

## Celiac Disease — How to Handle a Clinical Chameleon

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Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye, and barley) in genetically susceptible persons. The disease is associated with HLA-DQ2 in 90 to 95 percent of cases and with HLA-DQ8 in 5 to 10 percent of cases and is self-perpetuating in the continued presence of gluten.<sup>1</sup> It is the interplay between genes (both HLA and other types) and environment (i.e., gluten) that leads to the intestinal damage that is typical of the disease.<sup>2</sup> Under physiologic circumstances, this interplay is prevented by competent intercellular tight junctions, structures that limit the passage of macromolecules (including gluten peptides) across the intestinal epithelial barrier. Recent evidence suggests that the gluten-induced up-regulation of zonulin, an intestinal peptide involved in the regulation of tight junctions, is responsible, at least in part, for the aberrant increase in gut permeability that is characteristic of the early phase of celiac disease<sup>3</sup> and the subsequent abnormal passage of gluten into the lamina propria. The protein is deamidated by tissue transglutaminase in the lamina propria and is then recognized by antigen-presenting cells bearing HLA-DQ2 or DQ8, thereby triggering the autoimmune reaction of celiac disease.<sup>2</sup> Given the undisputable role of gluten in causing inflammation and immune-mediated tissue damage, celiac disease represents a unique model of autoimmunity in which, in contrast to all other autoimmune diseases, a close genetic association with HLA-DQ2, DQ8, or both; a highly specific humoral autoimmune response (autoantibodies against tissue transglutaminase); and most important, the triggering environmental factor (gluten) have all been identified. This information provides the rationale for the treatment of the disease based on complete avoidance of gluten-containing grains, a task complicated by the lack of a clear food-labeling policy.

Epidemiologic studies conducted during the past decade, using specific and sensitive serologic tests, have revealed that celiac disease is one of the most common lifelong disorders in both Europe<sup>4</sup> and the United States.<sup>5</sup> The clinical presentation of this condition can range from the typical syndrome of malabsorption (chronic diarrhea, weight loss, and abdominal distention) to symptoms and conditions that can affect any organ system ([Table 1](#)).<sup>5</sup> Since the onset of celiac disease may be atypical or even silent, many cases remain undiagnosed and thus carry a risk of long-term complications, including osteoporosis, infertility, and cancer.

**Table 1.** Atypical Clinical Manifestations of Celiac Disease.

In this issue of the *Journal*, the article by Mäki and coworkers confirms that celiac disease often goes undiagnosed, even in a country such as Finland, where the level of awareness of the disease is high.<sup>6</sup> Using the most sensitive and specific serologic tests available — tests for endomysial and tissue transglutaminase antibodies — combined with HLA typing, the authors screened a cohort of children whose serum samples had been collected seven years earlier. Fifty-six had positive serologic tests, only 10 (18 percent) of whom had been given a diagnosis of celiac disease between the serum collection in 1994 and screening in 2001. In 27 children, the diagnosis was confirmed by an intestinal biopsy at follow-up in 2001, suggesting that the prevalence of celiac disease among Finnish children is 1 case in 99 children. The prevalence of the celiac disease trait, defined as seropositivity for autoantibodies and an HLA haplotype associated with celiac disease, was even higher: 1 case in 67 children.

These results raise many interesting questions. How can a disease that, if not treated, is associated with a high rate of morbidity and increased mortality not be segregated by genetic evolution and thus remain one of the most frequent genetically based disorders in humans? One possible explanation is that gluten, a protein introduced in large quantities into the human diet

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only after the advent of agriculture, activates "by mistake of evolution" mechanisms of innate immunity (such as the zonulin pathway<sup>7,8</sup>) that are too important to the survival of the species to be eliminated.

Another question concerns the variables that dictate the duration of clinical latency and the type of symptoms that occur once celiac disease becomes clinically apparent. In recent years, the age at the onset of symptoms has increased and the clinical presentation has changed. These changes seem to be associated with the introduction of smaller amounts of gluten into the diet at older ages.

