

Celiac Disease and Nonceliac Gluten Sensitivity



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KEYWORDS

- Celiac disease • Gluten-free diet • Tissue transglutaminase • Autoimmune
- Children • Wheat allergy • Nonceliac gluten sensitivity

KEY POINTS

- Celiac disease is found in genetically susceptible individuals who carry the HLA DQ2 or DQ8 gene.
- Celiac serology testing is a good screening tool.
- The gold standard for diagnosis is still an upper endoscopy to acquire small bowel biopsies.
- Currently the only available treatment is gluten-free diet.
- NCGS can be considered in those without evidence of celiac disease and wheat allergy who have clinical improvement on a gluten-free diet.

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy that causes damage to the small intestinal mucosa when gluten, found in wheat, barley, and rye, is ingested, which only occurs in genetically susceptible individuals. Innate gluten sensitivity, adaptive gluten sensitivity, and autoimmunity are essential in the development of CD.¹

The prevalence of CD has been increasing worldwide, most likely because of greater awareness and better testing. Gluten has a high concentration of glutamine and proline residues referred to as prolamines, which are specifically found in wheat, barley, and rye. It is thought that under stressful situations, such as infection or surgery, the gliadin protein enters the lamina propria where it is deaminated by the enzyme tissue transglutaminase (tTG) and then it becomes attached to it to form a

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complex. This specific complex is then presented to the antigen-presenting cell resulting in secretion of proinflammatory mediators.² This process ultimately produces intestinal inflammation resulting in crypt hyperplasia and villous atrophy. CD should also be considered in certain populations with an increased prevalence of CD, such as those with selective IgA deficiency, first-degree relatives of patients with CD, autoimmune thyroiditis, type I diabetes, Down syndrome, Turner syndrome, and Williams syndrome.³

EPIDEMIOLOGY

CD occurs in genetically susceptible individuals, but the pattern of genetic inheritance is still somewhat obscure. The prevalence of CD is about 1% within the United States and Europe, and this may be even higher in certain Northern European countries.⁴ It is now becoming a common disorder in North Africa, the Middle East, and India. However, the diagnostic rates are low in these regions because of low availability of diagnostic facilities and poor disease awareness.⁵ It is thought that the increase in prevalence is also attributed to the adaptation of Western gluten-rich dietary patterns. Many new diagnoses are also being made through screening individuals who are at risk because of family history of CD.

SYMPTOMS

The range of symptoms present in CD is a wide spectrum. Individuals may have the classic symptoms of abdominal pain with diarrhea or constipation, neurologic manifestations, or be completely asymptomatic. Symptoms are described as typical, atypical, and latent. **Table 1** lists the specific symptoms according to their categories. The classic, or typical symptoms, usually emerge in the pediatric age and consist of diarrhea, abdominal pain, and weight loss, and poor growth. The atypical presentations include osteoporosis, dermatitis herpetiformis, peripheral neuropathy, short stature, delayed puberty, dental enamel hypoplasia, and anemia. A mild elevation of serum liver enzymes is well described as an initial presentation of CD in pediatric patients. Headaches, seizures, and psychiatric symptoms are also associated with CD.

The latent form of CD is defined as having a predisposing gene, normal biopsy findings, and weakly positive serologies.⁶ It is thought that environmental factors affect the disease’s clinical presentation, the time at presentation, and the characteristics of the disease.⁷ Theories are now emerging in regards to infectious agents playing a role, at least on the timing of the presentation.⁸

Table 1 Signs and symptoms of celiac disease		
Typical	Atypical	Latent
Diarrhea	Osteoporosis/fractures	Gene positive
Abdominal pain	Dermatitis herpetiformis	Weakly positive serologies
Bloating	Nonspecific transaminitis	Normal biopsies
Gassy	Fatigue	
Constipation	Anemia	
Alternating diarrhea and constipation	Migraines	
Failure to thrive/weight loss	Peripheral neuropathy	
Vomiting	Dental enamel hypoplasia	
	Short stature/delayed puberty	

