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Practical Insights on Multiple Sclerosis

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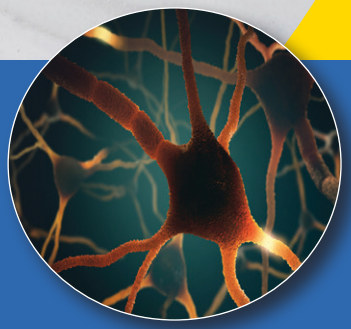

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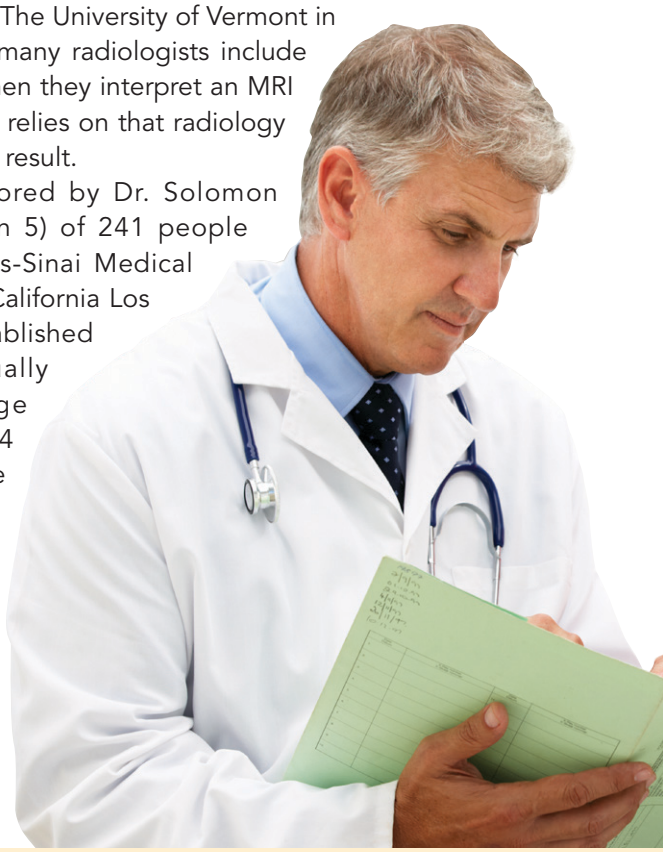
THE MISDIAGNOSIS OF MS

The diagnosis of multiple sclerosis (MS) can be difficult to make and is often delayed—in fact, people may have MS for several years before they receive a diagnosis. In recent years, too, it's been found that *misdiagnosis* of MS is a problem (where a person is labeled as having MS when he or she does not).

The reason for misdiagnosis? There is no single definitive test for MS. Clinicians rely on the details of a patient's symptoms and the results of a neurological examination, along with findings from magnetic resonance imaging (MRI) scans and blood work to make the diagnosis. Sometimes, too, they must test the spinal fluid to come to the conclusion that a patient has MS. But it's important to note that interpretation of the signs and symptoms suggestive of MS and of MRI and other test results requires a high degree of skill and experience, as well as understanding of the criteria for an MS diagnosis established by experts (known as the McDonald Criteria). It's not a 1 + 1 = 2 kind of situation, where a clinician can always pinpoint the diagnosis with a high degree of accuracy.

"Every person has their own unique version of MS, but the diagnostic criteria for the disease have been confirmed in large populations of people and are accurate if applied correctly," says Andrew J. Solomon, MD, Associate Professor of Neurological Sciences and Division Chief, Multiple Sclerosis, at Larner College of Medicine at The University of Vermont in Burlington. The catch is that many radiologists include MS as a possible diagnosis when they interpret an MRI scan, and if a neurologist only relies on that radiology report, a wrong diagnosis may result.

A recent study co-authored by Dr. Solomon found that almost 20% (1 in 5) of 241 people who were referred to Cedars-Sinai Medical Center and the University of California Los Angeles (UCLA) with an established diagnosis of MS were actually misdiagnosed. The average duration of misdiagnosis was 4 years, but some people were



Disclaimer: The goal of this publication is to provide patients with multiple sclerosis with the latest information about the disease and its treatment. The information provided in *MS Perspectives™* is not a substitute for the advice of your healthcare nurse or doctor. Please consult a qualified healthcare provider for individualized care and information.

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incorrectly labeled as having MS for up to 20 years, at an approximate cost of $10 million dollars to the healthcare system.

