Review Article

Diagnosing celiac disease: a review of diagnostic modalities of celiac disease

Arslaan Javaeed*

Student, Faculty of Education, University of Ottawa, Canada

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*Correspondence:
Dr. Arslaan Javaeed,
E-mail: ajava102@uottawa.ca

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ABSTRACT

Celiac disease is known as gluten-sensitive enteropathy. By enteropathy it simply means it is pathology of the gastrointestinal tract and that is why diarrhea (a common GI symptom) is usually one of the commonest presentations of celiac disease. So, it is safe to define celiac disease as an autoimmune disorder that mainly afflicts the small intestine. By autoimmune authors are referring to a disorder in which the body’s immune system works against the body itself. It is a chronic disorder where the sufferer is not able to tolerate gliadin, which is the alcohol soluble component of gluten. Gluten of course is a protein that is usually found in common foods like barley and wheat. Celiac disease which can also be regarded as celiac sprue has a genetic and immunological aspect to its etiology both of which would need to be considered when screening anyone for celiac disease.

Keywords: Celiac disease, Diagnosis, Screening

INTRODUCTION

The inflammatory response triggered when one with celiac disease ingests a gluten-rich or gluten-containing food, leads to poor digestion and absorption which could cause failure to thrive in babies as well as weight loss and electrolyte derangement. Celiac disease can usually occur in a spectrum. That is, the disease can be mild or severe depending on the symptoms and sometimes it may be entirely asymptomatic, i.e. without symptoms.¹ The prevalence of celiac disease in the United States is about 1 in 3000, this estimate suggests that a small proportion of western population is affected; about 1%. This however may not be the true picture when one considers the fact that there is a good number of underdiagnosis when it comes to celiac disease.²⁻⁴ According to international statistics, about 3 million people are affected in the United States and a similar number is seen in Europe as well. In Australia celiac disease is said to affect about 1 in 100 persons.⁵ There is however paucity of studies in Africa and Asia but it is suggested that certain populations in these regions show increase incidence of celiac disease. In the Middle East there are also few studies that can help ascertain its prevalence.⁶ It is also worthy of note that there are somewhat two age distribution when it comes to celiac disease. The first affects those in the young age group between 8-12 months and the second affects those in their 4th decade of life. It is said that about 20% of patients affected by celiac disease are usually in their 60s or older.⁷

In this article Author would be looking at the different methods that are employed in diagnosing celiac disease as well as recent techniques. First Author would consider history and examination, then we could look at laboratory modalities, imaging and histological techniques. Prognosis of celiac disease is excellent provided an accurate diagnosis is made which would lead to proper therapeutic interventions. In order to make an appropriate diagnosis the modalities below must be thoroughly employed as this will help to ensure the best prognosis for the patient.
**METHODS**

The first thing that was done was to get a list of literatures that were going to be used for this article. Then elimination was done based on the year it was written and the focus of the article. The literatures that were used were mostly 15 years old with exceptions of some significant ones that were reasonably older. Also, articles that focused more on diagnosis and not just epidemiology and management were considered first. This is because this area was going to be the main focus of this review. Most literatures were sourced from notable medical database and all are well referenced.

