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CELIAC DISEASE AS A MASKING CONDITION — THE ROLE OF EXTRAINTESTINAL SYMPTOMS IN DELAYED DIAGNOSIS

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ABSTRACT

Background: Celiac disease is a chronic autoimmune enteropathy caused by gluten in genetically predisposed people. It affects about 1% of the population. It was once seen mainly in children, but adult diagnoses are rising. Symptoms stem from immune reactions and nutrient deficiencies from gluten intake. Proper diagnostic tests allow quick diagnosis and treatment with a gluten-free diet (Durazzo et al., 2022).
Aim: This study intends to present the current state of knowledge regarding celiac disease, with particular emphasis on its extraintestinal manifestations. Their occurrence frequently represents a diagnostic challenge for physicians and may lead to inappropriate treatment management. This review intends to increase physicians' clinical awareness and encourage the use of appropriate, targeted diagnostic investigations.
Conclusions: The conducted literature analysis shows that celiac disease remains undiagnosed in a significant proportion of patients presenting with extraintestinal symptoms. Because gastrointestinal manifestations predominated in the past, physicians' diagnostic vigilance has diminished. Extraintestinal symptoms currently constitute a major diagnostic challenge and are increasingly observed, complicating and delaying accurate diagnosis. Untreated celiac disease may lead to serious complications that could be prevented through proper interpretation of these manifestations. Therefore, it is the key for physicians — particularly those working in primary care — to recognize these disease manifestations and quickly initiate treatment with a gluten-free diet, which markedly improves the prognosis of patients with celiac disease.

KEYWORDS

Celiac Disease, Extraintestinal Manifestations, Delayed Diagnosis, Atypical Celiac Disease, Gluten-Related Disorders

CITATION

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Introduction:

Celiac disease is a gluten-dependent autoimmune disorder occurring in genetically predisposed individuals. The presence of specific antibodies, the human leukocyte antigen haplotypes HLA-DQ2 and HLA-DQ8, and characteristic enteropathy are typical features of this condition. Activation of the immune response induces the production of proinflammatory cytokines, which affect cells throughout the body and result in villous atrophy in the small intestine. These processes are responsible for the development of characteristic symptoms, including diarrhea, abdominal pain, bloating, vomiting, and other gastrointestinal complaints.

The presence of extraintestinal manifestations, including anemia, reduced bone mineral density, fatigue, headaches, and other disorders affecting various systems, such as neurological or endocrine disturbances, constitutes a significant clinical problem. These manifestations are associated with gastrointestinal dysfunction resulting from impaired nutrient absorption and related nutritional deficiencies. Consequently, they may lead to abnormal functioning and damage to other organ systems.

Currently, depending on the studied population and diagnostic methods used, the prevalence of celiac disease in the general population ranges from 0.75% to 1.6%. Studies have shown that 60% of children and 62% of adults present with extraintestinal symptoms (Jericho et al., 2017); therefore, up to 75% of celiac disease cases remain undiagnosed (Kvamme et al., 2022). Although the disease was once considered a pediatric condition primarily, it is now increasingly diagnosed in adults. Moreover, the clinical presentation, once regarded as typical, is now frequently atypical, posing a major diagnostic challenge for physicians.

Because extraintestinal symptoms, which may often represent the only manifestations of the disease, overlap with the clinical presentation of many other conditions, they are frequently misinterpreted. This leads to numerous diagnostic errors and fragmented treatment approaches. As a result, establishing the final diagnosis of celiac disease may be significantly delayed — sometimes by several years — exposing patients to extended inflammation and the negative consequences associated with the lack of causal treatment.

According to current guidelines, the diagnostic process should include both intestinal and extraintestinal symptoms, the presence of IgA anti-tissue transglutaminase antibodies, measurement of total serum IgA levels, and typical histological findings on duodenal biopsy. Untreated celiac disease may lead to the development of malignancies, such as esophageal cancer, small intestinal cancer, and lymphoma, particularly enteropathy-associated T-cell lymphoma.

