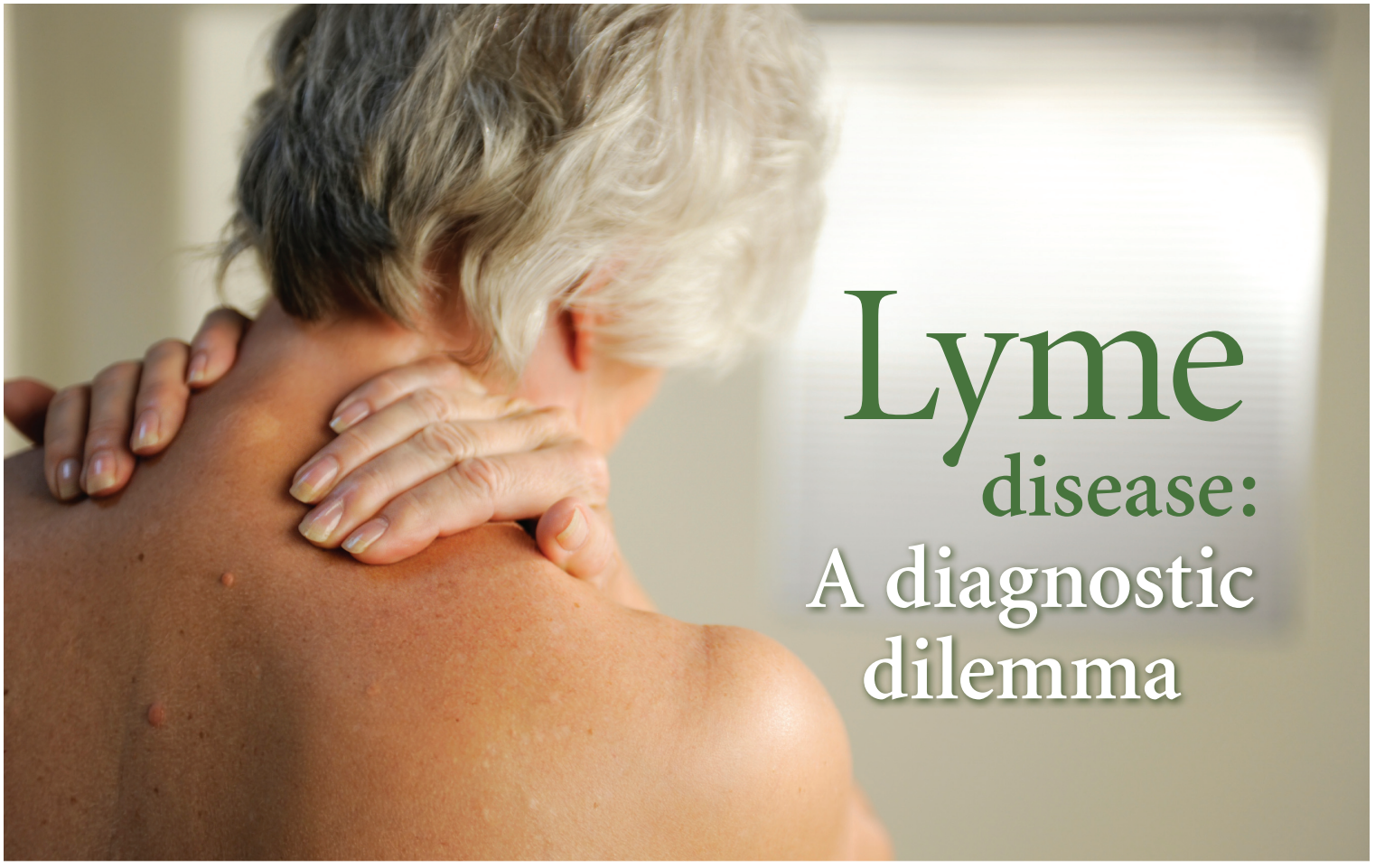

# Lyme disease: A diagnostic dilemma

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It is impossible to know the true prevalence of Lyme disease (LD), a bacterial illness transmitted through the bite of a tiny deer tick. Many cases go undiagnosed and the CDC admits that the disease is probably underreported by tenfold.[1] LD is caused by the bacterium *Borrelia burgdorferi* (*B. burgdorferi*), a genetically sophisticated spirochete with stealth pathology and numerous methods of immune system evasion. Like its close spirochetal cousin *Treponema pallidum* (the bacterium that causes syphilis), *B. burgdorferi* can cause disabling neurologic manifestations and present a puzzling diagnostic challenge. Because the disease is often missed in its early stages when treatment is most successful, years of needless morbidity and disability ensue for thousands of patients.[2] This article presents the diagnostic challenges inherent in the diagnosis of LD and provides information about when to suspect LD and how to test for it.

## Diagnosis of acute LD

The erythema migrans (EM) rash, commonly known as the "bull's-eye rash" due to its characteristic shape, is diagnostic of LD. If a patient presents with an EM rash, there is no need for serologic testing, per the CDC. The EM rash may appear at the site of the tick bite or elsewhere on the body; there may be one or there may be many.[1] However, if a patient presents with a history of a tick bite followed by symptoms of a headache, stiff neck, body ache, and low-grade fevers, LD should be highly suspect even in the absence of an EM rash.

## Missed diagnoses

There are numerous reasons why the diagnosis of early LD is missed, leading patients to progress to the much more serious and difficult-to-treat disseminated LD. Many healthcare practitioners mistakenly believe LD is not endemic to their state, causing them to omit the diagnosis from their differential or discount the patient's concerns in this regard. Unfortunately, practitioners may not realize that LD has been found in every state.[1] In states where *B. burgdorferi*-carrying ticks are not highly prevalent, the ticks may be carried in on the bodies of birds, pets, wild animals, or people. Furthermore, practitioners often do not obtain a thorough patient travel history that might raise suspicion to test for LD.

