Recent Advances in Neurology: Case Presentations

Jeffrey W. Ralph, MD
Assistant Clinical Professor
Director, UCSF Neuropathy Center

Patient 1

- 23 year-old man
  - Fatigue and weakness in the legs>>>arms.
  - No numbness.
- Family History
  - Mother—Sjögrens and rheumatoid arthritis
  - Father—hypothyroidism
- Exam
  - Cranial Nerves—normal (Mild ptosis?)
  - Normal muscle tone and bulk.
  - Mild weakness in proximal muscles.
  - Reflexes trace throughout.
  - Sensory examination—normal
- Labs
  - CK—Normal
  - Elevated tilters of anti-thyroperoxidase and anti-thyroglobulin antibodies.

Based on the details given, what do you think this is?

A. Motor neuropathy.
B. Neuromuscular junction disorder.
C. Periodic Paralysis.
D. His exam is essentially normal. This is a trick—there is no neurological diagnosis.
E. None of the above.

A Clue to the Diagnosis?

- Nerve Conduction Studies:
  - Normal sensory studies.
  - Low amplitudes of the compound muscle action potentials for multiple nerves studied in the upper and lower extremities.
- EMG
  - “Myopathic” motor unit action potentials.
How does this information affect your working diagnosis?

A. The low amplitudes for the motor responses suggest axon loss—this is a motor axonopathy or motor neuron disease.
B. Now a myopathy is most likely. (CK values can be normal in certain myopathies.)
C. I’m sticking with a neuromuscular junction disorder.
D. I hate reading EMG/nerve conduction studies. Next case please.

2 Hz REPETITIVE NERVE CONDUCTION STUDIES
Stimulate at Wrist and Record over Hand Muscle

A decremental response on low-frequency RNS can be seen in the following conditions?

A. Myasthenia gravis
B. Lambert-Eaton myasthenic syndrome
C. Myotonic disorder
D. ALS
E. All of the Above
LAMBERT EATON MYASTHENIC SYNDROME

NORMAL MUSCLE

LEMS

MOTOR NERVE CONDUCTION STUDIES
Stimulate at Wrist and Record over Hand Muscle

STIMULATE AGAIN AFTER 10 sec exercise

FACILITATION

EXERCISE
**Lambert Eaton Myasthenic Syndrome**

- Anderson et al., 1953
  - Myasthenia in a patient with a bronchial neoplasm
  - Prolonged apnea after succinylcholine administration
  - Direct muscle stimulation was normal
  - Increased sensitivity to d-tubocurarine
  - Normal cholinesterase levels

Anderson et al, Lancet, 1953, 1291-1292.

**LEMS**

- Defect of neuromuscular conduction associated with malignant neoplasms
  - Lambert, Eaton, Rooke
  - Abstract, American J. Physiology, 1956
  - Six patients with malignant tumors of the chest.
    - Proximal muscle weakness
    - Decreased or absent tendon reflexes
    - Increased fatigue
    - Slight improvement of strength with neostigmine
    - Patients very sensitive to d-tubocurarine
  - Electrophysiology
    - Low amplitude of motor action potentials although the strength of these muscles on voluntary contraction was essentially normal
    - Decline of response at rates of 1-10/sec
    - Marked facilitation at higher rates (up to 10 times initial amplitude) or after voluntary contraction

**Key Clinical Features**

- Proximal weakness in legs>arms
- Hyporeflexia
- Autonomic dysfunction
  - Dry mouth
  - Reduced sweating
  - Constipation
  - Erectile dysfunction
  - Pupillary light reflex may be affected
- Bulbar weakness uncommon; diplopia occurs occasionally

**Autoimmune Disease Mediated by Antibodies**

- Clinical response to plasma exchange
- Transfer of patients' sera into animals produces the pathophysiological features of LEMS
- Detection of antibodies P/Q-type VGCCs in patients
- Lambert and Elmqvist showed that there is a reduction of the quantal content of the EPP (biopsied intercostal muscle).

**Changes to the Nerve Terminal in LEMS**

**Lambert Eaton Myasthenic Syndrome**

- 50% of cases are associated with cancer.
  - Usually small cell lung cancer.
  - If a history of smoking and age >50 → cancer very likely.
  - 3% of patients with SCLC will develop LEMS
  - Tumor VGCCs trigger LEMS. Trigger for noncancer LEMS unknown.
- HLA Associations for Noncancer-LEMS
  - HLA-B8; HLA-DR3 and DQ2
  - These same associations are seen in young, female, Caucasian patients with MG.

**Long-Term Outcomes in LEMS without SCLC**

- Retrospective study of 47 patients
- Data collected from clinic visits over 10 year period
- “Favorable prognosis”
  - 88% of patients had improved strength
  - 43% had sustained clinical remission on immune therapy (corticosteroids plus azathioprine)
  - Two had a complete remission (not on any therapy)
  - 5 required only 3,4-DAP for symptom control
  - Lymphoma presented in 3 patients (related to azathioprine?)
  - 10 patients died (mean age at death was 70 years)
- Preserved proximal muscle strength predicted good outcome.

