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The Progression of Celiac Disease, Diagnostic Modalities, and Treatment Options

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Abstract

Celiac disease (CD) is an autoimmune disorder that affects genetically predisposed individuals who are sensitive to gluten and related proteins. It affects children and adults with increasing prevalence in the older age groups. Both adaptive and innate immune responses play role in CD pathogenesis which results in damage of lamina propria and deposition of intraepithelial lymphocytes. There are other proposed mechanisms of CD pathogenesis like gastrointestinal infections, intestinal microbiota, and early introduction of gluten. The diagnosis of CD is based on clinical symptoms and serological testing, though a majority of cases are asymptomatic, and small intestinal biopsies are required to confirm the diagnosis. Celiac disease is generally associated with other autoimmune diseases, and it is advisable to test these patients for diseases like type 1 diabetes mellitus, Addison's disease, thyroid diseases, inflammatory bowel disease, and autoimmune hepatitis. The patient with a new diagnosis of CD requires close follow-up after starting treatment to see symptom improvement and check dietary compliance. A newly diagnosed patient is advised to follow with a dietitian to better understand the dietary restrictions as about 20% of patients stay symptomatic even after starting treatment due to noncompliance or poor understanding of diet restrictions. The most effective treatment for CD is a gluten-free diet, but work on non-dietary therapy is in process and few medications are in the clinical trial phase.

Keywords

celiac disease, small intestinal biopsy, autoimmune diseases, serology, gluten, diet, therapy, treatment

Introduction

Celiac disease (CD) is an immune-mediated disorder affecting small intestine in genetically predisposed individuals. It results from sensitivity to gluten and related proteins.[1,2] The global prevalence of CD is 1%[3,4] though it does not represent the actual number of CD cases due to the vast majority of cases are asymptomatic and undiagnosed as reported in different studies. One study done in Italy showed 7:1 ratio of asymptomatic to symptomatic cases,[5] which is further reinforced by studies in which antibody testing performed for screening purposes.[6-9] Celiac disease is more prevalent in first- and second-degree relatives and people with other autoimmune disorders.[8,10]

Celiac disease results from an abnormal response to gluten which causes small intestinal injury and leads to malabsorption of nutrients. Celiac disease prevalence has increased 4 to 5 times in the last few decades, and the average age of diagnosis is the fifth decade of life in the United States.[11,12]

CD has 2 peaks of onset, one in early childhood around age of 2 years and the second in second to third decade of life.[13,14] As per Oslo's 2011 definition, CD can be classified as classic, non-classic, subclinical, silent, overt, potential, and refractory.[15,16] The other way of classifying CD is based on location and histological appearance. Based on location, it can be categorized as intestinal vs extraintestinal or a combination of both.[17]

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Table 1. Modified Histological Classification of Celiac Disease.

Type	Intraepithelial lymphocytes/100 enterocytes	Crypt hyperplasia	Villi
0	<40	Normal	Normal
1	>40	Normal	Normal
2	>40	Increased	Normal
3a	>40	Increased	Mild atrophy
3b	>40	Increased	Moderate atrophy
3c	>40	Increased	Complete atrophy

Histologically, CD was classified by Marsh and was later modified by Marsh-Oberhuber in 1999 (Table 1). Corazza proposed another classification but not widely accepted. Modified Marsh classification is the recommended histological classification by the Gastroenterology association but still not used widely.[18-20]

Pathogenesis

Celiac disease is an autoimmune disease affecting the genetically predisposed individuals in the setting of environmental trigger.[21] It results from abnormal T-cell response to gluten, which is found in cereal grain wheat, rye, and barley.[21,22] In genetically predisposed individuals, exposure to gliadin peptide which is a component of gluten leads to an adaptive immune response that causes damage to lamina propria.[23-26] In addition to adaptive response, innate immune response is the other factor which plays an important part in CD pathogenesis which can be seen by the presence of intraepithelial lymphocytes.[26,27] Celiac disease is common in families which is evident by the presence of specific HLA types HLA-DQ2 and HLA-DQ8 in almost all cases.[28,29] The intestinal microbiota is also considered another factor in the pathogenesis of CD leading to an immune response in addition to gluten and other environmental factors and this is shown in few studies.[30-34] Other factors considered and discussed in literature about CD pathogenesis are a shorter duration of breastfeeding, infections, and early introduction of gluten, but these are not proven with studies[35,36]; it is noted in one study that children who develop CD were consuming more gluten than those without CD.[37] European Society for Pediatric Gastroenterology, Hepatology, and Nutrition's current guideline is against high consumption of gluten in the first few weeks of life and it can be introduced after 4 months of age.[38]

