

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 chromosomal 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 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 led 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],