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Review

Mechanisms underlying celiac disease and its neurologic manifestations

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Abstract. The extra-intestinal manifestations of celiac disease (CD), including ataxia and peripheral neuropathy, are increasingly being recognized as the presenting symptoms of this autoimmune disease. Although there is a greater understanding of the pathogenesis of the intestinal lesions in CD the mechanisms behind the neurologic manifestations of CD have not been elucidated. In this article, the authors review the cellular and molecular mechanisms behind the histopathologic changes in the intestine, discuss the presentation and characteristics of neurologic manifestations of CD, review the data on the mechanisms behind these manifestations, and discuss the diagnosis and treatment of CD. Molecular mimicry and intermolecular help may play a role in the development of neurologic complications.

Key words. Celiac disease; gluten sensitivity; ataxia; peripheral neuropathy; pathogenesis; neurologic complications; ganglioside antibodies.

Introduction

Celiac disease (CD) has also been termed gluten-sensitive enteropathy because the small intestine is the main target of injury; however, the clinical manifestations are extremely diverse, suggesting the disorder is in fact a multi-systemic disorder [1].

CD is a T-cell-mediated, autoimmune disorder characterized by a close linkage to specific human lymphocyte antigen (HLA) alleles (DQ2 and DQ8) and precipitation by an environmental factor, gluten, which is the term for the storage proteins of wheat. Although gliadin, the alcohol-soluble fraction of gluten, has been most studied, other gluten proteins are probably also toxic to people who have celiac disease. Similar proteins in barley (hordeins) and rye (secalins) are toxic as well [2]. These proteins induce the inflammatory process in the intestine, while withdrawal results in regression of the process [3]. CD is a multi-genetic disorder associated with HLA-DQ2 (DQA1*05/DQB1*02) or DQ8 (DQA1*0301/DQB1*0302). Studies in siblings that have demonstrated a sib recurrence risk of 10% [4] and studies of identical twins in which there is a 70% concordance rate [5] suggest that the contribution of HLA genes in CD is less than 50%. The non-HLA chromosomic region most consistently linked to CD is located on the long arm of chromosome 5 [6, 7].

Other environmental factors, apart from gluten, also appear important for the development of CD. Breast feeding and the timing of gluten introduction in the diet [8], viral infections that promote the secretion of interferon

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alpha [9] and smoking [10] are some of the factors that appear to influence the development of the disease.
Recently it has been recognized that CD is one of the most common diseases encountered by physicians, occurring in 0.5%–1% of the population [11–13].

Pathogenesis

CD is a T-cell-mediated chronic inflammatory bowel disorder with an autoimmune component [14]. Loss of tolerance to gluten is a potential cause. The reason this occurs is obscure; however, changes in intestinal permeability secondary to alterations in intercellular tight junctions or in the processing of gluten are potential mechanisms [14, 15].
The immune response to gliadin takes place in two compartments: the lamina propria and the epithelium. The mechanism of the pathogenesis of the disease has been well established for the small intestinal lamina propria but not as well for the epithelium [14, 16].

Lamina propria

Gluten is digested in the intestinal lumen, and degraded to gliadin peptides and amino acids. A 33-amino acid (33mer) residue of gluten is resistant to digestion by gastric and pancreatic enzymes [17]. This 33mer is an ideal substrate for the ubiquitous enzyme tissue transglutaminase (tTG), present in the lamina propria, that is considered important in the pathogenesis of the disease. Tissue transglutaminase is a calcium-dependent enzyme that can deamidate glutamine residues into negatively charged glutamic acid groups [18–20]. Deamidation of gliadin creates negative charges that allow binding of gliadin peptides to the DQ2 or DQ8 grooves that have positively charged binding pockets present on the surface of antigen-presenting cells. While the gliadin fractions of gluten of have been the most studied peptides in the pathogenesis of CD, homology between the toxic epitopes of gluten and secalin- or hordein-derived peptides from barley and rye also exhibit T cell cross-reactivity [2]. Intestinal CD4 T cells that recognize deamidated peptides presented by DQ2 and DQ8 produce interferon-γ, which in turn provokes inflammation and villous atrophy [14]. This model implies that gliadin, tissue transglutaminase, HLA DQ2 or DQ8 and T cells are all essential for the development of CD. There is also evidence that deamidation by tissue transglutaminase is not always necessary, as gliadin-specific T cell reactivity will occur against some specific native gliadin peptides, especially in children. These reactions may contribute to the initial immune response to gluten [21].

