

Celiac Disease and Wheat Intolerance Syndrome: a Critical Update and Reappraisal

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ABSTRACT

Since the first description of celiac disease (CeD) by Samuel Gee in 1888 and the later “miraculous discovery” that bread was responsible for this condition following World War II in Europe there has been an exponential growth of knowledge regarding CeD. However, just when we thought that we knew everything there was to know about it, the disease is offering new challenges, with its presentation having significantly morphed over the years from cases of overt gastrointestinal symptoms, malnutrition, and atrophic villi on duodenal biopsies to that of largely extra-intestinal, subtle or mild symptoms. Along with these changes, unexpectedly a new parallel entity appeared a few years ago and is gaining ground: the so-called non-celiac gluten sensitivity (NCGS), an improper name since it should actually be referred to as wheat intolerance syndrome (WIS) given that the role of gluten in all such cases is far from demonstrated and the implication of an immune involvement suggested by the term “sensitivity” is still unfounded. Lastly, wheat can be an offender also through an IgE mediated allergy, whose presence must also be evaluated and ruled out in selected cases.

The practicing physician is therefore now challenged with the task of discerning which patients need to be assessed for one or the other of these disorders, and how.

This review aims at providing an updated, critical reassessment of these two entities.

Key Words: Non-celiac gluten sensitivity, gluten, allergy, pediatrics, adults

What is known:

- Celiac disease (CeD) is an autoimmune disease, triggered by the ingestion of gluten in genetically predisposed individuals
- So-called “Non-celiac Gluten sensitivity” is a term which describes people who report symptoms that respond to the withdrawal of gluten-containing foods from the diet, return upon their reintroduction, have no mucosal injury on duodenal biopsies, and for which CeD or wheat allergy have been ruled out

What is new:

- Advanced knowledge of possible environmental factors that may lead to the onset of CeD
- Emerging therapy options for patients with CeD
- “Non-celiac Gluten sensitivity” a misleading term, as role of gluten far from being defined. Better term proposed: Wheat Intolerance Syndrome.
- A possible algorithm to assist in the diagnostic process for patients suspected of wheat intolerance syndrome

CELIAC DISEASE (CeD)

PATHOPHYSIOLOGY & PRESENTATION

This complex autoimmune disorder is triggered by the ingestion of gluten (the major storage protein in wheat, barley, and rye) in genetically predisposed individuals (those presenting the human leukocyte antigen (HLA) class II genotypes defined as DQ2 and DQ8) leading to inflammation of the small intestinal mucosa.

Gluten is a heterogeneous protein complex. The gluten fractions that are toxic to celiac patients are a mixture of alcohol-soluble proteins called gliadins. Gliadins are rich in glutamine and proline residues, which even the healthy human intestine cannot fully digest ¹. As a result, intact gliadin peptides are left in the lumen, and some cross the intestinal barrier ². These fragments come into contact with the intracellular enzyme tissue transglutaminase (tTG), which deamidates them, leading to a change in shape and increased negative charge. The modified peptides are then easily captured by the HLA-DQ2 and/or DQ8 molecules expressed on the surface of the lamina propria-associated antigen-presenting cells (APCs) and are presented to CD4⁺ T cells leading to a cascade of reactions involving both innate and adaptive immunity and ultimately resulting in the intestinal damage ³.

A wide variety of clinical presentations have been described for CeD, including “Typical,” “Atypical,” “Silent,” and “Potential” forms. The typical form consists of gastrointestinal symptoms while the atypical form is characterized by predominantly extra-intestinal symptoms (see table 1). Silent CeD describes asymptomatic patients with positive blood serology and intestinal inflammation on biopsy; lastly, potential CeD includes patients with positive blood

serology who may or may not have symptoms, but show no apparent intestinal inflammation on biopsy.

Though the typical presentation was most prevalent in the early and mid-twentieth century, there appears to have been a dramatic change from the 1980s onward with a shift from classical gastrointestinal symptoms to higher rates of atypical and asymptomatic presentations⁴⁻⁶. Additionally, it has been found that, in general, presentations have become milder and poor growth less common⁷. The reason for this shift is uncertain, but may partly be the result of an increased awareness of the disease resulting in earlier detection and higher rates of screening at-risk individuals (see table 2).

