

Extraintestinal Manifestations of Celiac Disease

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Celiac disease is an autoimmune disorder that occurs in genetically predisposed individuals as the result of an immune response to gluten. It is present in approximately 1% of the population. Diarrhea has become a less common mode of presentation (<50% of cases) than it once was. Other presentations include iron-deficiency anemia, osteoporosis, dermatitis herpetiforme, and neurologic disorders, mainly peripheral neuropathy and ataxia. Arthritis is commonly found in patients with celiac disease when systematically sought. Overall, autoimmune diseases occur more frequently (three to ten times more) in those with celiac disease than in the general population. A gluten-free diet is the standard of treatment, although its effect on some of the extraintestinal manifestations remains to be determined.

Introduction

Celiac disease is a gluten-sensitive enteropathy that occurs in genetically predisposed individuals and responds to the withdrawal of gluten from the diet. Once considered a rare childhood disorder, celiac disease is now known to be a common condition that may have multiple complications. Nevertheless, the disease remains widely under-recognized. Use of new serologic markers in the diagnosis of celiac disease, in particular the antitransglutaminase antibody, has resulted in more efficient screening.

The development of celiac disease requires the histocompatibility molecules DQ2 and DQ8 as essential genetic factors, with the majority of patients carrying DQ2 alleles (DQA1*05/ DQB1*02). In the remaining patients an association with DQ8 (DQA1*0301/ DQB1*0302) is found. These histocompatibility locus antigen (HLA) genes occur in up to 40% of the white population [1••]. They are con-

sidered to confer only 40% of the genetic risk to develop celiac disease; the rest is attributable to non-HLA genes that have not been definitively identified. Overall, 10% of first-degree relatives of patients with celiac disease also have celiac disease. This number increases to 20% if there are affected sibling pairs in the family.

Epidemiology

Screening studies have revealed that celiac disease is very common, occurring in approximately 1% of the general population. This figure is based on studies of many populations internationally, such as the United Kingdom and the United States [2,3••]. Celiac disease occurs in all countries and regions populated by individuals of European origin (ie, Europe, Australasia, South Africa, Caribbean Islands, and South America) and in North Africa, the Middle East, and South Asia. The disease is considered to be underdiagnosed. As a result, symptoms may have a long duration before the diagnosis is established [4•].

Pathogenesis

Patients with celiac disease develop an immunologic reaction to toxic epitopes of the gliadin molecule; one fragment of the molecule, a 33-amino acid peptide, is resistant to digestion. These toxic fragments probably enter the mucosa during infections or result from an alteration in gut permeability. The immune reaction in the lamina propria is triggered when gliadin is deamidated by tissue transglutaminase, an enzyme that is present in most tissues. The deamidated gliadin subsequently binds to either DQ2 or DQ8 molecules on antigen-presenting cells (APC). An inflammatory process is then initiated by gliadin-restricted CD4 T cells, resulting in villous injury [1••]. The characteristic intraepithelial lymphocytosis is considered to occur by a different mechanism, one involving the innate immune system. Villous atrophy and intraepithelial lymphocytosis are the histologic hallmarks of the disease.

Diagnosis

Although small bowel biopsy is the gold standard for the diagnosis of celiac disease, serologic tests are important in

Table 1. Neurologic manifestations reportedly associated with celiac or gluten sensitivity

| Manifestation | Prevalence, % [study] |
|--|--------------------------|
| Peripheral neuropathy | 49 [9] |
| Headache | 46 [9] |
| Depression/anxiety | 31 [10] |
| Ataxia | 5.4 [11] |
| Migraines | 4.4 [9] |
| Epilepsy | 3.3–5.5 [12] |
| Less common manifestations | |
| Epilepsy with cerebral calcifications | |
| Dementia | |
| Cerebral vasculitis | |
| Brainstem encephalitis | |
| Progressive multifocal leukoencephalopathy | |
| Progressive myoclonic encephalopathy | |
| Huntington's disease/chorea | |
| Myoclonus | |
| Neuromyotonia | |
| Stiff-man syndrome | |
| Inclusion body myositis and polymyositis | |