**REVIEW OF LITERATURE**

Of the total world population, about 1% has celiac disease and this is despite the spate of under-diagnoses. Celiac disease patients are at increased risk of cancers like non Hodgkin’s lymphoma and small intestinal adenocarcinoma with the latter up to a 30 fold increase in risk with a 1.4 fold increase in death risk. The prevalence of celiac disease is also something that is worthy of note. Despite the 1% occurrence in the world general population, similar prevalence has been noted in places like Sweden among a younger age group (12 years) and in Finland among the older age group (52-74 years). Of course a setback to this prevalence study is the discovery that prevalence study carried out by serological testing alone i.e. tissues transglutaminase (TTG) and endomysial antibodies (EMA) would show a higher prevalence than confirmatory studies through small intestinal biopsies. This is no doubt due to the sensitivity of the latter however being an invasive screening test it is not recommended for such prevalence studies. We can also examine the prevalence of celiac disease among other different countries. For example two different biopsy confirmed studies revealed 0.7-0.8% prevalence in the United States. The disease appears to be commoner in the US among white people than African Americans or Hispanics. In Europe however there appears to be a varying degree of prevalence with low prevalence noticed in the United Kingdom and Germany while countries like Sweden and Finland have prevalence reports between 2-3% which is high in comparison to the world general population. Prevalence studies in Asia and Africa have not been well explored but few studies that have been carried out shows a low prevalence. For example the prevalence in China is low and this has been attributed to a possibly scare presence of the HLA haplotypes, DQ2 and DQ8 among the Chinese which has strongly been linked to celiac disease. In India, despite the fact that wheat is a stable food, the prevalence report from biopsy verified celiac disease is at 1% and the disease is rare in Saharan Africa, a case study of this is Burkina Faso where all the 600 people screened were negative for EMA or TTG antibodies. The incidence of celiac disease is also said to be on the rise. Data collected from North America has shown an increase in incidence right from the 1950s, this rise reached 17 per 100, 000 persons between the years 2008 to 2011. The rise is not peculiar to North America alone, data from the United Kingdom, also reveal a similar incidence that is placed at 19 per 100 000 persons between 2010 and 2011. The question now would be what is responsible for this rise in incidence. Some studies have attributed it to better diagnostic modalities but it is fair to state that this alone may not be the only reason. Therefore, it becomes tantamount to explore studies that have shown other possible risk factors for developing celiac disease and Author would be looking at some of them below. Studies have shown a strong correlation between gluten exposure and celiac disease. For example, studies done among refugee camps of the Saharawi people in Africa, and the Swedish infants born in the early 1990s that were formula fed, both populations with a high gluten load, the prevalence of celiac disease was over 1% among them. However, the relationship between breastfeeding patterns and the development of celiac disease has remained an issue of controversy. There was strong suggestion that factors like the timing and quantity of gluten introduction in infants play a significant role in the pathogenesis of celiac disease and this too owning to the celiac disease epidemic among infants in Sweden that coincided with a change in their feeding pattern. Despite this proposed correlation, three different prospective observational studies that were done recently did not show any association between breast feeding patterns and the subsequent development of celiac disease. These three studies were later corroborated by a two multicenter randomized clinical trial that were conducted in 2014 were there was no link found between the age of onset of gluten introduction and breast feeding with the subsequent predisposition to celiac disease.

Infant feeding has not been the only predisposing factors that studies have looked into, there have also been documented risks with infection, drugs, perinatal exposure and smoking and we shall also consider these risk factors below.

Celiac disease is an autoimmune disease and like other autoimmune diseases (e.g. type 1 diabetes mellitus), viral infections are said to play a role and this is the same for celiac disease. Gastrointestinal infections are one of the infections that has been linked to celiac disease, especially when the onset of infection is in early life and adulthood. However the results of this link has remained indeterminate as there have been reports of recall bias, and a clinical significance that only fits well in the context of disease trend. This has made it quite difficult to be definitive as to the true significance of viral infections in celiac disease. Conversely to this, a study done in the United States suggested that gastric colonization by Helicobacter pylori, which is notorious for causing peptic ulcer disease, confers some form of protection against celiac disease.
Next author could consider the role of drugs, for example, a study suggests that the use of proton pump inhibitors has been linked as one of the etiological causes of celiac disease.33 This suggestion however should be applied with caution especially considering the fact that PPIs are frequently used for symptomatic relief of ulcer, symptoms that could mimic an underlying celiac disease. So, it is unclear if the patients studied already had celiac disease for which the PPIs were given or the PPIs themselves played a role in the development of celiac disease in these patients. Another factor is the exposure to neonates during the perinatal period.

