Celiac Disease: Causes, Management and Treatment

Etoamaihe Chioma Jennifer*

Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria

*Corresponding Author: Etoamaihe Chioma Jennifer, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria.

Received: November 26, 2018 ; Published: March 27, 2019

Abstract

Celiac disease (CD) is an inflammatory disorder of the upper small intestine triggered by the ingestion of wheat, rye, barley, and possibly oat products. It was first discovered in the second century and more improvements have been made on it since then. It is highly prevalent in caucasians. It has several types grouped based on the symptoms they exhibit. The clinical feature of CD is characterized by a small intestinal mucosa with the absence of normal villi, resulting in a generalized malabsorption of nutrients. There is a strong genetic association with human leukocyte antigens (HLA-) DQ2 and DQ8 and currently unknown non-HLA genes. The precipitating factors of toxic cereals are the storage proteins, termed gluten in the field of CD (gliadins and glutenins of wheat, secalins of rye, and hordeins of barley). There is still disagreement about the toxicity of oat avenins. The structural features unique to all CD toxic proteins are sequence domains rich in Glutamine and Proline. Depending on the amino acid sequences, these peptides can induce two different immune responses. Both immune responses result in mucosal destruction and epithelial apoptosis. Additionally, stimulated T-cells activate B-cells that produce serum IgA and IgG antibodies against gluten proteins (antigen) and tissue transglutaminase (autoantigen). These antibodies can be used for noninvasive screening tests to diagnose CD. The current essential therapy of CD is a strict lifelong adherence to gluten-free diet.

Keywords: Celiac disease (CD); Human Leukocyte Antigens (HLA); Gluten-Free Diet (GFD)

Introduction

Celiac disease is a systemic immune-mediated disorder caused by the ingestion of gluten-containing grains (wheat, rye, and barley) in genetically susceptible persons [1]. It is one of the most common lifelong disorders on a worldwide basis, affecting approximately 1% of the general population. The frequency of celiac disease has increased in developed countries over the last decades, a finding that points out the causal role of possible environmental triggers additional to gluten [2]. Celiac disease (also referred to as celiac sprue, non-tropical sprue, and gluten-sensitive enteropathy) is an autoimmune disorder triggered by consuming a protein called gluten, which is found in wheat, barley and rye [1]. When a person with celiac eats gluten, the protein interferes with the absorption of nutrients from food by damaging a part of the small intestine called villi. Damaged villi make it nearly impossible for the body to absorb nutrients into the bloodstream, leading to malnourishment and a host of other problems including some cancers, thyroid disease, osteoporosis, infertility and the onset of other autoimmune diseases [2]. Celiac disease is a genetic disorder, meaning that it passes from parent to child via DNA. In some cases, stressful events such as pregnancy, surgery, infection, or severe emotional distress can trigger the onset of the disease [3].

Celiac disease is a chronic, immune-mediated enteropathy of the small intestine. In genetically predisposed individuals, it is triggered by gluten in food products [4]. Left untreated, Celiac disease may cause mal-absorption, reduced quality of life, iron deficiency, and osteoporosis, and there is an increased risk of lymphoma. The disease prevalence is 0.5 - 1.0%, but Celiac disease remains under-diagnosed. Clinically, Celiac disease presents with a broad spectrum of symptoms, with or without mal-absorption [5]. Knowledge of classical and
non-classical symptoms, as well as access to an appropriate diagnosis and counseling, are all crucial for the patients’ prognosis. The disease is associated with several autoimmune diseases, most importantly diabetes mellitus type 1 [6]. The diagnosis of Celiac disease is made by the presence of characteristic histopathological changes in duodenal biopsies in the form of crypt hyperplasia and villous atrophy, as well as by the remission of clinical symptoms and improved histology while the patient is on a gluten-free diet (GFD). The presence of Celiac disease antibodies and specific HLA (human leukocyte antigen) haplotypes may aid the clinical evaluation [7]. Patients with atypical symptoms and inconsistency between serology and histology can be a diagnostic challenge.

