MARY RENSEL, MD
Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic; specializing in clinical neuroimmunology.

R. PHILIP KINKEL, MD
Director of Medical Programs, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic.

A 40-year-old woman with a "windmill" pattern of sensory disturbance

ONE MORNING, a 40-year-old, previously healthy Caucasian woman awakens with a "pins-and-needles" sensation in her left fingers and hand. Within 4 hours the paresthesia spreads to involve sequentially her right hand, right foot, and left foot before ascending her legs to the waist. An evaluation at a local walk-in clinic leads to a diagnosis of food allergy, for which she is given antihistamines.

Her symptoms remain the same for 3 days. Then the paresthesia ascends further to a level above the breast, and she begins to note clumsiness in both hands, a "tight-band" sensation around her chest, severe unsteadiness while walking, and fatigue. She goes to the emergency department of a local hospital, and is transferred to the Cleveland Clinic after a computed tomographic (CT) scan of the head shows no abnormalities.

On admission she reports having had an upper respiratory tract infection 2 weeks previously. An extensive review of systems and past medical history reveals nothing else of clinical relevance. Her vital signs and general medical examination are normal.

Neurologic examination reveals no abnormalities of cognition, language, cranial nerves, or brainstem function. She holds her left hand in a slightly flexed posture but has no significant weakness or alteration of muscle tone in any limbs. Sensory examination reveals diminished stereognosis (ability to name a common everyday object placed in her hand with her eyes closed) in her left hand, diminished proprioception in the left fingers and toes, diminished vibratory sense up to the iliac crest bilaterally (on the left more than on the right), and a subtly diminished sensitivity to pinprick up to T3.

She walks with a wide-based gait and is unable to "tandem walk" (place one foot directly in front of the other when walking) or to maintain her balance with her eyes closed and her feet close together (Romberg's sign). With her eyes closed, she has difficulty touching her finger to her nose or her heel to her shin (ie, mild dysmetria); the deficit is much more marked on the left than on the right. Her reflexes are normal and symmetric. Babinski's sign is absent. There is no evidence of bowel or bladder dysfunction.

WHAT IS THE DIAGNOSIS?

1 Given this patient's history and neurologic findings, what is the most likely diagnosis?

- ❑ Guillain-Barré syndrome
- ❑ Transverse myelopathy
- ❑ Paraneoplastic sensory neuronitis
- ❑ Cervical spondylosis
- ❑ Subacute combined degeneration of the spinal cord (vitamin B_{12} deficiency)

This patient's history—the acute onset of paresthesia, beginning in the left hand and spreading in a "windmill" pattern (counterclockwise) to sequentially involve the other limbs before ascending to the chest—strongly suggests an acute transverse myelopathy beginning above the level of the C5 vertebral

TABLE 1

Causes of acute transverse myelopathy

Neoplastic disorders
- Metastatic carcinoma
- Lymphoma
- Astrocytoma, ependymoma
- Meningioma, Schwannoma

Infectious disorders
- Viral infections
  - Cytomegalovirus
  - Herpes simplex virus
  - Epstein-Barr virus
  - Human immunodeficiency virus
  - Herpes zoster
  - Influenza
  - Mumps
  - Hepatitis B
- Epidural abscess
- Bacterial infections
  - Syphilis
  - *Borrelia burgdorferi* (Lyme disease)
- Mycobacteria

Traumatic/degenerative disorders
- Herniated nucleus pulposus
- Spondylosis (acutely decompensated)
- Traumatic subluxation

Vascular disorders
- Atheroembolism, atherothrombosis
- Arteriovenous malformation (including dural AVM)
- Epidural hematoma
- Dissecting abdominal aortic aneurysm
- Hypotension
- Capillary telangiectasia

Inflammatory disorders (transverse myelitis)
- Autoimmune
  - Multiple sclerosis
  - Systemic lupus erythematosus
  - Sarcoid
  - Other connective tissue diseases
- Parainfectious
- Vasculitis
- Post-vaccination
- Radiation myelitis
- Paraneoplastic necrotizing myelitis

Metabolic
- Nitrous oxide intoxication (functional vitamin B_{12} deficiency)

Compression of the spinal cord requires immediate surgery

body in the left posterior column of the spinal cord. The tight-band sensation is further evidence of a myelopathic process. Her neurologic examination confirms the evidence of asymmetric posterior-column dysfunction involving the upper cervical spinal cord. The decreased sensation to pinprick up to T3 is most likely a false localizing sign.[1] Of importance, there is no evidence of disseminated involvement of the nervous system by history or examination.

