Slurred Speech and Difficulty Swallowing

Kirsten Gruis, MD, MS

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

CME is available 5/6/2008 - 5/6/2011

Copyright: 2008

American Association of Neuromuscular and Electrodiagnostic Medicine

2621 Superior Dr NW Rochester, MN  55901

The ideas and opinions in this Case Study are solely those of the author and do not necessarily represent those of the AANEM
CME Information
Product: CS22 - Slurred Speech and Difficulty Swallowing

Course Description
Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:
1. identify the basic pathophysiology at the neuromuscular junction in myasthenia gravis.
2. describe how to perform and identify abnormal repetitive motor nerve stimulation for a presynaptic disorder such as myasthenia gravis.
3. discuss the basics of administering treatment to patients with myasthenia gravis.

Release Date: 5/6/2008
Expiration Date: 5/6/2011. Your request to receive AMA PRA Category 1 Credits™ must be submitted on or before the credit expiration date.
Duration/Completion Time: 1 hour

Accreditation and Designation Statements
The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The AANEM designates both sections of this enduring material for a combined maximum of 1 AMA PRA Category 1 credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

How to Obtain CME
Once you have reviewed the materials, you can obtain CME credit by clicking on the link in the e-mail received when you purchased this product. Answer the questions and click submit. Once your answers have been submitted, you will be able to view a transcript of your CME by logging into www.aanem.org and clicking View Profile and then My CME.
Table of Contents

1. CME Information
2. History
3. Physical Examination
4. Electrophysiologic Data
5. Commentary V
6. Bibliography
Slurred Speech with Difficulty Swallowing

May 2008

CME Available from May 2008 through May 2011

Accreditation Statement: The AANEM is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education (CME) for physicians. The AANEM designates this educational activity for a maximum of 1 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity. This activity has been developed in accordance with the ACCME Essentials.

Presenting Symptom: Slurred speech and difficulty swallowing

Case prepared by: Kirsten Gruis, MD, MS

Affiliations: University of Michigan

Disclosures: No one involved in the planning of this CME activity have any relevant financial relationships to disclose. Authors/faculty have nothing to disclose.

Please note: The opinions expressed in these cases reflect the view of the authors and do not reflect official views or positions of AANEM. The AANEM is not liable for decisions made or actions taken by you or any third party in reliance on any of the information contained herein. Reference to any products, services, hypertext link to the third parties, or other information by trade name, trademark, supplier, or otherwise does not constitute or imply endorsement, sponsorship, or recommendation by the AANEM. Finally, we encourage you to read AANEM’s Privacy Policy.

Software Requirement(s): Each of the CME Application and Evaluation forms are online as PDF files, which can be viewed with Adobe Acrobat Reader software. Reader allows you to view, navigate, and print PDF files across all major computing platforms. To download a free copy of Reader, connect to the Adobe Acrobat site.

Appropriate Audience: Residents and practicing physicians.

Learning Objectives: After completing this educational activity, participants will be able to:
1) Identify the basic pathophysiology at the neuromuscular junction in myasthenia gravis.
2) Describe how to perform and identify abnormal repetitive motor nerve stimulation for a presynaptic disorder such as myasthenia gravis.
3) Discuss the basics of administering treatment to patients with myasthenia gravis.

Level of Difficulty: Basic.
Slurred Speech with Difficulty Swallowing

History

A 65-year-old man presents with an 18-month history of symptoms of slurred speech and difficulty swallowing. Symptoms are worse after prolonged talking and at the end of the day but symptoms never go away entirely.

Prior to continuing, please develop a differential diagnosis and list each possible diagnosis in order of likelihood.
Is there any additional information regarding the clinical history that might be helpful in clarifying your differential list or changing its order of priority?

Commentary I

Differential diagnosis would include: stroke (or another central nervous system disorder predominately affecting brainstem structures), motor neuron disease (amyotrophic lateral sclerosis [ALS]), neuromuscular junction disorder, or myopathy.

