Review Article

Symptoms of Celiac Disease – A disease with no symptoms

Tahreem Riaz[1], Muhammad Akram[1*], Umme Laila[1], Rida Zainab[1], Momina Iftikhar[1], Adonis Sfera[2], Pragnesh Parmar[3]

[1]Department of Eastern Medicine, Government College University Faisalabad, Pakistan
[2]University of California Riverside, Patton State Hospital, USA
[3]Additional Professor and HOD, Forensic Medicine and Toxicology, AIIMS, Bibinagar, Telangana, India
[*]Corresponding author email: **makram_0451@hotmail.com**

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Abstract

A wide range of gastrointestinal and extra-intestinal symptoms have long been linked to celiac disease, a complex autoimmune illness brought on by gluten consumption. A growing corpus of research, however, indicates that a sizable fraction of those who have celiac disease can experience mild or even no symptoms at all. The article investigates the mysterious idea of "Celiac Disease with No Symptoms," illuminating its prevalence, diagnostic difficulties, and clinical ramifications. We look at the potential long-term effects of untreated silent celiac disease as well as its potential public health implications. With an emphasis on the significance of early detection and intervention to lessen the pernicious effects of this frequently elusive disorder, this review highlights the need for increased awareness among healthcare professionals and the general public.

Key words

Celiac disease, Silent disease, Prevalence, Clinical Presentation, Diagnostic challenges.

Introduction

An abnormal autoimmune response against cereals containing gluten in susceptible individuals is what is known as celiac disease. Samuel Gee originally described celiac disease in 1888, but it wasn't until 1953 that it became obvious how important gluten was in the development of this disorder [1-3]. Gluten consumption causes enteropathy in people with celiac disease, which impairs the mucosal surface

and, as a result, results in improper nutritional absorption [4-7]. Due to the extensive range of clinical symptoms and the involvement of numerous human systems, celiac disease may be regarded as a syndrome. Contrary to other autoimmune diseases, celiac disease has unusual characteristics, such as the ability to completely repair mucosal damage and reverse the illness's chronic dynamics when gluten is completely avoided. On the other hand, undetected celiac disease may have serious effects on both adult and kid participants, according to recent research [8-10]. The complexity of celiac disease's presentation has been made clear by our increased understanding of the genetic predisposition, immunological responses, and environmental factors related to it. The possible long-term effects of untreated silent celiac disease, which can include nutritional inadequacies and an elevated risk of malignancies, also call for a careful analysis. The non-celiac gluten sensitivity (NCGS), in addition to celiac disease and wheat allergy, has been included as a third condition that is not thought to be caused by an immunological reaction. Despite the fact that a number of components are now known to be involved in the pathogenesis of NCGS, it is still largely unknown [11].

Considering these factors, this study seeks to explain the mysteries of celiac disease without symptoms and implores medical professionals to remain vigilant even in the absence of obvious clinical symptoms. In order to address this puzzling feature of celiac disease and ultimately improve the quality of life for individuals affected, we emphasize the critical role that public health initiatives, enhanced diagnostic techniques, and patient education play. The fact that celiac disease can present as a "disease with no symptoms" emphasizes how crucial early diagnosis and the adoption of a gluten-free diet are to preventing the pernicious effects of untreated disease.

Epidemiology of celiac disease

The scientific knowledge of celiac disease has changed over the past few decades as a result of a wealth of epidemiological data that has revealed unexpected tendencies and disproved long-held assumptions. One of the most common genetically based ailments affecting people is celiac disease, which was once thought to be rare in some nations, including the United States [12]. Recent studies have shown that the United States has a similar prevalence of celiac disease to Europe, which historically had a high frequency of the condition (1%–2%) [13, 14]. Nevertheless, despite great advancements in detection, it is still unclear how common this condition is overall. It is unclear if the discrepancy in reported frequencies between European nations is the result of different screening procedures, sample sizes, or actual variations in the prevalence of celiac disease [15].

The "iceberg model" aptly illustrates the fact that a significant number of cases continue to defy detection. While celiac disease is normally recognized in those who exhibit the traditional symptoms, there are many cases that go undetected and have unusual, mild, or even no symptoms at all [16]. Among healthy persons, a multicenter study from the United States found a prevalence of 0.75% (1 out of 133), which is consistent with research from populations in Europe and Australia [12]. Between 4.5% in those at high risk and 0.75% in those who are not, celiac disease is generally prevalent [12]. Families of celiac disease patients, children or adults exhibiting symptoms of the condition (such as diarrhoea, abdominal pain, and constipation), and people with conditions related to the condition (such as Type 1 Diabetes Mellitus, Down syndrome, anemia, infertility, or osteoporosis) are all considered high-risk groups [17].

