A SELF-TEST ON A CLINICAL CASE

ANDREW NAIDECH, MD, MSPH
Department of Psychiatry and Neurology and Department of Medicine, Tulane University Medical Center, New Orleans, LA

LEON WEISBERG, MD
Department of Psychiatry and Neurology, Tulane University Medical Center, New Orleans, LA

SARALA PALLIYATH, MD
Department of Psychiatry and Neurology, Tulane University Medical Center, New Orleans, LA

MARC KAHN, MD
Department of Medicine, Tulane University Medical Center, New Orleans, LA

Sudden weakness in a patient with lymphoma

A 42-YEAR-OLD WOMAN presented to the hospital for evaluation of weakness.

Seven months before, she had developed widespread lymphadenopathy, fevers, and night sweats and had lost 40 pounds. A lymph node biopsy established the diagnosis of angioimmunoblastic lymphadenopathy, an unusual T-cell lymphoma. Computed tomography (CT) revealed lymphadenopathy in supraclavicular, perihilar, and inguinal nodes. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) was started, but the patient was noncompliant with follow-up and underwent only four cycles over the next 7 months. Three months had passed since her last course of chemotherapy.

The patient said she began experiencing progressive difficulty walking 7 days previously, and subsequently developed a tingling sensation in both feet. She did not report incontinence, back pain, or headache.

Physical examination

The patient's vital signs were normal and remained stable throughout her present illness. No lymphadenopathy was present. The heart, lungs, skin, and abdomen were normal.

On neurologic examination, the cranial nerves were normal, but the patient could not lift either leg off the bed, dorsiflex or plantar flex the feet, or straighten or bend either leg at the knee. Her left arm was also significantly weak, distally more than proximally. There was mild impairment of sensation to vibration in the legs distally. Reflexes were present but depressed (1 on a scale of 0 to 4) in the upper extremities and were absent at the knees and ankles. The sensory examination was unremarkable. The Lhermitte sign (a shock-like sensation when the head is flexed) was absent. Anal tone was normal. The cerebellar examination was normal, allowing for her weakness.

DIFFERENTIAL DIAGNOSIS

1 What is the most likely diagnosis?

- ❑ Spinal cord compression
- ❑ Guillain-Barré syndrome
- ❑ Recurrent malignancy
- ❑ Stroke in evolution

Spinal cord compression should be considered in patients with a history of a malignancy who present with weakness in the legs or with trouble walking.

Suspect cord compression if a cancer patient has new weakness in the legs

Certain neoplasms, such as prostate carcinoma, have a particular affinity for the vertebral bodies and may cause early spinal cord compression. Lung, breast, and ovarian cancer are also common causes.

Patients with spinal cord compression tend to present with subacute to acute weakness in the lower extremities. Incontinence of bladder and bowel are common and worrisome signs. Sensation may abruptly stop at a certain dermatome, a symptom called a sensory "level." Reflexes are initially depressed but soon become brisk; the Babinski sign (extension of the great toe when scraping the sole of the foot) is usually present within a few days.

To establish the diagnosis, magnetic resonance imaging (MRI) with contrast is the test of choice; CT myelography may also be used. Treatment includes high-dose steroids, radiation, and consultation with a neurosurgeon for decompression of a mass.

Recurrent malignancy should be suspected in patients who are not compliant with

treatment or who have aggressive neoplastic disease. In this patient's case, however, a recurrence of lymphoma would be expected to cause symptoms similar to those she experienced before, such as lymphadenopathy and constitutional symptoms, not focal weakness. Since focal disease usually is caused by a focal process, such as a compressive mass, it would be unusual for a hematologic disease to present in this fashion.

Stroke (cerebrovascular accident) suggests an acute loss of blood flow to a portion of the central nervous system. Most strokes are intracranial, but some are due to occlusion of the vessels that supply the spinal cord (the anterior and posterior spinal arteries). These events are typically sudden and clinically resemble acute spinal cord compression.

Descriptive terms, such as "stroke in evolution," "rapidly improving neurologic deficit," and "stuttering transient ischemic attack (TIA)" lack objectively defined pathophysiology, and their use should be avoided.

Guillain-Barré syndrome is the most likely diagnosis, given the patient's presentation.

Guillain-Barré syndrome is a relatively common condition of the peripheral nervous system, not the central nervous system. An autoimmune disease, it leads to destruction of the myelin sheath around peripheral nerves. The presentation is typically subacute with progressive difficulty walking and ascending weakness into the arms and muscles of respiration. Reflexes are depressed. Urinary retention is unusual, and incontinence is very rare.

