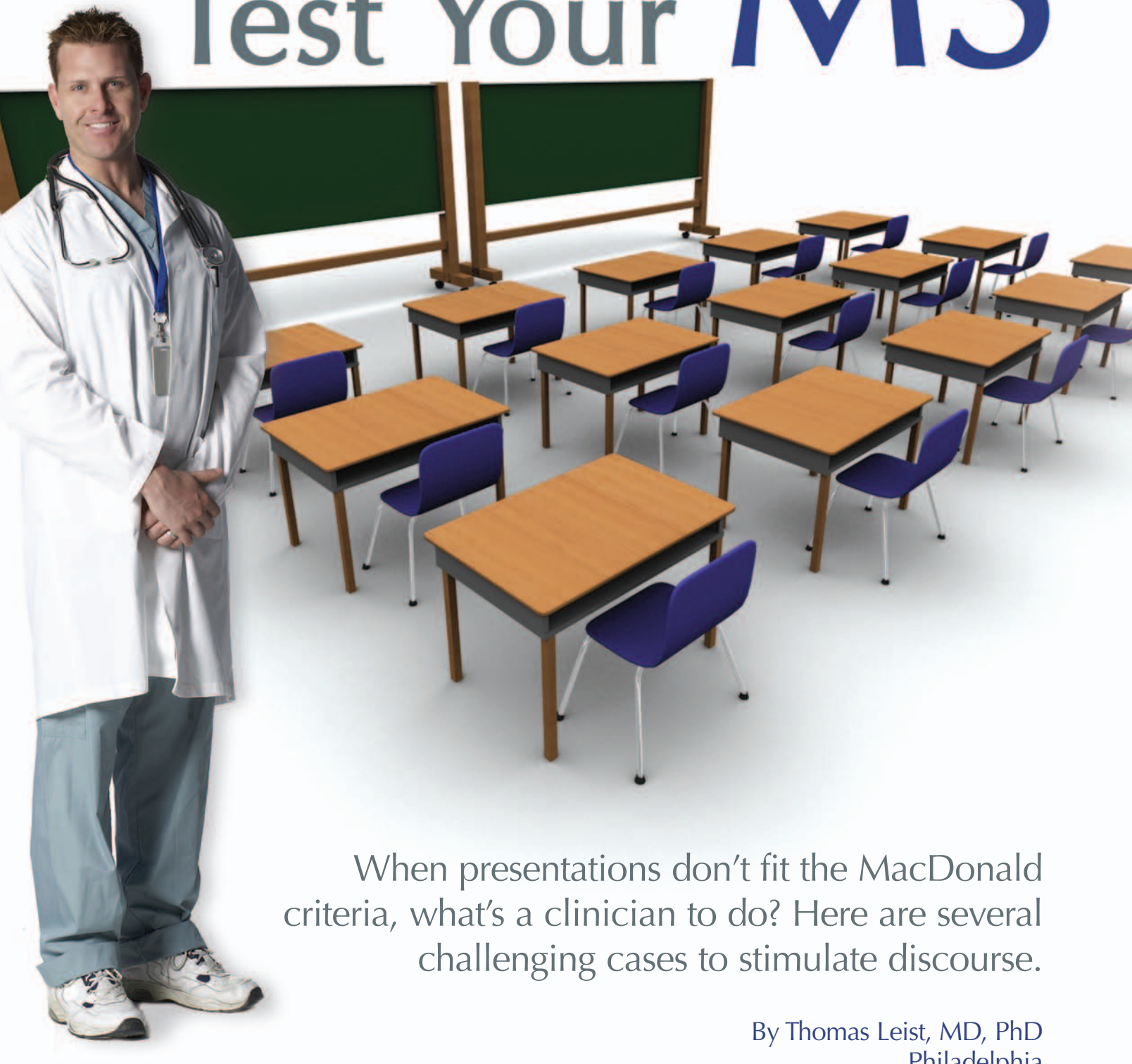
Grand Rounds:

Test Your MS



When presentations don't fit the MacDonald criteria, what's a clinician to do? Here are several challenging cases to stimulate discourse.