PREVALENCE

Though roughly 30% of the population contain the genes necessary to develop CeD (haplotypes DQ2 and or DQ8), only 1% of the population will actually develop the disease, a prevalence that is increasing worldwide over time⁸⁻¹³. The reason for this is unclear and though one may be quick to place blame on an increased content of gluten in “modern grains” or an increased consumption of gluten with time, these 2 hypotheses are wrong^{14,15} with the consumption of wheat flour (from all classes of wheat) actually dropping from 220 lbs. per person in 1900 to 134 lbs. per person in 2008 (Figure 1).

What other environmental factors may be contributing to the rising prevalence of CeD then?

Research is currently focusing on the impact of the mode of delivery^{16,17}, early life infections^{18,19}, exposure to antibiotics²⁰, infant feeding practices^{21,22}, birth season²³, and socioeconomic

status^{24,25}. It is currently thought that repeated early life infections, regardless of the source, may increase the risk for the development of CeD but that there does not appear to be a significant impact from antibiotic use^{18,20}. Additionally, recent studies have shown that the timing, quantity of gluten offered at its introduction and the relationship to breastfeeding do not appear to play a significant role in changing the natural course of CeD onset either^{21,22} (see²⁶ for a recent systematic review on this topic). At the moment, the most important factor found to have a significant impact on the development of CeD is possession of 2 copies of the HLA-DQ2 allele (the high-risk HLA genotype)²¹.

Currently, the favored hypothesis focuses on the role of the microbiota²⁷. In fact, the intestinal microbiota influences the development of the immune system and autoimmune diseases²⁸ and alterations in the intestinal microbial composition have been described in CeD patients, some of which normalize after treatment with a GFD²⁹. A recent study in mice showed that the intestinal microbiota can positively as well as negatively modulate gluten-induced immunopathology in the intestine and that intestinal microbiota changes may be a factor that increases CeD risk³⁰. This is clearly a rapidly evolving and exciting field and hopefully new discoveries and advances will be made in the coming years.

DIAGNOSIS

Currently, it is universally recommended that tTG IgA and total serum IgA be the first line of screening, given their very high sensitivity³¹⁻³³. Total serum IgA needs to be determined to guarantee that the patient is able to produce tTG IgA as celiac patients have higher rates of IgA deficiency than the general population (2%) and therefore may have a falsely negative tTG IgA

³⁴. Under these circumstances, both tTG IgG ³⁵⁻³⁷ and DGP IgG ³⁸ can be useful as markers of CeD as well.

In 2012, an ad hoc task force of ESPGHAN published revised criteria and produced an evidence-based algorithm that allowed skipping the duodenal biopsy under certain circumstances: namely, in children and teenagers showing a history and genetic asset compatible with CeD, tTG-IgA levels more than 10 times the upper limit of normal and a positive titer of EMA ³⁹. Although this simplified approach seems valid because it possesses a positive predictive value nearing 100%, it needs to be applied with great care. Children with gastrointestinal complaints diagnosed without endoscopy may have additional disorders that would go undiagnosed by skipping this procedure, though, as demonstrated by a retrospective study performed at the University of Chicago in which 12% of celiac patients were found to have additional diagnoses picked up at the time of endoscopy ⁴⁰.

TREATMENT

Strict, lifelong adherence to a gluten free diet (GFD) remains the only available treatment for patients diagnosed with CeD and should result in a complete return to health in the majority of cases (especially children).

With appropriate instruction from a trained dietician the GFD can be balanced and healthy.

However many patients initiate the diet without guidance and lean towards the convenience of processed gluten-free options leading to diets high in fat, sugar, and sodium without sufficient vitamin and mineral fortification ⁴¹ contributing to the weight gain seen in roughly 81% of CeD

patients started on a GFD ⁴². To insure that the patient is adequately educated, patients should receive an initial consult with a trained dietician and close follow up.

Alternate pharmacological therapies being evaluated for the treatment of CeD include enzymes to inactivate immunogenic gluten peptides in the human gastrointestinal tract ², agents that sequester gluten in the lumen ⁴³, modulators of gut permeability ⁴⁴ and of antigen presentation and immune responses including those that block tTG ⁴⁵ and HLA ⁴⁶, IL-15 inhibitors ⁴⁷, and the development of vaccines able to induce oral tolerance to gluten ⁴⁸.