Even if the practitioner does ask about a tick bite, the patient may deny one. More than 50% of patients do not recall a tick bite because the tick that transmits LD is the size of a poppy seed and may not be seen in the hair or body folds.[2] Because the tick injects an anesthetizing substance before taking its blood meal, victims usually do not feel a biting or itching sensation that would alert them to a tick attachment.[3] Furthermore, the *B. burgdorferi* bacteria may

be transmitted by the bite of insects other than ticks. It is still unclear what other vectors there may be for LD. Thus, a practitioner should not depend on the patient's memory of a tick bite to suspect an LD diagnosis.

The EM rash of LD is present only about 50% of the time,[4] and if a practitioner is not aware of this fact, LD diagnosis may be incorrectly ruled out based on the absence of an EM. There are also different presentations of the rash, and many are not in the "bull's-eye" pattern. The rash can be oval or round, light pink or bright red, solid or with one or many concentric circles, with or without pustules, and range in size from 5 to over 250 cm. The EM is often misdiagnosed as cellulitis, a spider bite, or tinea corporis.[4]

The symptoms of early LD are nonspecific and can be easily misdiagnosed as a minor virus. Even when LD is suspected it is often ruled out based on the results of a Lyme ELISA (enzyme-linked immunosorbent assay), a screening test that is only 40% to 50% sensitive.[5] Without understanding the sensitivity of the tests, practitioners may mistakenly rule out an LD diagnosis when the ELISA is negative.

## Late, disseminated LD

If early LD is missed, the infection proceeds to disseminate throughout the body, into the brain, and deep into the joints and other tissues. The disease may either progress immediately or the spirochetes may convert into a dormant cystic form, allowing the bacteria to lie in waiting. At *any* time in the future—from months to decades—when the patient is under emotional or physical stress that weakens the immune system, the dormant cysts can burst open, releasing intact spirochetes to invade all areas of the body.[6,7] Patients are typically assumed to be suffering from a psychosomatic illness because the symptoms often begin following a life stress. Because of this timing, it is understandable why practitioners do not consider the possibility of a reactivated, indolent, bacterial infection. Because LD can remain latent in the body indefinitely, a positive history of a tick bite or EM at *any* time in the patient's history is an important diagnostic clue.