Respiratory depression is the most feared complication of Guillain-Barré syndrome

ESTABLISHING THE DIAGNOSIS

2 What test(s) are likely to support establishing the diagnosis?

- ❑ MRI of the head
- ❑ CT of the spine
- ❑ MRI of the spine
- ❑ Lumbar puncture and cerebrospinal fluid analysis
- ❑ Nerve conduction studies

MRI of the head has gone from being an expensive, confirmatory test to a first-line procedure in many medical centers for the diagnosis of neurologic diseases, especially stroke. In this patient's case, however, the symptoms of distal bilateral weakness, abnormal reflexes, and lack of signs of cortical damage (such as aphasia) point to the spinal cord as the area of abnormality.

CT can be used to image the spine. The advantages are that it is relatively inexpensive compared with MRI and can be done very quickly. However, CT has poor soft-tissue resolution and does not show the spinal cord itself very well. Only axial images can be acquired in most cases. If MRI cannot be done to diagnose spinal cord compression, CT myelography can be performed by injecting contrast into the subarachnoid space and then acquiring images.

MRI of the spine is the diagnostic test of choice for imaging the spine and provides excellent contrast for soft tissue in a variety of planes of section, sagittal as well as axial. It also permits visualization of the intervertebral discs and the neural foramina. The sagittal sections allow a broad view of the spine above and below the suspected site of a lesion. If facilities permit, MRI should be the diagnostic test of choice to rule out a mass in the spinal cord; special sequences may also allow the diagnosis of spinal cord stroke to be made.

Lumbar puncture and cerebrospinal fluid analysis can provide valuable information. In bacterial meningitis the polymorphonuclear cell count will be elevated, and in viral meningitis the lymphocyte count will be high. If bacterial meningitis is suspected, empiric antibiotics should begin immediately and lumbar puncture should be performed as soon as possible to assist microbiologic diagnosis. In Guillain-Barré syndrome, a normal cell count (< 5 white blood cells per μL) with elevated protein is characteristic; the protein concentration may be normal early in the course, and this does not rule out the diagnosis.

Many physicians obtain an imaging study of the head before a lumbar puncture to rule out a mass that may elevate the intracranial pressure and lead to herniation during the withdrawal of spinal fluid. If there is no reasonable clinical suspicion of intracranial pathology, a lumbar puncture need not be delayed.

Nerve conduction studies and electromyography have assumed an important supporting role in the diagnosis of diseases of the peripheral nerves and muscles. Electrical activity of muscles is studied by inserting a needle electrode directly in the muscle. Bioelectrical potentials are amplified and displayed for analysis. Nerve conduction studies evaluate the motor and sensory function using surface recording electrodes over the muscles and nerves and stimulating different segments of the nerves. Nerve conduction velocities give information of the integrity of myelin; compound muscle action potentials and sensory nerve action potentials assess the integrity of axons.

In classic Guillain-Barré syndrome, nerve transmission is markedly slowed by demyelination (partially or completely blocked) or may show temporal dispersion of the action potential. The diagnosis may be made with electrodiagnostic studies alone, but the full pattern may take up to a week to appear.[1]

Case continued

In this patient, spinal fluid analysis showed a protein content of 227 mg/dL (normal 15–45), 5 white blood cells per μL, glucose 72 mg/dL (normal 50–100), and an opening pressure of 7 cm H_20 (normal 10–20). Cultures for bacteria, fungi, and viruses were negative.

Nerve conduction studies of the peroneal and posterior tibial nerves failed to excite recordable compound muscle action potentials from the extensor digitorum brevis and abductor hallucis muscles, respectively. No sensory nerve action potentials could be recorded from the sural nerve. The patient declined further studies.

MRI of the spinal cord revealed enhancement of the cauda equina, consistent with perineural inflammation; the cord was normal (FIGURE 1).

Guillain-Barré syndrome was diagnosed on the basis of the cerebrospinal fluid values and the findings on MRI and nerve conduction studies.

The original description of this syndrome[2] as "acute ascending paralysis" is credited to Octave Landry in 1859 when he described progressive weakness following a febrile illness. The syndrome was further described by Guillain, Barré, and Strohl,[3] who in 1916 documented the classic clinical features of acute weakness, areflexia, and mild sensory loss, and the laboratory findings of a normal white blood cell count and high protein level in the cerebrospinal fluid.

