Chapter 108 – Neuromuscular Disorders

Episode Overview:

1. List 4 components of the neuromuscular unit.
2. Describe the grading score for motor strength.
3. Compare myelopathy, motor neuron disease, neuropathy, neuromuscular junction disease, and myopathy with respect to history, strength, deep tendon reflexes, sensation and muscle wasting.
4. List 6 myelopathies, 2 motor neuron diseases, 4 neuropathies, 4 diseases of the neuromuscular junction, and 5 myopathies.
5. Distinguish upper motor neuron from lower motor neuron involvement.
6. What is the pathophysiology of myasthenia gravis?
7. What is one bedside diagnostic test for MG?
8. List 8 precipitants of a myasthenic crisis and describe 3 chronic therapies and 2 acute therapies.
9. What is the difference between myasthenia gravis and Lambert-Eaton myasthenic syndrome?
10. List 4 types of botulism toxicity. What is the mechanism of toxicity and typical clinical syndrome? What is the treatment?
11. What is tick paralysis?
12. What is the presentation / treatment of Polymyositis/Dermatomyositis?
13. What is periodic paralysis?

Wisecracks:

1. Clinically, how would you differentiate between a myasthenic crisis and a cholinergic crisis?
2. What is the presentation, timing and course of neonatal myasthenia?
3. What the differential diagnosis for a patient presenting with ascending muscle weakness, ptosis and diplopia?

Key Concepts:

- "In patients with acute neuromuscular weakness, complaints of difficulty in breathing or swallowing should heighten suspicion of bulbar involvement with possible airway compromise. In such patients, FVC of less than 15 mL/kg or maximal NIF of less than 15 mm H2O is a potential indication for mechanical ventilation.
- Patients with a neuromuscular decline in respiratory function can be given a trial of noninvasive ventilation.
- The edrophonium (tensilon) and ice bag tests can be useful bedside tests in the evaluation of a suspected new diagnosis of myasthenia gravis.
- Plasma exchange therapy and IVIG are both useful for the treatment of myasthenic crises with the choice dependent on which is available and preferred in the ICU.
- Botulism usually arises as a painless descending paralysis, often first affecting the cranial nerves and bulbar muscles, without sensory deficits or significant alteration of consciousness. The treatment is airway management and administration of antitoxin.
- Injection drug use remains an important cause of wound botulism outbreaks.
- Botulism must be considered in the evaluation of a weak and floppy infant.

- In hypokalemic periodic paralysis, the total body potassium level is not depleted, only shifted intracellularly: treatment should keep this in mind as potassium is administered with frequent checks of serum potassium levels.
- In newly diagnosed hypokalemic periodic paralysis, the patient should be evaluated and treated for hyperthyroidism if present."

Rosen's in Perspective

The approach to acute neuromuscular weakness is all about 3 things:

- Evaluate airway, ventilation and oxygenation
- Determine the location of the lesion (spinal cord, nerve, neuromuscular junction, or muscle)
- Consider the most common disorders that affect the area in question

[1] List 4 components of the neuromuscular unit.

Neuromuscular unit =

1) anterior horn cells of the spinal cord
2) peripheral nerve
3) the neuromuscular junction
4) muscle innervated

[2] Describe the grading score for motor strength

Grading Score for Motor Strength (Box 98.1)

- 5 = Normal Strength
- 4 = Weak but able to resist examiner
- 3 = Moves against gravity but unable to resist examiner
- 2 = Moves but unable to resist gravity
- 1 = Flicker but no movement
- 0 = No movement

[3] Compare myelopathy, motor neuron disease, neuropathy, neuromuscular junction disease, and myopathy with respect to history, strength, DTR's, sensation and muscle wasting.

Table 98.1

Disease	History	Strength	DTR	Sensation	Wasting
Myelopathy	Trauma, infection, cancer	Normal to decreased	Increased	Normal to Decreased	No
Motor neuron disease (ALS)	Progressive difficulty swallowing, speaking, walking	Decreased	Increased	Normal	Yes

Neuropathy	Recent infection, ascending weakness	Normal or decreased, distal>proximal	Decreased	Decreased	Yes
Neuromuscular junction disease	Food (canned goods), Tick exposure, easy fatigability	Normal to fatigue	Normal	Normal	No
Myopathy	Thyroid disease, previous similar episodes	Decreased, proximal>distal	Normal	Normal	Yes

[4] List 6 myelopathies, 1 motor neuron disease, 4 neuropathies, 4 diseases of the NMJ, and 5 myopathies

Myelopathies	Motor neuron diseases	Neuropathies	NMJ disease	Myopathies
1. transverse myelitis, HIV, MS 2. Spinal cord infarction, spinal SAH 3. SLE 4. SEA 5. Discitis 6. Burst #, neoplasm	1.Amyotrophic lateral sclerosis	1. Guillain-Barré syndrome 2.Toxic neuropathies 3. Diabetic neuropathy 4. Tick paralysis	1.MG 2.Lambert Eaton 3. Organo-phosphates 4. Botulism, tick paralysis, snake venoms, rx drugs	1.Polymyositis 2.Dermatomyositis 3.Polymyalgia rheumatic 4.Viral myositis 5.Metabolic disorders

[5] Distinguish upper motor neuron from lower motor neuron involvement

Motor Neuron	**DTR**	**Muscle Tone**	**Atrophy**	**Fasciculations**	**Babinski**
UMN	Increased	Increased	No	No	Present
LMN	Decreased	Decreased	Yes	Yes	Absent

[6] What is the pathophysiology of myasthenia gravis?

