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Review

Osteoarticular manifestations of celiac disease and non-celiac gluten hypersensitivity

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ABSTRACT

Celiac disease is a chronic inflammatory autoimmune enteropathy based disorder that is triggered by the ingestion of gluten in genetically susceptible individuals. The global prevalence of 1% to 2% represents only the tip of the iceberg. The diagnosis is confirmed by positive specific antibody, anti-transglutaminase or anti-endomysium, specific lesions of the small intestine and a response to strict gluten-free diet. The diagnosis is difficult and often delayed because the clinical variability is very large, ranging from digestive clinical presentation "classic" to "atypical" symptoms, often extra-intestinal, that are sometimes attributed to a concomitant disease or a complication. Among them, there are frequent musculoskeletal manifestations such as osteoporosis and osteomalacia. In the absence of risk factor, osteoporosis, in a premenopausal women or in a man less than 55 years, more is if it is severe and refractory to medications, need to rheumatologists on the track of celiac disease in the absence of digestive symptoms. Osteomalacia is related to secondary hypovitaminosis D malabsorption. Supplementation by calcifediol, water-soluble vitamin D, may be indicated. Celiac disease is associated with an autoimmune disease in almost 1/3 of the cases. Knowing these potential associations allows earlier diagnosis in patients whose only manifestation, a concomitant disease. Anemia, chronic fatigue or unexplained polyarthralgia are symptoms associated with celiac disease to look for specific antibodies. The aim of early diagnosis is to prevent the emergence of other systemic disorders and avoid complications such as bone fractures and cancer, especially intestinal lymphoma. Non-celiac gluten intolerance is a new entity defined by symptomatology similar to that of celiac disease induced by the ingestion of gluten and disappearing after crowding-out, among patients without specific antibodies and without intestinal lesion of celiac disease. This entity is a cause, at least in part, of increasing interest in gluten-free diet in the general population.

1. Definition and epidemiology

Celiac disease is a chronic autoimmune inflammatory bowel disease induced by the gluten peptide gliadin in genetically susceptible individuals. Gluten is found in most cereal grains including wheat, rye, and barley. Gluten is among the grain constituents that ferment during the production of bread, which makes the gluten-free diet burdensome. Over 95% of patients with celiac disease are positive for HLA-DQ2 and/or HLA-DQ8. When both these HLA types are absent, celiac disease is highly unlikely, perhaps even certainly ruled out.

Celiac disease has an estimated prevalence of 1% to 2% worldwide. The true prevalence is probably far higher, as the disease is underdiagnosed [1]. Prevalence estimates are increasing due to improved knowledge of the manifestations of celiac disease and to the introduction of highly sensitive and specific serological tests, most notably for anti-tissue transglutaminase antibodies type 2 (anti-tTG2). Fig. 1 describes the immunological mechanisms of celiac disease.

Perceptions of celiac disease have changed over the last two decades. Whereas the disease was previously thought to be a rare bowel condition, it is now viewed as a common multiorgan disease. In addition, other gluten-dependent immunological conditions have been identified, such as wheat allergy and non-celiac gluten hypersensitivity [2].

2. Clinical presentation of celiac disease

The diagnosis is difficult and often delayed due to the wide variety of clinical presentations ranging from the classic clinical picture

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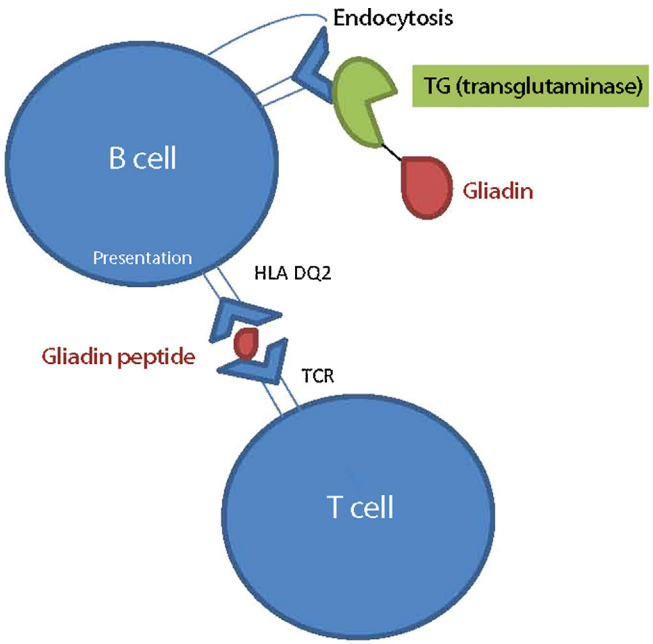

Fig. 1. Immunological mechanisms of celiac disease. Celiac disease is an inflammatory disease mediated by the T cells in the small bowel. The enzyme transglutaminase (TG) plays a key pathogenic role as the main autoantigen and the target of the specific antibodies. When tolerance to an autoantigen is lost, TG generates gliadin epitopes that bind more effectively to HLA DQ2/DQ8. TCR: T-cell receptor; HLA: histocompatibility leukocyte antigen.

to non-classic or atypical symptoms, some of which may be related to a concomitant condition or complication (Table 1) [3].

