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Neurologic Complications of Celiac Disease

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Abstract

Neurologic complications of celiac disease (CD) include ataxia and peripheral neuropathy, which can be the presenting symptoms and signs. Early diagnosis and intervention could prevent development of further neurologic and systemic complications. Questions remain regarding the prevalence of the neurologic complications, the pathophysiological mechanisms, and the effectiveness of therapy or response to a gluten-free diet.

Key Words: celiac disease, neuropathy, ataxia, gluten sensitivity, neurologic complications

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Celiac disease (CD) is an inflammatory small intestinal disease characterized by sensitivity to gluten, the storage proteins of wheat, and similar proteins found in barley and rye.[1] The immune reaction in CD occurs in the small intestinal epithelium and lamina propria. The mechanism of immunologic injury has been well characterized in the lamina propria.[2]

CD is a multigenetic disorder most strongly associated with the major histocompatibility complex alleles expressing HLA-DQ2 and DQ8 molecules.[3,4] To develop CD, HLA DQ2 or DQ8 and the ingestion of gluten are essential. Given the ubiquity of gluten-containing products in the Western diet and the fact that HLA DQ2 or DQ8 are present in up to 20% of the population, other genetic and environmental factors are suspected to play a role in the development of the disease. The reported incidence of CD has increased in both Europe[5] and the United States,[6] with improved ascertainment methods and increased awareness of the diverse clinical manifestations of the disease. In fact, CD is now recognized to be a very common condition with an incidence approaching 1% of the population.[4,7] This increased incidence has been accompanied by an increased awareness of the diverse clinical manifestations of the disease. A discussion of the basic science mechanisms underlying CD and their therapeutic implications is beyond the scope of this review and have been recently well described.[1]

The term "celiac disease" implies a disease characterized by an abnormal small intestinal biopsy with either clinical or histologic improvement following adherence to a gluten-free diet.[8] These patients may or may not have serologic evidence of the disease. The term "gluten sensitivity" has been used to describe 2 groups of patients: 1) those with gastrointestinal symptoms responsive to gluten withdrawal[9,10] and 2) those with positive antigliadin, antiendomysial, or antitransglutaminase antibodies.[11] The presence of HLA DQ2 or DQ8 has been used to suggest that "gluten sensitivity" is related to CD.[12]

Throughout this review, the terms CD and "gluten sensitivity" will not be used interchangeably. Use of the term CD will imply biopsy-proven cases, whereas "gluten sensitivity" will refer to patients with CD-associated antibodies who might not have undergone duodenal biopsy or whose biopsy results were not consistent with CD. Therefore, some patients with "gluten sensitivity" could in fact have CD if a biopsy (or repeat

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biopsy) were performed and showed the appropriate changes.

CLINICAL MANIFESTATIONS

The peak age of diagnosis of CD in adults is in the fourth to sixth decade,[13] but 20% of cases occur in patients who are older than 60 years of age.[14] Adults can present with extraintestinal manifestations, including iron-deficiency anemia, osteoporosis, infertility, elevated liver enzymes, and laboratory abnormalities secondary to deficiencies of folate or vitamins K and D.[15,16] Other associated inflammatory conditions include dermatitis herpetiformis, diabetes mellitus, autoimmune thyroiditis, and pericarditis.[15,17,18] There is an increased rate of the development of specific malignancies, including lymphomas.[19]

DIAGNOSIS

The diagnosis of CD has typically been based on the finding of CD-related antibodies (ie, elevated antigliadin [IgG and IgA], antiendomysial [IgA], or antitransglutaminase [IgA] antibodies) with confirmation by duodenal biopsy. Because of its superior sensitivity and specificity in comparison to antigliadin antibodies, the antiendomysial antibody (EMA) became the gold standard in serologic testing for CD. As a result of the complexity of this test and the discovery that tissue transglutaminase (tTG) is the primary autoantigen for EMA antibody, most commercial laboratories now test for anti-tTG antibodies by enzyme-linked immunosorbent assay using human recombinant or guinea pig tTG.[20]

