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Editorial

Neurologic manifestations of celiac disease

Proven, or just a gut feeling?

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Celiac disease (celiac sprue or gluten-sensitive enteropathy) is an inflammatory autoimmune disease of the small intestine that occurs in genetically susceptible (HLA $DQ2^+$ or $DQ8^+$) individuals upon exposure to dietary gluten.[1] Gluten (gliadin and glutenin, found in wheat, rye, and barley) comprises a family of proline- and glutamine-rich proteins. Celiac disease is common, affecting 0.5 to 1% of the Caucasian population, but incidence varies in different races. Classic symptoms, including chronic diarrhea and malabsorption, may occur in children or adults, but patients may be completely asymptomatic despite positive antibody and biopsy tests. Treatment with a strict, gluten-free diet results in cessation of gastrointestinal symptoms and normalization of antibody titers.

Immunopathogenesis of celiac disease. The strong HLA DQ2 or DQ8 haplotype association in celiac disease implicates a $CD4^+$ T-cell–mediated process because HLA DQ molecules present processed peptide antigens to $CD4^+$ T cells. $CD4^+$ T cells extracted from celiac disease-affected intestine respond to transglutaminase modified gluten peptides presented by HLA DQ2 or DQ8. Patients' peripheral blood T cells do not display such restriction. T cells in the gut are typically Th1 in phenotype, secreting large amounts of IFNγ. Both HLA-restricted $CD4^+$ T cells with $\alpha\beta$ T cell receptors and T cells bearing $\gamma\delta$ T cell receptors (presumably not HLA DQ–restricted) infiltrate the small intestine.[2]

While IgA and IgG anti-gliadin antibodies are found in the blood of celiac disease patients upon exposure to gluten-containing foods, they can be also found in many "normal" individuals (5–12%). Only a minority of gluten-sensitive patients (defined by presence of antigliadin antibodies) have classic celiac disease. This is distinct from autoantibodies to tissue transglutaminase (tTG), which are present in a high proportion of patients with active celiac disease (and rarely in "normal" individuals). tTG, an enzyme found naturally in gut endomysium, deamidates gluten peptides, rendering them negatively charged and able to stimulate T cells in the context of HLA DQ2 or DQ8.[1,2] Relevant gluten epitopes share abundant proline and (deamidated) glutamine residues. tTG activity is increased with local inflammation.

Neurologic manifestations of celiac disease. Many studies have presented proposed associations of celiac disease or gluten sensitivity with various neurologic syndromes. This possibility is intriguing because dietary intervention might then affect neurologic disease. This issue of *Neurology* includes four articles describing neurologic syndromes related to celiac disease or gluten sensitivity. The literature contains reports of several other neurologic syndromes that have been associated with gluten sensitivity. Interpretation of many of these studies is made difficult by nonstandardized antibody assays, referral bias, lack of blinding in treatment trials, the difficulty of maintaining a strict gluten-free diet for long periods of time, and the high prevalence of gluten sensitivity and undiagnosed celiac disease in the general population.

Ataxia? Hadjivassiliou et al.[3] have reported that gluten sensitivity presenting as ataxia may be a cause of sporadic idiopathic ataxia, so-called "gluten ataxia." They recently reported evidence of gluten sensitivity (presence of antigliadin antibodies) in patients with sporadic ataxia; 224 patients with ataxia, subdivided into idiopathic forms, hereditary forms, or multisystem atrophy (MSA), were compared with 1200 normal controls.[3] Antigliadin antibodies were

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detected in 41% in the idiopathic group, 14% of the hereditary ataxia group, 15% of the MSA group, and 12% of controls. A separate group of 44 sporadic–idiopathic ataxia patients from a London clinic had 32% prevalence of antigliadin antibodies. Almost half had evidence of axonal neuropathy in addition to ataxia.

Associations do not prove cause. Antigliadin antibodies may cause, exacerbate, result from, or be unrelated to neuronal degeneration. In support of a causal relationship, Hadjivassiliou et al.[4] showed that antigliadin antibodies and sera from most gluten ataxia patients, as well as one of five normal control serums, reacted with Purkinje cells. Other investigators[5] have not replicated this.

The prevalence of gluten sensitivity in hereditary ataxias has been reported to be as high as or higher than that in sporadic ataxias, suggesting that the relationship between gluten sensitivity and ataxia is complex, and not necessarily causative. In a large study in this issue, Abele et al.[6] prospectively assayed sera of 95 ataxia patients and 73 normal controls for IgG and IgA antibodies to gliadin. Ataxia patients included both idiopathic and hereditary forms. No significant differences between groups were observed, although a trend toward higher prevalence of antigliadin antibodies was noted for sporadic and autosomal dominant (AD) ataxias compared with normal controls and recessive ataxias.