History of celiac disease

The first description of CD is attributed to Aretaeus the Cappadocian, who lived in the second century AD. He noted the characteristics tool and chronic nature of the condition and observed that children could also be affected by the disease. In 1888, Samuel Gee, a physician working at the St. Bartholomew Hospital in London, provided a thorough description of the clinical features of childhood CD (Mulder, et al. 1993). During the first half of the past century, it was generally agreed that the treatment for CD was rest and diet. In 1924 Sidney Has described his treatment of childhood CD with a banana diet, but there was hardly any form of diet not frequently discussed at that time as a treatment for the disease. However, the relationship between gluten ingestion and the symptoms of CD was discovered by the Dutch pediatrician, Willem-Karel Dicke (1905 - 1962) [8]. He became the medical director of the Juliana Children’s Hospital in the Hague (The Netherlands) at the age of 31. Long before the start of the Second World War (1934 - 1936) he started experiments with wheat-free diets. At the end of World War II, during the 1944 - 1945 winter of starvation, the delivery of normal food such as bread to his young patients in his hospital was endangered this period and dietary studies convinced him even more that eating less cereals and more uncommon food products such as tulip bulbs improved the clinical condition of his patients and that a wheat-free diet had favorable effects on children with CD [8]. After World War II, in collaboration with Vande Kamer, a biochemist from the Netherlands Central Institute for Nutritional Research TNO in Utrecht, and with Weyers, a pediatrician from the Wilhelmina Children’s Hospital in Utrecht, he extended his research and demonstrated that gliadins, i.e. the alcohol-soluble fractions of gluten (wheat protein), produced fat malabsorption in patients with CD (Moulder, et al. 1993).

Literature Review

Celiac disease currently occurs in about 1% of the general population worldwide [9]. In Sweden this prevalence was first noted 15 years ago, and similar levels were subsequently reported elsewhere [10]; even higher levels have sometimes been reported in young (12 year olds in Sweden) and older people (aged 52 - 74 in Finland). In general, prevalence studies based on serology only (tissue transglutaminase (TTG) and endomysial (EMA) antibodies) report higher prevalence than screening that requires confirmation through small intestinal biopsy [2]. The differences in prevalence between countries cannot be fully explained by diagnostic criteria. Two recent studies indicate a biopsy verified prevalence of 0.7-0.8% in the United States, which is consistent with earlier data from North America [11]. The disease seems to be more common in white people than in African-Americans or Hispanics in the US. The disease seems to be more common in white people than in African-Americans or Hispanics in the US [12]. Data from Europe vary widely, with the United Kingdom and Germany having a low prevalence, while Sweden and Finland have perhaps the highest prevalence rates reported to date (2 - 3%) [13,14]. Reports on the prevalence of celiac disease outside of Europe and the US are less abundant. The prevalence of celiac disease in China is low (probably because of the scarcity of the necessary HLA haplotypes, DQ2 and DQ8, in the Chinese population) [15]. The prevalence of biopsy verified celiac disease in the Indian Punjab region, where wheat is a staple food, is 1% [16]. The disease is rare in people from sub-Saharan Africa-none of 600 people in Burkina Faso who were screened were positive for EMA or TTG antibodies [1].

CD occurs largely in Caucasians. The disease has been well documented in Asians from India, Pakistan, and Iran, but it is rare or non-existent among native Africans, Japanese, and Chinese [5]. Using simple serological tests, it has gradually become clear that the prevalence of CD in different countries in the Middle East, North Africa, and India where wheat has been the major staple food for many centuries is almost the same as that in Western countries. Clinical studies showed that presentation with nonspecific symptoms or no symptoms is as

common in the Middle East as it is in Europe. A high index of suspicion for CD should be maintained in all developing countries for patients who present with chronic diarrhea or iron-deficiency anemia [17]. CD is a common, but frequently unrecognized, disease. The disease is more frequent among females, with a female-to-male ratio of 2:3:1. Screening studies have shown that CD is severely under diagnosed, with a prevalence of 0.5 to 1% among the white population, both in adult and in children [18].

Clinical aspect of celiac disease

Types of celiac disease

Celiac Disease can be divided into different clinical phenotypes. We recommend the following terminology used by Ludvigsson [9].

Classical celiac disease: Mal-absorption syndrome with micronutrient deficiency, which is dominated by diarrhoea, fatigue, and weight loss. It often includes muscle weakness, muscle and bone pain, glossitis, aphthous stomatitis, and tooth enamel defects, and possibly lactose malabsorption. The patient’s biochemistry is usually affected.

