Epidemiology of Celiac Disease: What Are the Prevalence, Incidence, and Progression of Celiac Disease?

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Celiac disease (CD) is a chronic systemic autoimmune disorder induced by gluten proteins present in wheat, barley, and rye. Contrary to common belief, gluten enteropathy is a systemic disease rather than merely an ailment of the alimentary tract. Genetically susceptible persons develop autoimmune injury to the gut, skin, liver, joints, uterus, brain, heart, and other organs (Figure 1). The classical definition of CD included gastrointestinal manifestations (chronic diarrhea, failure to grow, weight loss, vomiting, abdominal pain, bloating, distention, and constipation), confirmed by a small bowel biopsy (SBB) with findings of villous atrophy, crypt hyperplasia, and normalization of the villous architecture in response to a gluten-free diet.[1,2] Previously, CD was thought to be a disease primarily of infancy; however, with the widespread delay in introduction of wheat into the infant diet, the clinical manifestations have become more subtle, and diagnosis is now typically made in older children and adults.[3–5] SBB is poorly accepted by a majority of patients with mild or no symptoms, and the pathologic examination of biopsy material is suboptimal in most settings. The use of SBB as a "gold standard" for diagnosis has significant limitations. It is occasionally false-negative because of patchy mucosal changes. Villous atrophy is often most severe in the proximal jejunum, typically not reached by endoscopic biopsy. This has led some to propose a new definition of CD, based on the presence of serum IgA autoantibodies to tissue transglutaminase (IgA TG) and HLA-DQB1*0201 or *0302 alelles.[6] These markers are increasingly used in screening for CD, but their true sensitivity and specificity are debatable. Although efforts to standardize IgA TG assays have been undertaken,[7,8] previous reports have likely overestimated the sensitivity and underestimated the specificity because of verification bias[9] caused by the lack of SBB studies in patients negative on TG screening.

Spectrum of CD

The current model of the natural history of CD (Figure 2) recognizes that, at certain points in time, the disease is not associated with obvious clinical signs and symptoms.

Latent CD precedes diagnosis of CD or follows successful treatment of active disease with a gluten-free diet (GFD). The SBB does not show villous atrophy and crypt hyperplasia, but there are increased γ/δ intraepithelial T cells, higher proportion of dividing epithelial crypt cells,[10] and subtle morphometric abnormalities of the enterocytes,[11] pointing to a low-grade ongoing inflammation in the gut wall. IgA TG or endomysial autoantibodies can be detected in many of these patients. Prospective studies have shown that individuals with latent CD develop symptoms and positive SBB while on gluten-containing diet.[12–14]

Active CD is characterized by intestinal and/or extraintestinal symptoms, villous atrophy and crypt hyperplasia, and strongly positive IgA TG and endomysial autoantibodies. However, the latter can be undetectable in occasional patients with coexisting IgA deficiency. Atypical presentation has become increasingly frequent, with nonspecific abdominal discomfort or extraintestinal symptoms[5] such as dermatitis herpetiformis, iron-deficiency anemia, hepatitis, cholangitis, hypertransaminasemia, coagulopathy, short statue, pubertal delay, osteopenia, arthralgia, aphthous stomatitis, dental enamel defects, alopecia, edema, infertility, depressive symptoms, and cerebellar ataxia. Dermatitis herpetiformis—an extremely itchy, bullous skin rash of the extensor surface of the limbs, trunk, and scalp—is a good example of a predominantly extraintestinal form of CD. Patients with dermatitis herpetiformis have IgA TG (80%–95%), HLA-DQB1*0201 (90%), and villous atrophy (75%, the remaining 25% have increased intraepithelial lymphocytes) and respond to GFD, yet they are often treated as if they had a different disease (eg, using Dapsone and not GFD).[15]

Abbreviations used in this paper: IgA TG, IgA autoantibodies to tissue transglutaminase; CD, celiac disease; GFD, gluten-free diet; SBB, small bowel biopsy.

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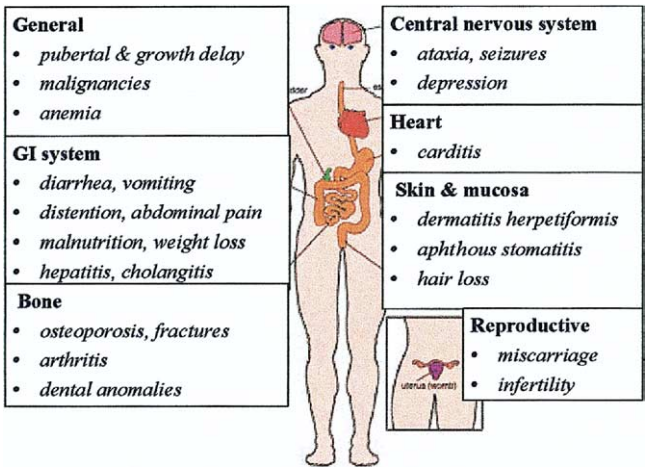

Figure 1. New paradigm: celiac disease is a multiorgan autoimmune disease caused by gluten intolerance.