Furthermore, it is becoming more and clearer that the prevalence of celiac disease is similar to that of European countries in non-industrialized nations, like North Africa, the Middle East, and India [18–20]. Given the global distribution of the causative components, the disease's diverse distribution is not unexpected. Notably, the Saharawi population in Algeria has shown the

highest known prevalence of celiac disease, surpassing the global averages and almost approaching 6% [16, 21, 22].

Clinical presentation of Celiac disease

The clinical presentation of celiac disease varies depending on parameters like age, the length of the disease, its severity, and the existence of extra-intestinal co-morbidities. Although celiac disease was once thought to be a pediatric ailment, adults are now being diagnosed with it more frequently [16]. There are numerous subtypes of celiac disease, each with its own unique clinical features: typical form, atypical form, asymptomatic form, latent form, potential form etc. [23].

Typical form

This variant often appears between the ages of 6 and 18 months and is characterized by common clinical symptoms linked to decreased intestinal absorption. It frequently follows the introduction of weaning meals containing prolamines. It is characterized histologically by crypt hyperplasia and villous atrophy.

Atypical form

With little or no gastrointestinal symptoms, atypical celiac disease is characterized by a prevalence of extra-intestinal symptoms. Adults and older children are more likely to experience it, and the typical signs of malabsorption are frequently missing.

Asymptomatic form

Individuals with this subtype display histological and serological abnormalities without displaying any clinical signs. It is usually seen in people who have a family history of celiac disease, in people who also have related autoimmune diseases like type 1 diabetes, or in people who have genetic disorders including Down syndrome, Turner syndrome, or Williams's syndrome.

Latent form

Latent celiac disease is found in people who had asymptomatic celiac disease in the past but continued to eat a gluten-containing diet. Although their serology may be positive, they may not show villous atrophy or other tissue abnormalities. Elevated endomysial antibodies in these patients may be a significant indicator of disease progression, according to some research.

Potential form

Those who lack a formal diagnosis of celiac disease but have the necessary genetic markers (HLA-DQ2/DQ8), positive serology results, and either normal or mildly abnormal histology are referred to as "potential" cases.

Refractory form

When malabsorptive symptoms and villous atrophy continue after following a strict gluten-free diet for at least a year, it is said to have refractory celiac disease. It is noteworthy that a portion of refractory individuals (about 5%–30%) do not respond to a gluten-free diet at all, while others may at first respond but then experience a resurgence of symptoms and intestinal damage. Based on intraepithelial lymphocyte counts, "Type 1" and "Type 2," two different subgroups of refractory celiac disease, have been identified [24].

Although celiac disease can develop at any age, two distinct age peaks are seen: one in childhood (often before the age of six) and the other in the fourth and fifth decades of life. The atypical forms often manifest later in life (after age 5) and are more frequently observed in adults, whereas the classical presentation is more common in the pediatric population and typically manifests early in life (between 6 and 24 months) [25]. This variety in clinical manifestations emphasizes the necessity of a broad clinical suspicion and thorough diagnostic strategy to correctly identify and manage celiac disease patients.

Celiac disease and associated conditions

Numerous other medical disorders, usually referred to as "associated conditions," are frequently linked to celiac disease and tend to manifest more frequently in people with the disease [26]. One of the most thoroughly

researched correlations of these conditions - which include genetic, autoimmune, and neurological disorders.

Autoimmune thyroid disorder

According to studies, autoimmune thyroid disorders such as hyperthyroidism (Graves disease) and hypothyroidism (Hashimoto's thyroiditis) are more common in celiac disease patients, ranging from 2% to 5%. It's interesting to note that these thyroid conditions might be identified before or after celiac disease is identified [27].

The HLA-DQ2 and DQ8 haplotypes are two genetic risk factors for both autoimmune thyroid diseases and celiac disease. Although the connection between these genetic markers and Graves' disease is less certain, they have been linked to Hashimoto's thyroiditis. Notably, those with Hashimoto's problem appear to be more likely than those with Graves' illness to acquire celiac disease [28]. Additionally supporting the role of genetic factors in the co-occurrence of these disorders is the reported connection with the gene encoding cytotoxic T lymphocyte-associated antigen-4 in addition to HLA markers [29].