(Adapted from Green et al. [8].)

the determination of who should be referred for biopsy. Participants in the National Institutes of Health consensus development conference on celiac disease suggested that IgA anti-tissue transglutaminase or endomysial antibody be used for serologic testing, given their high sensitivity and specificity of greater than 90% [5••]. Selective IgA deficiency is 15-fold more common among patients with celiac disease than in the general population, and as a result, both IgA and IgG tissue transglutaminase antibodies should be sought. However, concern has been expressed that the sensitivity of serologic tests is extremely variable in clinical practice, as reported by Abrams et al. [6].

Clinical Presentations

The focus of this review is the extraintestinal manifestations that make celiac disease a multisystemic disorder rather than a primary gastrointestinal disease. Over the past two decades the percentage of patients presenting in atypical ways, with so-called “silent celiac disease,” has increased. [7]. The spectrum of disease severity is very great. Some patients are totally asymptomatic (picked up by screening in at-risk populations), whereas others may present with a malabsorption syndrome or an enteropathy-associated T-cell lymphoma. The reason for the tremendously varied presentation is unclear. However, clinicians need to be aware that celiac disease does not

always present with intestinal symptoms, and they should be able to recognize the variety of its presentations.

The clinical classification of celiac disease depends on the presence of gastrointestinal symptoms, mainly diarrhea. Classical celiac disease is the diarrhea-predominant presentation, whereas silent celiac disease may be atypical (eg, anemia, osteoporosis, ataxia) or asymptomatic (detected by screening of at-risk groups, such as first-degree relatives or patients with type 1 diabetes or primary biliary cirrhosis).

Neurologic manifestations

Recognition of neurologic manifestations of celiac disease has increased. Neurologic and psychiatric disorders associated with celiac disease include cerebral ataxia, peripheral neuropathy, epilepsy, dementia, and depression. Table 1 provides a summary of the neurologic and psychiatric manifestations of celiac disease and gluten sensitivity.

Ataxia

Cerebellar ataxia occurs in celiac disease [13], and the term “gluten ataxia” has been expanded to include patients without celiac disease, though the association of symptoms and gluten sensitivity without celiac disease is controversial. Pellecchia et al. [14] demonstrated that improvement in the ataxia may occur with gluten withdrawal. The pathogenesis of the ataxia is considered autoimmune mediated [15]. Intravenous gamma globulin has therefore been beneficial in these patients [16].

Peripheral neuropathy

Peripheral neuropathy is the most common neurologic manifestation of celiac disease. Cicarelli et al. [9] reported an occurrence of signs of peripheral neuropathy in 49% of patients seen in an Italian celiac clinic. In addition, we have reported that celiac disease was present in 2.5% of patients evaluated for neuropathy [17]. Celiac disease was also found in 8% of patients with symptoms of neuropathy and normal electrodiagnostic studies. Appropriately, a skin biopsy will reveal evidence of a small fiber neuropathy, as reported by Brannagan et al. [18]. In our series the most common complaints were painful paresthesias of the limbs and occasionally of the face and variable sensory loss of large- and small-diameter sensory fibers. Motor weakness was rare and confined to the ankles, and gait instability occurred in 25% of the patients [17]. Antiganglioside antibodies have been identified in celiac disease-associated autoimmune neuropathies. Alaedini et al. [19] found that six patients with celiac disease were positive for one or more IgG antibody to GM1, GMD, GD1a, and GD1b gangliosides.

Epilepsy

Several studies have suggested an association between celiac disease and epilepsy. A high prevalence of epilepsy (3.5% to 5.5%) has been reported by Dalgic et al. [20] in

patients with celiac disease compared with normal control subjects. This appears to occur mainly in children rather than adults [21]. Nevertheless, seizure control has been reported to improve or stabilize in patients who adhere to a gluten-free diet, particularly if the diet is initiated shortly after the onset of epilepsy [22]. The uncommon syndrome of celiac disease, epilepsy, and cerebral calcification 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 those in Sturge Weber syndrome [23].