As for the other possibilities, Guillain-Barré syndrome and paraneoplastic sensory neuronitis are both excluded by the clinical features already mentioned and the presence of normal reflexes. Cervical spondylosis is unlikely, given the rapid onset of symptoms and no history of neck or radicular pain. Subacute combined degeneration of the spinal cord is a slowly progressive, symmetrical process with symptoms of posterior column dysfunction beginning in the lower extremities, and loss of distal reflexes on examination.

DIAGNOSTIC STUDIES FOR TRANSVERSE MYELOPATHY

2 What would be the most important initial diagnostic study to obtain?

- ❑ Cranial MRI
- ❑ Roentgenograms of the cervical spine
- ❑ MRI of the cervical spinal cord
- ❑ Lumbar puncture
- ❑ CT of the spine

A number of conditions can cause acute transverse myelopathy (TABLE 1). Although the history and demographic features frequently point to a likely etiology, direct imaging of the spinal cord is required in all cases to exclude compression of the cord, which would require immediate surgery.

Our patient is an otherwise healthy young woman with partial, asymmetric involvement of the cervical spinal cord, which was preceded by an upper respiratory tract illness. These features suggest postinfectious transverse myelitis as the most likely etiology. The only diagnostic study required at this point is a magnetic resonance imaging (MRI) scan of the cervical spinal cord with and without