"Misdiagnosis is a common problem confronting the MS specialist," reports *MS Perspectives'* advisor Barbara J. Green, MD, of the MS Center for Innovations in Care at Missouri Baptist Hospital in St. Louis. "The medical literature, including the Cedars-Sinai-UCLA study, increasingly identifies wrong diagnosis in anywhere from 15% to 60% of patients who are referred for specialty MS care."

Diseases That Can Mimic MS

Part of the misdiagnosis problem rests with the fact that many diseases can mimic MS, reports Dr. Solomon. According to his research, patients who have been misdiagnosed often are experiencing:

- migraine headaches;
- functional neurologic disorders that affect the way the brain functions, but can't be related to a structural problem (damage to the nervous system) the way MS can;
- neuromyelitis optica spectrum disorder (NMOSD), a disease that affects the optic nerve in the eye and the spinal cord (see the next article in this issue for more on that topic); or
- peripheral neuropathy, a disease where there is damage to the nerves located outside of the brain and spinal cord.

Sometimes, clinicians may quickly land on an MS diagnosis before they go through all of the other disease states that might have similar signs and symptoms or MRI findings. "Alternatively, I have seen a number of patients where the MS diagnosis was missed because the MRI presentation appeared more like a tumor or a stroke than MS," says Dr. Green. These patients underwent biopsy and were found to have an active inflammatory lesion suggestive of MS rather than a tumor, sometimes with the unfortunate result that the unnecessary surgery has led to seizures or a lessening of their neurological functioning.

"I also find that misdiagnosis can be patient-generated, especially because of access to the Internet and 'Dr. Google,'" says Dr. Green. "The range of MS symptoms allows people with a variety of physical complaints to mistake their symptoms as typical of MS. For example, MS is associated with numbness and tingling, but so are radiculopathies (diseases where there is damage to the nerve roots just outside the spinal cord), and neuropathies such as carpal tunnel syndrome." Likewise, MS can cause severe pain of a variety of types, but so can joint diseases, muscle diseases, headache syndromes, glaucoma, and fibromyalgia. And several urological and gastrointestinal diseases may appear to be like the bladder or bowel problems that are typically seen in people with MS.

"We don't want to suggest that all patients who have been diagnosed with MS need to question their diagnosis," says Dr. Solomon. But if you suspect you don't have MS, it is always a good idea to seek a confirmation of your diagnosis from another clinician.

Sometimes, patients may demand a specific diagnosis for their symptoms, according to Dr. Green. They may jump on MS when a community clinician raises it as a possibility. Patients may actually welcome the MS label and assume it, even if they have not met the specific diagnostic requirements, and may seek confirmation from an MS expert. "Undoing the diagnosis in that setting can be particularly difficult for patients," Dr. Green says.

Pitfalls of Misdiagnosis

The biggest problem with misdiagnosis of MS is that people are exposed to disease-modifying therapies (DMTs), sometimes for years. In the Cedars-Sinai/UCLA study, 72% of the people who were misdiagnosed were prescribed unnecessary DMTs, and 28% were prescribed DMTs that put them at risk for developing the often fatal infection known as progressive multifocal leukoencephalopathy (PML).

"DMTs are effective in preventing disability in MS when used early in the disease

course, and clinicians may feel pressure to put patients who they think have MS on them quickly," says Dr. Solomon. "But they also have side effects and significant risks. In some patients where a diagnosis is uncertain, rather than starting DMTs, additional evaluation and monitoring even over a short period may be prudent to confirm a diagnosis."

Of course, too, if people are being treated for MS when they have another medical problem, they are not getting treatment for the correct diagnosis and they may be suffering. Dr. Green suggests that "there is also a significant psychosocial impact on patients who have been misdiagnosed and then had the diagnosis 'revoked.' This can lead to a loss of trust in medical professionals, upsets in their home and workplace, and issues with their self-image."

What to Do If You Suspect You've Been Misdiagnosed

"We don't want to suggest that all patients who have been diagnosed with MS need to question their diagnosis," says Dr. Solomon. But if you suspect you don't have MS, it is always a good idea to seek a confirmation of your diagnosis from another clinician. If you can find one, you should consider seeing an MS specialist (even if you're seeing an MS expert currently). "Good neurologists will not be upset if their patients seek a second opinion," he says. The practice of medicine is both an art and a science, and the diagnosis can be tricky. "At the very least, getting confirmation will give you peace of mind that you are on the right course of treatment," he concludes.