Non-classical celiac disease: This condition is characterised by no or few gastrointestinal symptoms (e.g. abdominal pain, constipation, flatulence, and dyspepsia); however, extraintestinal manifestations are predominant (e.g. dermatitis herpetiformis, selective IgA deficiency, autoimmune liver diseases, diabetes mellitus type 1, autoimmune endocrine disorders (thyroiditis), certain neuropsychiatric disorders, osteopenia, and infertility) [9].

Symptomatic celiac disease: The presence of gastrointestinal or extraintestinal symptoms due to gluten ingestion [9].

Asymptomatic celiac disease: This condition is found in asymptomatic individuals or people with vague complaints, such as fatigue, which can only be identified after starting a GFD (the latter group can be described as having subclinical Celiac Disease) [9].

Potential celiac disease: This condition is found in asymptomatic individuals with positive Celiac Disease serology but with normal small intestinal histology. These individuals are considered at risk for later development of symptoms and/or mucosal lesions. This group can be difficult to differentiate from individuals with symptomatic Celiac Disease, because mucosal lesions in the proximal small intestine may be sporadic and patients’ habitual gluten intake may vary [9].

Refractory celiac disease: Refractory Celiac Disease is defined as persistent or recurrent symptoms (typically diarrhoea and weight loss) and signs of malabsorption that are accompanied by villous atrophy despite a strict GFD for at least 12 months and in the absence of other conditions [9].

Causes of celiac disease

Doctors don’t really know what causes the disease. Having certain genes; HLA DQ8 and HLA DQ2 can increase your chance of getting it. You are more likely to have these genes and get celiac disease if a close family member has the disease. Environmental factors, such as infections, may trigger changes in the small intestine of a person with these genes. Then, eating foods that contain gluten can trigger an abnormal immune system response. Over time, this response can cause digestion and absorption problems [19].

Celiac disease is a lifelong (chronic) condition that occurs when gluten triggers an abnormal immune system response that damages the small intestine. The small intestine is lined with tiny, finger-shaped tissues called villi. The villi create a large surface that absorbs vitamins, sugars, and other nutrients as food passes through the small intestine. When a person who has celiac disease eats gluten, the villi flatten out and the intestinal lining becomes damaged. This decreases the area that can absorb nutrients. In some cases, this inability to absorb nutrients may be bad enough to stunt growth and weaken bones. The loss of vitamins and minerals may lead to other problems, such as anemia, osteoporosis, or growth delays in children [20].

Symptoms of celiac disease

The symptoms of celiac disease vary greatly from one person to another. Some may have only one symptom, such as diarrhea or anemia, while others may have a number of symptoms. As the disease progresses, many systems of the body can be involved, including the reproductive, gastrointestinal and nervous systems. The blood, bones, teeth and skin can also be affected [15].

Celiac Disease: Causes, Management and Treatment

Some individuals with celiac disease have a positive blood test and a positive intestinal biopsy (tissue sample) but present no symptoms. This is called silent celiac disease [15].

Symptoms of celiac disease may include one or more of the following:

- Recurring abdominal bloating and pain
- Chronic diarrhea/constipation
- Vomiting
- Liver and biliary tract disorders ("Transaminitis", fatty liver; primary sclerosing cholangitis etc.)
- Weight loss
- Pale, foul-smelling stool
- Iron-deficiency anemia that does not respond to iron therapy
- Fatigue
- Failure to thrive or short stature
- Delayed puberty
- Pain in the joints
- Tingling numbness in the legs
- Pale sores inside the mouth
- A skin rash called dermatitis herpetiformis (DH)
- Tooth discoloration or loss of enamel
- Unexplained infertility, recurrent miscarriage
- Osteopenia (mild) or osteoporosis (more serious bone density problem [6].

Symptoms in children

Children tend to have the more classic signs of celiac disease, including growth problems (failure to thrive, chronic diarrhea/constipation, recurring abdominal bloating and pain, fatigue and irritability [6].

Dermatitis herpetiformis is an itchy, blistering skin disease that stems from intestinal gluten intolerance. The rash usually occurs on the elbows, knees, torso, scalp and buttocks. Antibodies to epidermal transglutaminase (eTG, also keratinocyte transglutaminase) are the autoantibodies believed to cause dermatitis herpetiformis.