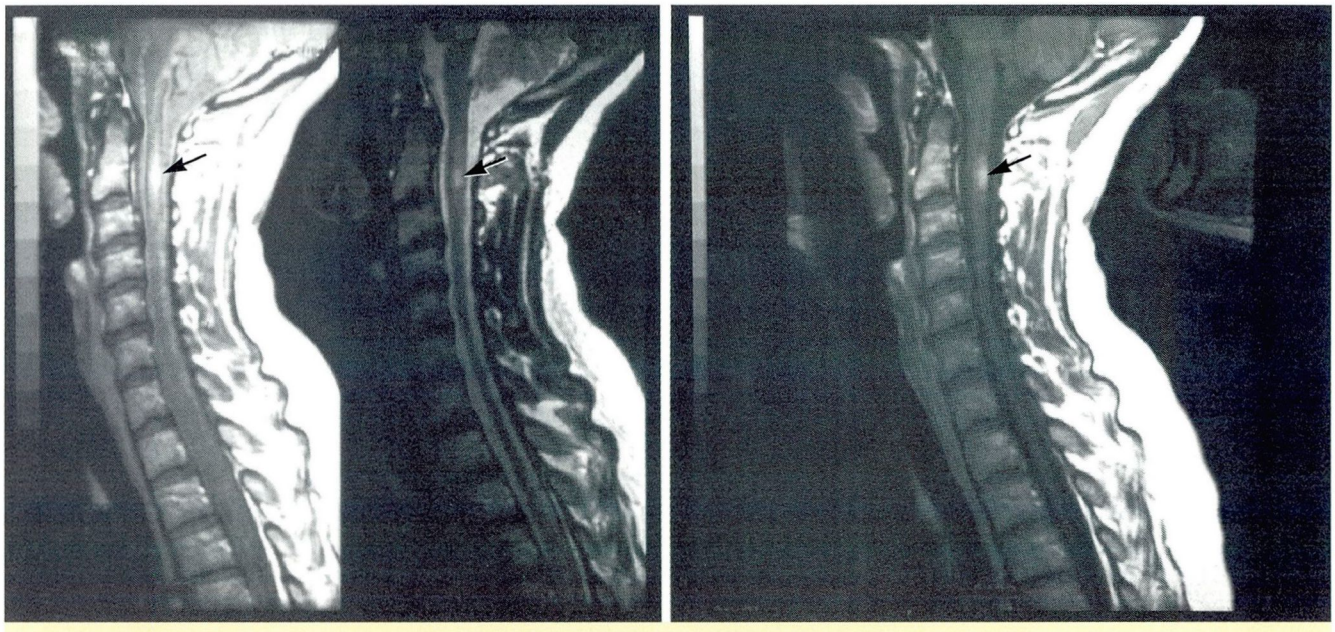

FIGURE 1. Left, T2-weighted sagittal magnetic resonance image of the cervical spinal cord showing an intramedullary, ovoid area of increased signal adjacent to the C2 vertebral body (arrow), predominately involving the posterior aspect of the cord and associated with mild cord swelling. Right, T1-weighted sagittal image following the administration of gadolinium, showing diffuse enhancement of the posterior aspect of the same lesion (arrow).

gadolinium. A standard roentgenogram or CT scan of the cervical spine would be useless, because these do not visualize the cord parenchyma.

The patient underwent an MRI scan of the cervical spine, which showed a discrete and well-circumscribed area of increased signal on the T2-weighted image in the posterior aspect of the spinal cord adjacent to the C2 vertebral body (FIGURE 1). This segment of the cord was also mildly swollen. Gadolinium enhanced this abnormality intensely and uniformly on the T1-weighted image. These features are classic for inflammatory demyelination involving a partial segment of the spinal cord, ie, partial transverse myelitis.

TRANSVERSE MYELITIS: COMPLETE OR PARTIAL

Transverse myelitis is a syndrome of inflammatory demyelination that on clinical examination appears to involve a segment of the spinal cord. Several disease processes can cause transverse myelitis, and these are often difficult to identify at the time of presentation (TABLE 1). The differential diagnosis is more diverse with subacute or chronic presentations than with acute presentations. The rest of this paper will deal exclusively with the more common acute presentations.

Standard x-rays and CT scans do not show the cord parenchyma

Of adults with transverse myelitis, one fourth to one third report having had a viral infection in the preceding month. In contrast, a greater fraction of children develop the syndrome after vaccination. Regardless of etiology, transverse myelitis usually develops over hours to several days, and causes its maximal deficits within 2 weeks in more than 80% of cases.[2]

Clinically, it is useful to distinguish complete transverse myelitis from partial transverse myelitis, although the clinical presentations may overlap.

Complete transverse myelitis

Complete transverse myelitis is less common than partial transverse myelitis, but tends to

TABLE 2

Common clinical presentations of partial transverse myelitis

SYNDROME	FEATURES
Posterior cord syndromes (sensory myelitis)	
Useless hand of Oppenheim	Diminished proprioception and stereognosis in one hand Complaints of clumsiness and paresthesia
Windmill syndrome	Paresthesia beginning in an upper extremity and spreading in a windmill pattern to involve all limbs (see text)
Ascending paresthesia syndrome	Paresthesia beginning in the feet and rising to a level on the trunk Frequently associated with a tight band sensation, mild gait instability, and mild bladder or bowel disturbance
Lateral cord syndrome (partial Brown-Sequard syndrome)	Ipsilateral hemiparesis or crural paresis Ipsilateral posterior column dysfunction (usually mild decrease in joint position sense or decrease in vibration) Contralateral decrease of pinprick sensation (although usually subtle and without a clear level on trunk)
Anterior cord syndrome*	Prominent weakness Paraparesis, tetraparesis Impaired bowel and bladder control Thermoanesthesia and analgesia below level involved Intact sense of position, vibration, and light touch
Conus medullaris syndrome	Paresthesia Numbness in a saddle distribution (sacral dermatomes involving perirectal area, perineum, and vagina), occasionally extending down back of legs to sole of feet Neurogenic bladder or bowel (can be mild) Diminished rectal tone Abnormal sensations within the rectum or vagina (pressure, fullness) Distal foot weakness (rare)

*Rare; always consider a vascular etiology with this syndrome

be more uniform in presentation and rapid in development.

Clinical presentation. Typically, the patient develops intrascapular or lower thoracic back pain followed by symmetrical, ascending numbness, paralysis, and bowel and bladder dysfunction. If flaccid tone and areflexia are present due to spinal shock, this disorder can be difficult to differentiate from Guillain-Barré syndrome. Variations on this pattern include initial asymmetric involvement of the cord, absence of pain, late or minor involvement of bowel and bladder function, and cervical cord involvement.