"Autoantibodies against the acetylcholine (ACh) receptor on the junctional folds on the post synaptic membrane" resulting in blockage of the acetylcholine receptors.

- With repeated stimulation increasingly fewer receptor sites are available for ACh binding
- Leads to muscle fatigue
- Fatigability and muscle weakness are the **hallmarks** of MG.

- Clinical progression = slow

- Multiple mechanisms:
    - Direct blocking of the receptor
    - Complement mediated destruction of the folds
    - Internalization and degradation of the receptors

Watch out for Myasthenic Crisis (MG with respiratory failure!!!)

NIF (negative inspiratory force) <15 → intubate!

[7] What is one bedside diagnostic test for MG?

Ice bag test

1. Measure pre-test ptosis
2. Apply ice to affected eye for 2 min
3. Improvement >2mm of ptosis is positive test

[8] List 8 precipitants of a myasthenic crisis and describe 3 chronic therapies and 2 acute therapies

General Precipitants:

- Infection
- Aspiration
- Medication changes
    - Eg. stopping anticholinergics
    - New medication that precipitates weakness
- Surgery
- Pregnancy
- Medications (Box 98.2)
    - Cardiovascular
        - Beta Blockers
        - CCB's
        - Quinidine
        - Lidocaine
        - Procainamide
    - Antibiotics
        - Aminoglycosides
        - Tetracyclines
        - Clindmycin
        - Lincomycin
        - Polymyxin B
        - Colistin
    - Other
        - Phenytoin
        - Neuromuscular Blockers
        - Thyroid Replacement

Treatment:

- BiPAP +/- IPPV
- Cholinesterase Inhibitors (pyridostigmine or neostigmine)
- Corticosteroids (caution in moderate to severe MG, can precipitate crisis)
- Intravenous immunoglobin (IVIG)
- Plasma exchange
- Thymectomy

[9] What is the difference between myasthenia gravis and Lambert-Eaton myasthenic syndrome?

Lambert-Eaton myasthenic syndrome = rare disorder.

- Almost 50% of cases are associated w/ small cell cancer of lung
- Autoantibodies cause inadequate release of ACh from nerve terminals
- Affects nicotinic (ie. peripheral) and muscarinic (ie. central) receptors
- With repeated stimulation, the amount of ACh in the synaptic cleft increases, leading to an increase in strength
- THIS IS = opposite of Myasthenia gravis, which gets more weak with repeat stimulation
- "The classic syndrome includes weakness that improves with use of muscles, particularly proximal hip and shoulder muscles; hyporeflexia; and autonomic dysfunction, most commonly seen as dry mouth. Management primarily focuses on treatment of the underlying neoplastic disorder, although IVIG has been reported to be useful."

[10] List 4 types of botulinum toxicity. What is the mechanism of toxicity and typical clinical syndrome? What is the treatment?

A) Food-Borne
B) Infantile
C) Wound
D) Inhalational / Unknown / Terrorism

Clostridium botulinum is an anaerobic, spore-forming bacterium. 3/8 toxins produced cause human disease (types A, B, and E).

Mechanism: toxin irreversibly binds to the presynaptic membrane of peripheral and cranial nerves = inhibition of the release of ACh at the peripheral nerve synapse.

- Block both voluntary motor and autonomic functions
- Will see improvement as new receptors are made

Clinical presentation:

- Classic = descending, symmetrical, flaccid paralysis. Loss of voluntary and autonomic function.
- ***PAIN AND SENSATION should be INTACT***
- The onset of symptoms is 6 to 48 hours after the ingestion

- Cranial nerves and bulbar muscles are affected first
- Look for the Ds: diplopia, dysarthria, and dysphagia,
- Because the toxin decreases cholinergic output, anticholinergic signs may be present: constipation, urinary retention, dry skin and eyes, and increased temperature and dilated, non-reactive pupils.
- *** presence of anticholinergic features helps differentiate botulism toxicity from myasthenia gravis.
- DTRs normal, slightly decreased
- Infantile botulism comes from C. botulinum spores that germinate and produce toxin in the high pH of the infant GI tract. "Botulism spores can survive in honey, so it is recommended that honey not be fed to infants. The clinical presentation includes constipation, poor feeding, lethargy, and weak cry; consequently, this diagnosis must be included in the differential diagnosis of the floppy infant."

- Treatment:
  - Supportive care +/- IPPV
  - heptavalent botulinum antitoxin (HBAT)
  - Human-derived botulism immune globulin (BabyBIG)
- According to LITFL:
  - notify public health
  - Antitoxin
  - Supportive
  - IV human botulism globulin
  - wound botulism: debride, penicillin

[11] What is tick paralysis?