Dermatitis herpetiformis is often associated with changes to the lining of the small intestine identical to those of celiac disease, but the disease may not produce noticeable digestive symptoms [21]. Doctors treat dermatitis herpetiformis with a gluten-free diet or medication, or both, to control the rash [22].

Symptoms in adults

Adults tend to have symptoms that are not entirely gastrointestinal in nature. Recent research has demonstrated than only a third of adult patients diagnosed with celiac disease experience diarrhea. Weight loss is also not a common sign. The most common sign of celiac disease in adults is iron deficiency anemia that does not respond to iron therapy [23].

Who should be tested for celiac disease and how often?

1. Children older than three years of age and adults, regardless of symptoms, if related to a close relative with biopsy confirmed celiac disease. A close relative is considered to be a parent, sibling or child. An aunt/uncle, grandparent or cousin with celiac disease may raise an individual’s risk for celiac disease somewhat, but not much higher than the risk of the average population [2].

2. In children younger than three, with symptoms, antibody testing may not always be accurate. However, young children with symptoms (especially failure to thrive or persistent diarrhea) should be evaluated by a pediatric gastroenterologist. Children need to be eating wheat or barley based cereals for some time, up to one year before they can generate an autoimmune response to gluten and have their blood tested [24].

3. Any individual who has a related autoimmune disorder, regardless of celiac symptoms, should be tested for celiac disease and if negative the test should be repeated on a periodic basis. These conditions include insulin-dependent diabetes mellitus (requiring insulin therapy), Hashimoto’s thyroiditis, Turner’s syndrome, Williams’s syndrome, Graves-disease and Sjogren’s disease [6].

4. Any person with Down Syndrome should be tested on a periodic basis.

5. Any individual who has experienced persistent miscarriage or infertility where a medical cause could not be found needs to be tested for celiac disease.

6. There are many other symptoms that could indicate the presence of celiac disease, including persistent gastro-intestinal symptoms, bone density problems, dental enamel hypoplasia, fatigue, and others. If you are concerned about your symptoms, ask your doctor about testing [11].

Diagnosis of celiac disease

CD diagnosis is not always easy to be performed. In around 10% of cases, there is difficulty in diagnosis due to conflicting serology, histology, and clinical findings. CD’s diagnosis must be considered in every patient presenting chronic diarrhea, abdominal distention, flatulence, iron-deficiency anemia, early onset osteoporosis, elevated transaminases, first and second degree relatives of the patients with CD, IBS, hypocalaemia, as well as in face of folic acid and liposoluble vitamins. There is no justification in literature, at the moment, for population screening for CD diagnosis [7].

HLA Typing is the first step for investigating relatives of CD patients. HLA typing excludes one third of 1st degree relatives and identifies individuals for evaluation with biopsy. It is also the clinical exam indicated if the individual presents negative serology and refuses to undergo biopsy. HLA allele DQ2 is identified in 90% - 95% of celiac patients, and HLA DQ8, in most of the others. Therefore, their absence has a negative predictive value next to 100%. HLA typing is useful also to exclude the disease in patients who, unwittingly, are already undergoing gluten-free diet or individuals in which diagnosis is not clear [7].

Serological diagnosis

Markers used are the antibodies anti-endomysial (EMA) and anti-tissue trans-glutaminase (anti-tTG), for being sensitive and specific for early CD’s diagnosis. Several studies have evidenced a high correlation among their results, thus it is not necessary to research both of them. The research of antigliadin antibody (AGA) performance is not comparable to test mentioned above and is disused [25].

Serum tests are responsible for recognizing that CD is not rare. Positive serum test suggests CD diagnosis, but duodenal biopsy is still gold standard. Positive serology may become negative after 6 - 12 months from the gluten-free diet introduction. Serum markers sensitivity is related to the extent of histological damage in CD, both at diagnosis and in the follow up to gluten-free diet adherence. Serum tests sensitivity will be high when there is the presence of total villous atrophy and its progressive decrease, as histological findings are less altered. Thus, negative serology does not exclude CD diagnosis. Serum tests may be used to evaluate the patient’s adherence to gluten-free diet. Antibodies become negative after 3 - 12 months of diet [26].
Biochemistry and treatment of celiac disease

Celiac disease (CD) is an inflammatory disorder of the upper small intestine triggered by the ingestion of wheat, rye, barley, and possibly oat products. The clinical feature of CD is characterized by a flat intestinal mucosa with the absence of normal villi, resulting in a generalized mal-absorption of nutrients [27].

