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EDITORIAL

Delay in the Diagnosis of Celiac Disease Today: An Underdiagnosed and Underestimated Disease

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ABSTRACT

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Celiac disease (CD) is a complex multisystem disease, a chronic, hereditary (genetics plays a key role in the predisposition to the disease), autoimmune enteropathy triggered by an environmental (dietary) factor, such as exposure to gluten proteins. Cereals containing gluten include wheat, oats, barley, and rye.

Contact of gluten with the intestinal mucosa produces characteristic, though not pathognomonic, damage ranging from increased lymphocytic intraepithelial infiltrate (LIE) to total villous atrophy. The consequence is a defect in the absorption of all nutrients (not just gluten), leading to deficiency states, often responsible for a wide spectrum of clinical manifestations, irreversible extraintestinal lesions, associated autoimmune diseases, serious complications, and death. The objective of this communication is to raise awareness among the medical community about the importance of early diagnosis and effective follow-up. Once diagnosed, patients adhere to a gluten-free diet (GFD), which not only normalizes their health (disappearance of symptoms, normalization of serological tests, and resolution of histological lesions in the vast majority of patients), but also improves their quality of life[1]. Furthermore, it prevents complications (often serious) and reduces long-term morbidity and mortality.
It is the most common food intolerance in the world (with a prevalence ranging mainly between 0.7% and 2.9% in the general population worldwide) and one of the most common genetically transmitted diseases in humans[2].

Celiac disease is an emerging disease with a universal distribution representing a serious hidden public health problem worldwide, with high and increasing healthcare costs and prevalence[3].

It has a homogeneous global distribution, as it is found in all countries of the world, regardless of race, with a high and increasing prevalence. The female-to-male ratio is 2/3:1[4].

In addition to celiac disease, other gluten-induced disorders also exist, such as dermatitis herpetiformis, gluten ataxia, wheat allergy, and non-celiac gluten/wheat sensitivity.

Since the 2nd century BC, there are written references to Cappadocia's Aretaeus (a Roman physician) calling these pot-bellied children who consulted him for recurring abdominal pain "koeliakos" (intestinal pain). Wilhelm Dicke's observations on the effects of rationing on Dutch children with celiac disease during World War II led to the identification of the toxicity of the gliadin fraction of wheat.

Celiac disease is considered a systemic condition as it damages the entire body. The autoimmune nature of the disease persists throughout life, so a gluten-free diet, which is currently the only treatment, must be strict and lifelong. This includes not only to food (cross-contamination should be avoided), but also to medications and cosmetics, among other factors[2].

Celiac disease is a "chameleon" process, also known as the great pretender, as it is widely disguised in its various forms of presentation, displaying a broad spectrum of varied and polymorphic manifestations, ranging from subclinical or completely asymptomatic cases with, few symptoms or those that are non-classical or even present a florid picture[5]. Symptoms may be intestinal (e.g., diarrhea, abdominal distension, abdominal pain) and/or extraintestinal (e.g., anemia, osteoporosis, endocrinological, gynecological, neurological, and/or psychiatric disorders)[6].

The proportion of known celiac disease cases in relation to those undiagnosed is between 3 and 10%, according to most authors (a celiac iceberg where the ice above the waterline represents the diagnosed cases and the submerged ice, of much larger size, represents the unknown cases). The diagnosis of celiac disease remains significantly underdiagnosed and underestimated primarily due to a lack of awareness of the frequency of celiac disease and its clinical variability[2].

The clinical pattern of the disease has changed in recent years, and today atypical forms of presentation are more common than classic forms, even in children[7]. Atypical presentations with non-classical symptoms are more likely to receive initial misdiagnoses. The longer the diagnosis is delayed and the longer the undiagnosed celiac patient (or that one who does not diet) is in contact with gluten, the greater likelihood of suffering from other irreversible extraintestinal lesions, serious complications associated autoimmune diseases (the likelihood of suffering from these is 5 to 10 greater than that of the general population) and death. In other words, the prevalence of autoimmune diseases, like other associated pathologies, irreversible extraintestinal lesions, serious complications, and mortality increases with the age of diagnosis[8].

The delay between the first symptoms and the diagnosis of celiac disease is unacceptably long for many people[9]. Untreated celiac disease results in a poor health-related quality of life (personal, family, school, work, social, and economic), but if celiac disease will be diagnosed and treated, the quality of life will improve to the level of the general population[1]. It truly presents a cloak of invisibility when it comes to late-onset disease in adults.

Children fully recover their intestinal villi, and absorption returns to normal within six months, or at most in two years[10]. This is not the case in adults, who in some cases never fully regenerate their villi or intestinal absorption.
Although malnutrition is a common manifestation of celiac disease in both children and adults, excess weight or obesity may also be present at the time of diagnosis. Therefore, excess weight in a patient should not exclude the suspicion of celiac disease[8].