Therefore, to prevent such serious complications, regular screening and increased awareness of celiac disease among physicians of various specialties are essential. Although strict adherence to a gluten-free diet may alleviate, and in some cases eliminate symptoms, doctors should remember that prevention is much better than treatment (Kowalski et al., 2025).

Aim of the Study:

This review paper aims to present the current state of knowledge regarding the pathogenesis and clinical presentation of celiac disease in patients with extraintestinal manifestations. The analysis and evaluation of the effects of these symptoms on the diagnostic process are fundamental to understanding their multifactorial nature and their nonspecific association with the gastrointestinal system. Misunderstanding their etiology, along with misinterpretation of diagnostic test results and patients' clinical symptoms, may lead to deterioration in health status and the development of long-term complications.

The findings derived from this study should encourage physicians to maintain heightened clinical care and to pursue more comprehensive diagnostic evaluation for this condition to preclude delays in initiating appropriate treatment for affected patients.

Literature Review Methodology

The literature review included original research articles, systematic reviews, and reports published in reputable medical and gastroenterology journals. Priority was given to publications from the past 10 years (2015–2025) to ensure the data's relevance and timeliness. Literature searches were performed using scientific databases such as PubMed, MDPI, *Scientific Reports*, Via Medica Journals, and the European Society of Medicine.

Pathogenesis of Extraintestinal Manifestations

Gluten is a complex of proteins, primarily gliadin and glutenin, which are rich in the amino acids glutamine and proline. By definition, celiac disease is an abnormal immune response to gluten, more precisely to the protein complexes it contains. The protein composition of gluten makes it resistant to proteolytic digestion. After entering the small intestine, gluten releases numerous immunogenic peptides that activate the gut-associated lymphoid tissue (GALT) in the intestinal mucosa. Activation of this tissue by gluten-derived peptides triggers an inflammatory process and a cascade of immune reactions.

The immunological mechanism proceeds as follows: gliadin binds to the CXCR3 receptor on enterocytes, inducing the release of zonulin. Zonulin disrupts tight junctions between epithelial cells, increasing intestinal permeability. Subsequently, activated dendritic cells secrete interleukin-15 (IL-15), which leads to the activation and proliferation of CD8+ intraepithelial T lymphocytes (IELs). This activation induces the expression of natural killer (NK) cell receptors, particularly NKG2D and CD94/NKG2C, consequently enhancing cytotoxicity against enterocytes through interactions with MICA and HLA-E. In the final stage, suppression of transforming growth factor-β (TGF-β) expression occurs, which is normally secreted by regulatory T lymphocytes (Treg) and FOXP3+ T cells. This inhibition results in loss of immune regulation, epithelial damage, and initiation of intestinal villous atrophy.

Another component of the immune response in celiac disease is tissue transglutaminase 2 (tTG2), which modifies gluten peptides via deamidation. These modified peptides subsequently bind to HLA-DQ2 and HLA-DQ8 molecules present on dendritic cells. This interaction leads to the activation of gluten-specific CD4+ T lymphocytes in the lamina propria and initiates the production of proinflammatory cytokines, including interferon-γ (IFN-γ), interleukin-21 (IL-21), and interleukin-2 (IL-2). IFN-γ promotes a Th1 immune profile, impairs regulatory T-cell (Treg) function, and increases the activity of cytotoxic CD8+ T lymphocytes. This results in intensified inflammation and contributes to villous atrophy in the intestinal mucosa (Patt et al., 2023).

One of the major risk factors for the development of celiac disease is genetic predisposition, particularly the presence of human leukocyte antigen (HLA) DQ2 and/or HLA-DQ8. These alleles significantly increase the risk of developing the disease. A 2023 study by Sare Aboulaghras and colleagues demonstrated that the DQ2 allele is the primary genetic risk factor for celiac disease. Both homozygous and heterozygous HLA-DQ2 status are more frequently observed in adults with this condition. Mechanisms of gluten peptide presentation by DQ2 further confirm the strong association between this HLA haplotype and celiac disease.