Headache

Gabrielli et al. [24] found migraine in 4.4% of patients with celiac disease, compared with 0.4% of normal controls. Both migraine and tension headache occur more frequently in celiac disease. In one celiac study, half of the celiac patients with headache (either migraine or nonspecific) had significant improvement with a gluten-free diet, indicating that the diet may improve headache in a significant proportion of people with celiac disease [25].

Depression

Common symptoms described in celiac disease include excessive anxiety, fatigue, and irritability, which are also found in depression, a common disorder in celiac disease patients [26,27]. In younger people these depressive symptoms may decrease after diagnosis and treatment of celiac disease, but the depressive symptoms did not improve in adults.

Schizophrenia and other behavioral disorders

Population-based studies reveal an association of celiac disease with schizophrenia [28]. However, the therapeutic implications of this relationship are unclear. In childhood and adolescence, disruptive behavior and depression have been noted in those with celiac disease [29]. More recently, a prospective study by Verkasalo et al. [30] revealed less achievement, as manifested by fewer college degrees and managerial positions, in those with silent, undiagnosed celiac disease compared with those without celiac disease. This finding was attributed to childhood behavioral problems. Little evidence is available to support an association with autism, though the use of a gluten-free diet (like that prescribed for celiac disease) is common.

Hematologic manifestations

Anemia is one of the most common manifestations of celiac disease, and it may be the only presenting sign in some patients with celiac disease. Iron deficiency, a predominant cause of anemia in celiac disease patients, was the mode of presentation in 8% of individuals seen in a US study [31]. These iron-deficient individuals with celiac disease included equal numbers of male and female patients, and diarrhea was not a complaint. In a study from the Mayo Clinic, celiac disease was identified as a cause of iron-deficiency anemia in 15% of patients undergoing esophagogastroduo-

denoscopic assessment (EGD) for iron-deficiency anemia [32]. In a prospective study by Karnam et al. [33], patients with iron-deficiency anemia without any obvious gastrointestinal cause underwent EGD, which revealed an incidence of 2.8% of celiac disease.

Duodenal biopsy should be routine when EGD is performed for iron-deficiency anemia. The pathophysiology of iron-deficiency anemia may be multifactorial; the most accepted mechanism is that iron is absorbed by the proximal duodenum, which is a primary region of involvement in celiac disease. Another mechanism, occult blood loss, has been identified in adults and children [34], though this was not confirmed in subsequent studies [35,36]. In a study of 26 adults with celiac disease and iron deficiency, a gluten-free diet was found to suffice for the correction of anemia in 94% and for the correction of iron deficiency in 55% of patients, suggesting that supplemental iron is unnecessary [37].

Deficiency of vitamin B₁₂ is more common than previously considered in patients with celiac disease [38]. It occurred in 12% of celiac patients in one series and was not associated with the degree of villous atrophy or diarrhea in either gender. Di Sabatino et al. [39] reported that hyposplenism is common at presentation of celiac disease and frequently improves with the diet.

Dermatologic manifestations

Dermatitis herpetiformis is considered to be celiac disease of the skin. It is strongly associated with the silent form of celiac disease, in which inflammatory small intestinal changes can often be found by histologic examination, even in the absence of any clinical gastrointestinal symptoms. Dermatitis herpetiformis is an extremely pruritic blistering condition that may occur anywhere on the skin but classically involves the extensor surfaces of the arms and knees and frequently involves the buttocks. The diagnosis can be made by finding granular IgA deposits in the papillary pits of the dermis. The course of dermatitis herpetiformis includes relapses and remissions, which are coincident with gluten exposure. A strict gluten-free diet can result in long-term remission. Hervonen et al. [40] reported that dermatitis herpetiformis is also associated with higher risk of T- and B-cell lymphoma of any site, whether gastrointestinal or extraintestinal. This increased risk can be prevented with the gluten-free diet but not by dapsone, which is frequently used to treat the skin lesions. Dermatitis herpetiformis is rare in children. Duodenal biopsy in patients with dermatitis herpetiformis reveals villous atrophy in 80%; the remainder of patients have a normal-appearing biopsy, though intestinal permeability is increased in all patients [41].