The symptoms of late, disseminated LD are many and varied. Because each body system can be affected, it is easy to see why the patient is assumed to be psychosomatic. Patients report having consulted specialists in rheumatology, cardiology, pulmonology, gastroenterology, psychiatry, neurology, endocrinology, otolaryngology, urology, and pain medicine in search of a diagnosis (see *Primary symptoms of LD*).

### Red flags

When a previously healthy individual suddenly develops panic attacks and anxiety, attention deficit or memory loss, severe insomnia, migraines, Bell palsy, tremors, or other puzzling neurologic symptoms, a disseminated LD diagnosis should always be included in the differential (see *Red flags for disseminated LD*).

### Common misdiagnoses

In some cases, LD patients have consulted numerous healthcare providers in quest of a diagnosis and may be labeled "doctor shoppers" or hypochondriacs. Undiagnosed LD patients are often known for their thick medical charts documenting many, seemingly unrelated diagnoses. These "diagnoses" are actually names of symptom complexes, and include fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, migraines, dysautonomia, plantar fasciitis, restless legs syndrome, gastrointestinal reflux, temporomandibular joint (TMJ) syndrome, and costochondritis[8,9] (see *Common misdiagnoses of LD*).

Some LD patients are misdiagnosed with serious, untreatable chronic conditions with no hope for recovery. When patients are assumed to have an autoimmune disease, they are even put on corticosteroids to suppress their immune system, an unfortunate outcome for a patient with a chronic infection. Per the author's experience, patients are often labeled "atypical" in their disease presentation, meaning that their disease process greatly resembles the given diagnosis but is missing some of the diagnostic features. Anyone with an atypical presentation of any of the diseases discussed below should be thoroughly evaluated to rule out the possibility of disseminated LD.

*Multiple Sclerosis (MS)*. The magnetic resonance imaging scans of patients with disseminated LD and patients with MS are indistinguishable, each revealing white plaques in the gray matter.[10] LD patients and MS patients share many symptoms in common including insomnia, anxiety, confusion, dizziness, weakness, numbness, balance problems, double vision, BP fluctuations, constipation, acid reflux, urinary urgency, and exhaustion. However, there are some important typical LD symptoms that are not typical of MS: joint pain, muscle aches, jaw and tooth pain, ringing in the ears, and a stiff neck. Some classic MS symptoms are missing in Lyme patients such as optic nerve inflammation, abnormal eye movements, spasticity, and muscle atrophy.

*Systemic lupus erythematosus (SLE)* is an autoimmune disease that can involve multiple organs and joints. Patients with disseminated LD often have positive antinuclear antibody tests with titers as high as 1:640.[11] For this reason, and because both SLE and LD share many nonspecific symptoms such as joint pain, muscle aches, and fatigue, practitioners are often tempted to presume an SLE diagnosis. These patients are labeled as "atypical" SLE by rheumatologists and usually don't respond to the immunosuppressive therapies

## Primary symptoms of LD[1,2]

**Musculoskeletal**
- Joint pain and stiffness
- Muscle pain and stiffness
- Loss of muscle tone
- Back and neck pain, stiffness
- Heel and foot pain
- TMJ

**Neurologic**
- Neuropathies
- Paresthesias
- Dizziness
- Cognitive disturbances
- Problems with concentration and short-term memory
- Hypersensitivity to touch, sound, light, and smell
- Tinnitus
- Drooping eyelid
- Transient blurred vision
- New-onset anxiety or panic attacks
- Clumsiness
- Depression
- Difficulty chewing or swallowing
- Hallucinations
- Headaches
- Involuntary jerking or muscle twitching
- Irritability
- Poor balance
- Sleep disturbances
- Speech difficulty
- Weakness of limbs

**Cardiac**
- Exhaustion
- Palpitations
- Shortness of breath
- Tachycardia
- Hypotension
- Hypertension
- Heart murmur
- Abnormal ECG
- Chest pain, tightness

**Endocrine**
- Low body temperature
- Sweats, chills
- Irregular menstrual cycle
- Loss of libido
- Worsening premenstrual syndrome
- Pelvic or testicular pain
- Milky breast discharge
- Hypertriglyceridemia
- Hashimoto thyroiditis
- Weight change (usually gain)