To summarize, the presence of HLA-DQ2/DQ8 indicates a genetic predisposition to celiac disease but does not confirm the disease itself. A negative test result generally excludes celiac disease as a possible cause of symptoms (Aboulaghras et al., 2023). In addition to HLA-DQ2/DQ8, many other immune-response-related genes may increase disease risk, although their individual contributions are smaller than those of HLA. Approximately half of the total genetic predisposition remains to be clarified and may involve epigenetic factors, small RNA molecules, and other mechanisms that call for further research (Tan et al., 2021)

Celiac disease is a disorder of digestion and nutritional absorption characterized by intestinal villous atrophy. This condition leads to the depletion of enzymes necessary for digestion, particularly brush-border enzymes. The disease initially involves the proximal small intestine and subsequently spreads to more distal segments. The proximal small intestine is responsible for the absorption of essential nutrients, including iron, folic acid, calcium, zinc, and magnesium. Furthermore, the jejunum and proximal ileum are responsible for the absorption of carbohydrates, fats, vitamin B6, and fat-soluble vitamins (A, D, E, and K). Vitamin B12, in contrast, is absorbed in the terminal ileum. The degree of intestinal mucosal damage correlates with the severity of nutrient deficiencies and associated symptoms, particularly in untreated patients with celiac disease (Kreutz et al., 2020; Therrien et al., 2020).

Epidemiology of Extraintestinal Manifestations

Typical symptoms occurring in celiac disease are well known and widely documented due to their frequency. Chronic abdominal pain, bloating, diarrhea, and weight loss are associated with a high probability of celiac disease in affected patients. Unfortunately, the presence of exclusively extraintestinal symptoms makes accurate diagnosis and treatment initiation more difficult, as their frequency and nonspecific nature often lead to misinterpretation.

According to a 2017 study by Hilary Jericho and colleagues, the prevalence of extraintestinal manifestations was 60% among children and 62% among adults. The frequency of selected extraintestinal symptoms is presented in the table below (Jericho et al., 2017).

Table 1. Prevalence of Selected Extraintestinal Manifestations in Children and Adults with Celiac Disease (Laurikka et al., 2018).

Short stature	33%	3%
Fatigue	28%	37%
Headaches	20%	24%
Anemia	40%	48%
Neurological symptoms	52%	24%
Osteoporosis	0%	23%
Infertility	—	5%

Despite the frequent occurrence of extraintestinal manifestations, some individuals with celiac disease do not present with characteristic intestinal symptoms associated with the condition. A 2022 study by Jan Magnus Kvamme and colleagues, involving 6,053 men and 6,928 women, found that the prevalence of celiac disease was approximately 1.47%. Importantly, around 75% of these cases remained undiagnosed, primarily because affected individuals often lacked typical intestinal symptoms and tended to underestimate or disregard their complaints (Kvamme et al., 2022).

The Most Common Extraintestinal Manifestations of Celiac Disease:

Hematological Manifestations

Celiac disease may lead to various hematological disorders due to impaired nutrient absorption in the small intestine. One of the most common complications is iron deficiency anemia, which occurs in more than half of patients with celiac disease and may sometimes represent the only observed manifestation of the disease. In some cases, anemia may also present as anemia of chronic disease or anemia associated with chronic inflammation (Seidita et al., 2022).

A 2021 study by Marleena Repo and colleagues suggested an association between iron deficiency in patients with celiac disease and abnormal expression of iron transport proteins. Increased ferroportin expression and decreased hephaestin expression were observed in children with celiac disease compared with healthy controls. However, further studies are required to fully understand the mechanisms underlying impaired iron metabolism in celiac disease (Repo et al., 2021).