A different pathway involving poor mineral absorption, particularly selenium insufficiency brought on by celiac disease, connects celiac disease with autoimmune thyroid diseases. As the thyroid is particularly sensitive to selenium insufficiency, Stazi, et al. [28] have noted that this reduced selenium absorption could directly contribute to harm in both the thyroid and intestines. Given this correlation, it is prudent to keep an eye out for signs of celiac disease in people with autoimmune thyroid illness and to be cautious of growth and pubertal development. Additionally, in some circumstances, thyroid abnormality screening in celiac disease patients may be necessary [30]. This emphasizes the significance of providing comprehensive care for people with celiac disease and autoimmune thyroid diseases.

Type 1 Diabetes

Type 1 diabetes is one of the most well-known and thoroughly studied diseases linked to celiac disease [31]. Children with type 1 diabetes had a 5- to 10-fold higher risk of celiac disease, according to studies like the one by Ludvigsson, et al. [32]. This elevated risk is, at least in part, a result of common genetic risk factors, particularly the existence of particular HLA genotypes. It's important to note that up to 75% of type 1 diabetes patients exhibit abnormalities in small intestinal biopsy tissue, and 5%–10% of them have antibodies associated to celiac disease [33]. Between 1% and 19% of those with type 1 diabetes have celiac disease, which varies greatly [27].

The early introduction of gluten-containing foods may be linked to an increased chance of acquiring autoimmunity, according to prospective studies in infants who are at high risk for developing type 1 diabetes and celiac disease [34–36]. However, there is still discussion and continuing study regarding the precise nature of the association between these two conditions [37]. Given the link between type 1 diabetes and celiac disease, it is crucial to take both diagnoses into account when treating patients. It is advised to regularly screen people with type 1 diabetes for celiac disease in order to enable early identification and timely intervention, thereby enhancing the general quality of life for those who are affected. To fully understand the intricate interactions between these two autoimmune diseases, more research is required.

Neurological disorders

A growing body of research [38] points to a possible connection between celiac disease and a number of neurological conditions. Data on the relationship between celiac disease and neurological disorders, however, are still fairly few. Ataxia is one of the neurological conditions that have been linked to celiac disease in some patients [39]. However, with estimated prevalence rates ranging from 1.2% to 5% [40], epilepsy appears to be the most common neurological disorder among people with celiac

disease. Individuals may respond differently to a gluten-free diet, and the clinical appearance of epilepsy in combination with celiac disease can range from focal to generalized seizures.

A distinct and somewhat uncommon illness called CEC (Celiac disease, Epilepsy, and Occipital Calcifications) was first identified in 1985. The incidence of celiac disease, epilepsy, and calcifications in the occipital region of the brain all co-occur in this syndrome [40]. Further implying the role of genetic variables in this association, Gobbi and colleagues hypothesized that those susceptible to CEC share the same HLA genotype as people predisposed to celiac disease [40]. While the particular pathways relating celiac disease to neurological diseases are still being investigated, they are believed to be related. These findings emphasize the significance of taking neurological problems into account in celiac disease patients, particularly in those who present with neurological symptoms that are not otherwise explicable. The neurological prognosis for these people may be improved by early detection and effective care.

Autoimmune Hepatitis and Liver Involvement

Involvement of the liver is rather prevalent in those with celiac disease [41]. At the time of diagnosis, 40% of adults and 54% of children with a traditional presentation of celiac disease had hypertransaminasemia, which is an elevation in liver enzymes [42]. On the other hand, about 9% of patients with chronic unexplained hypertransaminasemia have celiac disease [43, 44]. The introduction of toxins, inflammatory chemicals, and antigens into the portal circulation is thought to be the mechanism causing liver damage in celiac disease. All patients with persistent hypertransaminasemia of unknown etiology should undergo serological testing for celiac disease, according to Volta et al. [45]. This screening is important because it helps find cases where liver damage brought on by gluten consumption may be a contributing factor. Additionally, it's crucial to rule out gluten-related liver damage in people with autoimmune liver diseases or those who have severe liver diseases with no known cause. Patients who are under consideration for liver transplantation also require this assessment. Chronic hepatitis and liver cirrhosis can develop in people with undiagnosed celiac disease who regularly consume gluten [45, 46].