Spinal MRI findings may be normal during the first few days of complete transverse myelitis, or reveal only diffuse fusiform enlargement of the cord over multiple segments with little alteration in signal characteristics. More commonly, there is a diffuse increase in signal on T2-weighted images, extending over three or more segments of the cord, and associated with mild to moderate fusiform enlargement.[3,4] Gadolinium enhancement may occur but tends to be diffuse and poorly circumscribed.[4]

Prognosis. Of importance, complete transverse myelitis only rarely leads to multi-

ple sclerosis (MS). Although relapses can occur in an unknown percentage of cases,[5] numerous studies indicate that fewer than 5% of patients with complete transverse myelitis subsequently develop the disseminated involvement of the central nervous system suggestive of MS.[2,6,7]

Partial transverse myelitis

In stark contrast, partial transverse myelitis is a frequent initial manifestation of MS in young adults.

Clinical presentation. TABLE 2 lists common clinical presentations of partial transverse myelitis; the most common and difficult to recognize of these syndromes is sensory myelitis.

Patients with sensory myelitis usually experience ascending or descending paresthesia (pins and needles) involving one or more limbs, tight-band sensations around a segment of the trunk or limb which are at times painful, vague clumsiness of gait or limb movements, and subtle complaints of bladder dysfunction (ie, a slight increase in frequency, mild urgency, or mild hesitancy). Involvement of the cervical cord can result in Lhermitte's phenomenon—an electric sensation traveling down the spine and into the limbs with forward neck flexion.

Neurologic examination may reveal clear evidence of posterior column dysfunction, as in the case presented above, or only a subtle decrease in vibratory sensation. There is little if any weakness on examination. Pinprick and temperature sensation is usually normal, and reflexes are normal or brisk. Patients usually have some difficulty tandem walking or performing fine dextrous movements of the hand, depending on the level of involvement.

Because this syndrome is difficult to recognize, patients are often mislabeled as hysterical or suffering from stress. Alternatively, the tight-band sensations are misinterpreted as a sign of obstructive airway disease, cardiac disease, or an acute abdominal process (depending on the level of involvement), leading to unnecessary and often expensive diagnostic evaluations and treatments.

Spinal MRI findings in partial transverse myelitis usually differ from those seen with complete transverse myelitis. As in our patient, there is typically a well-circumscribed, ovoid area of increased signal on T2-weighted images that is confined to fewer than three vertebral body segments.[4] Diffuse enlargement of the cord is rare, although the cord may be slightly enlarged in the corresponding segments. At times there are multiple discrete areas of increased signal scattered throughout the cord, suggesting previous asymptomatic involvement. Acutely, there is intense and uniform gadolinium enhancement, which demarcates the area of clinical involvement within the cord.[8]

Less commonly, there is ring enhancement, which raises the specter of a neoplastic process. Neoplastic processes typically show significant cord enlargement, whereas partial transverse myelitis usually has mild or no cord enlargement. Unfortunately, there is considerable overlap in the MRI appearance, and differentiating the two processes can be difficult.

When partial transverse myelitis involves the thoracic spinal cord, conventional MRI techniques may reveal no abnormalities. Normal findings are less common with cervical cord involvement. If the MRI scan is normal and the diagnosis is still in question, then testing the somatosensory evoked potential of the posterior tibial nerves is a very sensitive technique to detect involvement of posterior columns.

Complete transverse myelitis rarely leads to MS, but partial transverse myelitis often does

FURTHER DIAGNOSTIC STUDIES

3 What is the next diagnostic study to obtain in this patient?

- ❑ Lumbar puncture for spinal fluid analysis
- ❑ Cranial MRI scan with gadolinium
- ❑ Cranial CT scan with contrast
- ❑ Visual evoked potential
- ❑ Somatosensory evoked potential

Cranial MRI is the most important diagnostic study to obtain, once inflammatory demyelination has been established as the likely etiology. This rule applies whether the syndrome involves the spinal cord (ie, partial transverse myelitis), optic nerve, or brainstem—three common initial manifestations of MS. Approximately 50% of patients with these syndromes have at least one typical periven-