The diagnostic value of serologic studies is limited by several factors, including false-positive or -negative values and variability in the sensitivity and specificity of commercially available assays. Antigliadin antibodies, particularly IgG antigliadin antibodies, could be positive in up to 12% of normal individuals[11] and are less specific than anti-tTG or antiendomysial antibodies.[21] In our experience, we have found a considerable number of patients with elevated IgA antigliadin and antitransglutaminase antibodies to have normal duodenal biopsies. There is also variability in the sensitivity and specificity of the commercially available assays for tTG.[22] Furthermore, IgA deficiency, which occurs more frequently in celiac disease, could yield false-negative results, so that quantitating immunoglobulin levels is useful in suspected patients.[1,15,23] Serologic studies could also be falsely negative in patients with CD, particularly those with mild enteropathy.[20,23,24]

Given the diagnostic limitations of these serologic studies, a small intestinal biopsy remains the gold standard against which the accuracy of antibody tests is compared. The classic small intestinal lesion in patients with untreated CD is characterized by villous atrophy. Crypt hyperplasia, increased intraepithelial lymphocytes, and the degree of villous atrophy can be determined by histologic examination of the biopsied lesions. The spectrum of findings can range from normal villous architecture with increased intraepithelial lymphocytosis to total villous atrophy in advanced cases.[25]

TREATMENT

A gluten-free diet has been the cornerstone of therapy for CD, and referral to a nutritionist specializing in CD is essential for proper education about which foods to avoid. Strict adherence to a gluten-free diet typically results in improvement of enteropathic symptoms, normalization of serologic markers,[26] and improvement of small intestinal mucosal abnormalities,[24] although *normalization* of histopathologic findings is not universal.[27]

NEUROLOGIC COMPLICATIONS

Background

Neurologic complications of CD were first described in the beginning of the last century. "Peripheral neuritis" in 2 patients with "sprue" was reported in 1908,[28] and

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ataxia and lower extremity anesthesia was reported in a patient in 1925.[29] In a landmark paper in 1966, Cooke and Smith described 16 patients with neurologic disorders associated with CD with 9 examined at autopsy. Ten patients had a severe, progressive neuropathy with prominent sensory ataxia and paresthesias in the legs.[30] Since then, there have been multiple reports of patients with biopsy-proven CD and neurologic dysfunction (Table 1). In a review of all such reports from 1964 to 2000, Hadjivassiliou et al. compiled 83 patients and found the most common neurologic manifestations to be ataxia and peripheral neuropathy, each occurring in 29 (35%) of the patients.[31] These percentages correlated with the percentages of ataxia or peripheral neuropathy occurring in their patients with "gluten sensitivity."

The incidence of neurologic complications in patients with CD has been estimated to be 6% to 10%.[32–34] Neurologic manifestations were noted in a higher percentage of patients (36%) with "probable gluten enteropathy" who did not necessarily have documented mucosal atrophy.[35] Neurologic complications, particularly peripheral neuropathy, however, can occur in as many as 23% of patients with CD who are well maintained on a gluten-free diet.[36]

Although there is a long history of reported neurologic complications associated with CD, the available literature consists primarily of case reports and relatively small, retrospective series, leaving unanswered many questions regarding the prevalence and diagnosis of these complications and their treatment or response to a gluten-free diet.

TABLE 1. Reported Neurologic Complications of Celiac Disease

Ataxia
Peripheral neuropathy
Epilepsy
Epilepsy and cerebral calcifications
Anxiety/depression
Headache
Dementia
Cerebral vasculitis
Encephalitis
Neuromyotonia
Inclusion body myositis
Polymyositis

ATAXIA

Ataxia is one of the more frequent neurologic syndromes associated with CD[12] and is often not suspected as a result of a lack of gastrointestinal symptoms or signs of malabsorption. The frequency of CD in patients with ataxia of unknown origin ranges from 12% to 15%,[37,38] whereas the frequency of "gluten ataxia" or "gluten sensitivity" and ataxia in patients with ataxia of unknown origin ranges from 12% to 41%.[12,37,39] One series, however, found no CD-associated antibodies in 32 patients with idiopathic cerebellar ataxia.[40]

