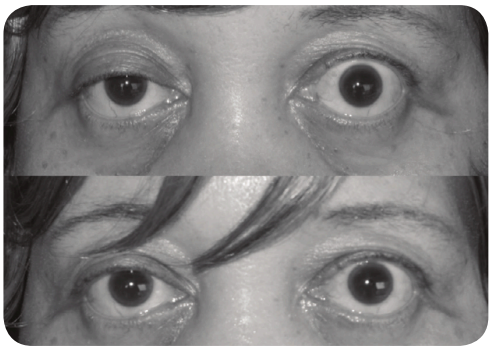

Figure 85.1 A biologically-female individual with myasthenia gravis demonstrating ptosis of the right eye before treatment (above) and after treatment (below) with edrophonium.

TREATMENT

- No curative method

MEDICATIONS

- Avoid MG-exacerbating drugs (e.g. aminoglycosides, tetracyclines, beta-blockers, quinidine)
- Acetylcholinesterase inhibitors
  - Symptomatic therapy
- Immunomodulating agents ↓ autoantibody production
  - Individuals with poor acetylcholinesterase inhibitor response
- Corticosteroids, other immunosuppressive agents

SURGERY

- Thymectomy, especially for thymoma; myasthenia often improves/disappears
- Rapidly worsening myasthenia/myasthenic crisis
  - Intubation
  - Plasmapheresis/intravenous immunoglobulin (IVIG)
  - Long-acting immunotherapy (e.g., corticosteroids, azathioprine)

MNEMONIC

Edrophonium vs. pyridostigmine

e**D**rophonium for **D**iagnosis py**RID**ostigmine is to get **RID** of symptoms