**Gastrointestinal and urinary**
- Abdominal pain and tenderness
- Bloating, gas
- Constipation
- Diarrhea
- Nausea
- Urinary frequency
- Constant thirst
- Irritable bladder
- Urine incontinence or retention
- Bowel incontinence or blockage

**Other**
- Easy bruising
- Hair loss
- Recurrent sinusitis
- Sore throats
- Tender glands
- Tooth pain
- Unusual rashes
- Shooting pains throughout body

indicated for the autoimmune disease. In addition, anti-DNA testing that is more specific for SLE is generally negative in Lyme patients.[11]

*Amyotrophic lateral sclerosis (ALS)* or *Lou Gehrig disease.* A few exceptional cases have been reported in which patients in wheelchairs who appeared to have terminal ALS were brought to full recovery by I.V. antibiotics following an LD diagnosis.[12,13] Any patient who has been diagnosed with ALS but has joint and muscle pain or severe cognitive issues should be highly suspect for disseminated LD as these symptoms are not common to ALS.

*Parkinson disease.* The following symptoms of Parkinson disease are also common to disseminated LD patients: tremors, difficulty with balance, slow movement, and muscle stiffness and aching. However, some classic Parkinson disease symptoms are NOT seen in Lyme patients including a shuffling gait, flat facies, and "pill rolling" in the fingers. There are no diagnostic lab tests or imaging studies to diagnose Parkinson disease: like LD, it is a diagnosis based upon a practitioner's clinical judgment. In a desire to find an answer for puzzling neurologic symptoms, practitioners can incorrectly presume a Parkinson diagnosis in patients with disseminated LD.

*Early-onset Alzheimer disease.* Because one of the most alarming symptoms of disseminated LD is sudden memory loss and confusion, middle-age patients have been diagnosed with early-onset Alzheimer disease when imaging studies are negative and the practitioner is at a loss for any other explanation. Several researchers have found that the *B. burgdorferi* bacteria may even have a role in the development of true Alzheimer disease as brain biopsies of Alzheimer patients are frequently positive for *B. burgdorferi* bacteria.[14,15] It is important to note that, unlike Alzheimer patients, LD patients are well aware of their cognitive decline and are frustrated and concerned about it.

*Autism spectrum disorder (ASD).* Children with disseminated LD may be labeled mildly autistic due to problems with language development and sensory integration disorder. Interestingly, an article by Bransfield et al suggests that *B. burgdorferi* may even have a causative role in the disorder in some children.[16] It is wise to thoroughly evaluate a child for disseminated LD when ASD is suspected.

## Testing for late disseminated LD

The CDC advocates a two-tier testing system for surveillance of LD in the general population. This system is modeled on diagnostic testing for HIV disease and utilizes an ELISA screening test followed by a confirmatory Western blot (WB). Unlike HIV diagnostic testing, however, the requirement for a positive result in the LD testing system is very restrictive in order to meet epidemiologic standards. For purposes of epidemiologic statistics the standard is to

err on the side of exclusion in order to assure homogeneity and uniformity of the disease population. Clearly, diagnosis and epidemiology are two different issues: it behooves the clinician to err on the side of inclusion, rather than exclusion, for diagnostic purposes so as not to miss a true case. Although the CDC advises practitioners that LD is a diagnosis that should be based upon clinical judgment rather than the result of lab testing, many practitioners who lack experience with LD incorrectly choose to use the CDC epidemiologic criteria for diagnostic purposes instead of making a diagnosis based upon clinical impression.[17]

Unfortunately, *B. burgdorferi* does not culture well in the lab, so it is necessary to test for the disease indirectly through the presence of antibodies. The standard two-tier protocol for LD testing is to initially screen with an ELISA test and follow with a WB only if the ELISA is positive. It is important for practitioners to be aware of the sensitivity and specificity of the tests they use. Due to *B. burgdorferi* strain variation and other factors (see following sections), the ELISA for LD has only about 50% sensitivity,[18] which would be considered unacceptable for HIV testing or any other disease state. In both acute and disseminated LD the WB test would more likely be positive than the ELISA. However, because of the standard two-tier testing protocol, which promotes the WB as a confirmatory test for a positive ELISA, the WB is often not used. Thus, the two-tier testing procedure is inadequate for diagnosis of LD because the ELISA is too insensitive and may miss as many as 50% of true cases.[18]

