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# Why Are There So Many Missed Diagnoses in Celiac Disease?

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## ABSTRACT

Celiac Disease is a chronic, multisystemic, autoimmune-mediated, genetic disorder that is triggered by the ingestion of gluten. This condition only develops in individuals with a specific genetic predisposition (HLA-DQ2/HLA-DQ8 haplotypes). Gluten is a group of proteins found mainly in wheat, barley, and rye (and in some oat products due to cross-contamination), and its consumption provokes an abnormal immune response that damages the lining of the small intestine [1]. This damage is characterized by atrophy of the intestinal villi—structures essential for nutrient absorption—leading to malabsorption and potentially resulting in nutritional deficiencies of varying severity which is characteristic, although not pathognomonic, ranging from an increase in intraepithelial lymphocytic infiltrate (ILEs) to total villous atrophy. Present a wide array of symptoms, affecting nearly every organ system [2,3].

At present, the only effective treatment is a strict and lifelong gluten-free diet, which can reverse inflammation, promote recovery of the intestinal mucosa, and prevent long-term complications. Comprehensive management also involves dietary education, clinical and nutritional follow-up, and monitoring for associated comorbidities[4]. Given its impact on quality of life and the need for sustained adherence to treatment.

It is an emerging disease that represents a serious hidden public health problem worldwide, with high and increasing prevalence and healthcare costs [5,6]. It has a global, homogeneous distribution, independent of race and age. The gender ratio is 2-3:1, with a higher incidence in women than in men.

There is written evidence of its existence dating back to the 2nd century BC, but it was only during World War II that gluten was identified as the toxin for these patients, leading to the adoption of a gluten-free diet.

We know that the number of missed diagnoses in celiac disease exceeds the number of confirmed cases. According to different authors, for every diagnosis that made, between three and ten cases remain undetected (with a global prevalence of approximately 1–2%) [2,3,7]. We also know how important is an early diagnosis, because it helps prevent complications—many of them serious—and associated conditions that, in general, do not reverse after starting a gluten-free diet if treatment begins too late[8,9]. When diagnoses are made in childhood and children adhere to a strict gluten-free diet, they typically do not develop complications or associated diseases later in life [2,10].

The aim of this communication is to analyze the main causes of underdiagnosis in celiac disease, raise awareness among healthcare professionals regarding non-classical clinical presentations, identify avoidable diagnostic errors, and promote increased clinical suspicion—particularly in at-risk populations—in order to shorten diagnostic delays and improve patient outcomes.

## So, what explains why these patients are not diagnosed early?

The reason is not a single one. Multiple factors overlap and stem both from the natural history of the disease and from the way celiac disease is (or is not) considered within healthcare systems.

**Celiac disease does not always look like "classic celiac disease."** For centuries, we held a fairly rigid image of the condition: chronic diarrhea, abdominal bloating and pain, weight loss, anemia, and growth retardation in children. This classical model still exists, but we know now it represents only a minority of cases[4]. Celiac disease is no longer confined to childhood; it can manifest at any age and shows no meaningful racial or regional differences[2,3].

**Clinical presentations vary widely.** Patients may be asymptomatic (silent)[11,12], have few or heterogeneous symptoms (oligosymptomatic), or minimize their symptoms because they have lived with them for years and perceive them as normal. This wide clinical spectrum often leads to misdiagnosis as functional gastrointestinal disorders or stress-related conditions[2,3].

**This broad spectrum makes confusion with other conditions more likely,** such as functional disorders or stress-related somatization. Misdiagnoses do occur, but the bigger issue is failing to think of celiac disease as a common, treatable condition-one that is often underdiagnosed and undervalued- and can be effectively addressed through a strict, lifelong gluten-free diet[13].

**There is a lack of cross-disciplinary awareness.** While pediatricians, gastroenterologists, and some internists are familiar with digestive and extra-digestive manifestations of celiac disease, most specialists do not recognize the symptoms and signs within their own fields. When each specialty looks only at its own "slice," celiac disease remains off the radar[2,13,14].

**There are problems in the diagnostic process, including preventable errors.** In gastroenterology, symptoms are often mild, heterogeneous, and nonspecific, and may resemble many other disorders, leading to delays[15] or overlooked diagnoses. We must know the disease in order to consider it and diagnose it.

**Even when celiac disease is suspected, procedures are frequently done incorrectly,** for example by starting a gluten-free diet before testing. This can normalize antibody results and improve intestinal mucosa, making diagnosis much more difficult-or impossible- later on[5].

**Failure to request total IgA testing.** If only specific IgA antibodies are measured without total IgA, selective IgA deficiency may be missed[6]. This deficiency is more frequent in people with celiac disease and can yield false-negative results. In adults in particular, there may be cases with negative serology even though the disease is active[3,6,16].

**Positive serology without confirmatory endoscopy and biopsy.** Sometimes, even with positive antibodies, clinicians do not request gastroduodenal endoscopy and duodenal biopsy- the gold standard, mostly in adults-[3,6,17] and instead rely on genetic testing, which has low positive predictive value (it does not confirm disease) and high negative predictive value (it almost rules it out)[18]. In both situations the result is not definitive, whereas a duodenal biopsy would be except in cases where antibodies are more than ten times above the normal limit, in which biopsy may not be necessary[4].

**Errors during biopsy sampling and interpretation.** Even with the duodenum in view, failure may occur if insufficient or poor-quality samples are taken. Sometimes endoscopy is performed for other indications and celiac-compatible mucosal patterns are found incidentally (reduced or absent folds, mosaic pattern, scalloping, fissures, grooves). In such cases, biopsies should be obtained. Samples must be taken from both the duodenal bulb and the second portion (at least 2 and 4 biopsies respectively)[11]. Specimens must be correctly oriented to avoid false positives, and interpretation should be done by a trained professional. Patchy involvement should also be considered, even within a same biopsy[19,20].