The epithelium

Pathologically, the development of intraepithelial lymphocytosis is an initial event in the disease. The intraepithelial lymphocytes (IELs) are predominantly CD8 T cells. Their presence was originally considered a phenomenon secondary to the CD4 T cell response in the lamina propria, because no gliadin restricted IEL could be identified. Marked IEL infiltrations, however, do not exist in other intestinal disorders associated with an inflammation of the lamina propria, such as Crohn's disease [16]. In addition, the significance of the IEL infiltration in CD is demonstrated by the major complications of the disease: refractory sprue and enteropathy-associated T cell lymphoma (EATL), which represents expansions of abnormal IEL.
The mechanisms responsible for IEL hyperplasia in CD are unclear; however, T-cell-mediated immune responses directed against damaged epithelial cells that express stress and interferon-γ-induced molecules (MIC and HLA E) have been suggested to be operative in CD [22, 23]. MIC and HLA E are recognized by the natural killer receptors NKG2D and CD94 present on IEL that are upregulated by interleukin (IL)15 [24–27]. A model that could account for the epithelial lesions is a dysregulation of this system of stress and damage recognition in the presence of high levels of IL-15 as found in CD. Upregulation of activating natural killer receptors by IL-15 [25] could lead to uncontrolled activation of IEL and villous atrophy [1, 28].

Manifestations of celiac disease

CD can present at any age in either gender, though women predominate with a ratio to men of 3:1. The classical presentation of CD is diarrhea with or without a malabsorption syndrome demonstrated by wasting, edema secondary to hypoalbuminemia, hypocalcemia, vitamin deficiency states and osteomalacia. This classical presentation encompasses most people who present with diarrhea. In the 1970s it became clear that presentation of celiac disease may be less dramatic. Deficiency of single nutrients such as iron, blood abnormalities secondary to hyposplenism and bone disease were documented to be frequent presentations [29–32]. The non-diarrheal presentations have lead to the use of the term 'silent celiac disease' [1]. Currently, less than half the patients diagnosed with CD present with diarrhea [33]. The predominant non-diarrheal presentations are listed in table 1.

Association with other autoimmune disorders

Autoimmune disorders occur 10 times more commonly in CD than in the general population. They include insulin-dependent diabetes [34], thyroid disease [35],

Table 1. Presentation of silent celiac disease

Children	short stature
	anemia
	neurologic symptoms
Adults	dermatitis herpetiformis
	anemia (iron, folate or B12 deficiency)
	reduced bone density
	apthous stomatitis, dental enamel defects
	infertility, recurrent miscarriage
	irritable bowel syndrome
	dyspepsia
	esophageal reflux
	neurologic symptoms
	autoimmune diseases

Table 2. Neurologic manifestations reportedly associated with CD or gluten sensitivity.

Peripheral neuropathy
Ataxia
Epilepsy
Epilepsy and cerebral calcifications
Anxiety/depression
Schizophreniform disorder
Dementia
Headache with white matter abnormalities
Cerebral vasculitis
Brainstem encephalitis
Progressive multifocal leukoencephalopathy
Progressive myoclonic encephalopathy
Huntington's disease
Myoclonus
Chorea
Neuromyotonia
Stiff-man syndrome
Inclusion body myositis
Polymyositis

Sjögren's syndrome [36], Addison's disease [37], autoimmune liver disease [38], cardiomyopathy [39] and neurological disorders. When both occur in a patient, the CD is frequently silent, and patients are initially diagnosed with the autoimmune disease.

The association of autoimmune disorders and CD is considered to be due to a shared genetic tendency (HLA alleles) and due to the presence of CD itself. There are several lines of evidence supporting the role of CD as an etiologic factor for autoimmune diseases. In a large, multi-center cooperative Italian study, the prevalence of autoimmune diseases was closely related to duration of gluten exposure with children diagnosed and treated at less than 2 years of age having no increased prevalence of autoimmune diseases [40], though this was not confirmed in a different Italian study [41]. In addition, patients with celiac disease at diagnosis have a higher rate of autoantibodies compared to those on a gluten-free diet [42], and in children with CD, diabetes-related and thyroid-related serum antibodies were noted to disappear on a gluten-free diet [43]. Several autoimmune diseases may improve on a gluten-free diet, including neurologic [44], cardiac [45] and renal diseases [46].

Neurologic manifestations of CD

Neurologic manifestations of CD have been described for nearly 100 years and are estimated to occur in 6–10% of patients with CD. Ataxia and peripheral neuropathy are the most frequently described manifestations [47]; however, numerous other manifestations have been described, particularly over the last decade, to be associated with CD or gluten sensitivity (see table 2). CD implies a disease process characterized by an abnormal duodenal biopsy with either clinical or histologic improvement following adherence to a gluten-free diet. 'Gluten sensitivity', however, describes both patients with gastrointestinal symptoms that are responsive to gluten withdrawal and patients with abnormally elevated antigliadin antibodies. As the degree of overlap between these two entities has yet to be determined, the distinctions between these two definitions should be recognized when reviewing the literature.