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Aptitude

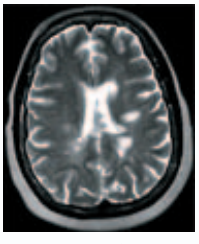
Multiple sclerosis in its protean manifestations remains one of the more consistently frustrating clinical challenges in the field of neurology. Even to those well-versed in the more classic clinical presentations of MS and its differential diagnoses, there are still quite a few gray areas in which information is limited and the neurologist is often bound to rely more on clinical instincts. When such a case is referred to your office by an internist who suspects MS, you may have to look beyond the textbook work-up to find the individual nuances that could change the diagnosis or require consideration of an entirely different approach.

As an opportunity to sharpen your diagnostic skills, this article presents four real-world cases that may not quite readily fit within the confines of the commonly accepted MS criteria but still task the clinical considerations and a path of action. Test your clinical acumen by developing your approach to the case scenarios provided. Space has been provided for you to write in your clinical impressions. Approaches chosen by the author are on page 52.

Case 1: Warnings Without Incident

A Caucasian woman in her mid-50s comes to your office. She had a brain MRI after complaining of neck pain and headaches following a low-velocity car accident in which she was involved as a restraint driver. Her MRI revealed at least six ovoid lesions directly abutting the lateral ventricles and some lesions in the juxtacortical area. In addition, there are several punctuate white matter lesions throughout the centrum semiovale. The patient denies any history of neurologic events, does not report any problems with gait, spasticity, bowel or bladder dysfunction. She denies ever having had visual problems beyond the need for reading glasses.

She has a history of borderline hypertension for which she is on an antihypertensive and a diuretic. She has had testing for diabetes, hyperlipidemia and hypercholesterolemia, all of which were reportedly within normal limits. She occasionally takes a non-steroidal analgesic for joint pain. Her family history includes hypertension, type II diabetes, and rheumatoid arthritis. The general examination is within normal limits with the exception of some point tenderness over the cervical spine. The neurologic examination is non-focal with the exception of symmetrically brisk reflexes at knees and ankles.



T-2 weighted image exhibiting multiple void lesions in periventricular location.

1. What course of action do you choose when dealing with a patient without MS symptoms who nevertheless presents with findings in line with demyelination on MRI?

2. What are some of the possible MS mimickers this patient could have, and what are the clues for them?

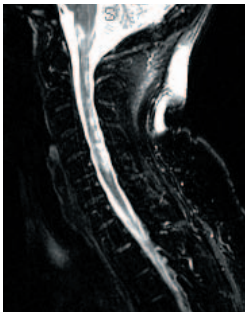
3. What tests can be done to better determine the presence of MS in this patient?

Case 2: When Symptoms and Scans Don't Add Up

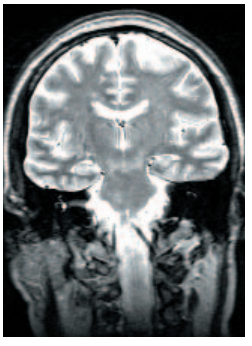
A 29-year-old African-American woman presents in October 2004 reporting band-like dysthesia, which she describes as a sensation similar to a vise clamped around her mid-abdomen. She also says she urinates frequently and her gait is off. She is admitted into the health center where she is treated with intravenous steroids, and completely recovers within three weeks.

In February 2005 she comes back to your examining room. The dysthesia has now moved to up above her mid-chest level, her balance is poor, she reports a burning sensation over her legs, and she suffers from bowel and bladder problems alternating from excessive frequency to constipation. An MRI reveals multiple confluent lesions in the cervical and thoracic cord; however, the brain MRI was negative. The patient underwent inpatient rehabilitation before being discharged. She was ambulating with a cane after then.

She returns in June 2005. This time she reports difficulties swallowing, weakness, dysthesia, urinary tension and reduced reflexes. A visual evoked potential showed a modest delay on the left side, the brain appears is still normal on MRI and the cord MRIs show abnormal signaling throughout with an extension in the lower brain stem. She undergoes plasmapheresis and later experienced some recovery.



