AANEM Case Study:

It is not Myasthenia Gravis

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No one involved in the planning of this CME activity had any relevant financial relationships to disclose. Authors/Faculty had nothing to disclose.

Reviewed and accepted by the 2013-2014 Website CME Committee of the American Association of Neuromuscular & Electrodiagnostic Medicine

Certified for CME credit 08/2014 – 08/2017
It is not Myasthenia Gravis

**Educational Objectives:** Upon completion of this case study, the participants will acquire skills to
1) recognize patterns of presentations in mitochondrial diseases related to Polymerase Gamma (POLG)1 mutations, 2) differentiate mitochondrial diseases from neuromuscular junction disorders, and 3) pursue appropriate investigation in patients suspected for mitochondrial diseases.

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EMG CASE: It is not Myasthenia Gravis
Jau-Shin Lou, MD, PhD

Case Information

<table>
<thead>
<tr>
<th>Presenting Symptom(s):</th>
<th>Fatigue, double vision, swallowing and speech difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-specific Diagnosis</td>
<td>Case-specific Diagnosis (e.g. inclusion body myositis): Sensory Ataxic Neuropathy, Dysarthria, and Ophthalmoparesis (SANDO)</td>
</tr>
<tr>
<td>Appropriate Audience:</td>
<td>Residents, practicing physicians, and academic physicians</td>
</tr>
<tr>
<td>Level of Difficulty:</td>
<td>Advanced</td>
</tr>
</tbody>
</table>

1. HISTORY

A 41-year-old woman presents with fatigue, double vision, swallowing and speech difficulties for 7 years. At age 33, she developed foot allodynia and numbness that has progressed up to calves after 8 years followed by tingling in both hands. At age 34, she started to experience progressive fatigue, proximal muscle weakness with difficulty walking up stairs. At age 35, she developed double vision that got worse when she was tired. She underwent Neuro-Ophthalmology evaluation and was noted to have frozen lateral and upward gaze, as well as fatigable ptosis, left worse than right. She was diagnosed with myasthenia gravis at that time and started on pyridostigmine with questionable improvement in fatigue. It was also noted that she had wide-based gait around that time. At age 35, she started to have swallowing difficulty, especially with liquids. Her speech also got slurred when she was tired. Recently, she discontinued pyridostigmine without any change in her symptoms. Treatment trials over the years included prednisone for 4 months, methotrexate and a course of IVIgG. Prednisone was discontinued due to suicidal ideation and worsening diabetes. Trials of methotrexat (up to 15 mg/week) and IVIgG showed no improvement of symptoms.

Past medical history includes:

- Hypertension
- Diabetes
- Obesity
- Psoriasis
- Depression/anxiety
- Polycystic Ovarian Disease
- Sleep apnea on CPAP
- S/P right carpal tunnel release

Medications:

Family history is negative for neurological disorders. She has 2 healthy sisters.

Previous diagnostic studies:

- Acetylcholine R binding and blocking Antibodies: negative
- MuSK Antibody: negative
- CK: 341 IU/L (normal range)
- Vitamin E, SPEP: normal
- Lactic acid (venous) 2.1 mg/dL (0.5-2.2 mg/dL)
- Friedreich's Ataxia DNA Test: negative
- Mitochondrial Myopathy mtDNA (MELAS, MERRF, NARP mutations): absent for common mutations
- MRI scan of brain (with or without enhancement?): normal
- CT scan of chest was normal without No evidence of anterior mediastinal mass or thymoma.

2. PHYSICAL EXAMINATION

- General – morbidly obese (4’11”, 261 lb, BMI 52.6)
- Mental status - normal
- Speech - mild dysarthria (any particular type?)
- Cranial Nerves - bilaterally impaired upward gaze and adduction; bilateral ptosis without fatigability on upward gaze. Normal corneal reflexes.
- Motor Examination - normal bulk, tone and strength in all muscle groups
- Sensory Examination - severely diminished to light touch, pinprick, temperature, vibration, and proprioception in both legs, distally worse than proximally
- Deep tendon reflexes - absent in legs and 1+ in arms.
- Plantar response is flexor.
- Coordination - mildly impaired bilateral finger-to-nose test and rapid alternating movements; wide-based, ataxic gait; positive Romberg’s sign
3. COMMENTARY

The patient has non-fatigable ophthalmoparesis, dysarthria, length-dependent sensory impairment to all modalities and ataxia. These findings indicate involvement of multiple areas of nervous system: multiple cranial nerves and/or cranial nerve innervated muscles and the sensory part of the peripheral nerves in a length-dependent pattern (if corneal reflex is present). The lesion cannot be localized to one anatomical site or system.