Moreover, a 2018 study conducted by Neha Berry and colleagues involving 103 patients with celiac disease demonstrated that iron deficiency anemia was present in 81.5% of participants. Other causes of anemia were also identified: folic acid deficiency occurred in 10.7% of patients, while vitamin B12 deficiency anemia was observed in 13.6% of cases. Although vitamin-related anemias occur less frequently than iron deficiency anemia, they should be considered during the diagnostic process. The research team also demonstrated a significant association between anemia severity and the degree of intestinal villous atrophy (Berry et al., 2018).

Table 2. Most Common Hematological Symptoms Associated with Nutrient Deficiencies in Patients with Celiac Disease

Iron	Microcytic, hypochromic anemia; fatigue; weakness; pallor of the skin and mucous membranes; brittle hair and nails; angular cheilitis
Vitamin B12	Megaloblastic anemia; glossitis; fatigue; weakness; neurological symptoms such as numbness and tingling of the extremities; depression
Folic Acid	Megaloblastic anemia; glossitis; fatigue; weakness; pallor of the skin and mucous membranes; neurological symptoms

Bone Manifestations

Reduced bone mineral density, known as osteopenia, is a common problem in patients with celiac disease and may lead to the development of osteoporosis. Bone changes are mainly caused by impaired calcium and vitamin D3 absorption in the small intestine, as well as by the release of proinflammatory cytokines due to chronic inflammation. During childhood and adolescence, adequate calcium intake is critical, as it plays a key role in achieving peak bone mass. A decrease in serum calcium levels stimulates parathyroid hormone (PTH) secretion, leading to bone demineralization. Vitamin D3 deficiency occurs significantly more frequently in individuals with celiac disease.

Approximately 30–60% of patients with newly diagnosed celiac disease present with osteopenia, while 18–35% have osteoporosis. Bone loss typically begins around age 35, peaks after age 50, and increases the risk of fractures. A 2015 study conducted by Katriina Heikkilä and colleagues demonstrated that the overall risk of any fracture in individuals with celiac disease is 30% higher, while the risk of hip fracture is increased by 69% compared with healthy individuals (Heikkilä et al., 2015). Therefore, performing densitometric testing in patients with suspected or confirmed celiac disease is of great importance. Strict adherence to a gluten-free diet is likely the only effective treatment capable of restoring normal bone mineral density in both children and adults (Lungaro et al., 2023).

Neurological Manifestations

Neurological symptoms may result from the deposition of immune complexes, their neurotoxic effects, and vitamin and nutrient deficiencies. Patients with celiac disease may develop various neurological disorders, including different types of peripheral neuropathies and gluten ataxia. These conditions are often observed in individuals without gastrointestinal symptoms.

Peripheral neuropathy is characterized by tingling, pain, and numbness caused by nerve damage, usually beginning in the hands and feet. The average age of onset is approximately 55 years. Gluten ataxia affects muscle control, making it difficult for patients to coordinate arm and leg movements and maintain a stable gait. It may also cause difficulties in performing fine motor tasks and visual impairments. The average age of onset is approximately 53 years (Mearns et al., 2019).

A 2019 study by Marios Hadjivassiliou and colleagues, involving 100 patients with celiac disease, reported the following findings: gait instability in 24%, persistent sensory symptoms in 12%, headaches in 42%, nystagmus in 11%, and distal sensory loss in 10%. Abnormal magnetic resonance imaging (MRI) findings were noted in 60% of participants, while 47% demonstrated abnormal cerebellar MR spectroscopy results (Hadjivassiliou et al., 2019).

A 2021 study conducted by Mohammad M. Fanaeian and colleagues included 1,000 patients with confirmed celiac disease. The results showed that headaches were more frequent in these patients (34%) compared with the control group (27%). Additionally, migraines occurred significantly more often in individuals with celiac disease (20%) than in healthy controls (12%). The study also demonstrated that women experienced both headaches and migraines more frequently than men — approximately 72% of individuals reporting headaches and 80% of those with migraines were women. In patients with celiac disease, migraines most commonly occurred without aura (76%), were unilateral, and were usually accompanied by nausea. Evidence suggests that a gluten-free diet may effectively alleviate headaches and significantly improve the course of migraines (Fanaeian et al., 2021).