**Misinterpretation of Disease Normalization.** Once a gluten-free diet is started, the patient's antibodies gradually decrease (those remain permanently stored in lymphocyte memory), and their villi rebuild. After a period of time, which is longer in adults than in children and varies from patient to patient, the antibodies and villi return to normal, which does not mean the patient is cured. Celiac disease is not curable; it simply means the person is now healthy if follows a gluten-free diet. This patient will never be able to ingest even traces of gluten again for the rest of their life. And we must dispel the belief held by some doctors that a patient whose blood antibodies levels have normalized is cured and can resume a normal diet[2,10].

**Risk groups must not be underestimated.** These groups carry a much higher probability of celiac disease than the general population (approximately 10–15%). Even if asymptomatic, they should be evaluated regularly. In most countries, systematic screening is not performed; therefore, an important alternative is active case-finding, particularly in primary care[2,4,13,14].

**Risk Groups**

- First- and second-degree relatives of people with celiac disease
- Type 1 diabetes
- Hashimoto's thyroiditis
- Spontaneous miscarriages, especially recurrent
- Male and female infertility
- Dermatitis herpetiformis
- Cerebellar ataxia
- Collagen vascular diseases
- Selective IgA deficiency
- Hypogammaglobulinemia
- Cystic fibrosis

- Down, Turner, Williams syndromes
- Dental enamel defects
- Recurrent mucosal ulcerations (e.g., aphthae)
- Chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease)
- Autoimmune cholangitis (primary biliary cholangitis, primary sclerosing cholangitis)
- Autoimmune diseases affecting various organs (like liver, pancreas, kidney)
- Antiphospholipid syndrome
- Metabolic syndrome
- Eating behavior disorders
- Multiple food intolerances
- Malabsorption syndromes and micronutrient deficiencies
- Immunodeficiency
- Cancer
- Other non-specific groups that should be studied include patients with: unexplained anemia, weight loss, growth delay, short stature, anorexia, chronic fatigue, chronic diarrhea, irritable bowel syndrome, cramps, edema, headaches, osteoporosis (even pre-menopause or in men), spontaneous fractures, tetany, recurrent infections, coagulation disorders and purpura, "brain fog," neuropathies, paresthesia, seizures, depression, unexplained hypertransami-nasemia, and many other less frequent manifestations[20].

This clinical heterogeneity explains why diagnosis requires a high index of suspicion and a combination of specific serologic tests with histologic confirmation through intestinal biopsy[21].

All associated conditions appear more frequently in people with celiac disease than in the general population. After 3–4 years of a strict gluten-free diet, their frequency returns to levels similar to those of the general population; this is why they are considered "risk groups."

In many cases, these associated conditions may be the first clinical manifestation of celiac disease. If celiac disease is diagnosed in time and a gluten-free diet is started, some of these conditions may partially or fully revert[22]. This underscores what could have been prevented with early diagnosis. The years lost before diagnosis represent accumulated damage[23].

There may also be confusion with other gluten-related disorders such as dermatitis herpetiformis, cerebellar ataxia, non-celiac gluten/wheat sensitivity, wheat allergy, and, of course, celiac disease itself.

All the symptoms and signs listed across different organs and systems can belong to multiple pathologies that do not have a diagnosis because they do not fully fit within them. **But should we not consider that some of them may be due to celiac disease?** By diagnosing and treating it (with a gluten-free diet), we can remove patients from the category of "undiagnosed"—a situation that ultimately represents a failure for the healthcare system.

All of the above mentioned is supported by different cited authors and is also based on evidence[24].

For uncertain cases, or for patients who started a gluten-free diet before evaluation, complementary methods are being developed and validated, such as interleukin-2 testing[25], measurements of intraepithelial leukocyte subpopulations, analysis of volatile compounds, the role of the intestinal microbiota in disease development is explored as an exciting frontier, and other emerging tools[5,26].

At the same time, artificial intelligence is advancing in three highly promising areas[27]:
**Automated histopathological analysis** to evaluate multiple cuts from the same biopsy, detect subtle lesions, and avoid missed diagnoses (this is the most advanced line of research)[11,22,28,29].

**AI-assisted interpretation of endoscopic images** to highlight patterns that the endoscopist's eye might miss or to define optimal biopsy sites, including in videocapsule studies[30]. And in unsuspected cases undergoing endoscopy for other reasons[31].

**Analysis of electronic health records** to define risk profiles and suggest testing-as an active search for risk groups- an intelligent screening approach. This is not magic: infrastructure, external validation, and regulation are still needed, but clinically serious results already exist[28,32,33].

## Conclusion

Celiac disease is common, treatable, and potentially silent. Underdiagnosis does not occur for a single reason but rather through a chain of factors: non-classical clinical forms, heterogeneous symptoms, lack of cross-disciplinary knowledge, preventable diagnostic errors, and insufficient active case-finding among risk groups.

We must find ways for these patients to receive an early diagnosis so they do not spend years moving between doctors and healthcare services with a disease that compromises their quality of life.

**This requires:**

- considering celiac disease in the presence of nonspecific symptoms or associated conditions (high index of suspicion)
- studying it correctly without skipping steps, and
- training different specialties to recognize it within their own clinical domains.

Because when diagnosis is early and the gluten-free diet is followed strictly and lifelong, many risk factors cease to be risks and become potentially modifiable. That changes the natural history of the disease.

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