When Is Celiac Disease Celiac Disease?

See "Progression of celiac disease in children with antibodies against tissue transglutaminase and normal duodenal architecture," by Auricchio R, Mandile R, Del Vecchio MR, et al, on page 413.

More and more often, the clinician dealing with children or adults suspected of celiac disease is coping with the diagnostic and therapeutic dilemma of the "potential celiac patient," that is, the patient who presents with elevated specific celiac serum antibodies but has a normal (or almost normal) duodenal biopsy. How to handle these people? Can we predict those who will evolve into full-blown celiac disease if left on a gluten-containing diet? Are we risking under-diagnosing or over-diagnosing celiac disease in these individuals? In their article, "Progression of Celiac Disease in Children with Antibodies Against Tissue Transglutaminase and Normal Duodenal Architecture" published in this journal, Auricchio et al[1] follow a large cohort of children with potential celiac disease to try to answer these questions.

There is a problem with both the under-diagnosis as well as the over-diagnosis of celiac disease. Under-diagnosis is a well-known, worldwide problem, which is particularly relevant in the United States where the rate of diagnosis has lagged behind other countries.[2,3] A considerable body of research has addressed why a substantial portion of patients with celiac disease are not diagnosed. Factors identified include minimal or absent symptoms, failure to test high-risk groups,[4] inappropriate interpretation of serologic testing, an inadequate number of duodenal biopsies,[5] and the inadequate pathological interpretation of duodenal biopsies.[6]

Over-diagnosis is when people are inappropriately told they have celiac disease when they do not. This latter group would be committed to a life-long, unnecessary gluten-free diet. This area, however, has not been investigated adequately.[7,8]

After the diagnosis of celiac disease, a gluten-free diet is advised. Because celiac disease is currently incurable, this commitment is life-long. Recent research has demonstrated that adherence to a gluten-free diet can become the major factor affecting quality of life.[9] This finding is especially evident considering social, functions such as eating out of the home and travel. In fact, the most vigilant patients, those with the greatest knowledge of the diet, have a lower quality of life[10] and may exhibit maladaptive eating behaviors that are forbearers of eating disorders.[11] Therefore, the diagnosis of celiac disease clearly requires great precision.

The diagnosis of celiac disease requires several steps: the patient, while eating gluten, contacts their health care provider; the clinician has the diagnostic consideration of celiac disease; serologic testing is ordered, most appropriately a tissue transglutaminase IgA antibody (tTG IgA), often combined with or followed by an anti-endomysium IgA antibody, particularly in children; and, if serologic testing is positive, an endoscopic duodenal biopsy is performed. In this setting, the findings of villous atrophy together with intraepithelial lymphocytosis indicates active celiac disease and dictates the prescription of a gluten-free diet. The circumstances may arise when, often surprisingly, a positive serology is not associated with the presence of villous atrophy. Instead, the duodenal mucosa may be normal or show only an intraepithelial lymphocytosis and a diagnosis of active celiac disease cannot be made. This intriguing subset of patients has been labelled as having "potential celiac disease."[12]

The cohort described by Auricchio et al[1] in this issue of *Gastroenterology* included 280 children. They had both positive tTG IgA and endomysial antibodies on $\geq$2 occasions and normal duodenal biopsies. Over a median follow-up time of 60 months (from a minimum of 18 months to a maximum of 12 years), 42 children (15%) developed villous atrophy, 89 (32%) lost their positive antibodies, and the remainder of these children had persistent positive serologic tests. The cumulative incidence of progression to villous atrophy was 43% at 12 years. In multivariate analysis, the baseline factors most strongly associated with development of villous atrophy were the number of $\gamma\delta$ intraepithelial lymphocytes, age (older age), and homozygosity for HLA DQ2. Adding to the analysis the persistence of positive tTG IgA at 2 years after diagnosis allowed the correct identification of patients who will develop villous atrophy 85% of the time.

As mentioned, this phenomenon of potential celiac disease can also be seen in adults.[13,14] Adults, too, if left on a gluten-containing diet, can progress to villous atrophy, lose their positive celiac antibodies, or persist with positive serologic tests without progression to villous atrophy (the latter perhaps meeting the definition of false-positive tTG?).

What should be the management of patients with positive serologic tests for celiac disease and normal biopsies? Ultimately, the management must be the result of a thorough, well-informed agreement reached between the expert doctor and the patient (or their caregivers), but general advice can be given as follows.

- First, the biopsy should be reviewed. Was an adequate number of pieces taken? It is recommended that $\geq$4 be taken from the descending duodenum and 1 or 2 from the bulb.[15,16] The bulbar biopsies are taken because the disease may be confined to the duodenal bulb, the so-called ultra-short celiac disease.[17]
- Second, biopsies should be reviewed by a second, specialist pathologist.
- Third, if confirmed as a patient with potential celiac disease, and if the patient has symptoms, a gluten-free diet should be commenced and evaluated for both clinical and serologic response.
- If asymptomatic, a wait and see approach is appropriate with interval biopsies every 2 years, if the elevated antibodies persist, as Auricchio et al[1] did.

For adults, a biopsy is usually recommended for the diagnosis of celiac disease.[18] However, for children the European Society for Paediatric Gastroenterology Hepatology and Nutrition has published evidence-based guidelines allowing diagnosis without a biopsy[19] in a symptomatic child with tTG IgA antibodies >10 times the upper level of normal, a positive anti-endomysium IgA antibody in a sample drawn on a different occasion, and consistent celiac HLA, because this approach has a positive predictive value nearing 100%.[20] It must be noted that none of the children in the study by Auricchio et al[1] who were labelled as having potential celiac disease were initially symptomatic or had tTG IgA levels that were >10 times the upper level of normal, thus reinforcing the concept that none of them would have been improperly labelled as having celiac disease even with these less restrictive guidelines. This biopsy avoiding policy may well be applied to adults in the near future.[21]

It is essential that diagnostic guidelines be followed to ensure that the diagnosis of celiac disease is well-founded. The disease, and its treatment, are considered life-long: we would not want a child or an adult to be committed to a socially restrictive diet unnecessarily; neither, of course, would we want to leave a patient with celiac disease on a harmful gluten-containing diet.

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Conflicts of interest
The authors disclose no conflicts.


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