DIAGNOSIS OF CELIAC DISEASE

Until the 1950s, CD was a clinical diagnosis based on observations focused on mal-absorptive features.⁹ Now, the first step in determining if a patient has CD is to obtain serologies. The sensitivity and specificity of detecting CD is now close to 95% or greater, despite its checkered past. The antigliadin antibodies were first developed in the 1980s, but showed a sensitivity and specificity between 80% and 90%. The endomysial antibody (EMA) was developed next in the mid-1980s, which was found to be highly accurate, but difficult to standardize. This assay requires monkey esophagus or human tissue as a substrate, and an individual reading the sample, adding to interobserver variability. Despite the disadvantages, the sensitivity and specificity of EMA is found to be greater than 90%.¹⁰ In the late 1990s, tTG was identified as a CD autoantigen and it has now become the test of choice not only for diagnosis, but also for monitoring CD, given its sensitivity of 99%.¹¹ The accuracy of deaminated gliadins is controversial. It seems to be the most sensitive and specific in those younger than 3 year old.¹² It is important to remember that a total IgA level should always be ordered to assess for selective IgA deficiency, because it is the most common immune deficiency in children. If this is truly present, it will lead to false-negative results. Of note, low levels of IgA that are not deficient will not affect the test specificity. However, if an individual truly has selective IgA deficiency, serologic testing offers little advantage over directly proceeding to intestinal biopsy to establish the diagnosis. **Table 2** lists the antibody tests available and their associated sensitivities and specificities.

HLA testing should also be considered during a work-up for CD. It is known that 95% of those with CD are HLA DQ2 positive and the rest are HLA DQ8 positive. However, about 40% of the general population also carries one of these genes, making genetic testing poorly specific.¹³ This test may be of benefit in those who are asymptomatic with negative serologies, but belong to an at-risk group. The high negative predictive value of genetic testing allows one to eliminate the possibility of ever developing the disease.

The gold standard for diagnosis is still with a small intestinal biopsy when an individual is consuming gluten, to document duodenal damage, mainly villous atrophy. Gross findings during an upper endoscopy include scalloping of the duodenal mucosa

Table 2
Serologic test comparison

	Sensitivity %	Specificity %
AGA IgA	69–85	73–90
AGA IgG	75–90	82–95
DGP IgA	74–99	90–99
DGP IgG	63–95	90–99
EMA (IgA)	85–98	97–100
tTG IgA	90–99	94–99
tTG IgG	45–95	94–97

AGA IgA and AGA IgG tests are no longer recommended as initial testing because of the inferior accuracy.

Abbreviations: AGA, antigliadin antibody; DGP, deaminated gliadin peptide.

From Hill ID, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40:1–19.

(Fig. 1). However, if this is not present, it does not exclude a diagnosis, because the microscopic changes are mainly consistent with a diagnosis. The characteristic histologic features include infiltration of lymphocytes in the epithelium (>25 lymphocytes per 100 epithelial cells), increased density and depth of crypts, and varying degrees of villous atrophy. This progression was first described by Marsh in 1992, and his scoring system, from stage 0 (normal) to stage 3 (villous blunting) subsequently modified by Oberhuber and colleagues,¹⁴ is now widely used by pathologists (Table 3 for Marsh classification).^{15,16} Biopsy findings are not necessarily pathognomonic and are seen in other conditions. Box 1 provides a list of other causes of villous atrophy occurring in the duodenum. It is the constellation of clinical, histologic, and serologic findings, and response to therapy, that ultimately provide a confirmation of a CD diagnosis (Figs. 2–4).

In 2012, the European Society of Gastroenterology, Hepatology and Nutrition published their guidelines for CD and suggested that a nonbiopsy diagnosis of CD could be considered in a certain patient population who has 10 times the elevation of tTg IgA, a positive EMA-IgA, and the presence of the HLA DQ2/8 haplotype. The subsequent resolution of symptoms and normalization of the tTG titer on a gluten-free diet (GFD) confirms the diagnosis.¹⁷ Although a nonbiopsy diagnosis of CD is desirable, there are potential risks of avoiding biopsy. Currently, there is no standardization of serologic tests for CD in the United States, because there are marked variations in antibody levels between commercial assays. There is also a possible risk of a false diagnosis of CD without the biopsy and placing a patient on a lifelong GFD. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition clinical practice guidelines differ in that they recommend a duodenal biopsy for the diagnosis of CD.³

