Lewis-Sumner Syndrome Associated with Inflixima

Davyd R. Hooper, MD, Steven K. Baker, MD, MSc, and Mark A. Tarnopolsky, MD, PhD

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American Association of Neuromuscular and Electrodiagnostic Medicine

2621 Superior Dr NW Rochester, MN 55901

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CME Information
Product: CS27 - Lewis-Sumner Syndrome Associated with Inflixima

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. develop a differential diagnosis of mononeuropathy multiplex.
2. differentiate Lewis-Sumner syndrome, multifocal motor neuropathy, and chronic inflammatory demyelinating polyneuropathy as separate clinical entities.
3. identify the potential role of tumor necrosis factor antagonists in the induction of autoimmunity directed towards the peripheral nervous system

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Lewis-Sumner Syndrome Associated with Infliximab

February 2009

CME Available from February 2009 through February 2012

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Presenting Symptom: Multifocal weakness and paresthesias (mononeuropathy multiplex).

Case Specific Diagnosis:

Case prepared by:

Davyd R. Hooper, MD, Neuromuscular and Electrodiagnostic Medicine, University of Manitoba

Steven K. Baker, MD, MSc, and Mark A. Tarnopolsky, MD, PhD, Departments of Medicine and Pediatrics, Neuromuscular Disease Clinic, McMaster University.

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Appropriate Audience: Electrodiagnostic and neuromuscular medicine residents and practicing physicians.

Learning Objectives: After completing this educational activity, participants will be able to:
1) Develop a differential diagnosis of mononeuropathy multiplex.
2) Differentiate Lewis-Sumner syndrome, multifocal motor neuropathy, and chronic inflammatory demyelinating polyneuropathy as separate clinical entities.
3) Identify the potential role of tumor necrosis factor antagonists in the induction of autoimmunity directed towards the peripheral nervous system.

Level of Difficulty: Intermediate/Advanced
Lewis-Sumner Syndrome Associated with Infliximab

History

A 47-year-old man experienced gradual onset of sensory loss in his right hand, which progressed up his forearm to the level of the elbow in addition to left facial paresthesias. He also noticed reduced grip strength, weak wrist extension, elbow flexion, and shoulder abduction. One month later he experienced a similar pattern of sensory loss and weakness in his left arm followed several weeks later by bilateral foot paresthesias and left leg weakness.

Commentary I

Based on the presentation there is subacute onset of multifocal weakness and sensory loss. This is suspicious for a mononeuropathy multiplex disease pattern or may less likely represent progressive central nervous system pathology (e.g., demyelinating diseases, multiple strokes).

History, Continued

Relevant previous medical history includes a diagnosis of rheumatoid arthritis resistant to treatment with sulfasalazine and hydroxychloroquine. He began intravenous infusions of infliximab 7 months prior to his presentation.

He was previously diagnosed with bilateral carpal tunnel syndrome and smokes 1 pack of cigarettes per day

Despite having facial paresthesias he denies any other bulbar symptomatology. There are no autonomic features such as bowel/bladder disturbance, dry eyes/mouth, palpitations, or presyncope.

Physical Examination

On examination there was reduced sensitivity to pinprick in the lower face. There was wasting of distal forearms and hand intrinsic muscles. Shoulder and finger abduction was Medical Research Council (MRC) grade 1. Elbow flexion and extension, wrist extension, and dorsiflexion were grade 3. Ankle eversion was grade 2. Knee extension was grade 4 on the right and grade 3 on the left. Muscle stretch reflexes were absent in the legs and reduced in the arms. Only the right biceps reflex was normal. Sensory examination revealed a mild stocking-type loss of pain perception to the level of the knee with a superimposed dense sensory loss in the deep peroneal distribution. A similar glove-type distribution of loss was present in the arms to the level of the elbow, and there was superimposed dense loss in the median distribution. Vibration sense was slightly reduced at the metatarsophalangeal joint bilaterally.

Commentary II

Infliximab is a tumor necrosis factor (TNF)-alpha antagonist which has been implicated with the induction of central nervous system demyelination and peripheral neuropathy as well as other auto-immune diseases. The physical examination is suggestive of a lower motor neuron injury with a pattern of mononeuropathy multiplex.