Second MRI (cervical spine fast spin late echo sequences) exhibiting multiple confluent lesions with extension into the medulla.



Second MRI (coronal T2 sequence) of the brain.

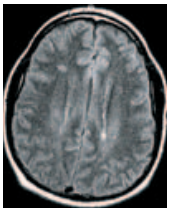
1. What tests should be performed?

2. What can we learn from the patient's response to plasmapheresis?

Case 3: Forgotten First Attack

A 45-year-old Caucasian woman describes a history of subtle, worsening changes to the way she walks over the past six months to a year. In the clinic she also reports nighttime cramps, difficulty initiating urination, and difficulty navigating stairs as she has a hard time keeping track of where her feet are.

An MRI shows two to three white matter lesions, two of which are ovoid and in direct periventricular location. The patient brought in spinal MRIs done on an open scanner that showed no clear cord-intrinsic lesions or disk disease. Her family history has no cases of MS or autoimmune diseases but there are signs of cardiovascular problems, as her father died of a stroke at age 55.



Flair sequence exhibiting two periventricular lesions.

She mentions she has had three children (the oldest of whom is 15) and no miscarriages; two of the children were delivered via Caesarian section. After repeated questioning, she remembers that shortly after her first child was born she lost vision in her left eye for about two weeks. She gradually regained sight without treatment, but she notes that when she drives at night she notices some difficulty making out contours with her left eye.

Visual evoked potentials were performed and were reportedly within normal limits. The examination exhibits spasticity, hyperreflexia in both lower extremities and some weakness in the left leg.

1. Does this patient have MS? Why or why not?

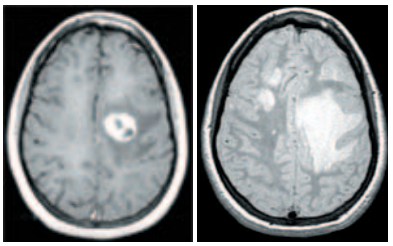
2. If she is assumed to have MS, where does she belong in the diagnostic spectrum? What tests can help us clarify this case?

3. Should the patient be put on immunotherapy? If so, what can the clinician expect from such treatment?

Case 4: Aggressive Onset

A 17-year-old Caucasian woman first has noticeable difficulties maintaining her balance in February. The problem is so pronounced that during a physical education class the teacher sent her to the school nurse for drug testing. Two weeks later, the patient cannot lift her left arm and is taken to the emergency room. The MRI shows a cervical spinal lesion and another lesion in the brachium pontis. She is treated with steroids and has good recovery following physical therapy.

One month later, she returns after experiencing loss of vision in her right eye. She started high dose of interferon two weeks prior. She is treated with another round of steroids. She experiences partial vision recovery. She is now having a hard time keeping up with her schoolwork even with a tutor. In June she suffers another attack. This time, she loses mobility in her left arm and left leg and experiences weakness in both lower extremities. An MRI of her brain and cervical spine shows new enhancing lesions. All tests reveal her to be negative for infective diseases, HIV or Lyme disease. She has no family history of MS or any history of illness before her first onset in February.



Tumofactive lesion with significant edema. Left image: T-1 enhanced sequence. Right image: FLAIR sequence.

1. Did the first immunomodulator fail in this case?

2. What other treatments may be effective ways of controlling this case?

3. Given that she is a 17-year-old female, how should we deal with the risk of amenorrhea?

Case 1: Warnings Without Incident

1. What course of action do you choose when dealing with a patient without MS symptoms who nevertheless presents with findings in line with demyelination on MRI?

This patient obviously does not fulfill the standard clinical criteria for a diagnosis of MS, although she has experienced clinical events. However, the MRI raises the issue of heretofore sub-clinical MS.

2. What are some of the possible MS mimickers this patient could have, and what are the clues for them?

The patient has a history of hypertension, which can be associated with white matter changes. Given this patient's past medical and family history adult onset diabetes and dyslepidemia and their possible vascular consequences remain distinct possibilities and a respective work-up is indicated if not tested within the last one to two years. The history of joint pain in combination with the mother's diagnosis of rheumatoid arthritis may raise the suspicion of an inflammatory arthropathy could also be associated with changes in the CNS.