A prospective study was done in Sweden examined data of risk factors in the perinatal period from more than eleven thousand celiac disease sufferers. It found some risk of celiac disease in patients that had an elective cesarean section compared to the general proportion of those who had cesarean section.34 A reason for this may be as a result of babies born though elective cesarean sections not entering the birth canal from where the babies would naturally get their bacterial gut flora constituted. This alteration in the gut flora of those born as a result of elective cesarean section is said to cause a predisposition that eventually gives rise to celiac disease. Finally, smoking is another risk factor that has been implicated even though data regarding this has been inconclusive. The general assumption is that smoking should predispose to celiac disease owning to its strong relationship with cancer similar to that with celiac disease and intestinal cancer. However, study in the UK suggests that smoking may confer some protection against celiac disease, while other studies actually found no relationship between celiac disease and smoking.35,36 In these predispositions from different studies, one thing can be safely deduced, and it is that the predisposition to celiac disease is multi-factorial and as such it would be impossible to state categorically one significant cause. In view of this, it is appropriate to state that celiac disease arises from a constellation of varying insults in the background of genetic predisposition rather than a singular underlying cause.

Pathophysiology and pathogenesis

Celiac disease is believed to arise from the interaction that occurs between environmental factors like gluten and the body’s immune system as well as genetic factors.

When celiac disease is considered immunologically, the disease can be described as that which chiefly occurs in individuals with the haplotypes of the DQ2 or DQ8 HLA type. So, what is gluten? Basically, gluten refers to the storage protein form for foods like barley, rye and wheat. Gluten proteins in the body are not completely digested by the body’s digestive juices of gastric and pancreatic peptidases, this is because gluten contains glutamines and prolamines and as a result even after its break down large peptides of amino acids are still left as shown in Figure 1.37

![Figure 1: Incomplete breakdown of gluten in human intestine and stimulation of immune system by peptides.](image)

These large peptides eventually pass into the intestine through the epithelial barrier via the paracellular or transcellular route. The way this route eventually influences the pathogenesis however is not yet properly understood. Immunologically, celiac disease arises from a dysregulation of both the innate and adaptive immunity. The innate immunity is described as the immunity an individual is born with and the adaptive immunity is also often referred to as acquired immunity. So, a break down in both of these two immune types is said to play a role in the pathogenesis of celiac disease. It has been suggested that an increase in the permeability of the intestinal epithelium that permits gliadens (which is the harmful part of gluten) to pass contributes to the early phase of the development of celiac disease. This is because gliaden is believed to activate the acquired immune system of eventual sufferer of celiac disease.

A study done by Lammers et al, demonstrates how gliadin may be able to pass the paracellular route into the intestinal mucosa.38 Their study proposed that gliadin binds to a chemokine receptor, the CXCR3 forming a gliadin-CXCR3 complex which in turns leads to the release of zonulin which disrupts the tight junctions, leading to the eventual passage. This is however not the only mechanism that has been proposed. Another study done by Matysia-Budnik et al, described what is now referred to as the excessive expression of a transferin receptor (CD71) among patients who were suffering from celiac disease.39 This receptor is believed to aid the transport of gliadin through a different process referred to as retro-transcytosis. This is not all regarding the transport of gliadin and its role in the pathogenesis of celiac disease. Schumann et al, described an epithelial translocation of part gliadin that is clinically significant in the pathogenesis of celiac diseases referred to as alpha2-gliadin-33mer.40 This epithelial translocation takes place.
via apical to basal transcytosis in the presence of interferon-gamma another cytokine that has been strongly linked to the immune pathogenesis of celiac disease. With these different studies, the possible mechanism that leads to the pathogenesis of celiac disease through the transport of gliadin via the gut epithelium either from the transcellular or paracellular routes has been put forth. Nevertheless, it should be stated that as these complex gliadin transport modalities are better understood a new therapeutic breakthrough in celiac disease may be on the horizon.

With regards the pathogenesis of celiac disease, there have also been other studies done in different areas one of them was done by Fina D et al, and this was to demonstrate the gluten-dependent rise expressed in the RNA and interleukin 21 of duodenal samples from celiac disease patients who were not treated. The relevance of the cytokine in maintaining the expression of T-bet and sustaining interferon gamma production was examined. Grose et al, was able to describe a systematic deficiency in the natural killer T cells and this is in combination with the already defective cytokine that is produced in celiac disease. The study was able to suggest that a deficiency in the immune regulation of natural killer T cells could have a role in the loss of immune tolerance among patients with celiac disease.

