NEUROUNO
Neuro Diagnostic Excellence
Update 3 – March 2014
UPDATE

Special Edition

Challenging Case Studies in Neurology

Case 1

Clinical Presentation

A 66-year-old woman presented to urgent care with progressive neurologic symptoms over the previous week. Her symptoms started with a pins and needles sensation in her chest. Over the next few days, bilateral leg weakness developed and she noted worsening vision and bladder control. On initial examination, she was alert and well-oriented. Pertinent physical findings included normal vital signs; normal chest, heart, and abdominal examination; and no evidence of trauma. Visual field testing showed large central scotomas bilaterally. Pupils were 3 mm on the left and 5 mm on the right, with an afferent pupillary defect on the right. Other cranial nerves were intact. Motor, reflex, sensory, and cerebellar examinations of the upper limbs were normal. In the lower limbs, strength was 2/5 in all groups tested. Knee jerks were 4+ bilaterally and ankle jerks were 4+ bilaterally, with sustained clonus. Bilateral Babinski signs were present. There was a sensory level at T4.

2. **This presentation is *least* consistent with a diagnosis of:**

- Guillain-Barre syndrome
- Multiple sclerosis (MS)
- Acute disseminated encephalomyelitis
- Neuromyelitis optica (NMO, also called Devic's disease)

The patient was admitted to the neurology service where magnetic resonance imaging (MRI) of the brain and spinal cord was performed (Figures 1 and 2).

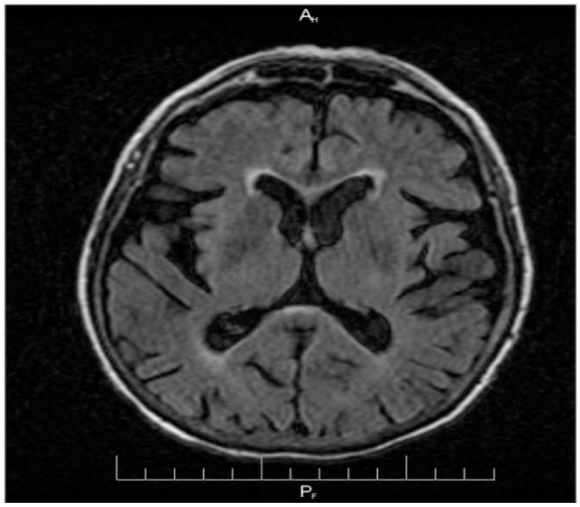

Figure 1.

Magnetic resonance imaging of the brain showing a mild degree of white matter changes around the ventricles on axial fluid-attenuated inversion recovery sequences. This was felt to be nonspecific, especially in view of the patient's age.

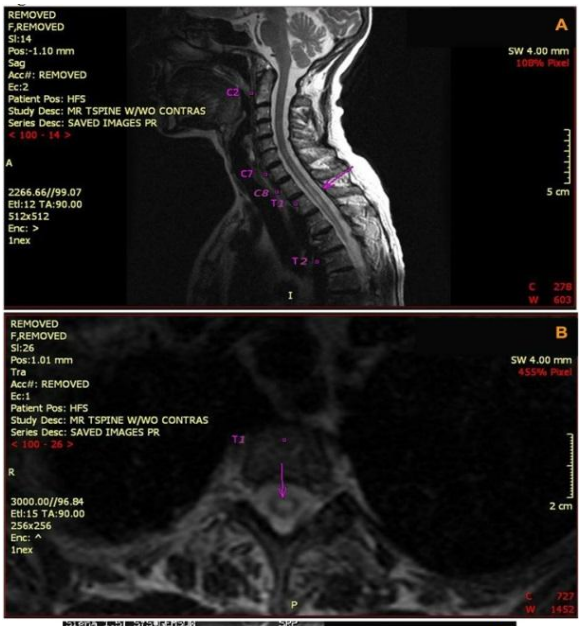

Figure 2.

Magnetic resonance imaging showed significant enhancement extending linearly down the cord from about C8 to T4. The enhancement appeared maximal at T1 where it is well seen on both the sagittal (a) and the axial (b) sections. A scan more than a year later (c) shows severe atrophy of the cord at the same areas.

In addition, visual evoked potentials were performed which showed bilateral optic nerve dysfunction.