Clarification regarding the temporal course of symptoms would be of benefit. Symptoms that happened suddenly with maximum severity at onset may represent a central nervous system lesion such as a stroke. Stroke like symptoms associated with dysphagia and dysarthria may include symptoms of hemi-body numbness or weakness and acute vertigo. Accompanying symptoms of bilateral limb weakness would be more suggestive of a neuromuscular disorder. Among neuromuscular disorders, symptoms of double vision (diplopia) and droopy eyelids (ptosis) would be suggestive of a neuromuscular junction disorder. Symptoms of fasciculations and muscle atrophy are more indicative of motor neuron disease. Lastly, symptoms of symmetrical proximal limb weakness with pain, arthralgias, and/or rash are suggestive of an acquired, inflammatory myopathy.

History, Continued

He reports no pain, rashes, muscle atrophy, fasciculations, cramps, ptosis, or diplopia. He reports his symptoms of dysphagia and dysarthria are gradually progressive and no numbness or vertigo. He describes difficulty arising from a seated position requiring him to use his arms to initiate this movement. He describes a 7-pound weight loss from difficulty swallowing. One month prior he had a transient episode of difficulty holding his head upright and shortness of breath with exertion. At that time he had a negative evaluation for cardiac disease.

If necessary, revise your differential diagnosis based on the additional clinical history. On which details of the physical examination should you focus at this point?

Commentary II

A stroke is unlikely given the progressive nature of his symptoms and lack of hemi-body numbness or weakness. Lack of ocular symptoms doesn’t exclude a neuromuscular junction disorder, and a prior episode of neck weakness with dyspnea that resolved would be consistent with this disorder. Symmetrical proximal leg weakness in combination with dysphagia may represent findings of a myopathy. Additionally, although the patients reports no symptoms of muscle atrophy or distal limb weakness, motor neuron disease with predominate bulbar symptoms also remains a possible diagnosis. Weight loss may be seen in all three diagnoses: inflammatory myopathy, neuromuscular junction defect and motor neuron disease.
Physical Examination

Extraocular eye movements are full, and there is no ptosis even with prolonged upward gaze. There is significant bilateral facial muscle weakness, with inability to close both eyelids tightly, pursing lips to whistle, or holding air in his cheeks. There is weakness of tongue protrusion and lateral tongue movements to resistance. He had a flaccid dysarthria to casual conversation. He has normal facial sensation, palate movement, and absent jaw jerk. The neck flexors are moderately weak. He has normal strength in the shoulder girdle, proximal upper arms, and hand intrinsics except for weakness of finger extensors bilaterally. There is mild weakness with hip flexion but otherwise full strength in thigh and distal leg muscles. There is no muscle atrophy in upper or lower limbs. He demonstrates difficulty rising from a seated position but is able to walk on his heels, toes and in tandem. Sensation to light touch and pin-prick is intact in all four distal limbs. Deep tendon reflexes are easily elicitable but without pathological spread and plantar responses are flexor bilaterally (no abnormal Babinski sign).

At this point, review your differential diagnosis and revise as appropriate.
Are there additional observations on physical examination that might be helpful in narrowing your differential list?

Commentary III

Physical examination findings include bilateral facial diplegia, distal upper limb weakness and proximal lower limb weakness without muscle atrophy, sensory loss or abnormal upper motor neuron (corticospinal tract) findings. A central nervous system disorder such as a stroke is excluded. The lack of muscle atrophy, fasciculations, and pathologically increased deep tendon reflexes make motor neuron disease (ALS) unlikely. A neuromuscular junction disorder and myopathy with both proximal and distal weakness are still possible diagnoses.

If necessary, revise your differential diagnosis based on the additional physical findings.
Design your approach to the electrophysiologic examination based on the existing data.