There is a group of patients who has positive serology and normal histology. They can be grouped in the latent form, but one needs to make sure that they are exposed to adequate amounts of gluten before biopsy. One also needs to determine if an adequate number of biopsies were taken from the bulb and second portion of the duodenum and their histologic orientation is correct. Capsule endoscopy is helpful in this group of patients to look for mucosal scalloping. Abnormal capsule endoscopy can be followed by push enteroscopy to obtain biopsy. In this subgroup of patients, HLA

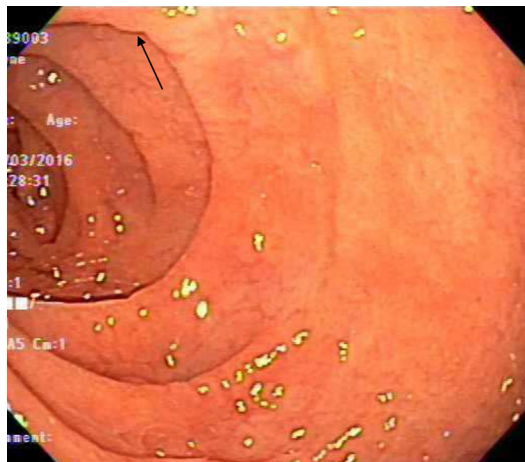


Fig. 1. Arrow pointing to gross finding of scalloped mucosa in the second portion of the duodenum on endoscopy.

Table 3 Histologic features and grading of celiac disease					
Marsh 0	Marsh 1	Marsh 2	Marsh 3A	Marsh 3B	Marsh 3C
No histologic changes	Increased IEL	Increased IEL with crypt hyperplasia	Increased IEL, crypt hyperplasia, partial villous atrophy	Increased IEL, crypt hyperplasia, subtotal villous atrophy	Increased IEL, crypt hyperplasia, total villous atrophy

Abbreviation: IEL, intraepithelial lymphocytosis.

typing is useful. If HLA DQ2 and DQ8 are negative, CD is unlikely. If positive, they can have potential CD-latent form and the next step is decided depending on each individual patient. If they are symptomatic, they can be placed on a GFD and the clinician would follow symptoms and serologies and consider rechallenging with a gluten-containing diet in the future. If they are asymptomatic, patients can stay on regular diet with close follow-up of their serology testing with potential rebiopsy in the future.

TREATMENT OF CELIAC DISEASE

Currently, the only available treatment of CD is a lifelong GFD. Treatment should only be started after diagnosis is confirmed by intestinal biopsy.

The goals of treatment are resolution of symptoms, maintenance of normal growth, and development and improvement of histology. Persistent villous atrophy and inflammation has been associated with increased morbidity and increased risk of malignancy. Adherence to the diet allows an individual to achieve a goal of histologic remission of their CD, which should occur within 1 to 2 years of strict diet adherence.¹⁸ Studies show that about 45% to 80% of children are adherent to GFD. There are times where diet adherence may be difficult, especially during adolescent years. The common complaints of the diet are that foods are less tasty and more expensive. There is also associated anxiety and a negative social effect leading to decreased quality of life, because one is constantly needing to be vigilant to avoid gluten contamination.¹⁹ Because of this, adolescents are in need of more psychosocial support and physician-dietician involvement with their daily routine and school life. But, a progressive decline

Box 1 Other causes of villous atrophy in the duodenum
Marasmus
Crohn disease
Giardiasis
Autoimmune enteropathy
Drug induced (ie, olmesartan)
Graft-versus-host disease
AIDS-associated enteropathy
Intestinal lymphoma
Tropical sprue

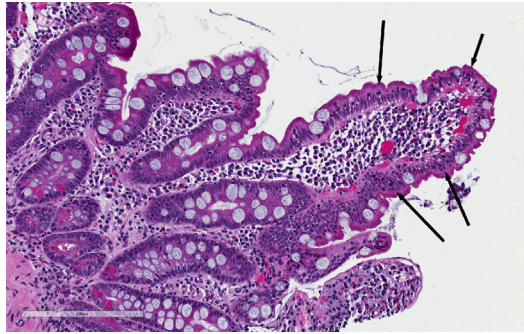


Fig. 2. Marsh 1 findings of increased intraepithelial lymphocytes (*arrows*), but architectural preservation of villi is present.

and eventual normalization of serology over 12 to 24 months of GFD is a good indicator of compliance with GFD.