2. **Based on the history, physical examination, and MRI findings, the most significant nervous system damage is probably localized to which of the following locations?**

- Periventricular white matter and spinal cord
- Spinal cord and peripheral nerves
- Spinal cord and optic nerves
- Cerebrum and cerebellum

3. **Which of the following blood tests is least important?**

- Sedimentation rate
- Tests for systemic lupus erythematosus and other connective tissue diseases
- Hexosaminidase A levels
- Stains, cultures, antibodies, and polymerase chain reaction for viruses and other infectious agents

4. **True or false: In cases such as this, modern MRI scanning has made a spinal tap obsolete and unnecessary.**

- True
- False

Laboratory Tests

Initial blood tests showed a normal sedimentation rate, complete blood count, and electrolytes. Liver function tests were normal. Tests for lupus and other antinuclear antibody tests were normal. The lumbar puncture showed that the cell count, glucose, and protein levels were within normal limits. Immunoglobulin G/albumin ratio was slightly elevated, although the immunoglobulin G index was normal. No bacteria were seen. Polymerase chain reaction and antibody studies for herpes and a wide range of other viruses were normal. Additional blood and spinal fluid was sent to an outside reference laboratory for additional studies.

5. **In considering some additional studies not explicitly mentioned above, which of the following has little relevance to this case?**

- Test for the 14-3-3 protein
- Test for aquaporin 4 antibodies
- Test for oligoclonal bands
- Test for myelin basic protein

The test for aquaporin 4 antibodies was strongly positive. Spinal fluid was negative for oligoclonal bands but positive for myelin basic protein.

6. **Taking all available information together, the most likely diagnosis is which of the following?**

- MS
- Muscular dystrophy
- NMO

Most Agreed Answers for the Questions

1. **Guillain-Barre syndrome** is a lower motor neuron disorder principally involving demyelination of the peripheral nerves and nerve roots. In patients with Guillain-Barre syndrome, reflex responses are decreased or absent and there is little or no sensory loss and no sensory level. The present findings indicate an upper motor neuron pattern of weakness. The sensory level as well as loss of bladder control strongly suggest spinal cord involvement. Thus central rather than peripheral demyelination would be a reasonable cause of the problem.

2. The history and physical findings -- plus MRI scans showing major **spinal cord abnormalities** extending linearly through multiple levels, but with only minor demyelination in the brain -- suggest spinal cord damage. The bilateral central scotomas plus the pupillary abnormalities strongly suggest optic nerve damage. This is confirmed by the visual evoked potentials. Often optic nerve lesions are too small to be seen in the brain MRI, even though they may be readily detectable by visual evoked potential testing. In some cases, but not in this one, optic nerve lesions can be seen on MRI scan.

3. Most commonly, **hexosaminidase A deficiency** causes what is called Tay-Sachs disease, a neurodegenerative condition that usually begins in infancy. It causes gradually progressive loss of strength and coordination as well as decreased cognitive function and blindness. Adult cases can occur, but the accumulation of deficits is gradually progressive and not sudden such as in this case. The sedimentation rate or tests for lupus or other connective tissue diseases might detect a vasculitis which could cause the sudden onset of deficits that we see here. Likewise, it is possible that a central nervous system infection could be the cause.

4. **False.** The spinal tap is still extremely important to check for evidence of infection, inflammation, and abnormal immunologic responses.

5. **The 14-3-3 protein** is to test for Creutzfeldt-Jakob disease, which presents as a rapidly progressive dementia and myoclonus. Such findings are not present in this case. The other 3 tests could be helpful in this case.

6. **NMO, or Devic's disease**, is the most likely diagnosis. NMO is an inflammatory demyelinating process that affects the central nervous system. There has been a long debate whether NMO should be considered to be simply a variant of MS. Some authorities still think it should be considered a variant of MS with a predilection for the optic nerves and spinal cord. However, about 70% of presumed cases of NMO show positive aquaporin 4 antibodies. In some cases (perhaps as many as 30%), oligoclonal bands are present, which are ordinarily considered somewhat specific for MS, but the majority of patients with NMO do not show oligoclonal bands. Myelin basic protein is not specific for either MS or NMO but can be seen in both as well as in many other diseases that damage central nervous system myelin.