Clinical Subtypes of CD

Celiac disease is clinically defined as classic, non-classic, subclinical, potential, and refractory.[16] Classic CD, however, affects both pediatric and adult population but mainly diagnosed between 6 and 18 months of age and presents with typical symptoms of malabsorption including diarrhea, failure to thrive, and weight loss. The atypical or non-classic form mainly present as extraintestinal manifestation of CD such as osteoporosis, abnormal liver function, vitamin deficiencies, anemia, neuropathy, or infertility, but patients with atypical disease can have gastrointestinal symptoms like reflux, bloating, or abdominal pain. The atypical form is usually diagnosed in high-risk population on screening. Subclinical form of CD also falls under atypical disease. Latent or potential form of CD is defined as normal small bowel architecture but positive serology and presence of HLA-DQ2 and/or HLA-DQ8. Refractory CD is the presence of symptoms even after strict dietary restriction for 6 to 12 months.[39,40]

Clinical Manifestations

Celiac disease is more common in females with F:M ratio of 2:1, and females are usually diagnosed at a young age with predominant symptoms of constipation and iron deficiency anemia.[13,15,41] Celiac disease diagnosis is challenging as the majority of patients are asymptomatic and the ones with symptoms vary significantly.[42] The symptomatic patients can have gastrointestinal symptoms in combination with extraintestinal manifestation or they can just present with extraintestinal symptoms.[17] Gastrointestinal symptoms like diarrhea, loss of appetite, malabsorption, failure to thrive, short stature, and delayed puberty are mainly seen in the pediatric population.[16,43] On the contrary, the adult populations rarely have the classic malabsorption symptoms, and they usually present with irritable bowel syndrome-like symptoms in association with nausea and vomiting, and the reason for their hospitalization is mainly electrolyte imbalance and cachexia.[44-46]

Celiac disease in its classic form presents with gastrointestinal malabsorption symptoms, but we need to be careful in diagnosing as about 40% of patients with CD are obese at diagnosis and constipation can be presenting symptom in 20% of patients.[15,16,47,48] Another rare presentation is the celiac crisis which presents as diarrhea and shows severe electrolyte disturbances.[48] In the past, majority of diagnosed cases were of symptomatic disease but now the non-classic and subclinical forms are increasingly diagnosed but the classic form is still the most common presenting type and makes about half of the diagnosed cases.[15,45]

Celiac disease is now seen more frequently in adults and older population, and the reason for this is better diagnosis

tools and understanding of the disease, although in most cases the disease is mild in this age group and the main presenting symptoms are nutrient deficiencies and iron deficiency anemia.[15,49]

Celiac disease is a multi-organ system disease, and few studies showed extraintestinal symptoms as the most common presentation.[15,45] Extraintestinal symptoms are seen in both children and adults and osteoporosis is the most common with a frequency of about 70% due to changes in calcium and vitamin D absorption.[44,45,50] Patients with severe osteoporosis and bone loss especially if they are young males should be worked up for CD even in the absence of gastrointestinal symptoms.[51] Bone disease is the main cause of morbidity in patients with CD and increases the fracture risk significantly as compared with the general population.[51,52] The second most common presentation is iron deficiency anemia which is seen in about 40% of cases secondary to inflammation and malabsorption of iron and commonly seen in newly diagnosed patients.[53,54] The other common manifestations are neurological symptoms such as headache, paresthesia, cerebellar ataxia, myoclonic syndrome, epilepsy with cerebral calcifications, anxiety, and depression, and it is associated with elevated levels of anti-gliadin antibodies.[45,55-57] Celiac disease affects the reproductive system in both males and females, so patients can present with unexplained infertility, recurrent abortions, miscarriages, early menopause, late menarche, or abnormality of sperms, and these changes are reversible with a gluten-free diet, so these cases need high suspicion and need a workup for CD even in the absence of malabsorption symptoms.[43,58-62] Undiagnosed pregnant cases of CD can lead to premature and small for gestational age babies.[61,63]

Other common extraintestinal manifestations of CD are abnormal liver tests known as celiac liver,[64,65] hyposplenism,[66] dermatitis herpetiformis,[45,67,68] aphthous ulcer,[45,69] dental enamel hypoplasia,[70] and acute and chronic pancreatitis.[71]