So even though the pathogenesis of celiac disease is still far from been completely understood, studies have been able to show different possible etiological factors, risk factors and environmental factors as well as immune factors and genetic factors which in combination or with the right predisposition could lead to the eventual development of celiac disease. Celiac disease is therefore not a disease that arises from a singular factor alone, but one whose pathogenesis is closely linked to first a dysfunction in the immune regulatory system as is the case with other autoimmune disease. The eventual development of celiac disease would then depend on the presence of these factors and a dysfunction in the immune system. The mechanism for the immune system dysfunction, even though not sufficiently understood, the aforementioned studies provide a good basis for further research into the pathogenesis of celiac disease.

DISCUSSION

History and examination

In the diagnosis of celiac disease, the medical history and physical examination is crucial. The prevalence of celiac disease in first degree relatives is about 10% and this does not just buttress the genetic etiology of celiac disease but also underscores the need to take a proper family history. So, a patient who presents with GI symptoms like diarrhea, flatulence, abdominal pain should be evaluated for age of onset, if symptoms are related or worse by certain meals and of course if any family member (especially first degree relatives) have similar history or any known medical condition like celiac disease. The physical examination may show features that point to malabsorption of nutrients, so there could be evidence of weight loss, pallor, cheirosis, glossitis, evidence of peripheral neuropathy and Trousseau sign may be elicited as a result of calcium deficiency. Both the medical history and physical exam is the first step towards diagnosing celiac disease.

Laboratory tests

The laboratory tests employed in diagnosing celiac disease include blood investigations that show derangement based on the pathogenesis of celiac disease, tests like hematological tests, electrolyte and stool tests as well as the more specific tests like the serological tests and genetic test.

General tests

Hematological tests

These tests help to detect anemia which can be present in celiac disease as a result of deficiency of nutrients needed by the body to ensure normal blood levels. Nutrients like iron and folate can become deficient as a result of celiac disease and this would lead to defective red blood synthesis and a resultant anemia. So, a drop in iron levels in a patient with some of the aforementioned signs and symptoms may be suggestive of celiac disease.

Electrochemical tests

In malnutrition that is seen in celiac disease, patients could become deficient in essential body electrolytes like potassium, calcium and magnesium casing hypokalemia, hypocalcemia and hypomagnesaemia respectively. There could also be presence of low protein (hypoproteininaemia). All these can be shown by doing an electrolyte test as well as test for serum protein which could be a pointer to celiac disease.

Stool tests

Steatorrhea which is seen in malabsorption of fats by the presence of bulky, foul smelling stools can be tested by a 72 hour fecal fat collection.

Specific tests

Serological tests

This is one of the mainstay tests for celiac disease. It involves checking for the presence of antibodies in the serum of patients suspected to be having celiac disease. Celiac disease is said to be an autoimmune disease, and so there is usually an elevation of certain antibodies in the blood of patients with celiac disease. These antibodies usually differ in sensitivity (to ability of a test to detect the presence of a disease) and specificity (the ability of a
test to detect the absence of a disease). The common antibodies that are checked in the serological tests for celiac disease are the tissue transglutaminase IgA, endomysial IgA and reticulin IgA. This is because they correlate better with mucosal damage in the GI tract. The tissue transglutaminase IgA has a sensitivity of about 98% and a specificity of about 95%. It must be noted that IgA remains the preferred immunoglobulin when testing for celiac disease, but some patients with celiac disease tend to be IgA deficient. For these patients, the IgG can also be used. There are also other antibodies that are commonly used for serological tests in patients with suspected celiac disease. There is the anti-deamidated gliadin peptide (DGP) and the antigliadin antibody which was first discovered in the 1980s. The latter’s use however has been discouraged as a screening tests as unlike the tissue transglutaminase IgA it has a low sensitivity and a low specificity.