Your Family Health History:
A Clue to Your Own Health

Like most people, whether they have multiple sclerosis (MS) or not, you may have a high risk for other diseases—but you don't need fancy tests to identify these illnesses and perhaps prevent them. Instead, putting together a simple family health history to see what types of diseases are common among people in your family, from cancer to heart disease to diabetes, may provide answers. In fact, in a study conducted by the Cleveland Clinic, expensive genetic tests missed some obvious cases where the family health history was very strong for cancer.

"I view family health histories as 'back to the future'," says Charis Eng, MD, PhD, a cancer geneticist at the Cleveland Clinic and the study's author. "It's the best-kept secret in health care." Plus, it's an inexpensive way to assess your risk.

To get on top of your family health history, follow these steps:

- Use the Centers for Disease Control and Prevention's "My Family Health Portrait" tool to get started. It can be found at: https://phgkb.cdc.gov/FHH/html/index.html
- Sit down with your parents and ask them about their personal health, as well as that of their siblings, parents, and grandparents. You might want to do this more than once, since people tend to forget significant details the first time around.
- Be sure to fully document both sides of your family's health history. Many women may think only their mom's health counts, while men may focus on their dads, but both sides contribute to the risk for disease.

NEUROMYELITIS OPTICA SPECTRUM DISORDER
NOT JUST A FORM OF MS

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease that attacks the central nervous system, particularly the spinal cord and the nerves in the eyes (known as the optic nerves). It is believed to affect more than 15,000 people in the United States and over 100,000 people worldwide, and impacts more women than men (almost 3/4 of people with NMOSD are female). It typically starts between 40 and 50 years of age, but can affect younger and older people, too.

In the past, NMOSD was not easily distinguished from multiple sclerosis (MS) and was treated with MS-directed disease-modifying therapies (DMTs). However, it's now known that NMOSD is a different disease from MS and develops when the body, for unknown reasons, mounts an immune response that targets the aquaporin-4 water channel—a channel that is found mainly in the brain, and in higher concentrations in the optic nerves and spinal cord. The immune system begins to produce antibodies that lead to sudden attacks of severe inflammation where this water channel is located.

Understanding Antibodies

The body's immune system normally produces antibodies to fight off bacteria and viruses. But with an autoimmune disease like NMOSD or MS, the body gets confused and starts to attack itself. In the case of NMOSD, aquaporin-4 antibodies begin to inflame and destroy astrocyte cells, cells that support nerve function in the brain and spinal cord. This can lead to severe nerve injury and damage to myelin, the fatty coating around nerve fibers in the optic nerves and the spinal cord.

Despite the recognition that NMOSD is not a form of MS, research suggests that it is one of the top-5 conditions that are misdiagnosed as MS. (See the previous article for more information on misdiagnosis.)

"Twenty years ago, NMOSD wasn't on anybody's radar screen and there was a lot of debate as to whether it even really existed," Brian G. Weinshenker, MD, a leading NMOSD expert and neurologist at the Mayo Clinic in Rochester, MN, reported at the 2019 meeting of the Consortium of Multiple Sclerosis Centers (CMSC). "In fact, many neurologists who dealt with MS told me that they had never seen NMOSD in their practice. Clearly, that wasn't the case—it was more a matter of not having the criteria to recognize it."

Today the diagnostic criteria exist, according to Dr. Weinshenker, helped by the discovery of a very specific aquaporin-4 antibody marker that can be tested for in the blood. Seventy percent of people with NMOSD will test positive for these antibodies, compared with 0% of people with MS. This allows clinicians to make a confident diagnosis in patients with just a single symptom compatible with NMOSD as long as they have a positive aquaporin-4 antibody test result. Clinicians should, however, go through a full range of tests to ensure the diagnosis is correct, including taking a full medical history, doing a neurological examination, and performing magnetic resonance imaging (MRI) scans and a spinal tap, eye and vision exams, and other tests. Dr. Weinshenker adds that the diagnosis can still be made by these other evaluations in some patients who do not have aquaporin-4 antibodies in their blood.

NMOSD Symptoms

Common symptoms of NMOSD include numbness, tingling, weakness in the legs and difficulty walking, and visual changes like blurriness or loss of vision in one or both eyes—all common symptoms of MS. Symptoms tend to be more severe in NMOSD than in MS, however; for example, many patients lose the ability to walk during an attack of spinal cord inflammation. People with NMOSD may also experience unique symptoms, such as severe nausea, vomiting, and hiccups, or narcolepsy-like sleep attacks, symptoms that are almost never seen during MS attacks.