Gluten

There are two main groups of proteins in gluten, called the gliadins and the glutenins. Upon digestion, the gluten proteins break down into smaller units, called peptides (also, polypeptides or peptide chains) that are made up of strings of amino acids—almost like beads on a string. The parent proteins have polypeptide chains that include hundreds of amino acids. One particular peptide has been shown to be harmful to celiac patients when instilled directly into the small intestine of several patients. This peptide includes 19 amino acids strung together in a specific sequence. Although the likelihood that this particular peptide is harmful is strong, other peptides may be harmful, as well, including some derived from the gluten in fraction [28].

It is certain that there are polypeptide chains in rye and barley proteins that are similar to the ones found in wheat. Oat proteins have similar, but slightly different polypeptide chains and may or may not be harmful to celiac patients. There is scientific evidence supporting both possibilities [27].

Human Leukocyte Antigens (HLA)

The most important genetic factors identified are HLA-DQ2 and HLA-DQ8, which are necessary but not sufficient to predispose to CD. The associations found in non-HLA genome wide linkage and association studies are much weaker. This might be because a large number of non-HLA genes contributes to the pathogenesis of CD. Hence, the contribution of a single predisposing non-HLA gene might be quite modest. Practically all CD patients carry HLA-DQ2 or HLA-DQ8, while the absence of these molecules has a negative predictive value for CD close to 100%.

There is a strong genetic association with human leukocyte antigens (HLA-) DQ2 and DQ8 and currently unknown non-HLA genes [24].

Pathogenesis

During the last decade, intense biochemical studies have contributed to substantial progress in understanding the general principles that determine the pathogenesis of CD [6]. The precipitating factors of the toxin are the storage proteins, termed gluten in the field of CD (gliadins and glutenins of wheat, secalins of rye, and hordeins of barley). There is still disagreement about the toxicity of oat avenins. The structural features unique to all CD toxic proteins are sequence domains rich in Gln and Pro. The high Pro content renders these proteins resistant to complete proteolytic digestion by gastrointestinal enzymes. Consequently, large Pro- and Gln-rich peptides are cumulated in the small intestine and reach the subepithelial lymphatic tissue. Depending on the amino acid sequences, these peptides can induce two different immune responses [27].

The rapid innate response is characterized by the secretion of the cytokine interleukin-15 and the massive increase of intraepithelial lymphocytes. The slow adaptive response includes the binding of gluten peptides (native or partially deamidated by tissue transglutaminase) to HLA-DQ2 or -DQ8 of antigen presenting cells and the subsequent stimulation of T-cells accompanied by the release of pro-inflammatory cytokines such as interferon-γ and the activation of matrix metalloproteinases. Both immune responses result in mucosal destruction and epithelial apoptosis. Additionally, stimulated T-cells activate B-cells that produce serum IgA and IgG antibodies against gluten proteins (antigen) and tissue transglutaminase (autoantigen) and can be used for non-invasive screening tests to diagnose CD. The current essential therapy of CD is a strict lifelong adherence to gluten-free diet [24]. The genetic determinants that confer susceptibility to the disease are, however, not yet fully understood. The most important genetic factor identified is the human leukocyte antigen (HLA)
Celiac Disease: Causes, Management and Treatment

locus. The HLA-DQ2 (DQA1*0501-DQB1*0201) haplotype is expressed in the majority of affected patients (90%), the DQ8 haplotype (DQA1*0301-DQB1*0302) is expressed in 5% [26]. An increased risk of celiac disease has been observed among persons who carry two DQB1*02 alleles (Liu, et al. 2014). The ability of these alleles in conferring individual susceptibility to celiac disease is related to their peculiar capacity to bind negatively charged peptides such as gliadin peptides resulting from the deamidation of gluten by the anti-trans-glutaminase. The HLA antigen results in the activation of T lymphocytes, whose secretion products play a key role in causing mucosal lesions (Catassi, et al. 2011). The associations found in non-HLA genome-wide linkage are much weaker. This might be because a large number of non-HLA genes contributes to the pathogenesis of celiac disease [4]. Hence, the contribution of a single predisposing non-HLA gene might be quite modest.