Ataxia

Ataxia has been frequently associated with CD and may present with a lack of gastrointestinal symptoms. The frequency of CD in patients with ataxia of unknown origin ranges from 12 to 15%, whereas, the frequency of 'gluten ataxia' or 'gluten sensitivity' in patients with ataxia of unknown origin ranges from 12 to 41% [47, 48]. The clinical presentation may be indistinguishable from other forms of cerebellar ataxia, with the main features including progressive unsteadiness of gait, stance and limbs. Myoclonus can also occur in patients with CD and ataxia. Antigliadin and antiganglioside antibodies have also been found to be prevalent in patients with hereditary cerebellar ataxia, suggesting that there may be a possible shared genetic origin between CD-associated ataxia and spinocerebellar degeneration [49].

Cerebellar atrophy may be detected by MRI in patients with gluten ataxia [50], and post-mortem findings have included atrophy, gliosis, Purkinje cell loss and degeneration of the posterior columns of the spinal cord in CD-associated ataxia [51]. Some studies of gluten ataxia have suggest an immune-mediated attack of the central nervous system as evidenced by the presence of lymphocytic cerebellar infiltation [50] and anti-Purkinje cell antibodies [52], although this has not been confirmed by others [53].

Peripheral neuropathy

Although the exact incidence of celiac neuropathy (i.e. peripheral neuropathy with biopsy-proven CD) is unknown, a recent study reported that 23% of patients with CD, well controlled by diet, had peripheral neuropathy versus a 4% occurrence rate in the control group [54]. At our tertiary care referral center, celiac neuropathy was found in 2.5% of the patients evaluated for neuropathy [55].

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. In our series of 20 patients, the common complaints included painful paresthesias in the limbs and occasionally in the face. Variable sensory loss of both large and small diameter sensory fibers was noted on physical examination. Motor weakness was rare and confined to the ankles. Gait instability was reported in 25% of the patients [55].

In addition to peripheral neuropathic signs and symptoms, patients have also been reported to have ataxia, or autonomic features, dysarthria or myoclonus [51]. Mononeuropathy multiplex is another peripheral neuropathy presentation that has been reported in a patient with CD [56].

Electrodiagnostic studies in patients with a predominantly sensory neuropathy have been normal, minimally abnormal [55] or have typically revealed only axonal changes [48]. Demyelinating changes have been rarely reported [57, 58].

Sural nerve biopsy studies have typically revealed axonal changes of wide-ranging severity without inflammatory deposits [55]. Demyelinating features have been detected in a patient with CD and a rapidly progressive neuromyopathy [58]. Quantitation of epidermal nerve fiber (ENF) density in skin biopsies is a useful method for confirming the diagnosis of small fiber neuropathy. Skin biopsies obtained from eight patients with celiac disease, neuropathic symptoms and normal electrodiagnostic studies revealed a decreased ENF density (i.e. below the 5th percentile) in five patients. The remaining three patients had morphologic changes and ENF densities in the low normal range [59].

Epilepsy

A chance association between CD and epilepsy may be possible as the prevalence of CD among epileptic patients has been reported to range from 1:40 to 1:127, depending on the screening method. Nevertheless, seizure control has been reported to improve or stabilize with adherence to a gluten-free diet, particularly if initiated shortly after the onset of epilepsy [47].

A unique syndrome of CD, epilepsy and cerebral calcifications has been described in both pediatric and adult populations. The calcifications occur mainly in the parieto-occipital region at the gray-white matter interface or in regions similar to the calcifications of Sturge-Weber syndrome. 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 [60].

Other neurologic manifestations

There are reports of patients with headaches and gluten sensitivity or celiac disease whose headaches improve following adherence to a gluten-free diet [61, 62]. Untreated patients with CD have been reported to have an increased incidence of mood disorders (such as anxiety or depression), which may respond to a gluten-free diet [63]. There have been case reports or small series describing other neuromuscular manifestations (e.g. inclusion body myositis, polymyositis, neuromyotonia [64]), movement disorders (e.g. Huntington's disease [65], chorea [66]) or cerebral abnormalities (e.g. cerebral vasculitis [67], progressive leukoencephalopathy [68]) to be associated with CD or gluten sensitivity. Screening for CD has been recommended in individuals with Down's syndrome as the frequency of CD could be as high as 4.6–7% [69].