Silent CD is characterized by the presence of IgA TG and endomysial autoantibodies, histologic lesions on SBB typical for CD, and CD-associated HLA-DQ genotypes in an asymptomatic individual. In retrospect, however, many patients or their relatives recollect typical symptoms.[16–18] Children with silent disease had decreased height z-scores that correlated with the degree of intestinal injury.[16,19] Silent CD has been suggested to cause nutritional deficiency of iron; zinc; folate; vitamins D, K, and E; osteoporosis[20]; lymphoma[21]; and neurological disease,[22] but the evidence is not very strong. There are no clear guidelines concerning the GDF in people with silent CD, especially those detected through serologic screening. However, preliminary reports appear to confirm that a GFD in silent cases prevents or reverses systemic complications such as delayed growth, weight loss,[23,24] or osteopenia.[10]

Prevalence

The proportion of people in a population who have CD at a specified time (prevalence rate) depends of course on definition of the disease. Figure 3 illustrates prevalence of preclinical (latent), undiagnosed (largely silent), and diagnosed (mostly active) CD in several European and US populations. Although the prevalence of *diagnosed* CD varied widely among these populations, the estimates of combined undiagnosed and diagnosed (or silent and active) CD were remarkably similar, between 0.7%–2.0% in most of the populations, including the United States. The prevalence of childhood CD has been reported to be between 1:285 and 1:77 in Sweden,[25,26] 1:99 (positive SBB) and 1:67 (presence of IgA TG and HLA- DQB1*0201 or *0302) in Finland,[6] and 1:230[27] and 1:106[18] in Italian schoolchildren. Generally, similar rates have been reported for non-European white populations, such as New Zealand,[28] Australia,[29] Argentina,[30] and Israel.[31]

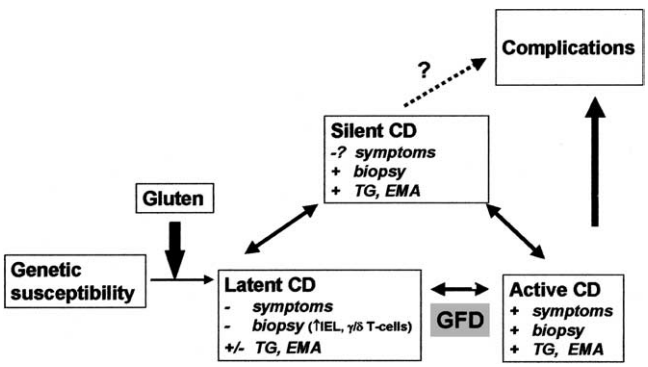

Figure 2. Natural history of celiac disease.

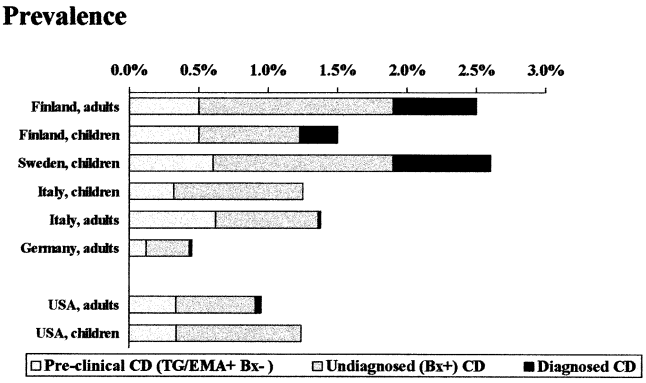

Figure 3. Prevalence of preclinical, undiagnosed and diagnosed CD based on work of Murray et al,[4] Mäki et al,[6] Carlsson et al,[26] Hoffenberg et al,[32] Fasano et al,[33] and Mustalahti et al.[55]

In the United States, cumulative incidence of persistent IgA TG positivity by the age of 5 years was 1:104 (95% CI: 1:49–221).[32] In US adults, the prevalence varied from 1:1750[4] (clinically diagnosed CD, including dermatitis herpetiformis) to 1:105[33] (presence of IgA endomysial antibodies). Ethnic-specific data for the US population are scarce; the cumulative incidence of persistent IgA TG in Hispanic children was reported to be more than 3 times lower than in non-Hispanic whites,[32] probably because of the low frequency of the HLA-DR3, DQB1*0201 haplotype in this population. CD is virtually unknown in East Asian populations who also lack this HLA haplotype; however, rates close to those in Europe have been reported from the Middle East and India. Although the disease is believed to be rare in Africa (and in African Americans), the highest prevalence has been reported for Saharavi in North Africa.[34]

The estimates based on seroepidemiologic studies suggest that, for each diagnosed case of CD, there may be 3–7 undiagnosed cases and that 1%–3% of the general