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Celiac Disease; its Epidemiology, Pathogenesis, Diagnosis and Treatment

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ABSTRACT

Celiac disease is an autoimmune disorder triggered by the presence of gluten in diet. Mainly it damages the small intestine. Typical symptoms of celiac disease are chronic diarrhea, nausea, vomiting, constipation and foul-smelling stools. Celiac disease produces a series of complications like lactose intolerance, nutritional malabsorption and deficiency of vitamins. This disease is mostly common in children, but adults and older people can also be affected by this. The only effective treatment for this disease is a lifelong gluten-free diet. Celiac disease is easily confusable with other disorders, so a proper examination is needed. This confusion is also the reason for delayed diagnosis. Celiac disease is spread all around the globe with varying statistics. Its patients have genetic variants that are responsible for initiating autoimmune and inflammatory reactions. Serological blood testing is the primary technique in diagnosis followed by endoscopy and biopsies.

Keywords: Celiac disease, epidemiology, pathogenesis

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Introduction

Celiac disease, also known as coeliac disease, is an autoimmune disorder [1]. It damages the mucosal lining of the small intestine and causes the individual to become intolerant to gluten, a protein mainly found in wheat, rye and barley [2]. Typical symptoms of coeliac disease are chronic diarrhea, nausea, vomiting, constipation and foul-smelling stools. Mostly this disease occurs in childhood but can develop at any age [3]. When a person with celiac disease comes in contact with gluten, his body carries out an abnormal immune response and starts to produce autoantibodies, these antibodies regard gluten molecules as invaders and the immune system produces inflammatory cells [4]. In small intestine, it causes an inflammatory reaction that damages the intestinal villi, hence leading to the poor absorption of nutrients, minerals and fat-soluble vitamins [5]. This malabsorption often results in weight loss, lack of energy, anemia (iron deficiency anemia due to iron malabsorption and megaloblastic anemia due to vitamin B12 malabsorption) and osteopenia [6]. There are also chances that the person with increased damage to small intestine may become lactose intolerant [7]. Celiac disease is not to be confused with wheat allergy as the latter is scarce and not autoimmune and has zero damage to small intestine [8]. The only effective treatment for celiac disease present is having a gluten-free diet all the remaining life. This treatment also causes intestinal mucosa to recover and improves symptoms [9].

Epidemiology

Samuel Gee in 1888 stated the first modern-day clinical description of coeliac disease in children. He suggested diet as the cure for this disease [10]. Back in the day, celiac disease was thought to be rare with a prevalence of 0.02% [11]. But with the passage of time, its cases began to increase. Now its statistics vary in different parts of the world. It is also seen that coeliac disease is more prevalent in women than in men [12]. Its estimated global prevalence is 1.4% with 80% of celiac cases remaining undiagnosed [13]. According to continents, its prevalence is in Europe (1 in 50), North America (1 in 133), Australia (1 in 70) and South America (1 in 100). The highest prevalence of CD is seen in Finland, standing at a staggering rate of 2.4% [14]. Early diagnosis of coeliac disease is necessary, however, it is seen that 20% of patients are diagnosed after 60 years of age because their symptoms are not very specific and are easily confusable with other diseases, like in old age acid reflux or irritable bowel syndrome is very common [15].

Pathogenesis

Patients with celiac disease carry genetic variants, either HLA-DQ2 allele or HLA-DQ8 allele [16]. However, 30% to 40% of the public without CD also carries at least one of the following alleles [17]. Given that, non-HLA factors also contribute to developing celiac disease. HLA-DQ2 and HLD-Q8 alleles are responsible for developing celiac disease but are not sufficient alone to do so [18]. 95% of patients with CD have HLA-DQ2 (90%) or HLA-DQ8 (5%) apart from its other five variants (DQ4, DQ5, DQ6, DQ7 and DQ9). Both DQ2 and DQ8 are genetically inheritable to the next offspring [19]. The receptors produced by these genes have a higher tendency to bind more strongly with the gliadin peptides, hence increasing the risk of celiac disease [20]. These isoforms bring forth the autoimmune mechanism by activating the T lymphocytes. Prolamins are the proteins present in food that initiate the immune reaction in CD [21]. Gliadin, wheat prolamin, affects enterocytes of the small intestine allowing large molecules around the tight junction. After causing some changes to tight junction, it causes an increase in intestinal permeability allowing peptides of larger than three amino acids to pass [22]. Gliadin also stimulates lymphocytes causing the release of interleukin-15 which damages the epithelial and mucosal cells. This response causes the immune system to carry out inflammation reactions by stimulating the inflammatory cells [23]. A 33 amino acid peptide activates specific T-cells. An excellent indicator of a patient having celiac disease is the presence of CD4+ T lymphocytes in lamina propria, the lining of mucous membrane and CD8+ T lymphocytes in the epithelial lining of the intestine [24]. CD4 T cells release cytokines that increase inflammatory reactions, injuring the intestinal lining [25].