Pathogenesis of neurologic manifestations of CD

While advances have been made in understanding the pathogenesis of the intestinal lesions in CD, the pathogenesis of the neurologic manifestations has yet to be elucidated. Current data point to molecular mimicry and intermolecular help as two possible mechanisms that could explain how ingested gluten can result in damage to the neuraxis.

Anti-ganglioside antibodies in celiac neuropathy

Several polyneuropathies are associated with elevated levels of antibodies to ganglioside molecules of the peripheral nerves. Antibodies against GM1 and GD1a gangliosides, for example, are often encountered in the motor axonal subtype of Guillain-Barré syndrome (GBS), while antibodies to GQ1b are closely associated with the Miller Fisher subtype of GBS [70]. Likewise, among chronic neuropathies, there is a high incidence of anti-GM1 antibodies in patients with multifocal motor neuropathy [71]. Serum anti-ganglioside antibody analysis has therefore proven useful as an aid in diagnosis and

follow-up of autoimmune neuropathic conditions. In celiac neuropathy, as many as 65% of studied patients were found to have raised antibody titers against one or more gangliosides [55, 72]. Such association seems to implicate an immune-driven mechanism in the pathogenesis of celiac neuropathy.

The immune process behind the rise in anti-ganglioside antibody activity in celiac neuropathy is unknown, but it could be related to other immune-mediated or inflammatory mechanisms, which have been described in celiac disease and in autoimmune neuropathies.

Anti-ganglioside antibodies might arise through antigen molecular mimicry and antibody cross-reactivity with foreign glycolipids or glycoproteins. In GBS, for example, IgG anti-ganglioside antibodies appear to be induced by infection with bacteria such as *Campylobacter jejuni* or *Haemophilus influenza*. These bacteria bear lipopolysaccharide (LPS) molecules that cross-react with gangliosides [73–75]. In these cases, the antibody specificities have been shown to correspond to the structure of the cross-reactive LPS oligosaccharides [76, 77], and production of anti-ganglioside antibodies with the same specificities has been induced by immunization of animals with the LPS species [78].

In CD, a mouse monoclonal immunoglobulin (Ig) G anti-gliadin antibody has been shown to cross-react with human cerebellar tissue, possibly indicating its involvement in CD ataxia, although the target antigen has not yet been characterized [52]. Such cross-reactivity is suggestive of the presence of common epitopes shared by gliadin and nerve components. Elsewhere, some gluten species have been shown to be glycosylated [79], possibly containing epitopes that mimic ganglioside carbohydrates, with the potential to generate antibody cross-reactivity. Although these studies are the subject of intense debate, they provide a basis for more in-depth characterization of the various gliadin proteins as a possible source of cross-reactive epitopes and investigation of their possible role in occurrence of anti-ganglioside immune reactivity in celiac neuropathy.

Another possible mechanism for inciting the antibody response against gangliosides is through neo-epitope formation and intermolecular help. Molecular modification that leads to formation of new epitopes plays an important role in CD pathogenesis. As stated earlier, enzymatic deamidation of gliadin molecules by tTG significantly enhances their stimulatory effect on T cells by creating acidic residues, which have higher affinity for DQ2 and DQ8 molecules [19, 20, 80]. The observed elevation of tTG levels in CD is also likely to increase its transamidating activity [81, 82]. Gliadin, an excellent substrate for tTG, can become cross-linked to molecules with glutamine acceptor groups, including tTG itself. It has been hypothesized that the gliadin-tTG complex can result in an immune response against tTG through the proposed process of intermolecular help, where tTG-specific B cells internalize the complex and present the gliadin portion to gliadin-sensitized T cells [83]. The same mechanism may be responsible for the immune response against gangliosides if tTG can catalyze the cross-linking reaction of gangliosides (or other molecules with ganglioside-like epitopes) with glutamine residues of gliadin, or if gliadin can form a non-covalent complex with ganglioside species in the gut mucosa. The ensuing gliadin-reactive T cell help could activate the ganglioside-specific B cells and generate anti-ganglioside antibodies in the absence of ganglioside-specific T cells.

The specific role of anti-ganglioside antibodies in celiac neuropathy, if any, is not yet known. There is, however, some indirect evidence of a pathogenic involvement of these antibodies in autoimmune neuropathies. Passive transfer of anti-ganglioside antibodies has been shown to result in myelin and axonal degeneration [84] and conduction block in animals [85, 86]. Binding of anti-ganglioside antibodies to the nodes of Ranvier and paranodal myelin of peripheral nerve has been demonstrated by several investigators [87, 88] and has been postulated to cause demyelination and conduction block after activating antibody- and complement-dependent lymphocytes. Correlation of clinical improvement with decreasing antibody titer in response to plasmapheresis [89] appears to lend further support for a pathogenic note.