In the differential diagnosis of a chronic disease affecting multiple anatomical sites and systems metabolic-toxic, infectious, immune-mediated and genetic/degenerative etiologies have to be considered. Mitochondrial disorders should be considered when the disease affects multiple systems. Chronic progressive external ophthalmoplegia (CPEO) can be seen in association with mitochondrial myopathies or neuropathies. Sensory Ataxic Neuropathy Dysarthria Ophthalmoparesis (SANDO) is one of mitochondrial disorders that can cause all of the patient’s findings. Other mitochondrial disorders can explain some of her symptoms but not all. Myasthenia gravis is a more common cause of ophthalmoparesis and dysarthria but it does not cause sensory deficits and ataxia, which are dominant findings on examination in our case. Also, the patient tested negative for acetylcholine receptor antibodies and the anti-MUSK antibody. Friedreich's Ataxia was excluded by DNA testing. There is no family history or cerebellar atrophy on MRI that would be suggestive of spino-cerebellar ataxia. Other differential diagnoses include generalized neuropathy such as chronic inflammatory demyelinating neuropathy (CIDP), or other immune-mediated neuropathy. CIDP can affect cranial nerves but it is quite unusual to have no motor deficit after years of symptoms, though pure sensory variants have been reported. Miller Fisher syndrome can cause ophthalmoparesis, ataxia and hypo/areflexia. But this is an acute disease that develops over a few days, less than 2 weeks, and not over years as in our case. Oculopharyngeal muscular dystrophy can also cause opthalmoparesis and dysarthria but cannot explain significant sensory loss and ataxia. Infectious causes are less likely given a chronic progressive course. Neurological complications of lyme disease can involve cranial nerve, especially facial neuropathy, but it does not typically cause pure sensory neuropathy. HIV infection can be associated with various neurological complications and cannot be excluded.

4. ELECTROPYHISIOLOGIC DATA

Limb Temperature: $\geq 32.0^\circ$ hand (FDI), $\geq 30.0^\circ$ foot (1st-2nd dorsal metatarsal)

Abnormalities graded 1+ to 4+, 1- to 4-
### Sensory Nerve Conduction Studies

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Peak Latency</th>
<th>Amplitude</th>
<th>Conduction Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neg Peak Lat. (ms)</td>
<td>Normal Lat. (ms)</td>
<td>uV</td>
</tr>
<tr>
<td>Medianus Sensory Right</td>
<td>Wrist - Dlg II</td>
<td>abs</td>
<td>&gt;12.0</td>
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<tr>
<td>Radialis Sensory Right</td>
<td>Wrist - Dlg I</td>
<td>abs</td>
<td>&gt;17.0</td>
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<tr>
<td></td>
<td>Forearm - Snuff box</td>
<td>abs</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td>Suralis Sensory Right</td>
<td>Post Calf 14cm - Lat. Malleolus</td>
<td>abs</td>
<td>&gt;4.0</td>
</tr>
<tr>
<td>Ulnaris Sensory Right</td>
<td>Wrist - Dlg V</td>
<td>abs</td>
<td>&gt;5.0</td>
</tr>
</tbody>
</table>

### Motor Nerve Conduction Studies

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Latency</th>
<th>Amplitude</th>
<th>Conduction Velocity</th>
<th>Neg Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset Lat. (ms)</td>
<td>Normal Latency</td>
<td>mV</td>
<td>Normal Amplitude</td>
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<tr>
<td>Medianus Motor Right</td>
<td>Wrist - APB</td>
<td>4.56</td>
<td>&lt;3.8</td>
<td>9.5</td>
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<tr>
<td>Elbow-Wrist</td>
<td>8.83</td>
<td>8.8</td>
<td>235</td>
<td>55.0</td>
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<tr>
<td>Peroneus Motor Right</td>
<td>Ankle - EDB</td>
<td>3.41</td>
<td>&lt;6.0</td>
<td>5.7</td>
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<td></td>
<td>Fib. head- Ankle</td>
<td>Tech Dif</td>
<td>Ab. knee-Fib. head</td>
<td>12.0</td>
</tr>
<tr>
<td>Tibialis Motor Right</td>
<td>Ankle - Abd hal</td>
<td>4.68</td>
<td>&lt;6.0</td>
<td>10.6</td>
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<tr>
<td></td>
<td>Knee-Ankle</td>
<td>10.9</td>
<td>Tech Dif</td>
<td>&gt;40.0</td>
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<tr>
<td>Ulnar Motor Right</td>
<td>Wrist - ADM</td>
<td>2.31</td>
<td>&lt;3.2</td>
<td>15.2</td>
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<tr>
<td>Bi Elb-Wrist</td>
<td>5.81</td>
<td>15.6</td>
<td>185</td>
<td>52.9</td>
</tr>
<tr>
<td>Ab Elb-Bi Elb</td>
<td>7.29</td>
<td>16.0</td>
<td>100</td>
<td>67.6</td>
</tr>
</tbody>
</table>
Summary:

- SNAPs are absent in right upper and lower extremities.
- The right median-APB CMAP has prolonged latency. Other motor nerve conduction studies in the right upper and lower extremities are normal.
- 3-Hz repetitive nerve stimulation of the right facial nerve over the right nasalis shows no decrement.
- EMG of proximal and distal muscles in the right upper and lower extremities are normal.
4. COMMENTARY

Electrophysiologic study show severe sensory neuronopathy/ganglionopathy. There is no evidence or demyelinating neuropathy or neuromuscular junction disorder. There is no evidence for demyelinating neuropathy, neuromuscular junction disorder or myopathy. These electrophysiologic findings limit the differential diagnosis to a limited list (see http://neuromuscular.wustl.edu/sensory-large.html). None of the other disorders causing a chronic sensory neuronopathy/ganglionopathy includes ophthalmoparesis and dysarthria in the clinical presentation. Of all these diseases only SANDO is known to cause ophthalmoparesis and dysarthria.

The patient has severe sensoryneuronopathy/ganglionopathy, sensory ataxia, dysarthria and ophthalmoparesis. These deficits are localized to the sensory part of the peripheral nerves and selected cranial nerves and/or the muscles they innervate. MRI brain does not show brainstem lesion that would affect cranial nuclei. Friedreich's Ataxia can cause similar findings (dysphasia, diabetes, abnormal eye movements, however, not ophthalmoparesis/plegia) but was excluded by negative DNA testing.

Polymerase Gamma (POLG1) DNA test detected a Heterozygous mutation, c.1399G>A(p.A467T) and a novel heterozygous missense variant, c.264C>G (p.F88L). The diagnosis of SANDO was confirmed.

There is no specific treatment for diseases related to POLG1 mutations. Management is supportive.

5. SANDO

Sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO) is a characteristic clinical triad. 78% of full SANDO syndrome have POLG mutation on Chromosome 15q26.1 which is mostly autosomal recessive but autosomal dominant was also reported. The mutations can be compound heterozygotes or homozygotes. Symptom onset is in young adult, but can also see at later age. Sensory neuropathy is typically the first manifestation, which can involve both large and small fiber. Small fiber loss may be an earliest feature. Sensory ataxia may manifest as pseudoathetosis. Motor involvement is variable. Patients can have normal, distal weakness or diffuse weakness. Gait difficulty is secondary to sensory ataxia. Tendon reflexes are typically absent or reduced. Later signs include progressive external ophthalmoplegia and ptosis. Cranial nerve involvements also cause dysarthria and facial weakness. Some patient may have CNS involvement and manifest as seizure or depression.

Electrophysiologic study can show axonal neuropathy or neuronopathy with absent or reduced SNAP amplitude. Needle EMG may see evidence of denervation (90%) in distal and/or proximal muscles. Myopathic features can be seen in proximal muscles.
Laboratory findings are non-specific. Lactate may be high in CSF and serum in some patients. Serum CK is normal or mildly elevated. In patient with CNS involvement, degeneration of cerebellum, spinocerebellar and dorsal column tracts may be evident. Thalamic lesions were reported in some patients. Muscle pathology is variable from normal to mitochondrial abnormalities such as ragged red fibers, COX + and COX -, and SDH+ muscle fibers. Mitochondrial oxidative enzyme activities are often normal.

The disease is progressive and there is no specific treatment. Management is supportive.

Polymerase Gamma (POLG) gene is located on chromosome 15q26.1. POLG1 is encoded for DNA polymerase alpha subunit, which is responsible for mtDNA replication. POLG1 mutation can cause a number of phenotypically heterogeneous mitochondrial diseases including

Progressive External Ophthalmoplegia (PEO) (most common); Ataxia neuropathy spectrum (ANS); Mitochondrial Ataxic Syndrome without Ophthalmoplegia (MIRAS); Sensory Ataxic Neuropathy, Dysarthria, and Ophthalmoplegia (SANDO); Mitochondrial DNA (mtDNA) depletion syndromes (MDDS); Alpers-Huttenlocher disease: Hepato-cerebral degeneration; Mitochondrial Neurogastrointestinal Encephalopathy syndrome (MNGIE).

The patient is now 44 years old. She continues to have worsening balance difficulty. She needs a walker and a wheelchair to get around. Motor strength is still full except for mild hip flexor weakness bilaterally.

**BIBLIOGRAPHY**