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CELIAC DISEASE DEVELOPS IN GENETICALLY PREDISposed individuals as a response to ingested gluten. *Gluten* is the term for the storage proteins of the cereal grains wheat, rye, and barley.[1] While virtually 100% of the population ingests these grains in one form or another and 30% to 40% of the population carry the genetic markers of the disease (HLA-DQ2 or type 8),[2] only 2% to 3% of those with genetic markers develop the disease.[2] This indicates that other genetic factors and environmental precipitants are necessary for disease expression. These factors are largely unknown, although breastfeeding, timing of gluten introduction, and gastrointestinal infections in childhood have been incriminated,[3,4] at least in the development of childhood celiac disease.

The diagnosis of celiac disease is dependent on finding characteristic, although not specific, pathological findings in duodenal biopsies.[5] These changes include inflammatory changes within the small-intestinal epithelium (intraepithelial lymphocytosis) and the lamina propria as well as various degrees of villous atrophy.[5] A range of pathological abnormalities exists, from intraepithelial lymphocytosis with normal villous architecture to total villous atrophy, all of which are considered part of the spectrum of gluten enteropathy or celiac disease.[5] However, there are several causes of intraepithelial lymphocytosis without villous atrophy in addition to celiac disease, such as *Helicobacter pylori* infection and tropical sprue.[6] It is therefore difficult to diagnose celiac disease in the setting of intestinal inflammation when villous atrophy is absent.[7] But in some clinical settings, such as the presence of symptoms, positive serologic results, and even the appropriate HLA type, patients with these inflammatory changes receive a diagnosis of celiac disease.[7]

Serologic blood tests that include antigliadin, tissue transglutaminase (tTG), and endomysial antibodies are used for triaging individuals for endoscopic biopsy. The tTG and endomysial antibodies are sensitive and specific for celiac disease, while antigliadin antibodies are not as sensitive or specific.[1]

See also p 1171.

Celiac disease is common, occurring in about 1% of the population,[8,9] although the majority of cases are undiagnosed.[10] The number of persons actually diagnosed as having celiac disease varies from country to country, depending on physician awareness of the varied clinical manifestations and the availability of blood tests for the condition.[11] The rate of diagnosis is high in some European countries such as Finland, where in some regions 70% of cases are diagnosed.[11] Within the United States, the rate of diagnosis is increasing, both in adults and children,[10,12] although only a small fraction (estimated at <5%) of cases are diagnosed.

Recent evidence from both Finland[13] and the United States[9] has demonstrated that the prevalence of celiac disease has increased markedly over a relatively short time. In the United States, the prevalence of celiac disease has increased 4-fold in the last 50 years.[9] These data are based on the analysis of stored serum samples and reflect a true increase in the prevalence of the disease, not just the number of individuals who are given diagnoses. The reason for this increase is not clear but may be related to environmental factors such as the changing nature of gluten or other factors related to diet.

Accompanying this increase in disease prevalence is a change in the clinical manifestations, so that the classic presentation of diarrhea and malabsorption syndrome is now less common than other presentations.[14] The disease now manifests more often as a multisystem disorder. Anemia, osteoporosis, peripheral neuropathy or ataxia, irritable bowel syndrome, and dyspepsia are all possible presentations. Many patients are asymptomatic, with the disease detected by screening performed because of their presence in a high-risk group such as being a family member or having an associated autoimmune disease, type 1 diabetes, or Down syndrome. Increasingly, those with autoimmune thyroid disease are also screened.

Patients with undiagnosed or diagnosed celiac disease appear to have an increased mortality risk. Based on studies that have examined stored serum samples for tTG antibodies and correlated the results with mortality data, those with

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undiagnosed celiac disease (positive anti-tTG results) have increased mortality compared with those with negative antibody levels.[9,15] The increased mortality applies to both men and women and is mainly from increased death due to malignancies.[15] Likewise, most studies have documented an increased standardized mortality rate for those diagnosed as having celiac disease,[16,17] although there are several issues in all the studies, including lack of population controls and children, small numbers of patients, and including only those seen in specialty clinics.

In this issue of *JAMA*, Ludvigsson and colleagues[18] used the unique Swedish health care number assigned to individuals, allowing them to be followed through the health care system. Patients with celiac disease were identified through the analysis of nationwide pathology data from all 28 pathology laboratories in the country. A biopsy showing villous atrophy is required for diagnosis of celiac disease in Sweden. Their study included more patients than all previous studies combined (3049 deaths in those with celiac disease) and demonstrated a significant modestly increased risk of death (hazard ratio [HR], 1.39) that applied to children as well as adults. Risk of death decreased with time after diagnosis of celiac disease but remained significantly elevated at 5 years after diagnosis. Cardiovascular diseases and malignancy were the main causes of death.

In their study, Ludvigsson and colleagues[18] also identified patients with inflammation but without villous atrophy in duodenal biopsies. These patients had pathological changes that may be part of the spectrum of celiac disease[5] but, in Sweden, do not acquire the diagnostic label of celiac disease and, therefore, are not traditionally advised to commence a gluten-free diet. This group of patients also had an increased risk of death (HR, 1.72).

An even more interesting group in the study, those labeled as having "latent celiac disease,"[18] also had an increased risk of death (HR, 1.35). These patients were defined by the presence of celiac antibodies (anti-tTG, antigliadin, or antiendomysial antibodies) and normal duodenal biopsy results. Some of these patients may have had celiac disease that was missed because of an inadequate number of biopsies. Villous atrophy may be patchy, and 3 biopsy specimens, as in the Swedish study, may fail to detect it.[19] In the United States, these patients may receive a diagnosis of "gluten sensitivity" due to the presence of symptoms and antigliadin antibodies but a normal biopsy result. Currently, patients who undergo serologic testing and have positive antigliadin antibodies in the absence of positive tTG antibodies or selective IgA deficiency are assumed to be healthy, lacking any disease. However, these patients have an increased mortality. This was noted in the current Swedish study[18] as well as in a study from Northern Ireland in which patients with gluten sensitivity (positive antigliadin antibodies but not celiac disease) had increased all-cause mortality compared with the general population (standardized mortality ratio, 2.41).[20]

Until recently, gluten sensitivity has received little attention in the traditional medical literature, although there is increasing evidence for its presence in patients with various neurological disorders[21] and psychiatric problems.[22] The study by Ludvigsson and colleagues[18] reinforces the importance of celiac disease as a diagnosis that should be sought by physicians. It also suggests that more attention should be given to the lesser degrees of intestinal inflammation and gluten sensitivity.

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