Whereas the ELISA is the quantitative test for antibodies, the WB is a qualitative test. The WB is a more sensitive test, although far from ideal. Interpretation of the blot is subjective and must therefore be read by a lab that is highly experienced in this area. *B. burgdorferi* antigens of various molecular weights are separated as distinct bands on the blot strips, and when a serum sample is washed over the strip, an antibody will adhere to its corresponding antigen causing that band to darken in direct relationship to the amount of antigen-antibody complexes formed. The interpretation of the WB test is subjective in that the technician must make a judgment call as to whether a band is negative, indeterminate, or positive based upon the darkness of the bands.

The author's clinical experience has shown that prescribing a 5-day course of metronidazole before a patient is tested can be helpful in two ways. First of all, metronidazole has been shown to open *B. burgdorferi*'s dormant cysts in vitro, releasing intact spirochetes.[6,7] The newly released spirochetes presumably prompt the immune system to produce antibodies against *B. burgdorferi*, thereby increasing the odds of a true positive test. Second, when LD patients take metronidazole, most will experience a Jarisch-Herxheimer ("Herx") reaction (intensification of symptoms) due to the immune system's recognition of new spirochetes and the resulting antibody response.[1] The "Herx" reaction is often described as feeling like a severe case of influenza. The presence of a "Herx" reaction is a clue in its own right that the patient may be harboring disseminated LD.

Neurologists would be surprised to discover that testing the cerebrospinal fluid (CSF) for *B. burgdorferi* antibodies is not the gold standard for neurologic LD that they assume it to be. In fact, studies have shown that in most cases of neurologic LD, *B. burgdorferi* is not isolated in the CSF.[19] Even for neurologic LD, the WB is still the best option available.

### Red flags for disseminated LD[1]

- Severe headaches of new type and intensity, with negative neurologic workup
- New onset of insomnia
- New onset of panic attacks or anxiety
- Joint pains with normal X-rays and negative rheumatologic workup
- A "flu" that never ends
- Unusual constellation of neurologic symptoms that a clinician has been unable to diagnose
- A neurologic illness such as MS or ALS that is labeled "atypical"
- Bell palsy (Lyme until proven otherwise)

### Common misdiagnoses of LD[1]

**LD is often misdiagnosed as:**
- Chronic fatigue syndrome
- Fibromyalgia
- Depression, anxiety, obsessive-compulsive disorder
- Somatization disorder
- SLE
- MS
- Parkinson disease
- ALS (Lou Gehrig disease)
- Early-onset Alzheimer disease
- Ménière disease
- Viral syndrome

**In children:**
- Failure to thrive
- ASD
- ADHD
- Learning disabilities

## Interpretation of the Western blot test results

Positivity on the WB is based on the presence of antibodies from certain predetermined bands. To properly interpret the WB, the practitioner should be aware of the specificity of each band. For example, if the reported test result is negative but there are bands present that are highly specific for *B. burgdorferi* bacteria, the practitioner should consider this

a significant finding pointing toward a positive diagnosis, especially when weighed with other factors such as history and symptoms.

There are nine *B. burgdorferi* genus-specific bands on the WB and the presence of any of these should raise high suspicion for LD. These bands are 18, 23, 31, 34, 37, 39, 83, and 93 kDa.[20] The CDC surveillance criteria for a positive immunoglobulin (Ig)-M include the presence of only two of these bands (23 and 39 kDa): the presence of any of the other seven bands is not regarded as significant. This approach to the blot interpretation is perplexing and illogical.[21]

Many practitioners, following the model of other bacterial infections, believe that if a positive Lyme IgM does not convert to a positive IgG by 6 to 8 weeks, there was never an LD infection to begin with. However, because the LD infection can remain active indefinitely, the IgM may remain elevated for months to years.[22] This has been one more complicated factor in the interpretation of the WB.