Electrophysiologic Data

<table>
<thead>
<tr>
<th>NERVE</th>
<th>SIDE</th>
<th>STIM SITE</th>
<th>RECORD</th>
<th>CM</th>
<th>AMPL uV</th>
<th>LAT ms</th>
<th>CV m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulnar</td>
<td>Right</td>
<td>wrist</td>
<td>5th digit</td>
<td>14</td>
<td>20 uV</td>
<td>3.3ms</td>
<td>58 m/s</td>
</tr>
<tr>
<td>Sural</td>
<td>Right</td>
<td>calf</td>
<td>ankle</td>
<td>14</td>
<td>12 uV</td>
<td>3.5ms</td>
<td>50 m/s</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NERVE</th>
<th>SIDE</th>
<th>STIM SITE</th>
<th>RECORD</th>
<th>cm</th>
<th>AMPL mV</th>
<th>LAT ms</th>
<th>CV m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulnar</td>
<td>Right</td>
<td>wrist</td>
<td>hypothenar</td>
<td>7</td>
<td>9 mV</td>
<td>3.0ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>below elbow</td>
<td>hypothenar</td>
<td>17</td>
<td>7.8mV</td>
<td>6.0ms</td>
<td>57 m/s</td>
</tr>
<tr>
<td>NERVE</td>
<td>SIDE</td>
<td>AMPL</td>
<td>REST% decrement</td>
<td>Post-activation facilitation immediately after exercise (%) decrement</td>
<td>Post-activation exhaustion 2-3 minutes after exercise (%) decrement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------</td>
<td>----------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulnar F-wave Right</td>
<td>wrist</td>
<td>hypothenar</td>
<td>7</td>
<td>9 mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>below elbow</td>
<td></td>
<td>17</td>
<td>7.8 mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peroneal Right</td>
<td>ankle</td>
<td>EDB (foot)</td>
<td>9</td>
<td>3.5 mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>below knee</td>
<td></td>
<td>19</td>
<td>3.0 mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal Accessory Right</td>
<td>Posterior SCM</td>
<td>Upper</td>
<td>3.4 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial Motor Right</td>
<td>preauricular</td>
<td>nasalis</td>
<td>2.0 mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Repetitive nerve stimulation performed with as much muscle/limb immobilization as possible. A train of 4 stimuli at 2 Hz is applied once a maximum CMAP is elicited. The decrement is calculated for each train as the difference between the first and fourth CMAP amplitudes. If a decrement is noted a repeat train of 4 stimuli is done to verify findings. The muscle is then exercised for 60 seconds and a train of 4 stimuli applied to assess “post-activation facilitation” (repair of a decrement and/or increment). After exercise a train of 4 stimuli is then repeated at regular one minute intervals continuing to 5 minutes to assess for “post-activation exhaustion”.

**NEEDLE ELECTROMYOGRAPHY**

INSERtional activity: N, sust, unsust
FIB: 0, 1+, 2+, 3+, 4+
OTHer: 0 or fascic, myotonia, myokymia
EFFort: N, decr
RECRuitment: N, inc or dec 1+, 2+, 3+, 4+
AMPlitude: N, inc or dec 1+, 2+, 3+, 4+
DURation: N, inc or dec 1+, 2+, 3+, 4+
POLyphasia: N, inc or dec 1+, 2+, 3+, 4+

<table>
<thead>
<tr>
<th>R/L</th>
<th>MUSCLE</th>
<th>INSER</th>
<th>FIB</th>
<th>OTH</th>
<th>EFF</th>
<th>REC</th>
<th>AMP</th>
<th>DUR</th>
<th>POL</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>FDIH (hand)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>
On the basis of both the clinical and electrophysiologic evaluations, formulate your diagnostic impression. List the most likely diagnosis first and follow in order with the other possibilities that are not excluded by the data. Eliminate those diagnoses not supported by the data.

Are there additional electrophysiologic data that you feel would further delineate the diagnosis? (Remember, collecting data that are not needed for the diagnosis is costly and uncomfortable for the patient.)

Make the final revisions of your diagnostic impressions.

**Diagnostic Impression**

This is an abnormal examination. There is electrodiagnostic evidence of a disorder of neuromuscular transmission of the kind seen in myasthenia gravis (MG).