3. What tests can be done to better determine the presence of MS in this patient?

An MRI of the cervical spine may help to delineate lesions in the cord, which if present may present independent of significant cervical disc disease and may support a diagnosis of demyelination even in a patient with co-morbid conditions. A visual evoked potential can also help determine injury along the visual system and may be supportive of a diagnosis of demyelination if found to be asymmetrically delayed. A follow-up MRI of the brain dependent on degree of clinical suspicion six to 12 months after the initial study may help to evaluate for occurrence of new lesions. A lumbar puncture may further help if visual evoked potentials are abnormal or MRIs exhibit changes.

In this case, the patient did not have spinal cord lesions, and the lumbar puncture did not exhibit oligoclonal bands or an increase in the IgG index. The patient elected to have the MRI repeated after one year, then again at the two- and three-year marks, to evaluate her lesions for any possible changes.

What can we learn from this patient?

This patient raises the issue of ongoing subclinical demyelinating disease a possibility that is not captured with either the Posner or MacDonald criteria. With increased imaging for different conditions patients with the overall profile described here are not infrequently seen clinical setting. While she may never have had an MS episode and there may be other possible causes for her symptoms, it would be premature to completely rule out MS in this case solely due absence of clinical events. It was elected to follow this patient expectantly to ensure stability of the initial findings.

Case 2: When Symptoms and Scans Don't Add Up

1. What tests should be performed?

This patient exhibits a myelopathic process with extending involvement if the cord. The appearance of the cord lesions which span multiple spinal segments is in line with findings Neuromyelitis optica (Devic's disease). The latter traditionally involves optic nerves and spinal cord. The patient in this case has a subtle involved of the visual systems as measured by the visual evoked potentials although the eye exam is unremarkable. The cerebrospinal fluid exhibited 45 white cells. Further testing reveals the presence of neuromyelitis optica antibodies (aquaporin-4) in the serum.

2. What can we learn from the patient's response to plasmapheresis?

This patient has CSF and brain and cord MRI findings in line with those observed in neuromyelitis optica. The lack of clear ocular involvement raises some issue of classification. While the patient initially had a good response to treatment with high potency steroids she became later refractory to this treatment but responded well to plasmapheresis.

This form of a necrotizing myelitis is more frequently observed in African-American patients and may, as in this case, exhibit relative sparing of the optic nerve This presentation may be considered as neuromyelitis without the optical presentation. This condition responds to a degree to plasmapheresis or an IVIg which can be combined with cytotoxic agents, but is generally unresponsive most MS therapies.

Unfortunately, this presentation is more often associated with a poor outcome particularly when it leads to respiratory compromise.

What can we learn from this patient?

This case should not be seen as advocacy for plasmapheresis during classical MS exacerbations. Here we had a patient who was initially considered to have recurring transverse myelitis but MRI and CSF findings delineate a picture more compatible with neuromyelitis optica. In this situation, the patient's ethnic roots require broadening of the diagnostic considerations even in presence of an incomplete clinical picture.

Case 3: Forgotten First Attack

1. Does this patient have MS? Why or why not?

It is not all that rare to encounter a patient with a history of a likely demyelinating event years prior who after many years of having no neurological complaints presents with more insidi-

ous onset of worsening symptoms. Very often as in this case the patient does not initially recall the previous clinical event. The MRI exhibits some lesions in an appropriate location for demyelination but their low number attests for the paucity of over clinical symptoms. Demonstration of presence of oligoclonal banding may be helpful.

2. If this patient is assumed to have MS, where does she belong in the diagnostic spectrum? What tests can help us clarify this case?

