Are You Aware of the Neurological Symptoms of Celiac Disease?

Celiac disease is associated with a wide variety of neurological disorders, even in its occult state. Here's why and how to make it part of your differential diagnosis.

By Meenakshi Gupta, MD, Mitchell Conn, MD and Gregg S. Gagliardi, MD

When patients present with ataxia or peripheral neuropathy, the differential diagnosis is long and complex. By contrast, in patients with epilepsy or headache the diagnostic work-up is typically straightforward. And yet, one possibility often overlooked in each of these cases is celiac disease. Neurologists need to both make room in their lengthy differentials during neuromuscular exams *and* stay alert during some seemingly routine work-ups for gastroenterologic symptoms that would give one pause—a pause sufficiently long enough to consider the possibility of celiac disease.

Celiac disease (CD) is a gluten-dependent autoimmune disorder that typically presents in adults with chronic diarrhea, bloating, weight loss, abdominal discomfort, steatorrhea and various types of malabsorption. But this constitutes only a small percentage of patients with gluten sensitivity. Many patients present with neurological manifestations even in the absence of an enteropathy.[1]

Table 1. Neurological Manifestations of Celiac Disease

- Peripheral neuropathy
- Epilepsy
- Cerebellar ataxia
- Headache
- Dementia
- Depression
- Myopathy
- Myelopathy
- Persistent fatigue
- Chronic progressive leukoencephalopathy

Because the spectrum of neurological manifestations associated with celiac disease (see Table 1) is wide, it is a challenge to physicians to recognize them as complications of prediagnosed CD or as initial presentations of CD.[2]

Several published papers have shown that the most common neurological disorders encountered with CD are peripheral neuropathy and ataxia. In a study of 215 patients with axonal neuropathy who were screened for gluten sensitivity, a possible etiology such as diabetes, vasculitis, paraneoplastic, or drug-related origin was established in only 75 patients, despite extensive investigations. Out of the remaining 140 patients, 47 (34 percent) were found to have a positive serology for gluten sensitivity. Of these, the symmetrical sensorimotor axonal neuropathy was the most common.[3] In another series, the evidence for peripheral neuropathy has been found in up to 49 percent of CD patients.[4] Thus, gluten sensitivity has been etiologically linked to a substantial number of idiopathic axonal neuropathies.

Gluten ataxia is one of the most frequent neurological syndromes that presents in the absence of gastrointestinal symptoms. The frequency of the condition in patients with ataxia of unknown origin ranges from 12 to 41 percent, whereas the frequency of biopsy-confirmed CD in patients with ataxia of unknown origin ranges from 12 to 15 percent,[5,6] Hadji-vassilou et al. reported positive antigliadin serology in 68 out of 224 patients who presented with sporadic ataxia.[7]

There are few case reports documenting other, less common neurological disorders such as myopathy, chronic progressive leukoencephalopathy and chronic headaches, but when should you suspect CD? Theoretically, there are several reasons for mass screening in CD but not enough evidence to support such a practice. Collin reports that screening asymptomatic individuals for celiac disease may even be harmful because a lifelong gluten-free diet is not easy to maintain, and the patients quality of life may deteriorate.[8] In contrast to screening, the best approach to diagnosing CD appears to be case identification especially in neuropathy, ataxia, migraine or epilepsy of idiopathic or cryptogenic cause.

Diagnostic Approach

The diagnostic approach to detecting CD has undergone important changes in recent years. The best screening tests for this disease are either serum IgA antiendomysial antibodies (EMA) or serum IgA anti-tissue transglutaminase (tTG). Both tests have extremely high sensitivity and specificity.

