

# Celiac Disease Diagnosis: Simple Rules Are Better Than Complicated Algorithms

Carlo Catassi, MD, MPH,<sup>a,b</sup> Alessio Fasano MD<sup>a</sup>

<sup>a</sup>Mucosal Biology Research and Center for Celiac Research, University of Maryland, School of Medicine, Baltimore; <sup>b</sup>Università Politecnica delle Marche, Ancona, Italy.

## ABSTRACT

Celiac disease is the only treatable autoimmune disease, provided that a correct diagnosis is achieved and a strict, lifelong gluten-free diet is implemented. The current diagnostic algorithm for celiac disease includes initial screening serological tests, followed by a confirmatory small intestinal biopsy showing the autoimmune insult typical of celiac disease. The biopsy, considered the diagnostic gold standard, has been recently questioned as a reliable and conclusive test for every case. Indeed, the wide variability of celiac disease-related findings suggests that it is difficult to conceptualize the diagnostic process into rigid algorithms that do not always cover the clinical complexity of this disease. Instead we find clinically useful the shifting to a quantitative approach that can be defined as the “4 out of 5” rule: the diagnosis of celiac disease is confirmed if at least 4 of the following 5 criteria are satisfied: typical symptoms of celiac disease; positivity of serum celiac disease immunoglobulin, A class autoantibodies at high titer; human leukocyte antigen (HLA)-DQ2 or DQ8 genotypes; celiac enteropathy at the small bowel biopsy; and response to the gluten-free diet.

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Celiac disease is the immune-mediated intolerance to dietary gluten, a protein contained in wheat, rye, and barley, affecting genetically predisposed individuals.<sup>1</sup> The clinical spectrum of celiac disease is wide, including cases with either typical intestinal (eg, chronic diarrhea, weight loss) or “atypical” extraintestinal (eg, anemia, osteoporosis, neurological disturbances) features, and silent forms that are occasionally discovered because of serological screening. Given the protean clinical presentation of celiac disease potentially involving any organ or tissue of our body, internists and general pediatricians are the first line of scrim-

mage facing the diagnostic challenges that this disease poses.

The typical jejunal damage associated with active celiac disease, showing villous atrophy, crypt hypertrophy, and increased intraepithelial lymphocyte count, was first described in 1957 by John Paulley in the UK. Since then, the histological analysis of small bowel biopsy specimens, initially taken by capsule and then by standard upper endoscopy, has become the gold standard for celiac disease diagnosis. The small intestinal biopsy is still considered a necessary investigation in the current guidelines of North American and European gastroenterological societies (“no small intestinal biopsy, no celiac disease”).<sup>2,3</sup> However, during these last decades, accurate tests have been added to the diagnostic tool kit, for example, the determination of serum immunoglobulin A (IgA) class anti-tissue transglutaminase (TTG) and endomysial (EMA) antibodies, IgG class anti-deamidated gliadin peptide antibodies, and human leukocyte antigen (HLA)-DQ2 and -DQ8 predisposing genotypes. As far as the small bowel biopsy is concerned, recently developed immunohistochemical techniques, particularly the detection of subepithelial IgA deposits, have

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Requests for reprints should be addressed to Alessio Fasano, MD, Mucosal Biology Research Center and Center for Celiac Research, University of Maryland School of Medicine, Health Science Facility II, Room S345, 20 Penn Street, Baltimore, MD 21201.

E-mail address: [afasano@mbrc.umaryland.edu](mailto:afasano@mbrc.umaryland.edu)

improved the diagnostic accuracy of this procedure. However, major limitations of conventional histology also have become clear, such as the frequent tangential artifact (a normal mucosa may appear atrophic when the specimen is not cut longitudinally), the poor specificity (particularly of minor lesions such as duodenal lymphocytosis), and patchiness of the mucosal damage (some sections appearing normal and others showing variable degree of damage).<sup>4</sup>

In many cases the clinical, serological, and histological findings are consistent and the diagnosis of celiac disease is straightforward. When celiac autoantibodies IgA-TTG and -EMA are found at high titers in a patient with typical symptoms, the probability of identifying a celiac enteropathy at the small intestinal biopsy is almost 100%.<sup>5</sup> In these cases, the small intestinal biopsy does not add any relevant information for celiac disease diagnosis and treatment.