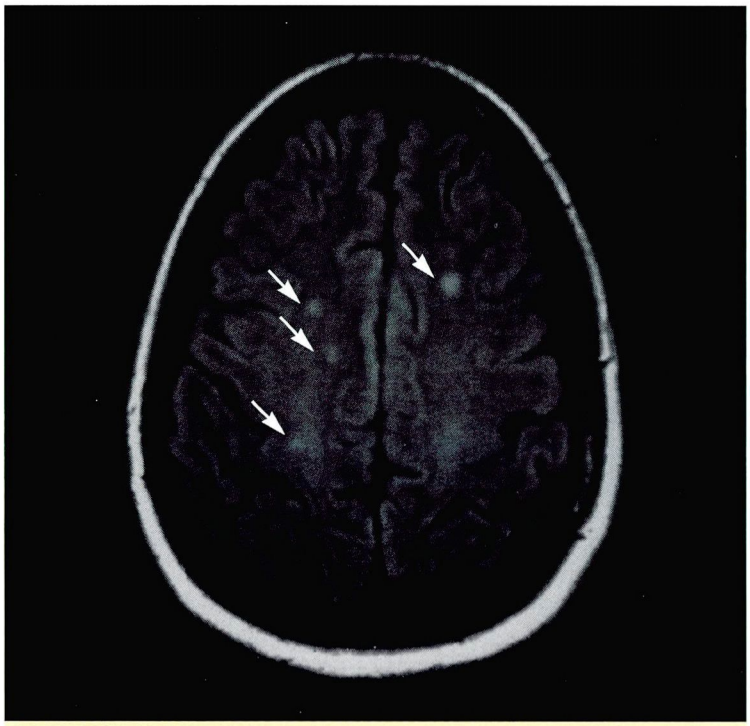

FIGURE 2. T2-weighted, fluid-attenuated inversion recovery (FLAIR) axial cranial magnetic resonance image showing four ovoid areas of increased signal involving the centrum semiovale dorsal to the lateral ventricles (arrows). The estimated lesion load is less than 1.23 cm^3.

tricular or deep white-matter lesion suggestive of MS.[9,10] These persons are at higher risk of later developing clinically definite MS, since 40% to 90% will experience a relapse involving another part of the central nervous system within 5 years (see below).[11,12,13] In the case under discussion, cranial MRI revealed four typical white lesions involving the centrum semiovale (FIGURE 2).

Most studies suggest that spinal fluid analysis provides little additional diagnostic or prognostic information if the cranial MRI findings are typical of MS.[14,15] The real utility of spinal fluid analysis is in cases where the cranial or spinal MRI is normal or atypical in appearance, or clinical features of the case suggest an unusual etiology such as vasculitis or an infectious process. Spinal fluid analysis should be obtained in all cases of complete transverse myelopathy after MRI imaging excludes a compressive etiology or complete block within the spinal canal. In these cases, spinal fluid analysis may help differentiate inflammatory etiologies. In addition, oligoclonal bands in the spinal fluid are an independent predictor of the subsequent development of MS.[15]

As mentioned above, somatosensory evoked potential studies are necessary only if the spinal MRI studies are normal. Cranial CT is of little use in evaluating inflammatory disorders of the central nervous system, and should not be routinely done. Visual evoked potentials provide sensitive information regarding asymptomatic demyelination within the optic nerves, an area not well visualized on cranial MRI. Therefore, this study is particularly useful to document disseminated involvement of the central nervous system if the cranial MRI is normal.

ARE ADDITIONAL TESTS NEEDED?

4 Should additional diagnostic tests be obtained to clarify the etiology of partial transverse myelitis in this patient?

- ❑ Yes
- ❑ No

Additional diagnostic testing remains a subject of controversy, generated in large part by pressures to reduce health care costs. The most useful and important studies to obtain in a case of acute transverse myelitis (ie, MRI scans) are also the most expensive. Moreover, certain studies, such as CT scans, electroencephalograms, and electromyelograms, are useless and should not be ordered without good reason. Between these two extremes are a number of tests that are useful in certain cases, but should not be ordered routinely.

We have described above how evoked-potential studies may be useful in certain scenarios. However, using somatosensory evoked potentials in evaluating this case would be an unnecessary and unjustified expense.