A third question concerns the complications of untreated celiac disease. Multiple studies that have focused on the biochemistry and toxicity of gluten-containing grains and the immune response to these grains suggest that patients with celiac disease should be treated, whether or not they have symptoms or associated conditions. However, no well-designed prospective clinical studies have addressed this point, nor do such studies seem likely to, given the ethical implications. Nevertheless, there is general agreement that persistent mucosal injury, with or without typical symptoms, can lead to serious complications in adults with celiac disease who do not strictly comply with a gluten-free diet.<sup>2</sup>

Perhaps the most controversial issue raised by the findings of Mäki and coworkers is the question of who should be screened for celiac disease. The prevalence of the disease and the burden of illness related to this condition, particularly if it is not treated, are so high as to potentially support a policy of screening of the general population. Celiac disease satisfies the five criteria of the World Health Organization for justifying general screening.<sup>9</sup> First, early clinical detection of the disease could be difficult, as suggested by Mäki et al. Second, with an overall prevalence approaching 1 percent,<sup>2</sup> celiac disease is a common disorder, causing substantial morbidity in the general population. Third, the screening tests for celiac disease are highly sensitive and specific, as demonstrated by many reports in the literature, including that by Mäki et al. Fourth, a treatment for the disease — a gluten-free diet — is available. Finally, if it remains unrecognized, celiac disease could increase the risk of life-threatening complications that are difficult to manage, such as intestinal lymphoma.

Nevertheless, the justification for screening of the general population for celiac disease will depend on the results of comprehensive, well-performed cost-effectiveness analyses. Although it is well established that complications may develop in the absence of treatment, the natural history of undiagnosed celiac disease remains unclear. Published studies have necessarily been limited to patients who have received a clinical diagnosis, an approach that ultimately leads to a biased estimate of the risks.<sup>2</sup> Despite the high sensitivity of the serologic tests for celiac disease, the positive predictive value of these tests decreases when they are used in the general population rather than in groups at increased risk.<sup>2</sup>

The appropriate age for screening and the need for periodic repetition of screening to rule out late-onset gluten sensitization are unclear.<sup>2</sup> The difficulties of treating patients with apparently silent celiac disease should also be considered. A five-year follow-up study revealed a 30 percent decrease in adherence to the gluten-free diet among patients in whom the disease was detected by screening, as compared with age-matched patients with symptomatic celiac disease identified during a regular diagnostic workup.<sup>10</sup> At the moment, the best epidemiologic approach to the diagnosis of celiac disease seems to be a systematic process of case-finding in which patients with symptoms or conditions, both typical and atypical ([Table 1](#)), known to be

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associated with the disease are targeted. Because of the high rate of morbidity related to untreated celiac disease and the typical delay in diagnosis,<sup>2</sup> increased awareness of the disease on the part of health care professionals, especially primary care physicians, and a low threshold for the use of serologic tests are pivotal both to alleviate the social and personal costs of the disease and to increase the quality of life of the many patients affected by celiac disease.

Dr. Fasano reports having served as a paid lecturer to Prometheus.

### Source Information

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### References

1. Dewar D, Pereira SP, Ciclitira PJ. The pathogenesis of coeliac disease. *Int J Biochem Cell Biol* (in press).
2. Schuppan D. Current concepts of celiac disease pathogenesis. *Gastroenterology* 2000;119:234-242. [[ISI](#)][[Medline](#)]
3. Fasano A, Not T, Wang W, et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. *Lancet* 2000;355:1518-1519. [[CrossRef](#)][[ISI](#)][[Medline](#)]
4. Catassi C, Fabiani E, Ratsch IM, et al. The coeliac iceberg in Italy: a multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr Suppl* 1996;412:29-35. [[Medline](#)]
5. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;163:286-292. [[Abstract/Full Text](#)]
6. Mäki M, Mustalahti K, Kokkonen J, et al. Prevalence of celiac disease among children in Finland. *N Engl J Med* 2003;348:2517-2524. [[Abstract/Full Text](#)]
7. El Asmar R, Panigrahi P, Bamford P, et al. Host-dependent zonulin secretion causes the impairment of the small intestine barrier function after bacterial exposure. *Gastroenterology* 2002;123:1607-1615. [Erratum, *Gastroenterology* 2003;124:275.] [[ISI](#)][[Medline](#)]
8. Clemente MG, De Virgiliis S, Kang JS, et al. Early effects of gliadin on enterocyte intracellular signalling involved in intestinal barrier function. *Gut* 2003;52:218-223. [[Abstract/Full Text](#)]
9. Fasano A. European and North American populations should be screened for coeliac disease. *Gut* 2003;52:168-169. [[Full Text](#)]
10. Fabiani E, Taccari LM, Ratsch IM, Di Giuseppe S, Coppa GV, Catassi C. Compliance with gluten-free diet in adolescents with screening-detected celiac disease: a 5-year follow-up study. *J Pediatr* 2000;136:841-843. [[CrossRef](#)][[ISI](#)][[Medline](#)]