The differential diagnosis of mononeuropathy multiplex is relatively broad:
Vascular: Vasculitic mononeuritis multiplex (primary or secondary vasculitis).
Neoplastic: Neurofibromatosis, infiltrative (e.g. lymphoma), amyloidosis.
Inflammatory (auto-immune): Multifocal motor neuropathy (MMN), Lewis-Sumner syndrome (LSS).
Hereditary: Hereditary neuropathy with liability to pressure palsy (HNPP).
Traumatic: Multiple mononeuropathies induced by trauma.

Electrophysiological Data

### SENSORY NERVE CONDUCTION STUDIES

<table>
<thead>
<tr>
<th>NERVE</th>
<th>SIDE</th>
<th>STIM SITE</th>
<th>RECORD</th>
<th>DISTANCE cm</th>
<th>AMPL microvolts</th>
<th>LAT msec</th>
<th>CV (m/sec)</th>
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</thead>
<tbody>
<tr>
<td>Radial</td>
<td>Right</td>
<td>Wrist</td>
<td>Thumb</td>
<td>10</td>
<td>8.4 (&gt;10)</td>
<td>2.0</td>
<td>50.0 (≥48)</td>
</tr>
<tr>
<td>Median</td>
<td>Right</td>
<td>Wrist</td>
<td>Thumb</td>
<td>10</td>
<td>6.4 (&gt;10)</td>
<td>2.65</td>
<td>37.7 (≥48)</td>
</tr>
<tr>
<td>Median</td>
<td>Right</td>
<td>Wrist</td>
<td>Ring Finger</td>
<td>13</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Median</td>
<td>Right</td>
<td>Wrist</td>
<td>Ring Finger</td>
<td>13</td>
<td>3.2 (&gt;10)</td>
<td>2.85</td>
<td>45.6 (≥48)</td>
</tr>
</tbody>
</table>

*Temperatures were maintained above 30° C in the feet and 32° C in the hands.
*Normal values are in parentheses.
*Abbreviations APB (abductor pollicis brevis), ADM (abductor digiti minimi), EDB (extensor digiti minimi)
Multiple partial conduction blocks are demonstrated.

**NEEDLE ELECTROMYOGRAPHY**

**INSertional activity:** N, sust, unsust  
**FIB:** 0, 1+, 2+, 3+, 4+  
**EFFort:** N, decr  
**RECruitment:** N, inc or dec 1+, 2+, 3+, 4+  
**AMPplitude:** 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>EFF</th>
<th>REC</th>
<th>AMP</th>
<th>DUR</th>
<th>POL</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Tibialis anterior</td>
<td>N</td>
<td>2+</td>
<td>N</td>
<td>Dec 1+</td>
<td>Inc 1+</td>
<td>Inc 1+</td>
<td>Inc 1+</td>
</tr>
</tbody>
</table>
Electrodiagnostic Interpretation

There is evidence based on motor nerve conduction studies of multiple partial conduction block. Hyperacute nerve injury such as infarction can look similar electrically but in clinical context of a subacute course this most likely represents conduction block from focal demyelination. The sensory amplitudes are slightly reduced. The slowing of the median studies and absent median sensory response from the ring finger most likely reflects his previous carpal tunnel syndrome. Needle EMG of selected weak muscles demonstrates active denervation and evidence of motor unit remodeling (reinnervation).

Further Investigations

Several investigations were undertaken to exclude conditions listed in the differential diagnosis including:

1. Antinuclear antibodies (ANA), anti neutrophil cytoplasmic antibody (ANCA), anti-GM1 antibodies, Anti-Hu antibodies, Angiotensin Converting Enzyme, vitamins D and E, hepatitis C serology, cryoglobulins, thyroid stimulating hormone (TSH), and vitamin B12. These were unremarkable.
2. Creatine kinase (CK) was mildly elevated at 227 U/L.
3. Rheumatoid factor was 569 U/L with a mildly elevated c-reactive protein (CRP) of 7.8 U/L. Protein electrophoresis showed a low level IgG lambda paraprotein.
4. A lumbar puncture performed 1 month after initial consultation showed mildly increased albumin at 0.37 g/L (upper limit of normal 0.24 g/L) with no elevation in leukocytes.