However, the following “borderline” situations are increasingly detected in clinical practice in both children and adults:

- Patients with so called “potential” celiac disease show positivity of serum celiac autoantibodies despite a (nearly) normal histological picture at the small intestinal biopsy. In many of these cases, the deterioration of jejunal architecture takes place over time. Implementation of the gluten-free diet is indicated in potential celiac disease, both for treating symptoms and for preventing late-onset complications.<sup>6</sup>
- Conversely, so-called seronegative celiac disease is characterized by clinical, genetic, and histological data indicating celiac disease in a patient lacking serum TTG and EMA antibodies. Seronegative celiac disease is likely to be underestimated due to the tendency to perform small intestinal biopsy only in patients with positive celiac disease serum markers (so called self-fulfilling prophecy).<sup>7</sup> A peculiar type of seronegative celiac disease is found in patients that also have IgA deficiency, who usually lack IgA but often show IgG class celiac autoantibodies.
- Diagnosis may be difficult in celiac disease patients showing modestly increased levels of serum celiac disease autoantibodies, as many of these subjects also have only slight enteropathy at the small intestinal biopsy (graded as 1 or 2 lesion by the Marsh-Oberhuber classification).<sup>8</sup> In these cases, the detection of subepithelial IgA anti-TTG deposits strongly suggests celiac disease.<sup>4</sup>
- The clinician is sometimes faced with the puzzling situation of “clear-cut” celiac disease in patients lacking the HLA-DQ2 or DQ8 haplotypes. Large multicenter studies have indeed shown that 0.4 % of celiac disease patients are both DQ2 and DQ8 negative.<sup>9</sup>
- Finally, prospective data on at-risk children suggest that serum celiac disease antibodies may disappear early in life, particularly when the titer is not very high. In symptom-free children it is, therefore, advisable to perform 2 or more antibody determinations on samples taken at least 3 months apart.<sup>10</sup>

**Table** Diagnostic Criteria for Celiac Disease (At Least 4 of 5 or 3 of 4 if the HLA Genotype Is Not Performed)

Typical symptoms of celiac disease\*  
 Positivity of serum celiac disease IgA class autoantibodies at high titer†  
 HLA-DQ2 or DQ8 genotypes‡  
 Celiac enteropathy at the small intestinal biopsy§  
 Response to the GFD¶

IgA = immunoglobulin A; GFD = gluten-free diet.

Notes: A family history of celiac disease adds evidence to the diagnosis; in symptom-free patients, particularly young children, it is advisable to confirm antibody positivity on 2 or more samples taken at least 3 months apart; in selected cases, a gluten challenge after at least 2 years of GFD might be required for diagnosis confirmation.

\*Examples of typical symptoms are chronic diarrhea, growth faltering (children) or weight loss (adults), and iron deficient anemia.

†Both IgA class TTG and EMA in IgA-sufficient or IgG class TTG and EMA in IgA-deficient subjects. The finding of IgG class anti-deamidated gliadin peptide adds evidence to the diagnosis.

‡HLA-DQ2 positivity includes subjects with only half the heterodimer (HLA-DQB1\*02 positive).

§Including Marsh-Oberhuber 3 lesions, Marsh-Oberhuber 1-2 lesions associated with positive celiac antibodies positive at low/high titer, or Marsh-Oberhuber 1-3 lesion associated with IgA subepithelial deposits.

¶Histological in patients with sero-negative celiac disease or associated IgA deficiency.

The above-mentioned wide variability of celiac disease-related findings suggests that it is difficult to conceptualize the diagnostic process into rigid algorithms that do not always cover all the facets of this chameleonic disease. Instead, we find operationally useful the shifting to a quantitative approach to celiac disease diagnosis that can be defined as the “4 out of 5” rule: the diagnosis of celiac disease is confirmed when at least 4 of these criteria are satisfied (Table). If the HLA genotype is not routinely performed, 3 of 4 criteria will suffice. This proposal apparently encompasses almost all of the typical and borderline situations that we have briefly listed above.

An important corollary of this rule is that the small intestinal biopsy may be avoided in selected cases, for example, very young children with typical symptoms of celiac disease (eg, parabola-shaped weight growth curve) and high-titer IgA class anti-TTG and EMA antibodies. This is good news for both patients and patients’ parents (who dislike this invasive investigation) and the health care system that pays for it. The small intestinal biopsy is still required in other less clear situations, for example, patients with minimal/absent complaints, or with modest/discordant elevation of celiac antibodies, or lacking the typical predisposing genotypes. In these situations, an accurate evaluation of small intestinal biopsy specimens taken at different levels, including quantitative morphometry and detection of IgA deposits, should find wider application (fewer biopsies, better biopsies). Finally, in questionable cases, a gluten provocation test (challenge) after at least 2 years of gluten-free diet should be considered.

In conclusion, we propose simple diagnostic criteria that could facilitate the ascertainment of celiac disease in clinical

practice. These rules should periodically be revised to take into account the continuous evolution of both advances in pathophysiological knowledge of the disease and diagnostic tools development. Given the permanent nature of the celiac condition, diagnostic accuracy remains a must. This requirement depends more on the level of expertise provided by the diagnostic center, in terms of clinical experience and diagnostic procedures, than on the rigid application of a protocol that always includes the small intestinal biopsy.

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