Spinal fluid analysis provides useful information in most cases, but may not be necessary if the cranial MRI findings are consistent with MS. Most neurologists obtain a number of serologic tests of blood and cerebrospinal

fluid when confronted with a case of inflammatory demyelination within the central nervous system. However, without historical clues or physical signs that point to an alternative diagnosis, these serologic tests are of limited utility.

For example, although physicians almost always obtain a serologic test for antinuclear antibody (ANA), 20% to 80% of patients with MS show elevations in ANA titers with no evidence of systemic lupus erythematosus or other connective tissue diseases.[16,17] Similarly, physicians routinely analyze the spinal fluid with expensive serologic or polymerase chain reaction techniques to detect *Borrelia burgdorferi*, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and other pathogens, even without evidence to suggest that these pathogens might be the cause of patient's clinical syndrome. Since no evidence exists to support these tests as screening serologic studies, we no longer obtain them unless there is a compelling reason.

The only tests we obtain in cerebrospinal fluid are a cell count and measurements of total protein, glucose, quantitative IgG and albumin for calculation of intrathecal IgG production, free kappa light chains, and oligoclonal bands. If this routine cerebrospinal fluid examination suggests an alternative etiology, then a frozen aliquot is sent for additional studies.

For all these reasons, we would not recommend any further testing for this patient.

PARTIAL TRANSVERSE MYELITIS AND MULTIPLE SCLEROSIS

5 Does this patient have multiple sclerosis?

- ❑ Yes
- ❑ No

This patient does not have clinically definite MS by any of the currently accepted criteria, ie, clinical or paraclinical evidence of disseminated involvement of the central nervous system occurring at multiple points in time. However, we would consider her at risk of developing MS.

WHAT IS THE PROGNOSIS?

6 What is this patient's risk of developing MS?

- ❑ High
- ❑ Intermediate
- ❑ Low

The immediate prognosis after a first episode of partial transverse myelitis is quite favorable. Although exact figures do not exist, roughly 80% to 90% of patients recover partially or completely within 1 to 6 months, regardless of treatment. The long-term prognosis depends on whether the patient develops clinically definite MS.

Risk depends on lesion load

Studies suggest that the risk of developing clinically definite MS correlates best with the "lesion load," irrespective of the type of syndrome a patient initially experiences.[13] (The lesion load is the volume of lesion on cranial MRI, which can only be calculated with special techniques not available in most practice settings.) Therefore, it makes little difference if a patient presents with partial transverse myelitis, optic neuritis, or a brainstem syndrome, which are all common initial presentations of MS. On the basis of lesion load at onset, we can distinguish three risk groups:

- High-risk: If the lesion load is 1.23 cm^3 or higher (usually, this corresponds to > 5–10 typical, discrete white matter lesions, depending on their size), the risk of clinically definite MS within 5 years is 90%.
- Intermediate risk: If the lesion load is less than 1.23 cm^3, as in this case, the risk of clinically definite MS within 5 years is 55%.
- Low-risk: If the baseline cranial MRI is normal, the risk is 6% to 16%, depending on the sample studied and the definition of a normal MRI.[11,13]

This patient has a lesion load of less than 1.23 cm^3, and therefore has an intermediate risk of developing clinically definite MS.

Once a person develops clinically definite MS, his or her long-term prognosis is still uncertain, since only 50% of patients with clinically definite MS become disabled within

Obtain spinal fluid if the MRIs are normal and there is no compression

10 years of diagnosis. Unfortunately, this percentage increases to approximately 80% after 30 years.

TREATING PARTIAL TRANSVERSE MYELITIS

7 What treatment should be offered this patient?

- ❑ Oral corticosteroids
- ❑ High-dose intravenous corticosteroids
- ❑ Interferon beta-1a (Avonex) or interferon beta-1b (Betaseron)
- ❑ Glatiramer acetate (Copaxone)

Traditionally, patients with monosymptomatic demyelinating syndromes (partial transverse myelitis, optic neuritis, or brainstem syndrome) are treated with corticosteroids if no improvement has occurred by the time the syndrome is diagnosed.