**Genetic test**

The next test that Author would consider for celiac disease is the genetic test. There is usually the presence of a specific human leukocyte antigen (HLA) that is seen in patients with celiac disease and it is reported that finding this HLA gene can help in diagnosing celiac disease. This also has its own setbacks as Author would soon see. Individuals suffering from celiac disease can have either HLA DQ2 and/or HLA DQ8 genes. The drawback of this is that a certain percentage of the normal population placed at about 25% to 30% will have these genes without having celiac disease. The presence of these genes however increases ones predisposition to having celiac disease from 1% to 3% when compared with the general population. This implies that as a first degree relative of one who suffers from celiac disease that would usually have about a 40% chance of developing celiac disease, this genetic test can help rule out the chance of them ever developing celiac disease if the aforementioned HLA genes are absent. This is why the test is said to have a high negative predictive value of >99%. 

**Dexa scan**

Due to the deficiency in nutrients as a result of the malabsorption that is seen in celiac disease, one of the nutrients that could be deficient is vitamin D, another is calcium both of which are needed for healthy bones. A resultant osteoporosis could ensue and may be present in patients with celiac disease. This is why a dixa scan would help show this, depicting any fracture risk that may be present in the bones.

**Gluten challenge**

Usually in the diagnosis of celiac disease one may not need a gluten challenge or gluten withdrawal test. The reason for this is that with the aforementioned antibody and genetic testing, one should be able reach a diagnosis. Gluten challenge also has some drawbacks in that it cannot be used in all members of the population. It is not recommended for use in children before the age of 5 years and it is also not recommended for those in the pubertal age.

Pregnant women should also not have a gluten challenge test done. So basically, a gluten challenge involves introducing gluten containing food to a patient with suspected celiac disease and watching the symptoms that would subsequently ensue. The recommended gluten food for a gluten challenge test is usually two slices of wheat containing bread giving daily for a period of 6 to 8 weeks. It must be stated that it is no longer recommended for diagnosing celiac disease, but it can still be used to support the diagnosis of celiac disease.

**Endoscopy**

The final diagnostic modality for celiac disease that Author would be looking at is endoscopy. This usually involves the use of a camera to view the inner part of the intestine. It could be used to view either the upper or lower GI. For celiac disease however, upper GI endoscopy is usually done. This has the advantage of been able to allow the physician to view the inner lining of the upper GI tract and also to take biopsy specimen that can be taking to the histological laboratory to make a confirmatory diagnosis of celiac disease.

During the upper GI endoscopy, biopsies are taken from different parts of the duodenum and/or jejunum, at least 6 to 8 biopsies need to be taking. This is to reduce the possibility of having a false negative test which can result if a normal part of the upper GI tract is biopsied. When the biopsied tissue is taking to the histological lab, lymphocytic infiltration and villous atrophy which would be the cause of the malabsorption seen in celiac disease are two strong pointers that would lead to the eventual confirmation of celiac disease in the patient. There is also the presence of hyperplastic crypts.

**Staging**

After the diagnosis of celiac disease is confirmed through histology, a staging is usually done to detect the severity of the disease based on the histological findings. There are 5 stages from stage 0 to 4:

- **Stage 0 - Normal**
- **Stage 1 - Increased percentage of intraepithelial lymphocytes (>30%)**
- **Stage 2 - Characterized by an increased presence of inflammatory cells and crypt cell proliferation with preserved villous architecture**
- **Stage 3 - Mild (A), moderate (B) and subtotal (C) villous atrophy**
- **Stage 4 - Total mucosal hyperplasia**
CONCLUSION

Even though most individuals diagnosed with celiac disease would be able to benefit from many modalities of current treatment, making a diagnosis is the crucial step to that. The above tests and imaging cover a good percentage of modalities that constitute the current trend in diagnosing celiac disease. It has been recommended that the genetic testing be used as a screening tool for celiac disease, especially for those with a family predisposition (a first degree relative with celiac disease). However, there are still some controversies regarding this. Nevertheless, it must be stated that with technological advancements, physicians currently have a wide range of tools at their disposal to accurately diagnose celiac disease as well as ruling it out in patients who may have symptoms that are similar to celiac disease.

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