The delayed progressive clinical course after and earlier demyelinating event can be viewed as in line secondary progressive MS. Besides disk and spinal disease diagnoses including Sjogren's, Lupus, HIV associated myelopathy, Behcet's, and HTLV-I associated myelopathy are among other differential diagnoses which can be considered in the appropriate setting. Treatment of the patient's symptoms with conservative strategies or medication is indicated. The role of disease modifying therapy is clearly less well established in cases such as this. It may also help to repeat the MRI of the cervical spine as the low field of an open scanner may lack the sensitivity we need to more thoroughly evaluate the lesions.

3. Should the patient be put on immunotherapy? If so, what can the clinician expect from such treatment?

Follow-up imaging of the brain after six to 12 months may help to visualize interval changes and if present on more than one subsequent scan may indicate the consideration of disease modifying therapy.

The currently licensed MS therapies have been found to be most effective in patients with relapses prior to initiation of treatment. Here, we have a patient who had one incident many years ago before presenting with this apparent progression. Whatever choice is made regarding treatment, it is important to include the rationale for the decision in the patient counseling and the plan for periodic evaluations should be outlined.

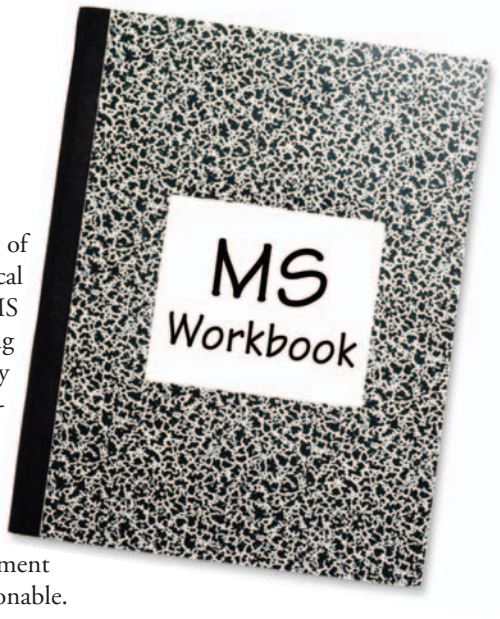
What can we learn from this patient?

One of the more important points from this case is that the patient did not remember her first attack and did not readily volunteer this information. It was only after repeated questioning that she recalled the incident. This shows the value of persistence when getting the patient's history, especially when asking about something he or she has recovered from.

Case 4: Aggressive Onset

1. Did the first immunomodulator fail in this case?

Clearly, we are looking at a very aggressive disease presentation. While a new attack after initiation of therapy could imply that the chosen therapy may not be fully effective this has to be viewed in the context of the rapid fire of clinical events in this case. MS lesions start developing some time before they become clinically apparent. Generally a window of about six months between start of treatment and evaluation of the on treatment effect is considered reasonable.



2. What other treatments may be effective ways of controlling this case?

Cytotoxic agents including cyclophosphamid (Cytoxan) and mitoxantrone (Novantrone) may be considered in an aggressive case such as this. Preplanned pulses with high potency steroids may also be useful second choice or adjunct therapy. Natalizumab (Tysabri)—when it returns to the market—could prove a good alternative for cases like this one.

In this case the patient was treated with four monthly doses of mitoxantrone and she was evaluated with a multiple-gated acquisition scan before each dose was administered.

3. Given that she is a 17-year-old female, how should we deal with the risk of amenorrhea?

Potential long-term consequences of cytotoxic agents have to be carefully balanced with treatment goals, particularly in young women. The issues of fertility were discussed and managed in close consultation by a gynecologist with the goal to reduce the potential risk for secondary amenorrhea.

What can we learn from this patient?

When treating a capricious and aggressive case of MS, we often have to make decisions about when to consider the initial course of therapy to have been a failure. In this case, the immunotherapy did not have enough time to become effective before her second attack, but this could be considered more of an exceptional case, due to her aggressive presentation, rather than as a shortcoming of the treatment.

It's also important to note than when you are diagnosing MS in a child or adolescent, you are treating both the patient and the parents. They will want to be very involved with each step of the process and understand what their child is going through. Their support can prove invaluable to maintaining treatment compliance and improving the patient's quality of life. **PN**

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