There is debate about whether screening for celiac disease should be performed on the entire population, or on whom, at what age, and which antibodies should be recommended[11]. In addition, mass screening for celiac disease meets most of the criteria listed for a mass medical examination by Wilson and Jungner, adapted by the World Health Organization (WHO)[8].
Although the disease is relatively easy to diagnose, based primarily on clinical suspicion, the socioeconomic

impact it causes is striking, as in many patients reach adulthood without a diagnosis requiring greater medical care and medications and therefore, demands much higher expenses on the part of the state, mutual insurance companies, or social security funds, and the patient. Clinical professionals must be aware of the diversity in the celiac disease presentation. Greater awareness among experts about the complexity of celiac disease presentation could contribute to improving the diagnostic process, especially in adults. These factors highlight the need for multifaceted strategies to promote timely diagnosis and avoid serious complications[12].

Although there is increasing training in celiac disease, the delay in diagnostic for patients without gastrointestinal symptoms remains long. While it has decreased in recent decades, it is highly variable and can take more than 10 years, especially in adult patients[13].

What could be the causes of this diagnostic delay: the systemic nature of the disease, with involvement of all organs, and the lack of specificity in its clinical manifestations[14]. Patients who minimize their symptoms (the so-called "silent celiac cases" are often patients accustomed to living with the disease and in poor health). Or specialist who fail to consider celiac disease with symptoms in other organs and systems (atypical symptoms) or in asymptomatic cases[12]. The health system (mutual insurance and social security) that leads the doctor to limit the time dedicated to each patient. Misdiagnosis, as often occurs when it is confused for example with irritable bowel syndrome (IBS) (in an unpublished study conducted in Córdoba, Argentina, 11% of patients diagnosed with irritable bowel syndrome were found to have celiac disease) and other conditions. The diagnosis of irritable bowel syndrome may be masking an undiagnosed celiac disease, since the overlap of symptoms between both is evident, and it should be considered one of the risk pathologies in which serological testing for celiac disease should always be performed. In socioeconomically disadvantaged populations, access to diagnostic testing and adequate medical care is limited, increasing the risk of underdiagnosis.

Selective IgA deficiency has a tenfold higher incidence among celiac patients than in the general population, must be considered when choosing the antibodies to be performed. Even though the detection of Total IgA and antitransglutaminase IgA (which is recommended as the test of choice for sampling by the London National Institute for Health and Clinical Excellence (NICE) guidelines)[15] is generally used for the initial assay and screening, detection of anti-endomysial IgA and/or antideaminated gliadin IgG are used for confirmation. The sensitivity and specificity of these antibodies is close to 100%. Although biopsy is no longer the gold standard in many cases, it remains very important, especially in adults in whom specific antibodies are often low or doubtful[16].

Psychological support is essential for many patients who struggle to accept their illness, deny it, or do not adhere to a diet (this often occurs when the diagnosed is made in adolescence), or for patients with pre-existing depression or other neuropsychological disorders[8].

The delay varies in different regions of the world, but screening would be important, even if it starts with at-risk groups (relatives of celiac disease, type 1 diabetes, autoimmune thyroiditis, irritable bowel syndrome, dermatitis herpetiformis, autoimmune diseases, Down syndrome, and other less common conditions). The cost-benefit factor is obviated in this case, as it allows for fewer patient visits for unrelieved symptoms, for diseases requiring medication, for young people disabled by other serious conditions, all of which could be eliminated with early diagnosis. And it is very important to consider the quality of life the patient regains[8].

It is also important not to overdiagnose the disease, and to do so the relevant differential diagnoses should be made, such as infections (Giardia lamblia), tropical sprue, collagenous sprue, drugs, common variable immunodeficiency (IgG, M, A), and other less frequent ones[5].

The importance of early diagnosis in celiac disease lies in reducing the risk of complications, since some autoimmune diseases are more frequently reported in patients with untreated (without a GFD) or undiagnosed, primarily asymptomatic celiac disease. Patients with long-term celiac disease (untreated or undiagnosed) are at high risk of benign and malignant complications, such as malignant lymphomas, small intestinal neoplasms, oropharyngeal tumors, unexplained infertility, osteoporosis, bone fractures, anemia, depression, autoimmune diseases, and others pathologies. In celiac patients diagnosed during childhood, adolescence or young adulthood, the incidence of complications and associated diseases is low because they have less exposed to gluten[17,18].

It is a need to increase awareness of celiac disease as a common public health problem and to intensify active case finding.

Addressing these challenges is essential to prevent long-term complications, reduce associated diseases (many of which are irreversible), improve the quality of life of patients with celiac disease, and reduce the burden on healthcare systems.

The potential for alertness likely lies in the need to systematically screen for the possibility of celiac disease in those with symptomatic or asymptomatic, classic or atypical clinical profiles, with intestinal or extraintestinal symptoms such as anemia, infertility, bone fractures, or chronic fatigue.

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