Foods that are allowed in a GFD include beans; nuts; fresh eggs; fresh meats, fish, and poultry; fruits; vegetables; and most dairy products. Meats should not be breaded, batter coated, or marinated. It is important to make sure foods are not processed or mixed with gluten-containing grains, additives, or preservatives. There are many grains and starches that are part of a GFD, including almond meal flour, corn, cornmeal, coconut flour, quinoa, pea flour, potato flour, sorghum, soy, and tapioca. Patients should always avoid all foods and drinks that contain rye and barley. Barley is found in such products as malt, malt flavoring, and malt vinegar. Patients should also avoid triticale, which is a cross between wheat and rye that was first bred in laboratories during the late nineteenth century in Scotland and Germany.²⁰ Unless labeled gluten free, patients should avoid beer, candies, salad dressings, sauces, or soup bases. There are breads made with corn, rice, or soy that also contain gluten. Patients should avoid oats unless it is specified as gluten free, and currently, 50 g of gluten-free oats is considered safe.

Cross-contamination is also another important topic to discuss with families. It occurs when gluten-free foods come into contact with foods that contain gluten. It can happen during the manufacturing process, such as when the same equipment is used to make a variety of products. If a product carries a gluten-free label, the Food and Drug Administration requires that the product contain less than 20 parts per



Fig. 3. Marsh 2 findings of crypt hyperplasia (*arrows*).

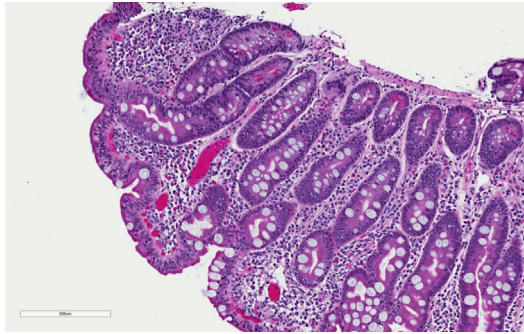


Fig. 4. Blunted villi seen, consistent with Marsh 3 disease.

million of gluten. However, the threshold of gluten in gluten-free products is under debate, because the consumption of even these trace amounts of gluten allowed by the Food and Drug Administration may be responsible for continuing symptoms seen by some patients with CD. In a study done by Faulkner-Hogg and coworkers,²¹ most patients with CD with persistent symptoms who switched to a no detectable gluten diet had either partial or complete resolution of symptoms. Therefore, it is important to provide patients with extensive nutrition counseling, because patients need to be aware that products labeled “wheat-free” may still contain gluten.

POTENTIAL RESEARCH TREATMENTS

Currently the GFD includes flour from rice, corn, soybean, and other less popular crops, which are poor in B vitamins and essential nutrients. They are also often devoid of flavor. Because of this, genetically modified gluten has been proposed, which thus far has shown to have a decreased immunogenicity in those with CD.²² Zonulin is extensively being studied, because it is an endogenous modulator of epithelial tight junctions. It is known that gliadin causes increased zonulin secretion leading to increased intestinal permeability, allowing the transport of gluten, which then triggers an inflammatory process.²² Larazotide acetate is being trialed because it has shown to decrease tight junction permeability by inhibiting zonulin receptors, which leads to stabilization of the protein connections of the intestinal epithelium. It has also shown a blunted response of tTG antibodies when exposed to gluten contamination.²³ In a study by Paterson and colleagues,²⁴ there was a 70% increase in intestinal permeability following a gluten ingestion in the placebo group, compared with those who received 12 mg of larazotide acetate. Although it is unlikely to be a cure and does not provide a free pass to continue eating gluten, it may well be considered maintenance therapy to improve symptoms and quality of life, while still in conjunction with a GFD.