Despite improved understanding of the relationship between neurological disorders and celiac disease, diagnostic delays remain common and may result in permanent nervous system damage. Strict adherence to a gluten-free diet may relieve symptoms of neuropathy, ataxia, headaches, and other neurological disorders.

Dermatological Manifestations in Celiac Disease

A 2021 study by Kapeel Dev and colleagues, involving 300 patients with confirmed celiac disease, found that the most common dermatological manifestation was dermatitis herpetiformis, occurring in 16% of patients, predominantly in men. The second most frequent condition was psoriasis, observed in 13.8% of patients and more commonly affecting women (Dev et al., 2021).

Dermatitis herpetiformis, sometimes referred to as the cutaneous form of celiac disease, typically presents with symmetrically distributed vesicles and papules located on the elbows, knees, and buttocks. Patients frequently undergo persistent pruritus, leading to scratching and excoriation. Importantly, individuals with dermatitis herpetiformis frequently do not exhibit gastrointestinal symptoms. Pathognomonic granular IgA deposits are found in the dermal papillae of affected subjects and are believed to originate from the intestine. The autoantigen targeted by cutaneous IgA antibodies is epidermal transglutaminase (TG3), which is closely related to tissue transglutaminase (TG2), the primary autoantigen in celiac disease.

The current understanding of the immunopathogenesis of dermatitis herpetiformis suggests that the process starts with latent celiac disease in the small intestine, accompanied by an autoimmune response that produces antibodies against tissue transglutaminase TG2 and, most likely, TG3. In the subsequent stage, immune complexes composed of high-avidity IgA antibodies directed against TG3 and the TG3 enzyme itself form and deposit within the dermal papillae. These mechanisms are supported by clinical observations related to treatment with a gluten-free diet (GFD). Adherence to a gluten-free diet leads to the disappearance of anti-TG2 and anti-TG3 antibodies in the serum, resulting in the resolution of skin lesions and regeneration of the small intestinal mucosa (Reunala et al., 2018).

Psoriasis, similarly to celiac disease, is an immune-mediated disorder. In individuals with celiac disease, impairment of the intestinal barrier function leads to the release of proinflammatory cytokines and activation of T lymphocytes. These immune cells may enter the bloodstream and accumulate within the epidermis and dermis. This process, combined with the fact that many patients with celiac disease have reduced vitamin D levels — a key factor toward maintaining healthy skin — may increase the risk of developing psoriasis (Li et al., 2022).

Endocrinological Manifestations

The association between thyroid diseases and celiac disease may be explained by genetic predisposition. Several immune system–related genes, such as HLA-DQ2, HLA-DQ8, and CTLA-4, are shared by individuals with celiac disease and patients with autoimmune thyroid disorders. Additionally, shared immunological mechanisms, including a Th1-type immune response and the production of proinflammatory cytokines, may link these two conditions. As a result, celiac disease is diagnosed more frequently in patients with autoimmune thyroiditis than in the general population. Studies indicate that approximately 4%–8% of patients with autoimmune thyroiditis also have biopsy-confirmed celiac disease. Although there is no conclusive evidence that a gluten-free diet alone treats autoimmune thyroid disorders, it may influence certain symptoms or immunological markers and may improve overall patient functioning (Ashok et al., 2022).

Type 1 diabetes mellitus, similarly to celiac disease, is an autoimmune condition. The risk of developing both disorders is increased in individuals with hereditary susceptibility and specific HLA haplotypes, particularly HLA-DQ2 and HLA-DQ8. Celiac disease occurs more frequently in individuals with type 1 diabetes than in the general population, with a prevalence of at least 5% in this group. In patients with type 1 diabetes, celiac disease often presents asymptomatically or with mild symptoms, which complicates diagnosis. Early screening for celiac disease in individuals with type 1 diabetes is essential, as delayed diagnosis may lead to complications such as growth retardation, anemia, or reduced bone mineral density during early life.