Shill et al.[7] (also in this issue) examined 22 ataxia patients for antibodies to gangliosides and antigliadin antibodies. Patients were selected to include equal numbers of idiopathic and hereditary ataxias. Fourteen of the 22 had antiganglioside antibodies, and nine of the 14 were also gluten-sensitive (i.e., antigliadin antibodies–positive). Seven of 12 patients with hereditary ataxias, all three with MSA, and one of seven with idiopathic ataxia had antigliadin antibodies. No relationship, outside high prevalence, was noted between the presence of antiganglioside Abs and hereditary or acquired ataxia or gluten sensitivity. In an earlier report from the same group, 50 patients with ataxia were examined for gluten sensitivity. Gluten sensitivity was detected in 27% (7/26) of sporadic and 37% (9/24) of AD ataxia patients.[8] When tested, more than half of both groups were also $DQ2^+$ or $DQ8^+$.

Neuropathy? Gluten sensitivity has also been implicated as a cause of neuropathy. In this issue, Chin et al.[9] report screening 400 neuropathy patients for antigliadin antibodies and anti-tTG autoantibodies. Twenty (5%) displayed antibodies to gliadin or tTG, and subsequently had confirmation of celiac disease by duodenal biopsy. These were not a random sample of neuropathy patients; 14 of the 20 were already diagnosed as having celiac disease, nine of whom were referred specifically for evaluation of celiac-associated neuropathy. Six of the 400 patients (1.5%) presented with neuropathy and were subsequently found to have celiac disease. Nerve biopsies in three patients revealed axonopathy. Electrophysiologic findings were surprisingly mild or normal. The authors concluded that celiac disease was more prevalent in patients presenting to their neuropathy clinic than in the general population. Thirteen of the 20 celiac disease patients also had antibodies to gangliosides, suggesting that the neuropathy in celiac disease patients might be mediated by antiganglioside antibodies.

Malignancy? Celiac disease may be associated with malignancy. In this issue, Gobbi et al.[10] report a 56-year-old woman with CNS lymphoma and a remote history of celiac disease. Her gastrointestinal symptoms had resolved with a gluten-free diet, but antigliadin antibodies were mildly elevated, suggesting that her diet was not totally gluten-free. Biopsy/PCR revealed T-cell lymphoma (with T-cell γ chain rearrangements) in her brain, stomach, and duodenum. It was presumed that the malignant $CD8^+$ $\gamma\delta$ T-cell lymphoma began in the small intestine, perhaps secondary to $\gamma\delta$ T-cell proliferation seen in intestines of celiac disease patients. An association of celiac disease with cancer would not necessarily support an association of celiac disease with neurologic diseases, given the differences in pathogenesis.

Diagnosis and treatment of celiac disease as related to CNS/PNS diseases. What does one make of so many, varied neurologic syndromes in association with celiac disease and gluten sensitivity? Given its high prevalence, if one looks for gluten sensitivity in enough patients, one is guaranteed to find positive patients. Association of antibodies to gliadin with hereditary cerebellar ataxias gives pause. Convincing association of gluten sensitivity with a specific neurologic condition requires large patient and control sample sizes and well-defined, reproducible diagnostic tests.

Should a patient with hereditary ataxia, antigliadin antibodies and no gastrointestinal symptoms be on a gluten-free diet? Although gluten-sensitive enteropathy clearly improves with a gluten-free diet, it is not clear whether neurologic symptoms are prevented, stabilize, or improve. Most supportive literature consists of case reports. Yet, some patients have been reported to develop nervous system symptoms despite a strict gluten-free diet. For these reasons, we do not recommend routine screening for celiac disease for any given neurologic presentation.

To determine the true association of the various neurologic disorders and celiac disease/gluten sensitivity, a multinational registry is needed. Given the frequency of an asymptomatic phenotype, more aggressive screening is needed to determine the true prevalence. To determine whether gluten sensitivity (with or without celiac disease) is causally related to the various neurologic syndromes, a controlled, randomized trial of gluten-free diet with compli-

ance confirmed by reduction of antigliadin antibodies is needed (admittedly a challenging task). Such a study should focus on young patients early in the process, as treatment of established neurologic disease with dietary restriction may not reveal an effect. If dietary gluten elimination alters the course of disorders associated with celiac disease/gluten sensitivity, a causal relationship would seem probable.

Also needed are more studies on the pathology of CNS diseases associated with celiac disease. Postmortem studies of two ataxia patients with associated gluten sensitivity revealed perivascular cuffing by $CD4^+$ and $CD8^+$ T cells, as well as Purkinje cell loss. Most imaging studies have not suggested an inflammatory CNS process.

Animal models of celiac disease could be helpful, and progress is being made in this area.[11] Such models would allow blinded controlled trials of gluten-free diet for associated neurologic disorders.

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