Therapeutic vaccines have also been considered with the aim of modifying the T-cell response. Although current studies show an induction of tolerance of gliadin peptides, it seems as if the vaccine may only be effective in patients with CD who are positive for the HLA DQ2 haplotype. There have been attempts to alter the immune response through infecting patients with CD with parasites. Unfortunately, further investigation was called into question because no benefit was observed in these clinical trials. Oral enzyme supplementation seems to be more promising, because researchers in Europe found that orally administered oligopeptidases allow the degradation of toxic gliadin peptides before they reach the small intestinal mucosa.²⁵

Ideally, the optimal degradation of gluten should take place in the stomach, which limits the immune response in the proximal small intestine.²⁶ Probiotics are currently popular, because they have demonstrated to have a beneficial effect in those with small intestinal bacterial overgrowth, lactose intolerance, and irritable bowel syndrome (IBS). Unfortunately, studies have not demonstrated a significant effect in those with CD.²⁷ It is well known that glucocorticoids and biologic therapies modulate the inflammatory reaction and are often used in refractory CD.

In summary GFD is the only treatment available for CD.

REFRACTORY CELIAC DISEASE

Refractory CD must be considered if symptoms persist, despite being on a GFD, and histologic damage of the small intestinal mucosa continues. Refractory CD is classified as type 1 and 2, where type 1 is responsive to corticosteroids. Type 2 is considered a premalignant condition where almost 50% of patients develop enteropathy-associated T-cell lymphoma within 5 years of diagnosis. Type 2 refractory CD is diagnosed from biopsy specimens that show monoclonality and occurs when an individual loses antibodies to tTG and there is infiltration of lymphocytes in the intestinal epithelium that lack expression of CD8, CD4, and TCRs.²⁸

MONITORING

Multiple guidelines call for routine monitoring of patients with CD, because this is a lifelong inflammatory condition. At time of diagnosis, all patients should have extensive nutrition counseling with an experienced dietician, because a GFD is the core management strategy. Patients should also be encouraged to join their local and/or national celiac support group.⁵ Patients should be examined every 6 months in their first year of diagnosis to monitor symptoms, dietary adherence, nutrition, and serologic features.^{29,30} It is recommended that tTG IgA should be measured after 6 months of adhering to a GFD. At this time, there should be a decline in the value, which provides an indirect indicator of dietary adherence and recovery. This marker should, again, be measured at 12 months after the diet to monitor adherence to the GFD. All patients should have annual hematologic and biochemical profiles. Because bone mineral density is one of the more common extraintestinal manifestations of CD, a dual-energy x-ray absorptiometry scan is recommended in the first year of diagnosis.³⁰ The most controversial aspect of monitoring patients with CD concerns the timing and role of repeat endoscopy with small bowel biopsies. Patients should understand that seroconversion with a GFD does not necessarily imply healing of the small intestine. The only accurate method available to verify intestinal healing is biopsy.³¹

NONCELIAC GLUTEN SENSITIVITY

According to the Oslo Definitions for CD, nonceliac gluten sensitivity (NCGS) is defined as being one or more of a variety of immunologic, morphologic, or symptomatic manifestations that is precipitated by the ingestion of gluten in individuals in whom CD has been excluded.³² Whereas gluten-related disorders is an umbrella term to describe all conditions related to the dietary exposure to gluten, NCGS specifically references a clinical scenario in which a patient has symptoms with gluten exposure and has resolution with removal of gluten, without having a diagnosis of CD. This was first described in 1980 by Cooper and colleagues³³ and has recently been the subject of much research to help diagnose, evaluate, and manage individuals who describe

symptoms that mimic other conditions, such as CD, wheat allergy, IBS, and lactose/fructose malabsorption.

Epidemiology

The incidence of NCGS is unknown. The condition is often self-diagnosed and managed with a GFD without the input of a physician. Cited rates of prevalence have ranged from less than 1% to 6% of the population.³⁴ This wide range is likely caused by different definitions and varying study designs. It is thought to be more common than CD, which is approximately 1% of the general population. There is a female predominance of 3:1, but no specific risk factors for the development of NCGS have been identified, nor have long-term consequences.³⁵

Pathophysiology

The pathophysiology of NCGS is also unknown. It had been shown that in contrast to CD, there is normal intestinal permeability. The duodenal mucosa of patients with NCGS does not show inflammatory marker expression when incubated with gliadin in vitro and there is also no basophil activation, as compared with patients with CD.³⁶ Wheat amylase-tryptase inhibitors, which are a family of proteins in wheat that are highly resistant to proteolysis, may drive the innate immune system toward an inflammatory state in NCGS and these amylase-tryptase inhibitors are proteins that are resistant to proteolysis.³⁷