Considering that patients with type 1 diabetes belong to a high-risk group for developing celiac disease and that symptoms may be subtle, regular serological screening is recommended. Strict adherence to a gluten-free diet may primarily improve glycemic control in patients with both conditions, whereas normalization of autoantibody levels is generally expected regardless of dietary changes (Flores Monar et al., 2022).

Reproductive System Manifestations

Celiac disease presents with a wide range of extraintestinal manifestations, including reproductive problems such as infertility and recurrent spontaneous miscarriages. Celiac disease should be considered as a potential underlying factor, since a direct cause of these disorders cannot be identified. Infertility in individuals with celiac disease is most often multifactorial, and proposed mechanisms include disturbances in immunoendocrine regulation as well as micronutrient deficiencies.

Malabsorption associated with celiac disease may lead to deficiencies of essential nutrients, including iron, selenium, zinc, folic acid, and vitamins A, D, E, and K. These nutrients are critical for proper gametogenesis, ovulation, implantation, and fetal development. Zinc and selenium, in particular, play important roles in sperm maturation and endometrial receptivity. The immunoendocrine mechanism is associated with the presence of anti–tissue transglutaminase autoantibodies and antithyroid antibodies, as well as increased levels of proinflammatory cytokines. These factors may impair angiogenesis within the endometrium and placenta. In men, immune-mediated processes may lead to reduced semen quality and impaired sperm function (Wieser et al., 2025).

Untreated celiac disease may also result in delayed menarche, irregular menstrual cycles, and premature menopause, ultimately shortening the reproductive period.

A study conducted in 2016 by Prashant Singh and colleagues demonstrated that women experiencing infertility had a 3.5-fold higher risk of being diagnosed with celiac disease compared with the control group. In cases of unexplained infertility, this risk increased sixfold. Among the 884 women with infertility included in the study, celiac disease was diagnosed in 2.3%, whereas among 623 women with unexplained infertility, the disease was identified in 3.2% (Singh et al., 2016).

Untreated celiac disease may lead to spontaneous miscarriages as a result of deficiencies in crucial nutrients such as zinc and selenium, as well as malnutrition frequently observed in affected individuals. These deficiencies negatively influence gonadotropin secretion, which may result in miscarriage or intrauterine growth restriction. Additionally, the presence of anti–tissue transglutaminase type 2 antibodies may interfere with implantation and proper placental development (Wieser et al., 2025).

In infertile patients with celiac disease, strict adherence to a gluten-free diet increases the likelihood of conception and a normal course of pregnancy, ultimately resulting in the birth of a healthy child. However, it should be noted that such a diet may lead to reduced intake of essential nutrients; therefore, appropriate supplementation is necessary (Krawczyk et al., 2022).

Extraintestinal Manifestations as a Cause of Delayed Diagnosis

Gastrointestinal symptoms are most commonly associated with disorders of the digestive tract, allowing prompt initiation of diagnostic evaluation for related conditions, including celiac disease. However, the presence of exclusively extraintestinal manifestations amounts to a considerable diagnostic challenge for patients. Due to the nonspecific nature of symptoms such as fatigue, headaches, or anemia — which frequently occur in many other, far more common population diseases — patients are often investigated for alternative diagnoses.

The performance of numerous diagnostic tests, frequently limited in scope and unable to identify celiac disease as the primary underlying cause, may lead to misdiagnosis. Initiating treatment directed toward an incorrectly diagnosed condition, as well as continuing diagnostic investigations that fail to examine the true source of the problem, may significantly delay the establishment of the final diagnosis of celiac disease. Another important factor is the lack of patient awareness of these symptoms, which often leads to their underestimation or neglect. Symptoms are frequently not severe enough to prompt patients to seek medical consultation or initiate diagnostic evaluation. They may also be overlooked because of their initially minimal impact on daily functioning and quality of life (Casella, 2025).