Most people also experience unpredictable relapses and remissions, with a build-up of neurological disability that develops as a result of the relapses. If left unchecked, NMOSD can lead to permanent paralysis, blindness, and even death.

NMOSD Treatments

While the cause of the disease is still unknown and it can't be cured, thanks to the ability to diagnose NMOSD accurately, Dr. Weinshenker says, "we can now intervene very early to stop the disease."

For a person who is having an attack of NMOSD, high-dose corticosteroids are typically given intravenously

(Continued on page 7)

Ask the Clinician

Is It a Real MS Relapse or Just a Pseudo-Relapse?

Q. What is the difference between a relapse and a pseudo-relapse?

Barbara J. Green, MD
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A. A pseudo-relapse is a term that is used to describe symptoms in a patient with multiple sclerosis (MS) that mimic a relapse but are due to some alternative explanation, such as:

- an infection or other illness,
- a menstrual period,
- medications,
- stress,
- fatigue, or
- exposure to hot weather or a hot tub.

The symptoms of a pseudo-relapse may be similar or even identical to those experienced during a previous relapse—for instance, blurred vision, tiredness, or walking difficulties. The episode differs from a true relapse, though, because the symptoms tend to go away quickly (within hours or days), whereas symptoms must last at least 24 hours and be separated from a previous attack by at least 30 days to be labeled a true relapse. In addition, the symptoms are not due to the development of new active lesions in the nervous system. Instead, they occur because a trigger is affecting your existing lesions and damaged nervous system and causing a temporary re-emergence of old symptoms.

Q. How can I tell symptoms of a pseudo-relapse from a relapse?

A. As Dr. Green says above, symptoms of a pseudo-relapse can be the same as, or very similar to, symptoms of a relapse. It's just the underlying cause and treatment that are different. That's why recognizing one from the other can be challenging—even for your MS provider. However, there are some symptoms that are more likely to be associated with a pseudo-relapse than a real relapse. In general, pseudo-relapses tend to affect the whole body instead of just one part. Symptoms can include a generalized feeling of weakness, tiredness, or increased pain or spasticity, changes in bladder or bowel function, and slowing of your cognitive (thinking and focusing) ability.

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Questions you can ask yourself to help identify a pseudo-relapse include:

1. Did my symptoms last continuously for at least 24 hours?
2. Do I have any symptoms of an infection, such as fever, chills, congestion, or changes in bladder or bowel function?
3. Have I become overheated or overtired in the past 24 hours?
4. Have I experienced an unusually stressful event in the past few days?
5. Have I started or stopped any medications over the past couple of days?
6. Have I been sleeping poorly lately?

Going through these questions will also help you communicate more clearly with your providers when you contact them to discuss the symptoms.

Q. Do pseudo-relapses need to be treated?

A. There are no long-term consequences related to MS that will occur because of a pseudo-relapse.

Because a pseudo-relapse isn't due to MS disease activity (a worsening MS lesion or the development of a new lesion) but rather to something that is affecting an existing lesion, removing the trigger for the symptoms typically resolves the problem. The trick is to find the cause of the symptoms and remove

that cause. So, for example, treating a urinary tract infection that is causing MS-like symptoms with antibiotics, correcting an imbalance of electrolytes (sodium, potassium, magnesium, etc.), or going indoors to an air-conditioned room on a very hot day may effectively stop a pseudo-relapse.

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We usually treat real relapses with corticosteroids to reduce inflammation in the body. But we don't want to treat pseudo-relapses with steroids, especially if they're caused by an infection; in that case, steroids could actually make the infection worse. We also don't want to subject your body to the potential long-term effects (loss of bone mass, weight gain, and the early development of cataracts, for instance) of repeated use of steroids unless absolutely necessary. We only want to prescribe steroids if the worsening of symptoms is due to a true worsening of the MS disease process.

Q. Do I need to tell my healthcare provider about a pseudo-relapse if my symptoms go away on their own?

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A. Absolutely. You should always report any MS-like symptoms to your clinician, even if you believe that they don't mean anything. Patients with MS need to be monitored and observed for true relapses—and there are instances where triggers for a pseudo-relapse, such as an infection, can lead to a true relapse. It's always better to tell your MS providers anything you notice so you can be reassured that you're not having breakthrough disease, your disease-modifying therapy isn't working, or that you have new damage (lesions that that can be seen on a magnetic resonance imaging scan). Recognition of a pseudo-relapse can also help you to avoid more pseudo-relapses by learning to recognize factors that can provoke these events. And there are cases where pseudo-relapses need to be treated, say with antibiotics for a urinary tract infection.