The American Gastroenterological Association recommends using IgA tTG for initial detection of possible CD.[9] Given the increased prevalence of IgA deficiency in patients with celiac disease, we propose to add IgA tTG to the work-up of all individuals with neurological disorders such as neuropathy, autoimmune diseases, ataxia, myopathy, recurrent migraines, refractory epilepsy, progressive encephalopathy, unexplained fatigue and encephalitis in the absence of positive routine diagnostic work-up or unbeneficial respective treatment. If serum IgA is low, serum IgG EMA and tTG can be obtained. Although used

Figure 1. The Neurologist's Algorithm for Celiac Disease Testing

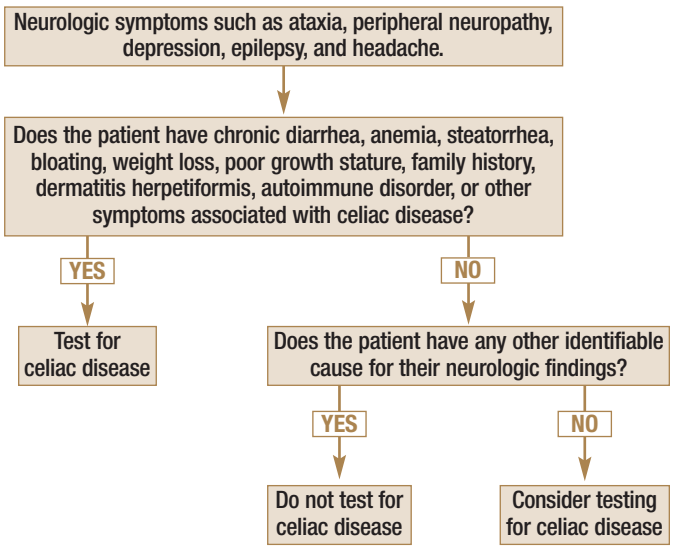

Table 2. Presentations of Celiac Disease

Common: diarrhea, weight loss, steatorrhea, bloating, anemia (especially iron deficiency), early-onset osteoporosis, nutritional deficiencies, excessive flatulence

Less Common: infertility, dermatitis herpetiformis, alopecia, abnormal liver tests, recurrent apthous ulceatios, neurologic manifestations (depression, ataxia peripheral neuropathy, seizure, migraine)

in the past, antigliadin antibodies are no longer the diagnostic test of choice. If these tests are positive, or if celiac disease is strongly suspected despite a negative serum test, the patient should be referred to a gastroenterologist for small bowel examination and biopsy.

Any patient with the above neurologic symptoms who also has a history of chronic diarrhea, malabsorption, weight loss, bloating, excessive bowel gas, family history of celiac disease, and skin rashes (*i.e.*, dermatitis herpetiformis), should undergo celiac testing. Furthermore, special attention should also be directed toward patients with unexplained iron deficiency, abnormal transaminases, diabetes mellitus, other autoimmune endocrinopathies, and IgA deficiency. Any of the above conditions in conjunction with neurologic findings would warrant a search for celiac disease. Harper et al. recently reported a case of a 30-year-old man with headaches, refractory seizures and MRI changes that emphasizes the importance of suspecting and screening for CD.[10]

Just as neurologists may be unaware of the GI symptoms that signify celiac disease, gastroenterologists need to be aware of the neurologic manifestations of CD. Management of patients with celiac disease can require careful coordination between the two specialties. Even for the most dedicated patients, maintaining a gluten-free diet can be extremely difficult. The development of neurologic symptoms in a patient with celiac disease may indicate disease progression and an issue with dietary compliance. Any patients with a known history of celiac disease should have a basic neurologic evaluation during all routine follow-up office visits. This should include an assessment for ataxia and evaluation for peripheral neuropathy.

The only treatment for patients with CD remains a gluten-free diet. Physicians should encourage patients with CD to contact a registered dietician.

Summary

Celiac disease is now felt to be more common than originally thought. As many as 1:133 people in the general population may have the disease. As a result, the diagnosis of celiac disease should be entertained in any patient who is undergoing a neurologic evaluation for unexplained symptoms such as ataxia, peripheral neuropathy, epilepsy, and headache. In order to determine which patients would best be served by celiac testing, a careful history should be obtained. A high index of suspicion is important in order to minimize diagnostic and therapeutic delay. **PN**

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