Consequently, autoimmune pathological processes may persist for extended periods, causing progressive damage and dysfunction affecting multiple organ systems. The long-term persistence of such a condition may lead to irreversible consequences and reduced quality of life in patients with undiagnosed or misdiagnosed celiac disease (Casella, 2025).

A study conducted in 2017 by Marco A. Paez and colleagues included 101 patients with biopsy-confirmed celiac disease. Among them, 49 patients presented with extraintestinal manifestations. Statistical

analysis reported in the article, performed using the Mann–Whitney test, demonstrated an average diagnostic delay of 2.3 months in patients with gastrointestinal symptoms, compared with up to 42 months in individuals presenting with extraintestinal manifestations. The table below presents the prevalence of selected nonspecific abnormalities in patients with gastrointestinal symptoms compared with those without.

Table 3. The prevalence of selected nonspecific abnormalities in patients with gastrointestinal symptoms compared with those without (Paez et al., 2017).

Abnormal thyroid-stimulating hormone (TSH) levels	15.5%	43.2%
Anemia	11.5%	69.4%
Abnormal bone density	41%	68%

The Importance of Screening

When Should Celiac Disease Be Suspected?

The clinical presentation of celiac disease has changed significantly over recent decades. The classical form of the disease, characterized by predominant gastrointestinal symptoms, is now observed less frequently than atypical and extraintestinal forms. Current guidelines point out the need for active case-finding in patients presenting with manifestations outside the gastrointestinal tract, as these may be the only manifestations of the disease.

According to the recommendations of the American College of Gastroenterology (ACG) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), serological testing for celiac disease should be performed in individuals presenting with unexplained systemic symptoms or laboratory abnormalities suggestive of malabsorption syndrome or autoimmune processes.

Chronic iron deficiency anemia of unknown etiology remains one of the most common indications for diagnostic evaluation. The ACG identifies persistent iron deficiency and unexplained anemia as key indications for serological testing for celiac disease, even in the absence of gastrointestinal symptoms.

Disorders of bone metabolism constitute another important group of extraintestinal manifestations. Reduced bone mineral density, osteopenia, and premature osteoporosis — particularly in youths or in patients with low-energy fractures — are recognized as indications for celiac disease testing in both ACG and ESPGHAN guidelines. These conditions frequently result from chronic malabsorption, including vitamin D and calcium deficiency and secondary hyperparathyroidism.

Neurological symptoms also represent an important group of extraintestinal manifestations. Current guidelines list peripheral neuropathy, ataxia, and epilepsy as clinical situations that justify screening for celiac disease, especially when no alternative cause has been identified. These symptoms may result from both vitamin deficiencies and autoimmune mechanisms.

Celiac disease should also be considered in patients presenting with chronic fatigue, impaired concentration often described as “brain fog,” and neuropsychiatric symptoms. According to ACG recommendations, chronic fatigue constitutes a valid indication for diagnostic evaluation.

In the field of endocrinology and reproductive health, diagnostic testing should be considered in cases of infertility of unexplained etiology, menstrual disorders, or delayed puberty. These disturbances may be associated with both nutritional deficiencies and coexisting autoimmune diseases.

Individuals presenting with the above unexplained extraintestinal manifestations, as well as their first-degree relatives, constitute a high-risk group for celiac disease and require an active case-finding strategy (Husby et al., 2020; Rubio-Tapia et al., 2023).

The Role of Serological Diagnostics

Current diagnostic algorithms for celiac disease are primarily based on serological testing, which serves to identify patients who call for further evaluation or small intestinal biopsy. The European Society for the Study of Coeliac Disease (ESsCD) recommends measuring IgA anti–tissue transglutaminase antibodies (anti-TG2 IgA) as the first-line test in cases of suspected disease. This test demonstrates high sensitivity and specificity, particularly in patients who are consuming gluten. Therefore, a gluten-free diet should not be initiated until the diagnostic process is complete.