Clinical Features

The prevalence of specific clinical features of NCGS is lacking, although there have been studies describing relative incidences of symptoms, both intestinal and extraintestinal in the study population. The manifestations can occur soon after ingestion of gluten and regress with gluten withdrawal. They then reappear when gluten is reintroduced in hours to days after re-exposure. NCGS, clinically, is similar to IBS with abdominal pain, bloating, and changes in bowel characteristics (diarrhea and/or constipation). There are also reported systemic features of “brain fog,” headaches, joint pain, fatigue, depression, extremity numbness, dermatitis, and anemia. Other features include weight loss, gas, glossitis, and behavior changes.³⁸ In children with NCGS, gastrointestinal symptoms tend to dominate, but the most common extraintestinal manifestation is reported to be fatigue.³⁹

Of note, as compared with the CD patient population, there is no increased prevalence of comorbid autoimmune diseases, such as type 1 diabetes mellitus and autoimmune thyroiditis, in patients with NCGS.⁴⁰ The psychiatric comorbid conditions of CD, such as anxiety and depression, are similar in patients with NCGS and CD. Whether there is a role of NCGS in neuropsychiatric illness is still being debated, because it has been implicated by some to be a cause of schizophrenia, autism spectrum disorders (ASD), and depression.⁴¹

ASD is the fastest growing group of developmental disorders in the United States that has long been associated with gluten sensitivity. Linking ASDs with CD has been unconvincing, because there has been no serologic evidence to support a relationship between the two disorders.⁴² However, one treatment modality, the gluten-free casein-free diet, has been popular in the management of children with ASDs. The role of a leaky gut enabling gluten peptides to advance to the blood brain-barrier and then interfere in neurotransmission has been suggested and there has been research into the prevalence of a leaky gut in children with ASDs to support this hypothesis.⁴³ Despite the popularity of the gluten-free casein-free diet as a treatment of ASDs, convincing evidence to support its use is lacking.

IBS and NCGS have significant clinical overlap. Some patients labeled with IBS may have improvement in symptoms with withdrawal for gluten from their diet. This was particularly true for the patients with IBS-D with HLA DQ2 and/or DQ8 genotypes who showed more frequent bowel movements on a gluten-containing diet and which was also associated with an increase in small intestinal permeability while on that diet.⁴⁴ Other than gluten, wheat, and wheat derivatives, there are other components that may trigger symptoms in patients with IBS, such as fructans, and therefore it is not clear to what component these patients may be responding to when gluten is eliminated. Patients with IBS also improve with the use of a FODMAP (fermentable oligo-, di-, and monosaccharide and polyols) diet, which removes highly fermentable, poorly absorbed, osmotic, short-chain carbohydrates, which can also be found in wheat. Whether it is the gluten or the FODMAP removal that results in clinical improvement is debatable. The difficulty of a clinical diagnosis in this condition, given its overlap with other diseases, is what is driving the need for the identification of specific biomarkers to help estimate the prevalence of this condition, and to aid in its diagnosis.

Evaluation

The frequency of self-diagnosis of gluten sensitivity has led to a large number of patients either presenting to the physician for evaluation while on a GFD or having tried it in the past. Of the utmost importance is determining whether or not the patient has CD. **Fig. 2** describes an algorithm to help differentiate between the two conditions. The specific antibodies for the diagnosis of CD are negative in patients with NCGS. However, some recent studies have shown this population may, in fact, have a high rate of positivity for AGA IgG. Patients with NCGS were demonstrated to have an elevated AGA IgG at 56.4% compared with 81.2% in untreated CD. This is far higher than the rates for autoimmune liver disease (21.5%), connective tissue disorders (9%), and healthy blood donors (2%–8%).⁴⁵ There are also concerns about the possibility of a wheat allergy arising in patients for whom a GFD results in symptoms improvement. In this population, IgE-based assays should also be considered.