Maddison et al., J Neurol Neurosurg Psychiatry 2001;70:212-217

**Which is not an effective therapy for LEMS?**

A. Pyridostigmine (Mestinon)
B. 3,4-Diaminopyridine
C. Prednisone
D. **Atropine**
E. Don’t ask me. I barely passed pharmacology.

**Therapy**

- 3,4-diaminopyridine
  - Blocks voltage-gated K+ channels → Prolongs nerve membrane depolarization → More Ca++ influx → More acetylcholine released.
  - Randomized, controlled trials showed benefit.
- IVIG—randomized trial showed benefit
- Plasmapheresis
- Steroids, azathioprine, and cyclosporine may benefit the disease.
Summary

<table>
<thead>
<tr>
<th></th>
<th>LEMS</th>
<th>MG</th>
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<tbody>
<tr>
<td>Tumor Association</td>
<td>SCLC (50%)</td>
<td>Thymoma (10-15%)</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Difficulty walking; autonomic symptoms; ocular symptoms uncommon</td>
<td>Ocular symptoms common (ptosis and diplopia); bulbar weakness in some</td>
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<tr>
<td>Examination</td>
<td>Depressed reflexes; Weakness Underwhelming</td>
<td>Normal reflexes; Ptosis; Ophthalmoparesis; Weakness easy to detect</td>
</tr>
<tr>
<td>Antibodies</td>
<td>VGCC</td>
<td>Ach R Abs (80%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>3,4 DAP, pyridostigmine, PLEX, IVIG, prednisone, azathioprine</td>
<td>Pyridostigmine, PLEX, IVIG, prednisone, azathioprine</td>
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Take Home Points

- Include LEMS in the differential diagnosis for exercise intolerance and weakness with normal CK levels.
- Patients may have overlapping diagnoses of LEMS and MG.
- Remember the role of 3,4 DAP in the treatment of LEMS.
- Is LEMS under-recognized in our patients presenting with CNS paraneoplastic syndromes?

Patient 2

- 60 year-old man with 18 mos. of muscle “tightness” and elevated CK levels. Muscle biopsy?
  - Started in calves → spread to other muscles
  - Worst after a period of rest; warm-up phenomenon
  - Difficulty getting out of chairs
- Exam
  - CN: Normal
  - Motor: Normal
  - Reflexes: Normal
  - Sensory: Normal
  - Gait: Normal

Patient 2

- Labs
  - T4 level mildly low → Started levothyroxine
  - CK 500-600s (Normal <350 U/L)
- EMG—Normal
What was seen...

60 year-old man with muscle tightness

My friends, let me tell you about rippling muscle disease.
**Summary: Rippling Phenomenon**

- Probably caused by abnormal regulation of calcium release from the sarcoplasmic reticulum.
- Rippling is electrically silent.
- The direction of rippling (wave) is perpendicular to the orientation of the muscle fibers.

**Which of the following contractions is NOT electrically silent?**

1. Muscle rippling
2. **Grip Myotonia**
3. Contracture in McArdle’s disease
4. Myoedema

**Electrically Silent Muscle Contractions**

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<tr>
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<th>Myoedema</th>
<th>Rippling Muscle Disease</th>
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<tr>
<td><strong>Response to muscle percussion</strong></td>
<td>Brief localized mounding</td>
<td>Linear indentation of the muscle that moves perpendicular to orientation of the muscle fibers</td>
</tr>
<tr>
<td><strong>Disease associations</strong></td>
<td>Cachexia; Myxedema; Rarely hereditary</td>
<td>Hereditary (Caveolin-3 mutations); autoimmune &amp; paraneoplastic (thymoma)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Muscle pain, cramps, stiffness (in hypothyroidism)</td>
<td>Stiffness; muscle pain</td>
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**Rippling Muscle Disease**

**Hereditary**
- Most cases associated with CAV-3 mutations (Note CAV3 mutations also cause limb girdle muscular dystrophy and cryptogenic hyperCKemia)
- Inheritance patterns
  - Autosomal dominant
  - Autosomal recessive

**Acquired**
- 1980: Alberta probably reported the first sporadic case.
  - "Increased mechanical muscle irritability syndrome."
- 1989: Ricker named and defined the entity.

**Main Symptoms**
- Stiffness ± Weakness
  - Stiffness; Weakness if MG also present

**CK**
- Hereditary: Midey elevated
- Acquired: Midey elevated

**Treatment**
- **Hereditary**
  - ??
- **Acquired**
  - Immunosuppressive medications; Given benign natural history, may not be necessary

**Disease Associations**
- Hereditary: N/A
- Acquired: Myasthenia gravis
  - Thymoma

**Other lab findings...**
- Hereditary: N/A
- Acquired: + Anti-striated muscle antibodies

**Symptom Onset**
- Hereditary: Childhood
- Acquired: 33-60 years old

**SUBJECTIVE vs. OBJECTIVE STIFFNESS**

Which of the following conditions is NOT associated with increased muscle tone on exam ("objective stiffness")?