**Commentary V**

Motor nerves terminate at the neuromuscular junction (NMJ) and communicate with corresponding muscle fibers. The motor nerve “presynaptic” membrane releases acetylcholine to subsequently bind to a receptor on the “postsynaptic” muscle membrane resulting in an endplate potential (EPP). Normally, the EPP is 3- or 4-fold higher than the threshold needed to generate a muscle fiber action potential resulting in muscle contraction. The “safety factor” is defined as the ratio between the EPP and this threshold potential. Any pathological process that results in lowering the EPP (and subsequently reducing the safety factor) can block NMJ function resulting in motor weakness. In myasthenia gravis (MG) the EPP is reduced by autoimmune pathology at the postsynaptic muscle membrane and acetylcholine receptors.

Repetitive motor nerve stimulation (RNS) is an electrophysiologic technique that is used to detect a reduced EPP in NMJ disorders. By applying 4-5 stimuli at a slow rate (2-3 Hz) the neuromuscular junction function is stressed. With each subsequent stimulus, the EPP is reduced as less acetylcholine is available for release. A normal NMJ withstands this stress given the safety factor. However, in any pathological process that results in lowering the EPP (and subsequently reducing the safety factor) can block NMJ function resulting in motor weakness. In myasthenia gravis (MG) the EPP is reduced by autoimmune pathology at the postsynaptic muscle membrane and acetylcholine receptors.

<table>
<thead>
<tr>
<th>R</th>
<th>EDC (extensor digitorum communis)</th>
<th>0</th>
<th>0</th>
<th>0</th>
<th>M</th>
<th>Inc 1+</th>
<th>N</th>
<th>Dec 1+</th>
<th>Inc 1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Biceps brachii</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>R</td>
<td>Triceps</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>R</td>
<td>Deltoid</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>R</td>
<td>Anterior Tibialis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>R</td>
<td>Medial Gastrocnemius</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>R</td>
<td>Vastus Lateralis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>R</td>
<td>Short head biceps femoris</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>R</td>
<td>Gluteus Medialis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>Inc 1+</td>
<td>N</td>
<td>Dec 1+</td>
<td>Inc 1+</td>
</tr>
</tbody>
</table>
Brief exercise stimulates mobilization of acetylcholine that is available for release at the NMJ. This results in a transient increase in the EPP, but only for a few seconds. Therefore, when RNS is performed after exercise, the subsequent EPPs are larger and less likely to decrease below threshold for muscle fiber activation. This phenomenon is termed “post-activation facilitation” or potentiation, and will result in a “repair” of a previously detected decrement at rest. This response is recorded in the column labeled “Immediately after exercise (%) decrement” in the table above. Repair of a decrement after brief exercise differentiates a NMJ disorder such as myasthenia gravis from a decrement that can occur in disorders with severe motor axonal loss such as ALS.

If slow rates of RNS are delivered a few minutes after exercise, the EPP is even smaller than at rest, resulting in a larger decrement. This phenomenon is termed “post-activation exhaustion” and likely results from temporary depletion of immediate stores of acetylcholine reserves in the motor nerve terminal. This response is recorded in the column labeled “2-3 Min after exercise (%) decrement” in the table above. Once this acetylcholine depletion is replenished, post-activation exhaustion resolves.

A higher physiological temperature (limb temp ~35° C) results in decreased sensitivity of the acetylcholine receptor and reduced acetylcholine half-life in the NMJ by increasing acetylcholinesterase activity. Therefore, higher temperatures may increase detection of a decrement in a diseased NMJ. Acetylcholinesterase inhibitors (pyridostigmine, Mestinon, etc.) increase available acetylcholine and reduce detection of a decrement with RNS. Therefore, these medications are held for at least 12 hours prior to RNS testing.