The patient's MRI: Before

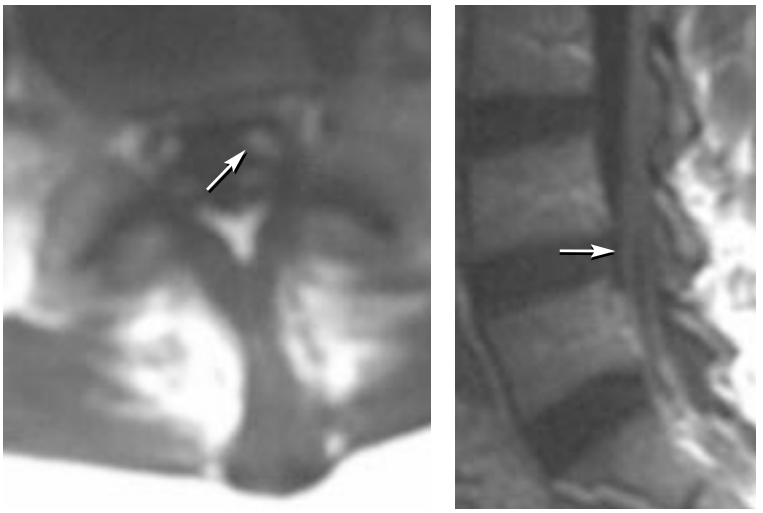

FIGURE 1. Axial (left) and saggital (right) MRI images of the lumbar spine. The nerve roots in the cauda equina are clearly seen (arrows), consistent with perineural inflammation.

The most feared complications of Guillain-Barré syndrome are respiratory depression, which occurs from demyelination of the phrenic nerves that innervate the diaphragm, and autonomic instability, which occurs from demyelination of the vagus nerves. Patients with moderate to severe symptoms should have the vital capacity and negative inspiratory force monitored by a respiratory therapist and have a cardiac monitor. Respiratory distress may require mechanical ventilation until treatment leads to improvement.

MRI is the diagnostic test of choice for imaging the spine

TREATMENT

3 Which of the following can be used as treatment of Guillain-Barré syndrome?

- ❑ Plasmapheresis
- ❑ Intravenous immune globulin (IVIG)
- ❑ Corticosteroids
- ❑ Cyclophosphamide

Guillain-Barré syndrome is an autoimmune disease, and its treatment is aimed at suppressing the immune system and removing antigens that lead to autoimmunity.

Both **plasmapheresis** and **IVIG** are effective, either alone or with the addition of corticosteroids. A large prospective randomized trial found plasmapheresis and IVIG to be comparably effective, and the combination of plasmapheresis and IVIG did not seem to be better than either one alone.[4] Therefore, the choice of IVIG or plasmapheresis depends on the availability at each institution.

Corticosteroids alone are not usually effective enough to have a meaningful impact.

Cytotoxic agents (eg, cyclophosphamide) are no longer used in acute disease, although they are sometimes used for chronic peripheral nerve disease.

ETIOLOGY

4 What likely led to this patient's contracting Guillain-Barré syndrome?

- ❑ Infection with *Campylobacter jejuni*
- ❑ Not known (idiopathic)
- ❑ Malignancy (paraneoplastic syndrome)
- ❑ A side effect of chemotherapy
- ❑ Viral infection (human immunodeficiency virus or cytomegalovirus)

Treatment includes suppression of the immune system

***Campylobacter jejuni* infection.** Clarification of the role of C *jejuni* has greatly improved our understanding of this disease. The risk of contracting Guillain-Barré syndrome is greatly increased in the first few months after infection with C *jejuni*.[5] A preceding diarrheal illness and isolation of the organism portend a worse prognosis.[6] No formal trials of antimicrobial therapy and outcome have been conducted.

Idiopathic. Although symptoms of an antecedent C *jejuni* infection (eg, respiratory symptoms, diarrhea) are common in patients with Guillain-Barré syndrome, the exact cause of this disease is usually not found.

Certain **chemotherapeutic agents** have well-documented neurotoxicities. The agents most commonly associated with peripheral neuropathy are vinca alkaloids (vincristine and vinblastine), platinum compounds (cisplatin and carboplatin), and taxol; damage is typically dose-related.

As in Guillain-Barré syndrome, patients with chemotherapy-induced neuropathy usually report distal weakness and loss of sensation, and the physical examination and ancillary studies are consistent with a peripheral neuropathy. Unlike Guillain-Barré syndrome, however, the course is chronic (weeks to months) rather than subacute (over a few days to a week). Some improvement may occur after withdrawal of the offending agent. There is no specific treatment.