The predominant clinical findings include progressive ataxia of gait, stance, and limbs sometimes accompanied by eye movement abnormalities, dysarthria, dysphonia, pyramidal signs, or memory deterioration.[12,33,39,41–45] Myoclonus can also occur in patients with CD and ataxia,[46] and some of these patients were reported to have antigliadin antibodies in the cerebrospinal fluid.[47] Of note, antiglutamic acid decarboxylase autoantibodies have been associated with cerebellar ataxia[48] and could also occur in CD-associated ataxia.[49]

CD-associated ataxia often lacks particular clinical features that would distinguish it from other forms of cerebellar ataxia.[38,50] Furthermore, there is some evidence suggesting a possible shared genetic origin between CD-associated ataxia and spinocerebellar degeneration.[51] In 1 series of 5 patients with CD and dementia, 2 of the patients were sisters who had cognitive dysfunction and a progressive spinocerebellar ataxia, presumed to be hereditary.[51] Antigliadin and antiganglioside antibodies have also been found to be prevalent in patients with hereditary cerebellar ataxia.[52,53]

Of 18 patients with ataxia and CD, cerebellar atrophy was detected by magnetic resonance imaging in 12 patients (66%), with

radiographic findings ranging in severity from vermian atrophy to frank atrophy of the vermis and bilateral hemispheres.[12,38,39] Postmortem findings included cerebellar atrophy, gliosis, Purkinje cell loss,[30] and degeneration of the posterior columns of the spinal cord.[12] An immune-mediated direct insult to the central nervous system was suggested by the finding of lymphocytic cerebellar infiltration[12] and anti-Purkinje cell antibodies,[54] although in another study, no autoantibodies were found.[55] In one patient with myoclonic ataxia and CD, there was selective symmetric cerebellar hemispheric atrophy, Purkinje cell loss, and cerebellar astrocytosis with cerebral and brainstem preservation.[46]

In early case reports of patients with biopsy-proven CD, the response to a gluten-free diet was mixed[33,45,46,56]; however, a more recent study of patients with "gluten ataxia" found improvement in the treatment group when compared with the control group after 1 year on a gluten-free diet.[57] Intravenous immunoglobulin treatment (IVIg) has also produced a marked improvement in some patients with either gluten ataxia[39] or CD.[48]

PERIPHERAL NEUROPATHY

Peripheral neuropathy is a common neurologic complication of CD[31] with the symptoms frequently antedating the diagnosis.[30,58,59] Although the incidence is not known, a recent study indicated that 23% of patients with CD who were well controlled by diet had peripheral neuropathy versus a 4% occurrence of neuropathy in the control group. Even patients with CD who did not have the neuropathy diagnosis demonstrated higher heat, pain, and touch thresholds when compared with control subjects, suggesting a subclinical neuropathy.[36]

At our tertiary referral center, we found celiac neuropathy (ie, peripheral neuropathy and biopsy-confirmed CD) in 2.5% of the patients evaluated for neuropathy. Furthermore, CD was found in 5% of patients with symptoms of neuropathy *and* normal electrodiagnostic studies, making CD an important diagnostic consideration in the evaluation of "small-fiber" or idiopathic sensory neuropathies.[59,60] The majority of the 20 patients with celiac neuropathy reported painful limb paresthesias, with the unusual feature of facial or oral paresthesias in 30%. Five patients (25%) reported mild gait instability. The predominant finding on examination was a sensory neuropathy with variable involvement of large and small fibers. Motor weakness was absent except in 2 patients in whom it was confined to the ankles. Seven patients (35%) had impaired balance noted with Romberg testing or tandem walking.