Diagnosis

The mainstay of CD diagnosis is based on clinical features in combination with serology testing and histological findings. Antibodies used for CD diagnosis are anti-tissue trans-glutaminase (anti-tTG), anti-endomysium, and deamidated gliadin peptide (DGP). The preferred single test is anti-tTG antibodies with a sensitivity of 93% and specificity of 94%. Although the anti-endomysial antibody test is most specific than all other serological tests, it is a qualitative test, operator dependent, and difficult to perform.[72-76] Studies done on DGP, in the beginning, were promising about its role in the diagnosis of CD, but over the course, data showed a decrease in its specificity, so now IgG-DGP is sometimes used for diagnosis in children aged <2 years but DGP-IgA lacks accuracy and not used in current practice.[72,77,78] To increase the sensitivity of serological testing, British society of Gastroenterology recommends sequential testing with tTG-IgA and DGP-IgG.[79] Even with the advancement in serology testing and easy availability still, none of these tests are 100% sensitive or specific which makes intestinal biopsy an important component for the diagnosis.[46,80]

The best method to establish the diagnosis is based on the "4 out of 5 rule," in which 4 out of these 5 criteria need to be present to diagnose someone with CD. These include classic signs and symptoms, antibody positivity, HLA-DQ2 and/or HLA-DQ8 positivity, intestinal damage, and clinical response to the gluten-free diet.[81] The current guidelines for the diagnosis of CD are based on case findings in which all populations with high risk need to be tested, but this is not proven beneficial and U.S Preventive service Task Force (USPSTF) has recommended against it.[75,79,82,83] In the pediatric population, intestinal biopsy can be avoided if a child has typical symptoms and signs of CD in combination with high titers of anti-tTG, detectable endomysial antibody, and HLA-DQ2/HLA DQ8 positivity, as recommended by the European Society for Pediatric Gastroenterology Hepatology and Nutrition,[84,85] but these criteria are not used worldwide,[85] so biopsy is still needed in the majority of the pediatric and almost all adult cases to establish the diagnosis.

Endoscopy with small intestinal biopsy is the gold standard test in adult patients and mandatory for establishing the diagnosis of CD.[86] Endoscopists need to be vigilant while taking duodenal biopsies as CD results in patchy mucosal changes, mainly involve the proximal intestine, with only 10% of cases will show changes in the duodenal bulb. So during endoscopy, at least 4 to 6 biopsies, out of which 2 from duodenal bulb and 4 from second part of the duodenum is needed for accurate diagnosis.[14,87] Celiac disease lesions can be differentiated into 5 stages based on histology as defined by Marsh and later modified by Oberhuber.[20] But studies have shown these systems are not used widely by pathologists due to disagreement on grading, so a more uniform grading system is needed.[88]

There are certain conditions like enteric infection, congestive heart failure, and a chronic liver disease which can lead to false-positive results due to cross-reactivity of antibodies.[89] On the contrary, patients need to be on a gluten-containing diet "gluten challenge" (>3 g gluten/day for at least 2 weeks) before getting tested, otherwise, there are chances for false-negative results.[75,89,90] A patient with CD has a higher prevalence of IgA deficiency as compared to the general population which is another reason for false-negative results, so in IgA-deficient patient anti-DGP IgG antibodies or tTG-IgG antibodies should be performed.[75,91]

There are cases in which serology is negative, but antigen haplotype DQ2 and or /DQ8 and histological changes like villous atrophy are present, this is called seronegative CD and it can result from strong antigen-antibody complexes deposition in mucosa which leads to decreased antibody entry into circulation.[91-93]

HLA typing is a good way of ruling out CD, but it cannot be used for the diagnosis.[84] HLA typing is used for the

diagnosis of seronegative CD as well a screening tool for seronegative first-degree relative of a patient with CD.[84,94]

The presence of low hemoglobin, elevated transaminases, and bone-specific alkaline phosphatase on routine blood work can provide clues about CD diagnosis. Iron deficiency is one of the most common extraintestinal manifestations, though you can also see normocytic or macrocytic anemia due to malabsorption of vitamin B12 and folic acid in CD.[53,95-97]