Diagnostic Impression

This 47-year-old man presented with subacute multifocal weakness and sensory loss in a pattern of mononeuropathy multiplex. This affected the limbs as well as the face (bulbar involvement). The electrodagnostic examination demonstrated multiple partial conduction block as seen in the inflammatory demyelinating neuropathies. CSF analysis showed only mild elevation of albumin. This clinical and electrodiagnostic presentation is most consistent with Lewis-Sumner Syndrome.

Commentary III

Lewis-Sumner Syndrome (LSS) is an inflammatory neuropathy characterized by a mononeuropathy multiplex onset with persistent conduction block on nerve conduction studies. The other clinical entities with similar features are Multifocal Motor Neuropathy (MMN) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

Saperstein et al. published a case series further characterizing LSS. Consensus criteria for MMN were published in 2003. One of the key features to differentiate MMN vs. LSS is objective sensory involvement. Although patients with MMN may complain of sensory symptoms the physical and electrodiagnostic examination must be normal in MMN for a formal diagnosis to be made.

The following table compares these 3 conditions.
<table>
<thead>
<tr>
<th>Weakness</th>
<th>CIDP</th>
<th>MMN</th>
<th>LSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric</td>
<td>Proximal and distal</td>
<td>Multifocal upper limb predominance</td>
<td>Multifocal</td>
</tr>
<tr>
<td>Sensory</td>
<td>Symmetric</td>
<td>No objective</td>
<td>Multifocal, Pain</td>
</tr>
<tr>
<td>Cranial Nerves</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Cramp/Fasciculation</td>
<td>+/-</td>
<td>Prominent</td>
<td>+/-</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Areflexia</td>
<td>Reduced in weak</td>
<td>Asymmetric reduction</td>
</tr>
<tr>
<td>Motor NCS</td>
<td>CB, slowing</td>
<td>Prolonged DL</td>
<td>CB</td>
</tr>
<tr>
<td>Sensory NCS</td>
<td>NCS Low/absent</td>
<td>Normal</td>
<td>Low/absent</td>
</tr>
<tr>
<td>CSF protein</td>
<td>Elevated</td>
<td>Normal</td>
<td>Mild elevation</td>
</tr>
<tr>
<td>Antibodies</td>
<td>None</td>
<td>IgM GM1</td>
<td>None</td>
</tr>
<tr>
<td>Steroid responsive</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*CB = conduction block
*DL = distal latencies
*NCS = nerve conduction study

Treatment of Lewis-Sumner syndrome (LSS) consists of immunomodulatory therapy including IVIg, and corticosteroids acutely, with steroid sparing agents such as azathioprine, cyclosporine, and mycophenolate added for long-term management.

**TNF-alpha antagonists and Neuropathy**

TNF-alpha antagonists (infliximab, etanercept, adalimumab) are a class of medications used in a wide spectrum of auto-immune diseases with extensive use in rheumatologic conditions. Their addition to treatment of arthritic conditions has greatly improved care and outcomes for these patients.

Over the last 10 years accumulating evidence implicates these agents in the induction of both central and peripheral nervous system disease. Central nervous system disease mostly involves multiple sclerosis like demyelination. Peripheral nervous system conditions described in association with these agents include Guillain-Barré syndrome, multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), LSS, axonal sensorimotor polyneuropathy, pure sensory neuromopathy, and small fiber neuropathy.

It is usual for there to be a delay from initiation of therapy to onset of neuropathy. Studies of patients undergoing treatments with TNF-alpha antagonists have demonstrated a delayed induction of autoantibodies including ANA and dsDNA. This happens as early as 14 weeks with peak antibody levels at 30 weeks. In support of the hypothesis that antibodies may be induced towards epitopes within the peripheral nervous system, antiganglioside antibodies were induced in 2 cases of CIDP reported by Richez et al.

Management strategy for these conditions is unclear. The TNF-alpha antagonist should be discontinued in all cases. In some cases, symptoms have resolved after discontinuing the agent and following along clinically. The majority of cases of neuropathy associated with TNF-alpha antagonists have required ongoing immunomodulatory therapy; usually with IVIg.
Patients who develop weakness or sensory symptoms while undergoing treatments with TNF-alpha antagonists should have a careful assessment of both the central and peripheral nervous system.

**Bibliography**


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