The mode of presentation may differ between children and adults. The clinical manifestations tend to diminish with advancing age. Non-classic symptoms often occur in patients with limited manifestations. Many of them involve from extra-intestinal sites. At the bone, for instance, osteoporosis or osteomalacia may develop. Thus, patients with celiac disease may present to the rheumatologist, whose task is then to establish the diagnosis of celiac disease in order to allow early and appropriate treatment, thereby decreasing the risk of malignant and nonmalignant complications [4]. Celiac disease is associated with a 1.35-fold (HR) overall increase in the risk of cancer at any site. Other complications include intestinal lymphoma, small-bowel tumors, oropharyngeal tumors, unexplained infertility, osteoporosis, and fractures [5]. Older age at diagnosis of celiac disease may be a strong risk factor for complications. The risk of lymphoma is about 8% to 10% but diminishes with early treatment [6]. The prevalence of intestinal lymphoma is increasing in lockstep with that of celiac disease [7]. Cancer usually develops at the stage of well-established celiac disease but may be inaugural [4].

The symptoms may be limited or absent. At the slightest doubt, screening tests should be performed in first- and second-degree relatives of patients with celiac disease (prevalence, 10% and 5%, respectively).

3. Diagnostic tools

3.1. Specific antibodies

The first-line investigation to evaluate suspected celiac disease is a serum assay of IgA-tTG2 antibodies. If the result is negative, the patient should be tested for IgA deficiency. In the absence of IgA deficiency, celiac disease is highly unlikely. If the IgA-tTG2 assay is positive, IgG-tTG and, in some cases, endomysial antibodies should be assayed.

3.2. Bowel biopsy

A bowel biopsy must be obtained if the serological tests are positive. The modified Marsh classification distinguishes four stages: 0, normal mucosa (known as the pre-infiltrative stage); 1, excess intraepithelial lymphocytes; 2, crypt hyperplasia; and 3, villous atrophy [8,9]. Stages 1 through 3 require a strict gluten-free diet. A response to the diet serves as a further diagnostic test. A normal mucosa rules out celiac disease. Serum assays of tTG antibodies are helpful for monitoring adherence to the diet and convincing patients of its usefulness, as the titers decline after 6 to 12 months without gluten.

4. Osteoarticular manifestations

4.1. Osteoporosis and osteomalacia

The bowel makes a major contribution to bone homeostasis both in healthy individuals and in patients with various gastrointestinal diseases. Vitamin D is absorbed by the ileum and involved in the intestinal absorption of calcium and phosphorus, as well as in their reabsorption by the kidneys, under the influence of parathyroid hormone. Therefore, good bowel function is essential to bone mineralization [10]. Osteoporosis is the most common consequence of undiagnosed and/or untreated celiac disease. Thus, osteoporosis is found in up to 75% of patients with celiac disease, independently from the presence of gastrointestinal symptoms, and may develop in non-menopausal women and in men younger than 55 years of age. The risk of severe osteoporosis refractory to medications is particularly high in patients with celiac disease. Compared to unaffected individuals, patients with celiac disease had a 1.43% higher risk of fractures [5]. A 2005 study of routine serological screening among bone-clinic patients showed celiac disease in 3.4% of patients with osteoporosis and only 0.2% of patients without osteoporosis, supporting routine serological testing of patients

Table 1
Clinical presentations of celiac disease.

Classic presentation	Non-classic presentations
Chronic diarrhea Failure to thrive/weight loss	*Gastrointestinal:* Recurrent abdominal pain, bloating, gastroesophageal reflux, vomiting, constipation, irritable bowel syndrome
Malabsorption syndrome: - micro/normo or macrocytic anemia (iron, folic acid, and vit. B12 deficiencies)	*Other:* Chronic asthenia, tooth enamel damage, recurrent oral ulcers, impaired reproductive capacity, neurological disorders (peripheral neuropathy, epilepsy, ataxia, migraine), psychiatric disorders, osteoporosis and osteomalacia, unexplained polyarthralgia
- edema due to hypoalbuminemia Steatorrhea	*Autoimmune diseases associated with celiac disease* (Table 2): Dermatitis herpetiformis, juvenile idiopathic arthritis, Sjögren syndrome, primary biliary cirrhosis, autoimmune hepatitis, thyroiditis, type 1 diabetes, Addison's disease, etc.