A. Stiff Person syndrome
B. Neuromyotonia (Isaac's syndrome)
C. Myotonia Congenita & Rippling Muscle Disease
D. Strychnine poisoning

**Take Home Points**
- Rippling muscle disease is a benign myopathy associated with muscle hyperexcitability
- Some muscle contractions (including muscle rippling) are electrically silent
- In the diagnostic process, consider the distinction between subjective and objective stiffness
- If a patient complains of stiffness or tightness, GO AHEAD AND PERCUSS THE MUSCLE!!
Patient 3

- 28 year-old woman with right rotator cuff injury
- Underwent RIGHT posterior brachial plexus block in preparation for shoulder surgery
- Severe pain upon injection
- Loss of consciousness → Respiratory arrest
- Procedure was performed
- Post-procedure, reported deafness then tinnitus
- OTHER SYMPTOMS
  - Severe pain in LUE
  - Weakness and numbness in the RUE
  - Constipation

Patient 3 Exam

- CN: Normal. No miosis, anhidrosis, ptosis.
- Motor: Proximal > distal weakness in the RUE
- Reflexes: Depressed in the RUE except the right triceps reflex was brisk
- Sensory: Light touch, vibration, and pain sensation impaired in RUE; LUE exam normal
- OUTCOME: Pain improved with gabapentin; modest improvement in strength on follow-up.

Which test would you order?

A. MRI brain
B. EMG/NCS of the RUE
C. MRI of the cervical spine
D. MRI of the brachial plexus
E. Multiple diagnostic tests

Patient 2

T2-weighted MRI scan showing linear cord signal abnormality spanning the C3 to C7 levels, localizing to the right gray matter.

EMG/NCS of the right upper extremity was normal
Cervical Myelopathy after Transforaminal Epidural Corticosteroid Injection

Pre- (left) and post-procedure (right) sagittal T2-weighted MRI scans. On the right, there is T2 prolongation within the cord spanning the C2 to C6 levels.

Possible Mechanisms of Injury
- Direct puncture and injection into the cord.
- Intra-arterial injection
  - Damage to the Vessel
    - Occlusion → Cord Ischemia
    - Dissection → Embolism → Cord Ischemia
  - Damage by Injectant
    - Embolism → Cord Ischemia
    - Toxic effects (scant evidence)
- Intra-neural injection
  - Central (centripetal) spread of the injectant
  - Injectant infiltrates cord
  - Injectant reaches subarachnoid space (detected in CSF)

Anatomy of the Cervical Cord
The close associations of the vertebral artery, spinal radicular artery, and nerve root are depicted. (Adapted from Mayo 2004)

Is there experimental evidence that a substance injected into a peripheral nerve can 1) reach the spinal cord and 2) cause a myelopathy?

A. No, and no
B. Yes, and no
C. Yes and yes
D. I abstain
Efocaine Story

- Introduced in 1950s
- 1% procaine, 0.25% procaine hydrochloride, and 5% butyl-p-aminobenzoate in 2% polyethylene glycol-300, 78% propylene glycol, and water
- Promoted as a safe, long-lasting anesthetic
- In the 1950s, Moore and colleagues reported 11 patients who developed bilateral leg weakness after its use, and another two patients died.
  - 10 received paravertebral intercostal nerve blocks
  - 1 had a lumbar sympathetic block

Efocaine, Part II

- Moore and colleagues injected Efocaine plus methylene blue into nerve roots of a killed monkey.
  - Immediate centrad spread, slowing only momentarily at the dorsal root ganglion.
  - Substance reached the spinal cord in two to five minutes, spreading up and down the surface cord subpially
  - After 10-15 minutes, the spinal fluid became tinged
- Moore and colleagues injected 0.5 to 1.5 cc of Efocaine into the lumbar nerves of 11 anesthetized monkeys
  - Respiratory paralysis developed in three monkeys
  - In all the surviving monkeys, leg weakness developed ipsilaterally to the site of injection.
  - Elevated anesthetic levels were seen in most of the monkeys’ CSF. (The levels were the highest when the resistance to the injection was the least.)
- Injection of miniscule amounts of penicillin intraneurally, could lead to a severe myelopathy.

A Similar Case

- Cochrane (Muscle & Nerve 2007)
  - Posterior brachial plexus block for shoulder surgery
  - Patient experiences severe pain upon injection
  - Respiratory arrest → Intubation → Surgical procedure completed
  - Ipsilateral arm paralysis and anesthesia; contralateral impairment of pain and temperature sensation
- Intraneural injection suspected
  - Severe pain upon injection
  - Needle placement was determined by electrical stimulation
  - Careful depth marking was done before injection
  - Free fluid was seen in the cord
Which of the following precautions may prevent this complication from occurring?

- Avoid sedation when nerve blocks are performed
- Immediate cessation of procedure if patient reports pain
- Fluoroscopic or CT guidance should be performed for all transforaminal epidural injections.

Take Home Points

- Injections into the neck region may rarely cause a cervical myelopathy.
  - Neurological deficits can be severe
  - And permanent
- Be aware that the peripheral nerve is a potential "highway" to the CNS.
- The precise mechanism of injury is often unclear.
- Despite our ignorance, common sense practices (e.g., don't do nerve blocks in sedated patients) may prevent this complication.

Thanks for your attention!