Other dermatologic manifestations associated with celiac disease include alopecia areata, viteligo, and psoriasis. Celiac disease occurs more commonly in those with psoriasis than would be expected [42], and it has been reported to reverse with a gluten-free diet [43]. Alopecia areata, also a chronic autoimmune disorder, occurs more

commonly in association with celiac disease [44]. Contrary to an earlier report, alopecia does not improve with a gluten-free diet [45]. Finally, chronic urticaria has been reported to improve in patients diagnosed with celiac disease who have commenced a gluten-free diet [46].

Oral mucocutaneous and facial manifestations

The presence of recurrent aphthous ulcers should prompt the physician to screen for celiac disease, given that aphthous ulceration is present in 10% to 40% of patients with untreated celiac disease. Other manifestations include Sjögren syndrome [47] and dental enamel defect [48]. Recently a large forehead, as described by Finizio et al. [49], was proposed as a sign of celiac disease. This is considered to be due to a proportionally smaller mid-third of the face, compared with the forehead.

Hepatic manifestations

Ranging from asymptomatic transaminasemia to severe hepatic failure, liver disease is recognized as a frequent extraintestinal manifestation of celiac disease. Hypertransaminasemia may be present in up to 40% of patients, including both adults and children, and is usually reversible with a gluten-free diet [50]. Celiac disease is detected as the cause of approximately 10% of cases of cryptogenic hypertransaminasemia [51] and should be sought by serologic testing in all cases. The exact cause of the liver abnormalities is unknown. Biopsies have shown nonspecific hepatitis as well as steatosis.

Primary biliary cirrhosis, sclerosing cholangitis, and autoimmune cholangitis are also associated with celiac disease [52]. It should be noted that the diagnosis and treatment of celiac disease in those with severe liver disease may result in improvement of liver function [53].

Blood test abnormalities

Various abnormalities in blood test results have been associated with celiac disease. The more common ones include hyperamylasemia and hypocholesterolemia. Elevated serum amylase, due to macroamylasemia (in which the pancreas is normal), has been found more commonly among untreated celiac patients than in those on a gluten-free diet (16.8% and 7%, respectively) [54]. Celiac disease is associated with hypocholesterolemia, especially low high-density lipoprotein. One study found that all patients with celiac disease and iron-deficient anemia had a cholesterol level of less than 156 mg/dL [55]. We have found that men have lower cholesterol than women [56]. Our study demonstrated that significantly low HDL cholesterol is improved by a gluten-free diet in those with celiac disease [57].

Bone disease

Reduced bone density is common in patients with celiac disease [58]. Studies have shown that screening of osteoporotic patients with celiac antibodies is beneficial in diagnosing patients with silent celiac dis-

ease [59]. Celiac disease has been found in 2% to 7% of patients with osteoporosis, and worsening T scores have also been found to correlate with more severe celiac disease. Sanders et al. [60] indicated that, among 431 patients presenting for bone-density determination, the prevalence of celiac disease was 1.2% in patients with osteopenia, and it was 2.1% for those with osteoporosis. The yield of screening postmenopausal women with osteoporosis for celiac disease is low, and this practice is not considered worthwhile [61].

Rheumatologic presentations

Among the extraintestinal manifestations of celiac disease, arthritis is common [62]. In many case reports arthritis is the presenting symptom in both adults and children. In one study of 200 celiac disease patients, by Lubrano et al. [62], arthritis was present in 26% of those with celiac disease versus 7.5% of normal control subjects. The arthritis was seronegative and oligoarticular, similar to the other enteroarthritis. Sacroiliitis was present in 14 of 22 patients with celiac disease who had undergone bone scintigraphy. Luft et al. [63] tested sera of patients with various rheumatologic disorders, including Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis, for the presence of tissue transglutaminase antibodies. They found an increased incidence of celiac disease only among patients with Sjögren syndrome (10%). A study by Rensch et al. [64] of patients with systemic lupus erythematosus found no patients with endomysial antibodies.