Tissue transglutaminase (tTG) enzyme modifies gluten peptides by deamidation or transamination. Transglutaminase is cross-linked with gliadin, which is mostly covalently linked, and produces new epitopes that develop autoantibodies against tTG which are responsible for causing further damage in the intestine [26].

Diagnosis

In most cases, there is a great delay in the diagnosis of celiac disease. Several tests are available for the diagnosis of celiac disease. Still, none of them could be of any use if the patient is already having a gluten-free diet because once the intake of gluten is stopped, the patient's small intestine begins to improve and the number of antibodies in the body starts to decrease within months. So, it is recommended to have gluten in amounts equal to 1 slice of bread every day in your diet, 2-3 weeks before diagnosis [27].

Serological blood testing is the primary diagnostic technique in ensuring celiac disease. In this testing, the presence of antibodies in the blood is detected. If the number of antibodies is higher than normal, it signals an increase in immune activity probably against gluten [28]. Test with anti-tissue trans-glutaminase (anti-tTG) antibody is suggested as the first priority because it has sensitivity and specificity of 93% and 94% respectively [29]. Other antibodies that help in the diagnostic process are anti-endomysial antibodies and deamidated gliadin peptide (DGP). Anti-tTG and anti-endomysial antibodies are both used for the diagnosis of patients with CD because of their high sensitivity. However, they have a drawback that they are only present in 30-89% of patients with villous atrophy and in less than 50% who suffer from mucositis [30]. Children younger than two years are diagnosed with celiac disease by anti-DGP antibodies [31]. Serological blood tests are highly efficient in patients with total villous atrophy as compared to patients with partial villous atrophy [32]. So, after these antibody tests, endoscopy is still recommended. Biopsy of the duodenum or jejunum is performed, however, not all areas of the intestine may be equally damaged, so it is advisable to take 4 to 6 biopsies [33]. In some cases, if the person is already having a gluten-free diet, a gluten challenge is suggested to check if a person has coeliac disease by histological analysis of the intestine [34]. However, gluten challenge is discouraged for children below 5 years and during periods of pubertal growth. A person has more chances of developing coeliac disease if his first-degree relatives (parents, siblings and offspring) are diagnosed with CD. About 1 in 10 is at risk of developing CD in case of first-degree relatives [35]. Deficiencies like Fe, B9, B12, Ca and vitamin D are also seen in coeliac disease. If the deficiency of these nutrients is reported, the patient may have coeliac disease, in this way they help diagnose CD [36]. Hypothyroidism is also common in patients living with celiac disease, so a thyroid function test is also suggested [37]. A diagnostician must also keep a keen eye on any signs of osteoporosis and osteopenia [38]. Patients with unexplained weight loss, mouth ulcers, growth and gut problems can also be screened for celiac disease [39]. However, these complications may be due to other problems, not necessarily CD.

Treatment

Early detection of a disease is the key to avoiding severe complications. The most effective treatment of coeliac disease is sticking to a lifetime gluten-free diet [40]. Once the gluten is in the gut, no medicine is strong enough to prevent the damage caused by gluten in the intestinal lining. It is necessary to start a gluten-free diet as soon as possible [41]. As the patient is on a lifelong gluten-free diet, the dietitian must ensure to set a balanced and flavorful diet plan that might help the patient to feel good and positive. A play of colors in the meal might play the trick. There are also gluten-free products on the market. But they are expensive and are difficult to find easily [42]. The main focus of concern is that these products should not only be rid of gluten foods but also from any cross-contamination from gluten-containing items as minor traces of gluten might sneak into them and trigger the disease [43]. According to research, our body can tolerate 10mg of gluten per day without damaging the intestine and triggering any symptoms, however, more research is needed to drive any reliable results [44]. Some people might have refractory celiac disease in which the symptoms continue to occur even though the patient has already been on a strict gluten-free diet for the past 12 months. Unknown exposure to gluten or infusion of gluten from unknown sources might be the reason for this [45].

Several researches are underway to develop a treatment for celiac disease that can reduce the need for dieting. Genetically engineered gluten-free wheat crops might allow the patient to have wheat. Gene editing techniques like CRISPR might be useful in future in this regard [46]. Moreover, the ingestion of a combination of enzymes prolyl endopeptidase and cysteine endopeptidase causes the degradation of gluten and helps in its digestion, reducing the severity of the symptoms and degree of damage to intestinal mucosa [47].

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