Other presentations of neuropathy and CD include a rapidly progressive syndrome similar to acute inflammatory demyelinating polyneuropathy.[30,61] A mononeuritis multiplex presentation has also been reported in patients with "gluten sensitivity"[58] and in patients with CD.[62] In the latter case, muscle biopsy revealed evidence of perivascular and perineural lymphocytic infiltration, and clinical motor deficits resolved with oral prednisone.[62]

Electrodiagnostic studies in the majority of patients with celiac neuropathy have been normal or only minimally abnormal.[59] A chronic, axonal neuropathy affecting both motor and sensory fibers has been the most frequently reported electrodiagnostic abnormality.[36,63] Demyelinating electrodiagnostic features have been reported in fewer cases.[61,64]

Sural nerve biopsies have revealed mild–severe chronic axonopathies without evidence of immune deposits.[59] Others studies have reported Wallerian degeneration,[63] inflammatory cell infiltrates in the spinal nerve roots,[64] and a "sparse lymphocytic infiltrate" in a patient with an axonal neuropathy and ataxia.[12]

In the series of 16 patients by Cooke and Smith, electron microscopy revealed gross disorganization of the internal structure of the terminal expansions of the axons and a variety of other unusual appearances, includ-

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ing possible phagocytosis of degenerating axoplasm by Schwann cells.[30]

The prominent pain, sensory loss, and often normal nerve conduction studies suggest that small-fiber involvement could be an early manifestation of celiac neuropathy. Preliminary skin biopsy studies at our center have revealed reduced intraepidermal nerve fiber densities in a number of patients.

Vitamin deficiencies have rarely been found to be a significant reason for peripheral neuropathy, and the response to a gluten-free diet has not been well characterized. Peripheral neuropathy has been reported to develop or worsen despite compliance with a gluten-free diet[30,36,59]; however, there are case reports describing patients who, following dietary indiscretion, had clinical deterioration and developed either an axonopathy[63] or demyelinating neuropathy,[61,64] which improved with resumption of the gluten-free diet.

The exact effect of a gluten-free diet remains to be determined in a systematic fashion.

Other reported neuromuscular manifestations of CD include case reports of acquired neuromyotonia, inclusion body myositis, and polymyositis.[58,65]

EPILEPSY

The incidence of epilepsy, mostly of the complex partial type, in patients with CD has been reported to range from 3.5% to 5.5%.[32,66] Because many cases of CD with absent, mild, or atypical features could go unrecognized, the prevalence could be higher. Approached from a different perspective, the prevalence of CD among patients with epilepsy has been estimated to be from 1:40 to 1:127, depending on the method of screening for CD.[67–70]

A peculiar syndrome of celiac disease, epilepsy, and cerebral calcifications has been described in the pediatric[71,72] and adult[73] populations. Several studies have examined this syndrome from different perspectives: 24 of 31 (77%) patients with epilepsy and cerebral calcifications were found to have CD; 5 of 12 (42%) patients with CD and epilepsy were found to have cerebral calcifications[74,75]; and 8 of 16 patients with bilateral occipital calcifications and epilepsy were found to have biopsy-proven CD.[76] The calcifications occur mainly in the parietooccipital region at the gray–white matter interface or in regions similar to the calcifications of Sturge-Weber syndrome.[77–79] There could be white matter hypodensities surrounding the calcifications, which resolve after adherence to a gluten-free diet,[80] although it is not clear whether the calcifications themselves resolve with diet.[81] Occipital lobectomy has been performed in cases of intractable epilepsy or severe intracranial hypertension with beneficial results.[82,83]

The etiology of syndrome is uncertain but has been related to reduced central nervous system folate levels secondary to folate malabsorption.[72,75,84] Patients with epilepsy and cerebral calcifications *without* histologic evidence of CD were noted to have the same HLA phenotype as those with CD, suggesting a genetic linkage between CD and this calcifying angiodysplasia.[75]

Seizure control has been reported to improve or stabilize with adherence to a gluten-free diet, particularly if initiated soon after the onset of epilepsy.[67,75–81,84]

The incidence of cerebral calcifications and epilepsy have also been observed to be less in patients with CD who are following a gluten-free diet versus those following an unrestricted diet.[85]

HEADACHE

Although the prevalence of migraine has not been found to be increased in patients with CD when compared with the general population,[32] there are reports of improved headache control[86,87] and improved single-photon emission computed tomography (SPECT) scan findings[88] following adherence to a gluten-free diet.