   Typically there is not as much brain demyelination in NMO as there is in MS. However, there are some cases in which the brain in NMO looks similar to a brain in MS and some cases cannot be definitely classified as one or the other. Based on the distribution of demyelination affecting only the optic nerves and multiple contiguous sections of spinal cord and the presence of aquaporin 4 with negative oligoclonal bands, most neurologists probably would consider the present case to represent NMO rather than MS. However, it would be acceptable to call this a case of the Devic's variant or the NMO variant of MS. Muscular dystrophy is a muscle disease and not a disease of either central or peripheral nerves. It does show weakness but weakness of gradual onset. There is no sensory loss or blindness. It would not be a reasonable diagnosis in this case.

Case 2

Clinical Presentation

A 29-year-old, right-handed black man with 2 weeks of persistent nausea and vomiting presented to the emergency department for evaluation. The patient denies any other associated neurologic symptoms. He did not experience fever, chills, or prior weight loss and had no recent illnesses, vaccination, exposure to infectious individuals, or travel-related exposure to disease. On occasion he would have an electrical shock-like sensation to the extremities when bending the neck in a flexed position.

The patient's medical history was significant for bilateral optic neuritis, and he has been legally blind for the last 10 years. In addition, he has a history of beta-thalassemia trait and had inguinal hernia repair. The patient denies taking any medications and has healthy parents with no significant medical problems. He denies any alcohol or intravenous drug abuse but has a smoking history of 1 pack per day for the last 8 years.

The man was admitted to the hospital for further evaluation. He underwent an extensive gastrointestinal workup including endoscopy and antral biopsy, the result of which was benign with only minimal chronic inflammation. Computed tomography (CT) of the chest and abdomen revealed patchy opacity in the right upper lobe and 2 small liver lesions. A neurology consult was then obtained.

Neurologic Examination

At admission, the patient's vital signs and general physical examination were within normal limits. On neurologic examination, he was alert and oriented with normal speech, language, and cognitive functions. Cranial nerves revealed visual acuity of minimal perception to light in both eyes, pupils bilateral 6 mm nonreactive to light, and funduscopic examination revealed a minimally pale fundus. The rest of the cranial nerves were within normal limits. Motor examination showed normal strength throughout, with muscle stretch reflexes of 2+ in all 4 extremities. Plantar response was bilateral downgoing. Sensory examination was normal to light touch, pin, and position but reduced vibrations up to the ankles. No finger-to-nose or heel-to-shin dysmetria was seen. The patient had cautious gait because of his blindness but otherwise could satisfactorily walk on his toes, heels in tandem, with negative Romberg's sign.

1. **In this patient, where would the electric shock-like sensation be localized?**

- Corticospinal tracts
- Spinothalamic tracts
- Posterior column tracts
- All of the above

Laboratory tests

The following laboratory tests were unremarkable: blood counts, electrolytes, glucose, blood urea nitrogen, creatinine, liver function tests, coagulation studies, thyroid function tests, vitamin B12 levels, urine drug screen, HIV test, erythrocyte sedimentation rate, antinuclear antibody, antithyroid antibody, angiotensin-converting enzyme, anticardiolipin antibody, antistreptolysin O, Lyme disease antibody, and ceruloplasmin levels. Cerebrospinal fluid (CSF) revealed pleocytosis (52 lymphocytes) with absent oligoclonal bands and elevated protein levels to 68. CT head scan without contrast was unremarkable.

2. Which of the following tests should be considered next?

- Magnetic resonance imaging (MRI) with and without contrast
- Magnetic resonance angiogram
- Magnetic resonance venogram
- All of the above
- None of the above -- the diagnostic workup is complete

The neurological localization of the patient's problem is in the brain stem. In addition, given the patient's history of optic neuritis, one of the major differential diagnoses to be considered is neuromyelitis optica for which MRI of the brain with and without contrast was obtained (Figure 1 and Figure 2). The MRI revealed a contrast-enhancing lesion in the posterior aspect of the lower medulla. The patient was then on intravenous solumederol 500 mg twice daily for 5 days. His vomiting stopped within 24 hours, but nausea remained persistent for almost 3 days.