Diagnosis of CD

The diagnosis of CD has traditionally depended on the presence of an abnormal small intestinal biopsy, obtained via upper gastrointestinal endoscopy, together with an improvement on a gluten-free diet [90]. Histopathologic features include an intraepithelial lymphocytosis, crypt hypertrophy, villous atrophy, abnormal epithelial cells and increased chronic inflammatory cells in the lamina propria.

Serologic testing has made the ability to screen for CD, available to all physicians. It can be employed for one of three purposes: (i) triaging patients for biopsy, (ii) following patients on a gluten-free diet or (iii) screening patients at risk for developing CD.

Of the commercially available serologic tests that aid in the diagnosis of CD, no one test is ideal. The use of multiple serologic tests increases the diagnostic yield. These include anti-endomysial antibodies (EMAs), IgA; anti-tTG antibodies, IgA; anti-gliadin antibodies (AGAs), both IgA and IgG; and a total IgA level. The EMAs and anti-tTGs are auto-antibodies, while the AGAs are antibodies to a food component.

The EMA and anti-tTG antibodies are highly sensitive for celiac disease [91], though sensitivities depend on the

degree of villous atrophy [92, 93]. The EMA test is an immunofluorescence assay requiring either monkey esophagus or human umbilical cord as the substrate. As a result the test is relatively expensive and labor intensive. The discovery that tTG was the main autoantigen for the EMA enzyme-linked immunosorbent assay (ELISA) [18] prompted the development of testing for tTGs. Anti-tTG antibodies are less specific, however, and have been reported to be positive in the presence of liver disease, diabetes and severe heart failure [94–96].

Tests for antibodies to gliadin were the first serologic studies available, and they remain in use as moderately sensitive, but relatively nonspecific, markers of CD. These antibodies may be present in inflammatory bowel disease [97], collagen vascular disease [98] and in many healthy people [99]. However, combining AGAs, with other serologic tests increases the sensitivity of the serologic tests [100], thus increasing the overall detection rate of CD.

Patients suspected of having CD should also be screened for selective IgA deficiency, since this occurs 10–15 times more commonly among people with CD compared to the general population [101]. Quantitative immunoglobulin studies in these patients will reveal an absent total IgA level; therefore, to detect CD, they should be tested for both IgG and IgA antibodies to endomysium, tTG or gliadin.

Both the anti-tTG and the EMA titers correlate with the severity of villous atrophy [93, 102]. As a result, in the presence of partial villous atrophy either antibody may be negative.

Because of the high specificity of EMAs for CD, some may consider a biopsy unnecessary for confirmation of the diagnosis in the presence of a positive EMA level. A biopsy, however, is considered to be more definitive than serologic resting for a diagnosis that requires lifelong treatment with a rigorous diet. A biopsy also provides a baseline for subsequent biopsies in the event that the patient does not respond to the diet.

Therapy of CD

The treatment for CD is a lifelong, gluten-free diet. This involves adoption of a diet free of wheat, barley and rye [1]. The diet is especially difficult to follow, since wheat flour is added to many processed foods and is universally used during food preparation in the food industry. Furthermore, inadequate food labeling for gluten is a problem in the United States. Patients should see an experienced dietician; however, within the United States most obtain most of their information from support groups. Substitute gluten-free grains are available, including corn, rice, teff and millet.

Oats are generally regarded as safe for most patients with CD and dermatitis herpetiformis [103, 104] because they lack the required toxic amino acid sequences, though there are issues with contamination with other grains. A few patients with celiac disease do mount an immune response to the oats and develop villous atrophy [105]. Patients who are stable on a gluten-free diet and who use oats as part of their gluten-free diet should be monitored for intolerance to them.

There are limited data to suggest that ataxia associated with gluten sensitivity responds to a gluten-free diet [44]. Peripheral neuropathy has been reported to develop or worsen despite compliance with a gluten-free diet [51, 54, 55]; however, there are case reports describing patients who, following dietary indiscretion, had clinical deterioration and developed either an axonopathy [106] or demyelinating neuropathy [57], which improved with resumption of the gluten-free diet. The exact effect of a gluten-free diet on the neurologic manifestations of CD remains to be determined in a systematic fashion.

Conclusion

Neurologic manifestations, such as ataxia and peripheral neuropathy, are increasingly recognized to be the presenting features of CD. Although strides have been made in understanding the pathogenesis of the gastrointestinal manifestations of CD, the mechanisms behind the neurologic manifestations remain to be elucidated.

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