Human immunodeficiency virus (HIV) has a myriad of effects on the nervous system, and peripheral HIV neuropathy is well described, especially in patients with severely depressed CD4 counts (usually less than 50). There may be symmetric distal sensory peripheral neuropathy, sensorimotor peripheral neuropathy, acute demyelinating polyneuropathy, or chronic demyelinating polyneuropathy.

Our patient was HIV-negative.

Cytomegalovirus also causes a polyradiculoneuropathy. It is a pathogen in immunocompromised patients, which is not the case in this patient.

Paraneoplastic neurologic syndromes are indirectly related to neoplasm; these include myasthenia gravis (when accompanied by thymoma), Eaton-Lambert syndrome, and the stiff-person syndrome. Most are believed to be due to molecular mimicry—the phenomenon of antibodies directed against an invading or abnormal protein (such as a cancer cell or infectious agent) reacting against normal host tissue.[7] T-cell as well as humoral mechanisms may be involved. In these cases, neurologic dysfunction occurs as a result of the neoplasm, although neither macroscopic nor microscopic metastases are found. Although onconeural antibodies are not newly described,[8] interest has quickened in recent years.

Some conditions have an animal model (Lambert-Eaton myasthenic syndrome and myasthenia gravis), but many do not (paraneoplastic encephalomyelitis, paraneoplastic cerebellar degeneration, stiff-person syndrome).[9] Work with animal models is hampered because neither transfer of serum from affected patients to animals nor immunization of animals with paraneoplastic antigens

reproduces the disease in most cases.[10] In other neurologic diseases, such as myasthenia gravis, passive transfer does induce disease.[11]

Treatment for paraneoplastic neurologic syndromes centers around treating the cancer itself or suppressing the immune system. This may be dangerous, however, in the case of tumors that arise from immune suppression such as lymphomas.

We suspect that our patient had a paraneoplastic syndrome, although angioimmuno-blastic lymphadenopathy and Guillain-Barré syndrome have not been reported previously to coincide, and it would be practically impossible to prove.

PROGNOSIS

5 What is the prognosis of Guillain-Barré syndrome?

- ❑ The patient is likely to have a permanent neurologic disability
- ❑ There is likely to be a chronic course with exacerbations and remissions
- ❑ The prognosis cannot be determined at this time
- ❑ The prognosis is good

In general, the prognosis with or without treatment is usually good: more than 90% of patients make a full neurologic recovery. Treatment shortens the course of the disease, but does not alter the eventual outcome.

The patient's MRI: After

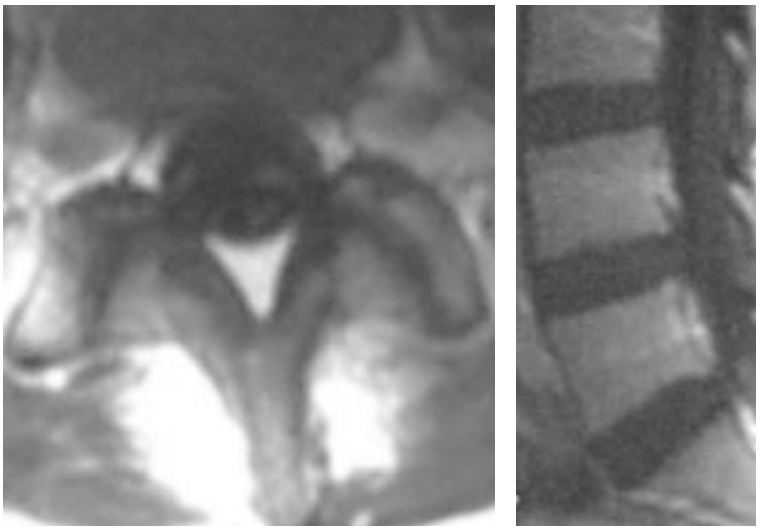

FIGURE 2. One month later, after treatment, repeat MRI showed that the enhancement in the cauda equina had almost completely resolved.

Case continued

The patient began treatment with plasmapheresis three times a week. She experienced dramatic improvement in her strength, and at the end of 2 weeks she was able to walk with minimal assistance. Repeat MRI of the lumbar spine at 1 month showed almost complete resolution of the enhancement of the nerves in the cauda equina (FIGURE 2). On follow-up 2 months after discharge, the patient had only very mild weakness; by 4 months after discharge, the neurologic examination, including reflexes, was completely normal.

More than 90% of patients with Guillain-Barré make a full recovery

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ADDRESS: *Andrew Naidech, MD, MSPH, Department of Psychiatry and Neurology, Tidewater Building, TB52, Tulane University Medical Center, 1440 Canal Street, New Orleans, LA 70112-2715.*