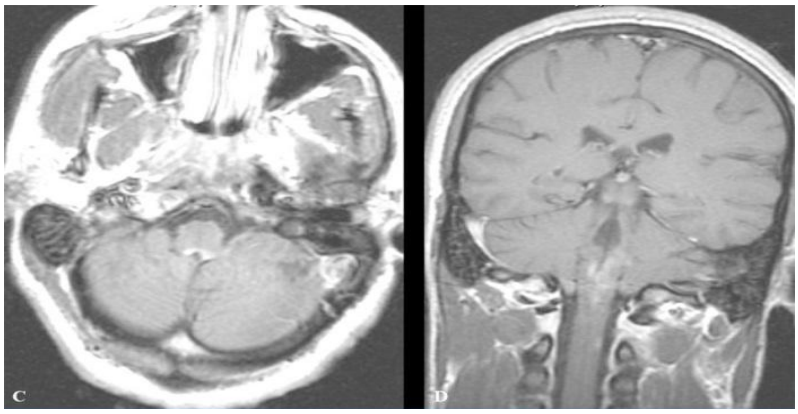

Figure 1. Magnetic resonance imaging of the head. Sagittal T1 images without contrast (A) and with contrast (B) revealing contrast-enhancing lesion in the posterior aspect of the lower medulla (arrow).

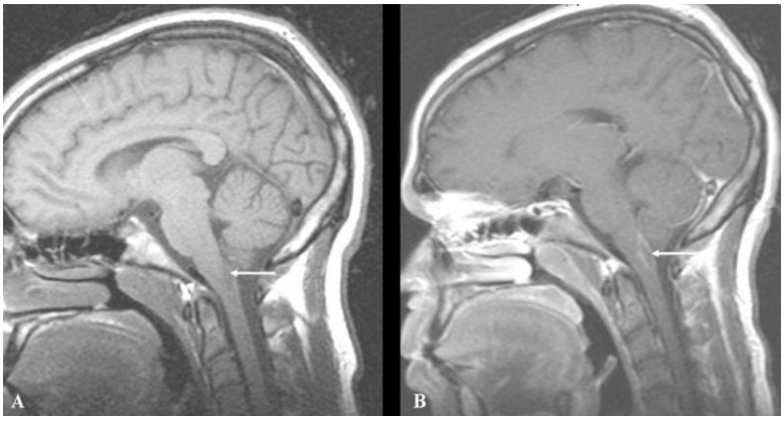

Figure 2. Magnetic resonance imaging of the head. Axial T1 postcontrast (C) and coronal postcontrast (D), revealing extent of the contrast-

3. Which of the following antibodies are the most helpful in making the diagnosis?

- Acetylcholine receptor antibody
- Neuromyelitis optica (NMO)-immunoglobulin G (IgG) antibody
- Anti-Hu antibody
- Anti-Purkinje cells antibody
- Anti-Yo antibody

Most Agreed Answers

1. Posterior column tracts
2. Magnetic resonance imaging (MRI) with and without contrast
3. Neuromyelitis optica (NMO)-immunoglobulin G (IgG) antibody

Case Summary

NMO, or Devic's syndrome, came from the French physician, Eugene Devic. NMO is a rare syndrome characterized by the combination of acute or subacute optic neuritis and transverse myelitis. Optic neuritis precedes transverse myelitis by almost 3 months in 80% of cases. NMO has acute and often fulminant monophasic attacks of optic neuritis and myelitis. Relapses, even though less frequent, can be devastating, with blindness and paraplegia. Unlike multiple sclerosis, NMO has involvement that is

limited to the optic nerve and spinal cord. The CSF profile of NMO shows pleocytosis with absent oligoclonal banding.

Persistent nausea and vomiting can be very distressing to patients and their families. The causes of the nausea and vomiting are multifactorial and include both peripheral and central causes. Different medications are effective at various neurotransmitters. Nausea is mediated through the autonomic nervous system. Neuroanatomically, the 2 main centers are the vomiting center (VC) and the chemoreceptor trigger zone (CTZ). The CTZ is the area postrema of the fourth ventricle and acts as the entry point for emetic stimuli and humeral substances. It remains sensitive to toxins or chemical stimuli. VC is seen in the dorsolateral border of the medulla and integrates the emetic response. Whereas the VC is within the BBB, the CTZ is outside the BBB and therefore responds to stimuli from either the CSF or the blood.

The treatment of NMO has been challenging. Most cases are progressive despite aggressive therapy that includes high-dose corticosteroids, azathioprine, cyclophosphamide, plasma exchange, and intravenous immunoglobulin. Recent evidence from the Mayo Clinic indicates success with mycophenolate in relapse frequency as well as in disability in patients with NMO spectrum disorders. Because some patients do respond to some of the therapeutic options, it is reasonable to try one or more of the therapies in these cases.