NMOSD (Continued from page 5)

to reduce inflammation in the body. If steroids don't work, plasma exchange (where the liquid part of blood is replaced with a plasma substitute) may be performed to reduce the amount of aquaporin-4 antibodies in the blood.

To lessen the risk of relapses, the Food and Drug Administration approved the drug eculizumab (brand name Soliris®) in June 2019—a significant step forward in fighting this devastating illness.

In a randomized clinical trial published in *The New England Journal of Medicine*, relapses were significantly reduced in people who received Soliris® versus a placebo every 2 weeks. Just 3 of 96 people (3%) on the active drug had relapses compared with 20 of 47 people who received a placebo (43%).

Soliris® is in a category of drugs known as monoclonal antibodies, and is given by an infusion over 35 minutes. The infusion is administered weekly for 5 weeks and then every 2 weeks after that. Patients must be monitored for at least 1 hour after receiving the infusion to make sure they don't have an allergic or other reaction to the drug, which can range from fever to hives to rare instances of drops in blood pressure and difficulty breathing. There is some risk of serious infections, including bacterial meningitis (an infection of the brain that can cause death). Other serious side effects are much less common, but can include kidney and blood cell disorders, and blood clots.

These potential complications, as well as the high cost of Soliris® (more than $500,000 a year), may appear daunting. However, the risk of NMOSD relapses and the accompanying progression of disability far outweigh the risk of taking the drug for most people with this rare disease.

Two other monoclonal antibodies, inebilizumab and sartalizumab, have been studied in large clinical trials with positive results as well. Rituximab (Rituxan®), an older antibody therapy, is not FDA-approved for NMOSD but has often been used to prevent attacks.

NMOSD Resources

Consult these sources for more information about NMOSD

- **Guthy-Jackson Charitable Foundation**
  https://guthyjacksonfoundation.org/
- **Mayo Clinic**
  https://www.mayoclinic.org/diseases-conditions/neuromyelitis-optica/symptoms-causes/syc-20375652
- **National Multiple Sclerosis Society**
  https://www.nationalmssociety.org/What-is-MS/Related-Conditions/Neuromyelitis-Optica-(NMO)

Support Programs for MS Disease-Modifying Therapies (DMTs)

Aubagio,® Genzyme Corporation:
www.aubagio.com, 855-MSONE2ONE (855-676-6326)

Avonex,® Biogen:
www.avonex.com/en_us/home/above-ms-program/join-biogen-support.html, 800-456-2255

Betaseron,® Bayer HealthCare:
https://www.betaseron.com/why-betaseron, 844-788-1470

Copaxone,® Teva Neuroscience:
http://copaxone.com/AboutSharedSolutions.aspx, 800-887-8100

Extavia,® Novartis:
www.extavia.com/info/PatientSupport/patient-support-program.jsp, 866-EXTAVIA (866-398-2842)

Gilenya,® Novartis:
www.gilenya.com, 800-GILENYA (800-445-3692)

Glatiramer Acetate Injection, Mylan:
www.glatirameracetate.com/en/patient-support, 844-695-2667

Glatopa,® Sandoz:
www.glatopa.com, 855-452-8672

Lemtrada,® Genzyme:
www.lemtrada.com, 855-MSONE2ONE (855-676-6326)

Mavenclad,® EMD Serono:
www.mslifelines.com, 877-447-3243

Mayzent,® Novartis:
www.mayzent.com, 877-MAYZENT (877-629-9368)

Ocrevus,® Genentech:
www.ocrevus.com, 844-OCREVUS (844-627-3887)

Plegridy,® Biogen:
www.plegridy.com, 800-456-2255

Rebif,® EMD Serono:
www.mslifelines.com, 877-447-3243

Tecfidera,® Biogen:
www.tecfidera.com, 800-456-2255

Tysabri,® Biogen:
www.tysabri.com/en_us/home/join-biogen-support/join-biogen-support.html, 800-456-2255

MS News, Support, and Self-Help Groups

Can Do Multiple Sclerosis
www.mscando.org

MS Views & News
http://www.msviews.org/msviewsandnews4

MS World
www.msworld.org

Multiple Sclerosis Association of America
http://mymsaa.org, 800-532-7667

Multiple Sclerosis International Federation
www.msif.org

Multiple Sclerosis Foundation
www.msfocus.org, 888-MSFOCUS (888-673-6287)

National Multiple Sclerosis Society
www.nationalmssociety.org, 800-344-4867

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