Figure 1: Structure of prolamin.

Figure 2: Structure of glutelin.

Treatment for celiac disease

The only current treatment for celiac disease and its skin form, dermatitis herpetiformis, is maintaining a strict gluten-free diet for life. Complete avoidance of gluten enables the intestine to heal, and the nutritional deficiencies and other symptoms to resolve [19]. Children tend to heal more quickly than adults. Following a strict gluten-free diet also reduces the risk of developing many of the serious long-term complications related to untreated celiac disease [29]. Adjusting to a gluten-free diet can be challenging, since it involves knowing what foods contain gluten, and determining possible hidden sources of gluten in food products and medications. It also involves a number of lifestyle changes since many commonly eaten foods must be avoided, including pasta, most breakfast cereals and certain snacks, most breads and other baked goods including cakes, cookies, doughnuts, bagels, etc [7]. Wheat flour and wheat starch are also frequently added as a thickener or stabilizer to soups, sauces, and processed meats and fish, including wiener, sausages, and imitation seafood. Barley is used in the manufacture of beer and of malt, a flavoring agent commonly used in food. To avoid hidden sources of gluten in the diet, knowledge of potential sources of gluten and careful reading of food ingredient lists is essential [7].

Management of celiac disease

CD diagnosis and lifelong gluten-free diet introduction must not be firm without compatible histological findings, regardless of the results of serological tests. However, it is also not advised to affirm a diagnosis based only on the histological diagnosis, because the disease does not compromise uniformly intestine, and alterations are not observed exclusively in CD. In spite of these problems, intestinal

Celiac Disease: Causes, Management and Treatment

biopsy is considered ‘gold standard’ diagnosis. Patients who present persistently positive serology and negative biopsy probably have latent CD [19].

Conclusion

In conclusion, Celiac Disease like all other diseases though does not have a cure but can be controlled. People with such symptoms as unexplained weight loss, irritable bowel syndrome and children with Dermatitis Herpatiformis should test for celiac disease [22]. Gluten intolerant individuals are also at risk of having it as well as down syndrome sufferers and people whose close relatives suffer from this disease [15].

The clinical feature of CD is characterized by a flat intestinal mucosa with the absence of normal villi, resulting in a generalized malabsorption of nutrients. There is a strong genetic association with human leukocyte antigens (HLA-) DQ2 and DQ8 and currently unknown non-HLA genes. The protein in various foods that worsen CD are the; gliadins and glutenins of wheat, secalins of rye, and hordeins of barley (There is still disagreement about the toxicity of oat avenins). The structural features unique to all CD toxic proteins are sequence domains rich in Glutamine and Proline. The high Proline content renders these proteins resistant to complete proteolytic digestion by gastrointestinal enzymes. Consequently, large Pro- and Gln-rich peptides are cumulated in the small intestine and reach the subepithelial lymphatic tissue. Depending on the amino acid sequences, these peptides can induce two different immune responses. The current essential therapy of CD is a strict lifelong adherence to gluten-free diet [30-32].

Numerous analytical methods for gluten determination have been developed, mostly based on immunochemical assays, mass spectrometry, or polymerase chain reaction. So far, only two enzyme-linked immunosorbent assays have been successfully ring-tested and are commercially available. During the last decade, future strategies for prevention and treatment of CD have been proposed. They are based on the removal of toxic epitopes by enzymatic degradation or gene engineering and on blocking parts of the immune system. However, any alternative treatment should have a safety profile competitive with gluten-free diet [25].

Acknowledgements

I wish to acknowledge my dearest supervisor, Obioma Benedeth Eze for her patience and kindness in guiding me through the making of this seminar.

I also wish to acknowledge my parents for their continuous support financially and otherwise.

And finally, my friends for staying by me and encouraging me through this period.

Bibliography


---

**Volume 14 Issue 4 April 2019**

© All rights reserved by Etoamihe Chioma Jennifer.