Bilateral occipital calcifications and CD have also been described in association with

migraine-like headaches, with a gluten-free diet having no influence on the headache.[89]

PSYCHIATRIC MANIFESTATIONS

An increased prevalence of depressive and anxiety symptoms has been described in patients with CD, particularly those with onset at an early age.[90–94] A dramatic resolution of depressive symptoms in response to a gluten-free diet has been reported in some patients.[94]

In 1 patient with a "schizophrenic disorder" and hypoperfusion of the left frontal lobe by SPECT scanning, adherence to a gluten-free diet was followed by resolution of the psychiatric and radiologic abnormalities.[95]

OTHER NEUROLOGIC DISORDERS

Isolated cases of dementia and CD have been described.[50,96] A single case of cerebral vasculitis and CD was reported in a 51-year-old man who developed seizures unresponsive to medical therapy. Brain biopsy revealed a mononuclear infiltrate in arterial vessels with no granulomatous changes, and prednisone and cyclophosphamide therapy resulted in clinical and radiographic improvement.[97]

Mostly asymptomatic white matter lesions have been described in 15 of 75 pediatric patients with CD who were following a gluten-free diet.[98] There are also case reports of progressive leukoencephalopathy[99,100] and an atypical subacute encephalitis[101] associated with CD.

CONCLUSION

As awareness increases of the heterogenous clinical presentation of CD, more patients who present with neurologic disorders will be found to also have CD. It is important for physicians to be familiar with the neurologic complications of CD, particularly ataxia and peripheral neuropathy, which occur in a substantial number of patients. Given that neurologic complications of CD often precede or occur in the absence of classic gastroenteropathic symptoms, an increased awareness and low threshold for testing populations with typical and atypical symptoms or conditions is warranted, because an early diagnosis and intervention could prevent further complications.[57]

Neurologic complications are also frequent in patients with "gluten sensitivity," ie, patients with elevated antigliadin, antiendomysial, or antitransglutaminase antibodies. The degree of overlap between this entity and CD has yet to be determined.

Currently, we recommend screening patients with idiopathic ataxia or peripheral neuropathy with serologic tests, including antigliadin (IgA and IgG), antitransglutaminase (IgA), or antiendomysial (IgA) antibodies, recognizing, however, that these tests could be negative if there is minimal bowel involvement or IgA deficiency. If these tests are abnormal (particularly the IgA antigliadin or antitransglutaminase antibody levels) or if there is a strong clinical suspicion of CD, referral to a gastroenterologist for a duodenal biopsy is warranted.

Nutritional deficiencies, if present, are easily correctible; however, these have rarely been found to be the cause of neurologic complications. Instead, immunologic mechanisms are suspected to be responsible for the neurologic disease. Patients with CD are known to be predisposed to developing other autoimmune diseases,[102–104] and perhaps even trace amounts of gluten might stimulate the immune system. Consistent with the proposed immune mechanisms are the findings of antiganglioside antibodies in celiac neuropathy,[59,105] anti-Purkinje cell antibodies in the ataxia of CD,[54] and a beneficial response of the ataxia to IVIg.[48]

For now, a gluten-free diet remains the cornerstone of therapy, although its ultimate effect on the neurologic complications remains unclear. Ataxia, seizures, and peripheral neuropathy with demyelinating features could be more responsive than the other complications.

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Given the frequent lack of adequate controls and the variety of definitions, inclusion criteria, and follow-up periods in the existing literature on neurologic complications of CD, there is clearly a need for prospective, long-term studies that use reliable, standardized measures.

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