Another puzzling factor in the LD testing dilemma is that test results are counterintuitive and do not compare to what the patient and practitioner may be accustomed to seeing in other disease states. Practitioners may assume that the more positive the test, the sicker the patient and vice versa. Because LD testing screens for antibodies against *B. burgdorferi*, a stronger positive test is seen in patients with robust immune systems that are successfully attacking the bacterial foe. On the contrary, those who are sickest or who have had the disease for a very long time often test weakly positive or negative on WB tests due to "immune fatigue" or antibodies being tied up in immune complexes. The paucity of antibodies in the sickest patients is one of the reasons for negative results on the ELISA and WB tests for LD.[23]

## Other tests to assist in diagnosis

Two published works by Stricker and Winger[24,25] have suggested that a particular subset of natural killer (NK) cells is indirectly proportional to severity of disseminated LD. This subset of CD57+NK cells is below normal in those with severe disease and generally increases to the normal range with successful treatment. Therefore, a below-normal CD57+NK cell count can help the practitioner diagnose disseminated LD when the antibody test results are not clear.

Other published studies[26,27] have described an association between the C4a complement protein level and infection/inflammation. Generally speaking, the more severe a patient's infection, the more elevated the C4a level. When a patient has been diagnosed with LD, an elevated C4a level can indirectly give an indication of severity of disease and serve as a marker for purposes of following treatment progress. Unlike the CD57+NK cells, which are uniquely associated with disseminated LD, the C4a may be elevated in many inflammatory disease states. However, when LD has been diagnosed, it can be assumed that the C4a level is associated with that infection.

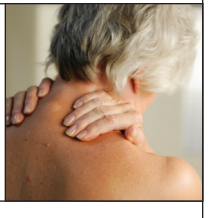
## Putting the puzzle together

The diagnosis of LD is complex and multifactorial and each factor should be considered a clue in the diagnostic puzzle. The diagnosis cannot be made without enough pieces of evidence to enable the big picture to emerge. It is not appropriate to rule out the disease based on a negative test and/or the lack of an EM or a known tick bite. As reviewed throughout this article, there are many other considerations in the diagnosis of disseminated LD.

The author has formulated a system to assist clinicians who may be new to the diagnosis of LD, especially the late disseminated form.[28] Because testing is unreliable, the following factors should be considered in cases in which the patient's LD tests are negative but other factors are suspicious. These eight factors are pieces to the diagnostic puzzle, and per the author's clinical experience, it can be assumed that if at least five factors are present, the patient is highly suspect for LD. The eight factors are:

1. History of a tick bite and/or EM at any time in the past
2. Positive history of tick exposure risk (highly endemic area, risky behaviors)
3. Bands specific to LD present on the patient's WB
4. History of a positive LD diagnosis at any time (may have been insufficiently or improperly treated)
5. Flulike symptoms when on antibiotics (Jarisch-Herxheimer reaction)
6. Typical LD symptoms, including exhaustion, joint and muscle pain, insomnia, stiff neck, cognitive decline
7. Below-normal CD57+NK cell count
8. Elevated C4a complement protein level.

***The diagnosis of LD is complex and multifactorial. Each factor should be considered a clue in the diagnostic puzzle.***



## Treatment

The treatment of LD is not within the scope of this article. It is a complex and controversial topic worthy of an entire book. There are two standards of care for the treatment of

both acute and disseminated LD espoused by the International Lyme and Associated Diseases Society (ILADS) and the Infectious Diseases Society of America (IDSA). More information is available on each organization's website: http://www.ilads.org and http://www.idsociety.org.

## Conclusion

Diagnosing either acute or disseminated LD can be a challenge for NPs. Due to inconsistencies in presentation and patient history, lack of practitioner knowledge and experience about the disease, and unsatisfactory testing methods, the diagnosis is often overlooked. When the diagnosis is missed, patients may suffer years of painful and debilitating symptoms as well as the stigma of an incorrect psychiatric diagnosis. NPs would do well to educate themselves about the problems with LD diagnosis so as not to overlook or misdiagnose this disabling disease.

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