Treatment

At present, the main and only effective treatment for CD is a gluten-free diet for life and strict avoidance of wheat, barley, and rye is needed.[46,98,99] Strict adherence to gluten-free diet results in resolution of symptoms within days to weeks, negative serology, and normalization of villous atrophy.[47,100] Although a gluten-free diet is very effective in treating CD, still it comes with many disadvantages, including high cost, nutrient and mineral deficiencies, psychological impact, constipation, and cardiovascular disease risk.[100-103] To avoid these negative effects of a gluten-free diet, it is recommended to have a regular follow-up with a trained dietitian who carries expertise in treating patients with CD.[104,105] One main reason for non-adherence to a gluten-free diet is wrong online information about gluten products, cross-contamination, presence of a small amount of gluten in medications, social pressure in adolescence, and for all these reasons close follow-up with dietitian and enrollment in a CD support group is recommended.[106-109]

Nonresponsive and Refractory CD

There are about 20% of patients in which diarrhea, abdominal pain, and fatigue persist even after starting a gluten-free diet and in these cases either the initial diagnosis of CD was made wrong or the patient is non-compliant with a gluten-free diet or gluten contamination.[110-113] So in the cases of deliberate gluten ingestion or food contamination, a dietitian referral is recommended to get more information about the gluten-free diet and possible contamination.[111] Persistent symptoms after 12 months of treatment can be due to other conditions like microscopic colitis, irritable bowel syndrome, and lactose intolerance, so for that reason, duodenal biopsies and colon biopsies are recommended to find the actual cause of symptoms.[110,113,114] In few patients, even after strictly following the diet restriction for 12 months, symptoms and villous atrophy persist labeled as refractory CD. The refractory CD has 2 subtypes and duodenal biopsies are required to look for aberrant T-cell population found in type 2 which is severe form and associated with worse outcomes.[115-117] Refractory CD type 1 is treated with steroids or azathioprine in combination with steroids, open-capsule budesonide, and aggressive nutrition is commonly used as first-line therapy. There is no agreement on the treatment of refractory CD type 2, although steroids, cyclosporine, cladribine, and stem cell transplant are considered.[118-121] Patients with type 2 refractory CD are at increased risk to develop T-cell lymphoma.[120]

New Treatments

It is a need of time to develop non-dietary therapies for CD as about 40% of patients are not satisfied with the only dietary treatment.[122] There are recent advances in dietary therapies and few drugs are in the clinical trial phase and the most promising ones are larazotide acetate and gluten-specific proteases ALV003 or latiglutenase.[123-125] Larazotide acetate is a zonulin antagonist, an oral peptide designed to tighten adhesions between intestinal cell linings and prevents gluten from crossing the epithelial barrier. It has shown effectiveness in relieving symptoms in patients who are on a gluten-free diet as compared to a placebo plus diet.[126] Latiglutenase, an oral mixture of recombinant gluten targeting proteases, targets gluten, breaks it into small fragments before reaching duodenum so in theory to prevent the pathological damage caused by gluten. In a large study done by Murray et al, there was no difference between latiglutenase and placebo in symptoms or histological improvement.[124,127] A monoclonal antibody against interleukin-15 and a vaccination called Nexvax2 are currently under investigation.[128]

Follow-up

Patients diagnosed with CD need close and well-arranged follow-up. Strict adherence to gluten-free diet results in improvement of clinical symptoms in 4 weeks and more than half of the patients' symptoms resolve completely within 6 months. In serological testing, there is a noticeable decrease in antibody titers after 6 months, so the first follow-up is advised to be scheduled after 6 months of the diagnosis, followed by every 12 to 24 months.[47,129] The histological changes take more time to correct, so it is advisable to repeat biopsy after 1 year of treatment and even better if done after 2 years to confirm complete healing.[130]

Celiac disease is associated with conditions like autoimmune thyroid disease, type 1 diabetes, inflammatory bowel disease, autoimmune hepatitis, autoimmune gastritis, primary biliary sclerosis, and adrenal insufficiency, so physicians need to be vigilant and keep a close eye on these conditions and check anti-nuclear and other organ-specific antibodies during follow-up visits. In newly diagnosed cases, it is recommended to get the basic blood work including complete blood cell count, vitamin B12, folate, vitamin D, calcium level, liver function test, serum albumin, copper, zinc, and vitamin A and E.[45,75,79,131]

Newly diagnosed adult patients are advised to undergo bone density testing as osteopenia and osteoporosis are very common. It is recommended by the British Society of gastroenterology to measure bone density after 1 year of a

gluten-free diet in patients older than 55 years with other risk factors for osteoporosis.[75] The ones with osteopenia or osteoporosis need calcium and vitamin D replacement and repeat bone scan in 2 years.[132,133] Celiac disease can present as wide range of clinical symptoms and can be associated with multiple autoimmune conditions. A prompt diagnosis and initiation of treatment carry high importance to prevent associated complications.

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