Simultaneous assessment of total serum IgA levels is also essential, as selective IgA deficiency occurs more frequently in patients with celiac disease and may lead to false-negative results. In such cases, IgG-based serological tests are recommended, particularly anti-TG2 IgG antibodies or antibodies against deamidated gliadin peptides (DGP IgG), despite their slightly lower diagnostic value.

Anti-endomysial antibodies (EMA) exhibit very high specificity and may be used when the diagnosis is ambiguous. Although duodenal mucosal biopsy remains the reference standard for diagnosing celiac disease in most cases, current guidelines allow diagnosis without biopsy in selected adult patients whose anti-TG2 IgA levels exceed 10 times the upper limit of normal. They are confirmed in a second blood sample.

Genetic testing for HLA-DQ2 or HLA-DQ8 is not routinely performed; however, it may be useful in cases with diagnostic uncertainty. This approach may increase diagnostic reliability and reduce the need for invasive procedures (Al-Toma et al., 2025).

Discussion

The way celiac disease manifests in patients has changed significantly over the years. In the past, it was primarily associated with gastrointestinal complaints; however, these symptoms now represent only a proportion of cases. In many individuals, the first manifestations occur outside the digestive system, which makes diagnosis more challenging. Studies indicate that a substantial number of patients remain undiagnosed for extended periods. Nonspecific symptoms such as chronic fatigue, anemia, or headaches often lead patients to consult multiple specialists before their immunological origin is recognized.

Extraintestinal manifestations of celiac disease have a complex etiology and are not entirely due to malabsorption. Although nutrient deficiencies play an important role, an increasing number of studies point out the significance of autoimmune reactions and systemic inflammation. Autoantibodies directed against tissue transglutaminase may damage tissues outside the gastrointestinal tract, which may explain why some patients experience severe neurological or dermatological symptoms despite relatively preserved small intestinal morphology. Iron deficiency anemia remains the most common extraintestinal manifestation of the disease and is often treated without identifying its underlying cause. However, when anemia remains despite supplementation and no obvious source of blood loss is identified, further diagnostic evaluation is necessary. A similar approach should be applied to bone health. Reduced bone mineral density in young persons without typical risk factors warrants consideration of celiac disease as a possible cause, particularly given that chronic inflammation may further accelerate bone resorption.

Neurological manifestations represent a particular diagnostic challenge because they are nonspecific and may have multiple etiologies. Studies indicate that neurological changes may improve only partially despite strict adherence to a gluten-free diet, pointing out the importance of early diagnosis. When diagnosis is delayed, nerve damage and other complications may become permanent.

Celiac disease frequently coexists with other autoimmune disorders, which adds further complexity to the diagnostic process. Individuals with certain hereditary predispositions are at increased risk of developing multiple autoimmune diseases, making the identification of celiac disease more difficult. Physicians should consider screening for celiac disease in patients with diagnosed autoimmune disorders, even in the absence of gastrointestinal symptoms.

The introduction of highly sensitive serological testing has significantly facilitated the diagnosis of celiac disease. However, the effectiveness of these tests depends on physicians' decisions to use them. To shorten the time to diagnosis, easy access to testing and greater awareness of the disease's diverse clinical presentation are essential. Celiac disease should be regarded as a systemic disorder instead of only a disease of the small intestine. Extraintestinal manifestations are common and often represent the primary presentation of the disease. Their early recognition may accelerate diagnosis and prevent long-term complications.

Conclusions

The clinical phenotype of celiac disease continues to pose a diagnostic challenge, as extraintestinal manifestations — particularly in adults — commonly hinder recognition of the disease beyond the commonly associated gastrointestinal symptoms. These manifestations may delay accurate diagnosis and therefore require increased diagnostic vigilance to shorten the duration of untreated disease and prevent serious complications. Consequently, implementing screening strategies proves essential to lower this risk and enable patients to maintain proper functioning and a good quality of life.

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