RNS of proximal nerves such as the facial, spinal accessory, axillary and musculocutaneous motor nerves are 2-3 times more likely to demonstrate a decrement than distal motor nerves. Recently, Petretsk et al. demonstrated that RNS of the radial nerve, recording at the extensor indicis proprius (EIP), was more likely to detect a decrement than RNS of the ulnar nerve in patients diagnosed with MG. Given our patient had finger extensor weakness, a radial nerve RNS may have been a better choice to demonstrate a decrement than the ulnar nerve. Additionally, Lo and colleagues demonstrated that abnormal RNS of the hypoglossal nerve, recording at the tongue, appears to correlate well to bulbar dysfunction in patients with MG. Rubin et al. demonstrated only 5-7% of patients with MG will have a decrement with post-exercise exhaustion when no decrement was detected at rest. Therefore, if no decrement =10% is detected by RNS at rest, it may be reasonable to skip post-exercise exhaustion techniques and proceed with single-fiber EMG (SFEMG), a more sensitive electrophysiology test for MG. In the present case additional electrophysiological studies such as SFEMG are not needed as the abnormalities with spinal accessory and facial RNS are sufficient to confirm the clinical diagnosis of MG.

Although previous studies assessing the utility of RNS for the diagnosis of MG have been very heterogeneous, the estimated sensitivity of RNS is 79% for the diagnosis of generalized MG. If RNS is normal and the diagnosis of MG is suspected, an abnormal SFEMG of the extensor digitorum communis (EDC) muscle approaches a sensitivity of 98% for generalized MG. Normal SFEMG testing essentially excludes a diagnosis of generalized MG. Acetylcholine receptor antibody testing is quite useful given a very high specificity for the diagnosis of MG, but only 80-90% of patients with MG will have an abnormal antibody titer.

In the present case concentric needle electromyography (CN EMG) has excluded a progressive neurogenic process with both active denervation and reinnervation that would be seen in ALS type motor neuron disease. CN EMG does demonstrate rapid recruitment of voluntary motor unit action potentials (MUAPs) which were short in duration, mildly polyphasic and varied in configuration of consecutive discharges in weak muscles (EDC and gluteus medialis), while strong muscles showed normal MUAPs. MUAP variation may be seen in disorders of the NMJ but also in motor neuron disease and disorders with recently reinnervated muscles. In a NMJ disorder MUAP variation is secondary to blocking of individual muscle fiber components of the MUAP secondary to reduction in the EPP. The presence of small MUAPs with rapid recruitment may lead to an erroneous diagnosis of a diffuse myopathy. However, RNS studies are used to distinguish a NMJ disorder from a myopathy.
In general, patients with MG are treated with immune modifying therapy in attempt to achieve disease remission while minimizing side effects of therapy. At the time of MG diagnosis and sometimes with an exacerbation of symptoms, all patients should undergo chest CT to evaluate for thymoma. If thymoma is detected, thymectomy is performed. Patients with MG are often screened for autoimmune thyroid disease given their frequent association. Patients with moderate-severe symptoms are treated with acute therapy (intravenous immunoglobulin (IVIG) or plasmapheresis) and high dose prednisone. Remission is generally achieved after 2-3 months of acute treatment and/or high dose prednisone. Once remission is achieved, prednisone is gradually tapered. Additional immunosuppressive agents (azathioprine, cyclosporine or mycophenolate) are added early in the disease course if remission is difficult to obtain with acute treatment, symptoms exacerbate while tapering high dose prednisone, or the patient is intolerant to prednisone.

In this case the patient was admitted to the hospital for the first several days of treatment to monitor for complications and/or acute decline. He was treated with seven plasmapheresis treatments, 60 mg of daily prednisone, and Mestinon over the course of three months. Chest CT and thyroid testing were normal, and the patient was prophylactically treated for steroid-induced osteoporosis and peptic ulcers. Eight weeks after starting therapy the patient had significant improvement in symptoms. Twelve weeks after therapy started remission of symptoms was achieved. At that time he began a steroid taper with azathioprine being added once he had undergone some reduction in prednisone. After an additional three months he was tolerating azathioprine well at 2 mg/kg and undergoing further reductions in his prednisone.

Bibliography