An acute, ascending, flaccid paralysis:

- Rocky Mountain region = US Pacific Northwest, and Southwestern Canada & east coast of Australia.
- Pathogenesis not fully understood = thought that a salivary toxin is injected while the tick feeds.
- Toxin functions like botulinum toxin to decrease the release of ACh from the presynaptic membrane of the neuromuscular junction
- Similar to Guillain-Barré syndrome, botulism, and myasthenia gravis.
- Symptoms onset 1-6 days after **Female** tick has attached,
- ***"There may be associated ocular signs, such as fixed and dilated pupils, that can help distinguish it from Guillain-Barré syndrome***

Treatment: supportive care. REMOVE TICK

[12] What is the presentation / treatment of Polymyositis/Dermatomyositis?

Risk Factors:

- Any Age
- Adults > Children
- Sarcoidosis
- Hypereosinophilic syndromes

- Malignant Neoplasms (breast, ovary, lung, and gastrointestinal tract, and lymphoproliferative disorders)
- Active viral / Bacterial infection

Presentation = weakness, pain, and tenderness of the muscles involved.

- Proximal muscle weakness predominates
- Difficult get up and go - hard to get out of chairs and weakness lifting the arms over the head.
- Often pain and tenderness in proximal muscles
- Decreased reflexes = decrease in strength
- *** NO Fasciculations ***
- Atrophy is a very late finding.

Dermatomyositis (more often kids) has classic skin findings:

- Periorbital heliotrope
- Erythema and swelling of the extensor surfaces of joints
- The facial rash is usually photosensitive, can also involve the exposed areas of the chest and neck

Elevated CK and CRP/ESR can NOT distinguish between neuromuscular causes and inflammatory myopathies (as both can be elevated in either condition)

Treatment:

- Prednisone 1 to 2 mg/kg/day
- If steroids ineffective: consider azathioprine (initial dose of 50 mg/day) or methotrexate (initial dose of 15 mg/week)

[13] What is Periodic paralysis?

Think about in acute, **painless** myopathies. Collectively, these disorders (hyperkalemic and hypokalemic forms and thyrotoxic periodic paralysis) cause periodic paralysis.

- Causes:
  - Hypokalemia / Hyperkalemia
  - Hypocalcemia / Hypercalcemia
  - Hypomagnesemia
  - Hypophosphatemia
  - Disorders of thyroid, parathyroid, or adrenal glands.

Hypokalemic and Hyperkalemic forms

- Rare hereditary disorders of ion channels
- Intermittent attacks of flaccid extremity weakness
- Hypokalemic form >> hyperkalemic form
- Associated w/ an inherited genetic mutation.
- Personal or family history of similar episodes
- Typical story is weakness after a large meal (carb load, increase insulin, more shift)
- Lower limbs > upper

Thyrotoxic periodic paralysis

- Acquired not genetic
- Almost identical presentation to kalemic forms of periodic paralysis
- Some overlap with clinical syndromes of thyroid and potassium forms
- Look for other hyperthyroidism symptoms (anxiety, emotional lability, weakness, tremor, palpitations, heat intolerance, increased perspiration, and weight loss despite a normal or increased appetite)
- In either hyperthyroidism or hypokalemia neuromuscular weakness likely related to sodium-potassium adenosine triphosphatase (Na+/K+-ATPase) pump = a rapid shift of potassium from extracellular to intracellular compartment.

Treatment: treat underlying electrolyte abnormality and thyroid dysfunction

Wisecracks:

[1] Clinically, how would you differentiate between a myasthenic crisis and a cholinergic crisis?

First off, cholinergic crisis (due to excess pyridostigmine) is so bloody rare it should barely be on your radar, always treat as MG crisis first. However, with your tensilon test (aka, edrophonium, which is an acetylcholinesterase inhibitor) the myasthenic patient will get better, the cholinergic crisis will become much weaker

[2] What is the presentation, timing and course of neonatal myasthenia?

According to UpToDate: “Transient neonatal myasthenia gravis occurs in 10 to 20 percent of infants born to mothers with myasthenia gravis. Most mothers of affected infants have active clinical disease, although some may have no evidence of myasthenia or may be in remission.”

- Maternal AChR antibodies transfer to fetus: causes clinical disease
- Rarely, there are persistent myopathic sequelae related to the fetal acetylcholine receptor inactivation syndrome (FARIS).
    - Elevated levels of maternal AChR antibodies directed against the fetal subunit of the AChR receptor, causing abnormal endplate development of the embryonic neuromuscular junction in a subset of infants. The facial and bulbar musculature may be particularly susceptible to permanent injury caused by this process.
- Typically presents within hours of birth
- Signs always present by third day of age
- More severely affected infants have a history of polyhydramnios and may have arthrogryposis multiplex (multiple joint contractures) at birth
- Recovery with treatment usually within several weeks

[3] What the differential diagnosis for a patient presenting with ascending muscle weakness, ptosis and diplopia?

- Gullian-Barre
- Myasthenic / Lambert Eaton Syndromes
- Botulism
- Hypomagnesemia / hypocalcemia
- Snake venom
- Tick paralysis
- Long list of drugs (phenytoin, beta blockers, pesticides, etc.)