Diagnosis of celiac disease

Clinical assessment, serological tests, and confirmatory procedures can all be used to diagnose celiac disease. The initial screening and diagnosis of celiac disease mostly relies on serological tests. The main serological tests used to make the diagnosis include the following:

In Vitro Gluten Challenge Test

The use of in vitro gluten challenge tests to measure gluten-sensitive immune activation in celiac disease has been the subject of research in recent years. In these experiments, the immunological response to gluten exposure is reproduced using cultured cells from the duodenal mucosa [47]. With this strategy, it may be possible to investigate immunological responses to gluten at the cellular level, shedding light on the disease's cause and maybe assisting in diagnosis and treatment. It is important to remember that in vitro testing is still a relatively new concept and is still being studied.

Genetic Analyses

It is not always advised to perform genetic testing for the HLA-DQ2 and HLA-DQ8 alleles in celiac disease patients. Instead, it is mentioned when the diagnosis is ambiguous or debatable. Only very small percentages (0.4%) of celiac disease patients are negative for both the DQ2 and DQ8 alleles, according to large multicenter studies [48]. It is helpful to rule out the tendency to celiac disease when these alleles are lacking (HLA-DQ2/DQ8 negative) in particular in family members of people with celiac disease. Particularly in cases of possible celiac disease, HLA testing can be a useful tool because it can either confirm a diagnosis (if positive) or assist rules it out (if negative). Additionally, it may be necessary to investigate additional reasons of these histological abnormalities when individuals

have villous atrophy in the absence of HLA-DQ2/8 and negative serology. Numerous other conditions that can cause malabsorption and exhibit similar histological findings to celiac disease include lactose intolerance, bacterial overgrowth, Crohn's disease, and a number of infectious diseases (such as Giardia lamblia, Cryptosporidium, Microsporidium, Cytomegalovirus, Herpes virus, and Whipple's disease).

Anti-Tissue Transglutaminase Antibodies (tTGA)

Using an enzyme-linked immunosorbent assay (ELISA), IgA anti-tissue transglutaminase antibodies (tTGA) are the main target of the serological diagnosis of celiac disease. These antibodies have a high specificity of approximately 96% and a sensitivity of up to 97%, giving them an overall diagnostic accuracy of 98%. Due to their better specificity (about 100% compared to 91% for tTGA), IgA anti-endomysial antibodies (IgA EMA) are used as a confirmatory test in situations when tTGA is positive. However, tTG-IgG testing is advised in those with concurrent IgA deficiency, which is present in 2%–10% of celiac disease patients. It's significant to remember that IgA deficiency can result in "false negative" results. With a specificity of around 100%, a sensitivity of roughly 94%, and an overall diagnostic accuracy of 97%, IgA EMA is thought to be the most precise test. It is important to note that EMA is normally identified through indirect subjective immunofluorescence, and that in cases of IgA deficiency and in children older than 2 years, these antibodies may produce falsely negative results [49].

Anti-Gliadin Antibodies (AGA)

Anti-gliadin antibodies (IgG and IgA) were originally employed; however, because to their very low sensitivity, specificity, and diagnostic accuracy, they are no longer advised as routine testing. They might not be very helpful, nevertheless, in identifying celiac disease in young children [50].

DeamidatedGliadin Peptides

The use of IgA and IgG antibodies to deamidatedgliadin peptides in more recently created immunoassays has virtually supplanted the detection of antigliadin antibodies. Clinicians may choose serial testing, which involves combining many tests, to increase diagnostic accuracy.

Treatment of Celiac disease

Gluten-Free Diet

A stringent, gluten-free diet for the rest of one's life is the main and most efficient treatment for celiac disease. This entails fully cutting off wheat, barley, rye, and all products derived from those grains from your diet. In those with celiac disease, even trace levels of gluten can set off an immunological reaction and harm the small intestine. Reading food labels carefully, being aware of processed food's hidden sources of gluten, and choosing naturally gluten-free foods such fruits, vegetables, lean proteins, rice, and gluten-free grains are all necessary for successfully adhering to a gluten-free diet. Developing a gluten-free eating plan that is both safe and well-balanced can benefit greatly from working with a qualified dietician who specializes in celiac disease.

Medications

Celiac disease sufferers can struggle with on-going symptoms or other issues even when they strictly avoid gluten in their diet. Healthcare professionals may recommend drugs in certain circumstances to treat particular problems. For instance, significant inflammation or autoimmune reactions may be treated with corticosteroids or other anti-inflammatory medications. Medications can also be used to treat symptoms like discomfort or diarrhoea. However, these drugs are often seen as supplements to a gluten-free diet rather than as a replacement for it.