Genotyping remains a component of the diagnostic algorithm in several scenarios. It may be necessary to evaluate patients already on a GFD in whom serologic testing is not an option, and in patients with borderline serology to help determine whether obtaining histologic evidence is warranted. Patients with NCGS have a prevalence rate for HLA-DQ2 and DQ-8 of approximately 50% as compared with 95% in CD and 20% of the general population.⁴⁶

In patients with NCGS there is biopsy evidence of mild inflammation of the mucosa (Marsh 0–1) as compared with partial or subtotal villous atrophy and crypt hyperplasia in patients with CD.⁴⁷ The level of CD3⁺ intraepithelial lymphocytosis present in those with NCGS is somewhere between healthy control subjects and patients with CD. There are other possible histologic findings in patients with NCGS, such as activated circulating basophils and increased incidence of eosinophilic infiltration in the duodenum and/or the ileum.^{38,48}

Diagnosis

For the clinician, it is important to keep the diagnosis of NCGS as a possibility for patients presenting with intestinal and extraintestinal complaints that improve on a GFD, but also not to mistake it for CD or a wheat allergy. These two conditions should always be excluded before diagnosing NCGS. A diagnostic algorithm shown in **Fig. 5** rests on excluding CD by obtaining celiac serologies while on a gluten-containing diet. If these serologies are negative and the patient is not IgA deficient, then the patient is unlikely to have CD and NCGS may be the more likely diagnosis. Other

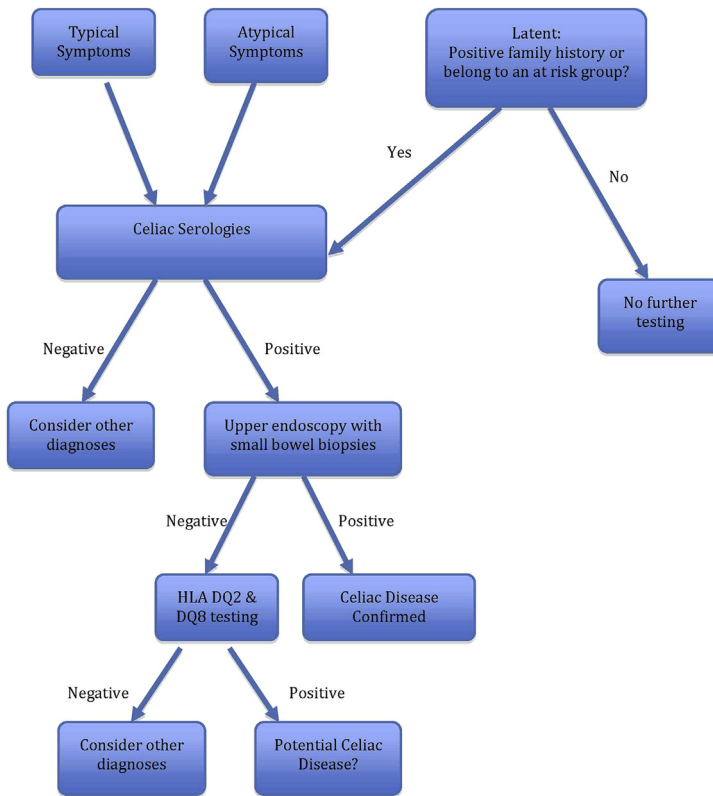


Fig. 5. Approach to diagnosing Celiac Disease.

supportive factors of this diagnosis include a lack of a personal history of autoimmune disease or family history of CD and absence of the features of malabsorption. If this is the case, further testing is not warranted. Those with equivocal serology would benefit from HLA typing to determine whether a biopsy is needed.⁴⁹ Once CD and wheat allergy are excluded, the patient should be placed on a GFD for at least 4 to 6 weeks. This typically results in significant improvement in several days and a subsequent gluten challenge should then be done to confirm the diagnosis.

Management

It is preferable to institute a gluten-limited diet in patients diagnosed with NCGS only after CD has been excluded. The need for a complete GFD versus a gluten-diminished diet depends on the patient's clinical response. Patients who remain on a GFD require nutritional support to ensure that macronutrient and micronutrient requirements are being met. In addition, because it is unknown whether this is a permanent or transitory condition, it is important to reassess the patient periodically (eg, every 6–12 months). This is particularly true of the pediatric population in whom dietary restrictions are onerous and may lead to other nutritional deficiencies. If the symptoms persist despite a gluten-restricted/GFD, other diagnoses should be entertained, such as lactose intolerance, IBS, fructose malabsorption, and small intestinal bacterial overgrowth.

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