Autoimmune diseases and endocrine diseases

Autoimmune diseases occur in those with celiac disease three to ten times more frequently than in the general population [56,65]. These diseases include thyroid disease [65], autoimmune hepatitis and cholangitis [52], primary biliary cirrhosis [66], type 1 diabetes mellitus [67], Sjögren syndrome [68], Addison's disease [69], peripheral neuropathy [18], psoriasis [42], and cardiomyopathy [70]. Table 2 provides a summary of diseases associated with celiac disease. The association with these other autoimmune diseases is thought to be secondary to shared HLA alleles, a common immunologic mechanism, and the presence of celiac disease itself. Duration of gluten exposure, as determined by age at celiac disease diagnosis, was considered to be an important factor in the risk of development of an associated autoimmune disease. This suggests that earlier celiac disease diagnosis may prevent the development of the autoimmune diseases in these patients; however, recent studies have refuted this possibility [65].

Reports exist of improvement of various autoimmune diseases in patients with celiac disease who are following a gluten-free diet. These diseases include neuropathy [17], cardiomyopathy [71], and thyroid disease [65]. However, most associated autoimmune diseases do not improve after a gluten-free diet, and diagnosis of celiac disease does not

Table 2. Other diseases associated with celiac disease

| Category | Manifestation |
|-----------------------------------|--|
| Neurologic | Peripheral neuropathy [9] |
| | Headache [24,25] |
| | Depression/anxiety [27,28] |
| | Cerebellar ataxia [13,14] |
| | Epilepsy [21,22] |
| Endocrine | Type 1 diabetes mellitus [67] |
| | Autoimmune thyroid disorders [65] |
| | Addison's disease [69] |
| | Alopecia aerate [44] |
| Cardiac | Idiopathic dilated cardiomyopathy [76] |
| | Autoimmune myocarditis [71] |
| Hepatic | Primary biliary cirrhosis [77] |
| | Autoimmune hepatitis [78] |
| | Autoimmune cholangitis [79] |
| Rheumatologic | Oligoarticular arthritis [62] |
| | Juvenile arthritis [80] |
| | Sjögren syndrome [68] |
| Other | Anemia [32] |
| | Osteoporosis [51] |
| | Turner syndrome [81] |
| | Down syndrome [82] |
| | Dental enamel defects [83] |
| | Sarcoidosis [84] |
| Recurrent acute pancreatitis [85] | |

(Adapted from Lee and Green [75].)

protect patients from the development of the associated autoimmune diseases [65].

Celiac disease has been found in 4% to 8% of women with unexplained infertility [72]. Recurrent spontaneous abortion is considered the main problem. However, others have not found this association [73]. Despite the contradictory evidence, some case reports show successful treatment of infertility after the diagnosis and dietary treatment of celiac disease [74].

Inflammatory bowel disease

Inflammatory bowel disease occurs more commonly in patients with celiac disease, including ulcerative colitis and Crohn's disease [86].

Gluten sensitivity without celiac disease

Gluten sensitivity without celiac disease is a controversial area. Patients are encountered with either neurologic or gastrointestinal symptoms that respond to a gluten-free diet despite the absence of celiac disease. It is certainly worthwhile to exclude celiac disease as a possible diagnosis with the appropriate HLA testing and a gluten challenge in these patients. However, patients are often adamant about their symptom improvement.

Conclusions

The varied clinical presentations make the diagnosis of celiac disease challenging. A host of diseases associated with celiac in turn give rise to multiple extraintestinal manifestations. Non-diarrhea-predominant presentations and silent celiac disease are the most frequent.

Substantial progress has taken place in our understanding of celiac disease in the past decade. Celiac disease is a multisystem autoimmune disorder that is currently believed to affect 1% of the general population, and patients are increasingly diagnosed after the extraintestinal complications and manifestations of the disease have been recognized. It is therefore important for clinicians of all subspecialties to be aware of the varied symptoms and diseases associated with celiac disease and to consider performing celiac serologies liberally.

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