Supplements

People with celiac disease frequently have nutrient malabsorption, which can result in a lack of vital vitamins and minerals. Healthcare

professionals may provide supplements to meet particular nutrient demands depending on the deficits of each patient. Iron, calcium, vitamin D, and vitamin B12 are typical supplements. To choose the right supplements and dosages, it is crucial to regularly monitor nutrient levels via blood testing.

Consultation with dietician

It is extremely useful when consulting with a licensed dietician who specializes in celiac disease. These professionals can offer specialized advice on starting and sticking with a gluten-free diet. They can support people in making informed food decisions, developing meal planning, and ensuring they get enough nutrients while avoiding gluten. Dieticians can assist people in locating suitable substitutes by staying current on the latest gluten-free goods.

Complications of undiagnosed Celiac disease

Untreated celiac disease carries a high risk of developing a number of problems that can impact different bodily systems. Consuming gluten, which is frequently found in wheat, barley, rye, and their derivatives, causes this autoimmune condition. When the immune system reacts to gluten, it damages the small intestine and causes chronic inflammation, which impairs the absorption of nutrients and results in a number of health issues. Malnutrition resulting from reduced food absorption, which leaves a person deficient in essential vitamins and minerals, is one example of this. Children who have this deficiency may have symptoms like weariness, weakness, anemia, and slowed growth. Chronic vitamin D and calcium malabsorption can also raise the risk of osteoporosis and other bone conditions, rendering people more prone to fractures and bone discomfort. Chronic diarrhoea, constipation, abdominal pain, bloating, and recurring mouth ulcers can all be caused by long-term gluten intake, which can also exacerbate gastrointestinal symptoms and harm the intestinal lining.

Women may experience delayed adolescence, irregular menstruation, and an increased chance of miscarriage, while males may experience decreased sperm quality and quantity. The neurological side effects of celiac disease have been linked to headaches, migraines, peripheral neuropathy, and even seizures. A skin disorder known as dermatitis herpetiformis that causes itchy, blistering skin rashes is strongly related to celiac disease. It frequently affects the scalp, buttocks, elbows, and knees, and if left untreated, it can hurt. Additionally, the likelihood of acquiring numerous autoimmune problems increases because celiac disease is usually linked to other autoimmune diseases such type 1 diabetes, rheumatoid arthritis, and thyroid disorders. Uncontrolled celiac disease over a prolonged period of time may increase the risk of several malignancies, including intestinal lymphoma and small bowel adenocarcinoma.

An individual's quality of life can be greatly impacted by psychological and behavioral conditions as anxiety, sadness, mood swings, impatience, and cognitive impairments. Additionally, there may be liver problems such as non-alcoholic fatty liver disease and increased liver enzymes. Some people with celiac disease may experience cardiovascular problems like hypertension and a higher risk of heart disease, though this is less common. For the prevention and management of these potentially life-threatening consequences, early identification and rigorous adherence to a gluten-free diet are imperative. For maintaining the best possible health and well-being, it is essential to seek medical assessment and treatment for suspected celiac disease as soon as possible. Plants are also useful in various conditions [51-55], so funded research [56] can be done on usefulness of plants and nanoparticles [57, 58] in celiac disease.

Conclusion

The clinical presentation of celiac disease, which is typically characterized by gastrointestinal pain and a variety of systemic symptoms, continues to be a mystery to medical professionals. The idea of "Celiac Disease with No Symptoms" has been discussed in this review; it refers to an illness

that defies expectations by showing no obvious symptoms or discomfort. It is clear that a sizable percentage of people are affected by silent celiac disease, even though prevalence rates vary throughout populations and age groups. There have been discussions on the intricacies of genetics, immunology, and environmental triggers as contributing causes to this phenomenon. Furthermore, it is important to not undervalue the possible effects of untreated silent celiac disease. Continuous intestine damage and systemic inflammation can cause a variety of long-term health issues, including as malnutrition, osteoporosis, infertility, and an elevated risk of several types of cancer, even in the absence of obvious symptoms. Therefore, regardless of the symptomatology, early diagnosis and detection of celiac disease remain of utmost importance. The importance of maintaining a high index of suspicion for celiac disease, especially in patients who come without the typical symptoms, is stressed by this review's conclusion. In order to reduce the potential health costs linked to this enigmatic ailment, it is essential that we continue to explore the processes underlying asymptomatic celiac disease and develop better diagnostic techniques. Understanding that celiac disease can present as a "disease with no symptoms" is essential for promoting early intervention and enhancing the quality of life for those who are affected.

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