Oral corticosteroids questioned

Until recently, the treatment of choice was an oral corticosteroid in tapering doses for 1 to 3 weeks (eg, prednisone 60 to 120 mg/day or an equivalent), even though controlled studies were totally lacking. This practice was brought to an abrupt halt following the publication of the optic neuritis treatment trial (ONTT).[18]

The volume of T2 lesion determines the risk of MS

This study randomized 457 patients with monocular optic neuritis to receive one of three treatments:

- Intravenous methylprednisolone (1,000 mg/day) for 3 days followed by oral prednisone (1 mg/kg/day) for 11 days;
- Oral prednisone (1 mg/kg/day) alone for 14 days; or
- Placebo for 14 days.

Although recovery of function occurred more rapidly in the IV methylprednisolone group, there was no significant difference between the three groups with regard to recovery at 6 months. More importantly, the prednisone-alone regimen not only provided no benefit to visual recovery, but was associated with a significant increase in the risk of relapse in the same or contralateral eye in the following 2 years: the rate was 30% in the prednisone-alone group, 14% in the IV methylprednisolone group, and 16% in the placebo group.[10]

As part of a preplanned secondary analysis, the 388 patients entered into the ONTT with truly monosymptomatic optic neuritis (ie, excluding patients with clinically definite or probable MS) have been followed for the past 5 years.[10,11] Unexpectedly, the IV methylprednisolone group had a lower rate of developing clinically definite MS within the first 2 years than did the placebo or oral prednisone-alone groups. This benefit was seen primarily in the subgroup of patients with abnormal cranial MRI scans at study baseline. Among patients with two or more cranial MRI abnormalities, clinically definite MS developed in 36% of the placebo group, 32% of the prednisone-alone group, and only 16% of the IV methylprednisolone group within 2 years.

As expected, this treatment effect was no longer apparent at 3 and 5 years, but the significance of these findings remain: early treatment with a high dose of IV methylprednisolone has a beneficial effect on the natural history of a monosymptomatic demyelinating syndrome. This finding has never been replicated in well established cases of clinically definite MS.

These results raise a number of important questions:

- Why does oral prednisone by itself result in an increased rate of relapses in optic neuritis, whereas high-dose IV methylprednisolone decreases the relapse rate and the short-term risk of developing clinically definite MS?

A number of hypotheses have been raised, but the answer is currently not clear.[19]

- Are the results from the ONTT applicable to other monosymptomatic demyelination syndromes (ie, partial transverse myelitis or brainstem syndrome)?

We feel the answer is yes, given the similar natural history of these syndromes after controlling for MRI and cerebrospinal fluid abnormalities. Nevertheless, further studies will be required to definitively answer this question. We elected to treat the patient under discussion with IV methylprednisolone according to the ONTT protocol. We do not feel it is acceptable at the current time to treat monosymptomatic demyelinating syndromes with oral prednisone alone.

• Can the short-term effect of IV methylprednisolone on the development of clinically definite MS after a monosymptomatic demyelinating syndrome be extended with other therapies such as pulses of IV methylprednisolone given regularly, interferon beta (Avonex or Betaseron), or glatiramer acetate (Copaxone)?

The answer to this question is unknown but is currently under investigation in a phase III clinical trial involving 55 centers in North America. In this study, with the acronym "CHAMPS" (Controlled trial of *H*igh-risk subjects in *A* Multiple sclerosis *P*revention Study), patients with monosymptomatic demyelinating syndromes (ie, partial transverse myelitis, optic neuritis, brainstem syndrome) of less than 2 weeks' duration and with two or more abnormalities on cranial MRI receive a course of IV methylprednisolone and then are randomized to receive either interferon beta-1a or placebo. The primary endpoint of the study is the time until clinically definite MS develops. Until this study is completed, all treatments for monosymptomatic demyelinating syndromes other than IV methylprednisolone must be considered experimental.

Our patient elected to enter this clinical trial and has remained asymptomatic following her complete recovery within 1 month.

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ADDRESS: *R. Philip Kinkel, MD, Mellen Center for Multiple Sclerosis Treatment and Research, U-10, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195; e-mail kinkelr@cesmtp.ccf.org.*

A study of interferon beta is underway

HIGHLIGHTS FROM MEDICAL GRAND ROUNDS

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