Of these treatment modalities, gluten-specific enzymes able to cleave the highly resistant proline and glutamine bonds within the gliadins' molecules, thus degrading the immunogenic epitopes within the gluten protein in the stomach, are among the most promising: ALV003, an orally administered mixture of 2 recombinant gluten-specific proteases (cysteine endoprotease isoform b-2 and SC prolyl endopeptidase) had shown impressive and very promising activity vs. placebo in significantly preventing the mucosal damage induced by gluten exposure in CeD patients ⁴⁹. However, a recently completed, and as yet unpublished, multicenter clinical trial in symptomatic CeD patients with significant mucosal injury despite maintaining a GFD, failed to show improved mucosal healing compared to placebo, most likely due to a heightened attention to the GFD by the patients recruited (Daniel Adelman, personal communication). It is worth mentioning here that none of the currently marketed "glutenases" have any capacity of detoxifying gluten ⁵⁰, whereas the Prolyl EndoPeptidase from *Aspergillus niger* (AN-PEP) appears effective in vitro ⁵⁰, but clinical trials assessing efficacy are pending.

Larazotide acetate (AT-1001) is Alba Therapeutics's investigational product, a novel tight junction regulator. In fact, it has been hypothesized that blocking gluten entry via the paracellular pathway (a pathway already altered in celiac patients) would prevent gluten toxicity.

In a multicenter study published in 2015⁵¹ Larazotide acetate at the lowest dose tried (0.5 mg) significantly reduced signs and symptoms in CeD patients on a GFD better than placebo. These results are certainly encouraging and the drug is now entering phase 3 trials, likely to begin in late 2016 (info available on <http://www.innovatebiopharma.com/inn-202.html>). However, one must note that no data has been provided so far supporting its ability to reduce intestinal inflammation.

As for preparations binding gluten in the gut, hence preventing its contact with the gut immune system, the polymer BL-7010 has shown efficacy in an animal model⁵² and is currently undergoing Phase 1 clinical trials.

A desensitizing vaccine (NEXVAX2 - ClinicalTrials.gov Identifier: NCT00879749) that uses three dominant gluten peptides administered subcutaneously to induce a tolerogenic response in CeD patients is under development. So far, it has been shown to be safe for intradermal injection of CeD and clinical trials on safety and efficacy are on their way.

Additionally, as patients with active CeD are thought to have gut dysbiosis research is also underway to better understand the role for probiotics for these patients. Currently no evidence-based recommendations exist though⁵³⁻⁵⁵ and given lower levels of regulation, cross contamination of probiotics may occur raising potential concern for their indiscriminate use⁵⁶.

A final area of potential interest is Helminth therapy. Parasitic helminths have been found to be efficient down regulators of host immune responses in efforts to promote their own survival ⁵⁷. Specifically *Necator americanus*, a hookworm that can persist in the small intestine of mammalian hosts, has shown beneficial effect in CeD leading to gluten tolerance with reduced clinical symptoms, stable marsh changes and intraepithelial lymphocyte counts on intestinal biopsy, reduced intestinal IFN gamma expressing T-cells, and increased T regs ⁵⁸, an effect that the same group was able to associate to increased microbial richness ⁵⁹. Adverse side effects such as anemia are possible, though, and clearly additional studies addressing safety and efficacy are needed.

What do celiac patients hope for alternative treatment? A recent survey of 256 CeD adult patients at our center (J. Tomal, D. McKiernan, S. Guandalini, C.E. Semrad and S. Kupfer, manuscript in preparation) showed that CeD patients are significantly more interested in taking a novel therapy that protects against inadvertent gluten cross contamination while on a GFD than in one that protects against intentional gluten consumption. In addition, they appear are more interested in protection against bowel inflammation than symptom control. Similar findings have recently been reported also from a survey on adult CeD patients in Italy ⁶⁰.

While it is likely that some of the alternatives may come to fruition in the next year or 2, a true “cure,” although certainly possible, might take much longer ⁶¹.

WHEAT ALLERGY

A second, well known disorder related to gluten ingestion in children is wheat allergy, which will be very briefly touched here. Wheat is in fact a rather common food allergen and in predisposed subjects it may elicit an allergic response, typically an immunoglobulin E (IgE)-mediated phenomenon. In infants and young children, IgE-mediated reactions to wheat may well include gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhea. Unlike CeD, though, the onset is often more rapid, within minutes to 2 hours from the time of ingestion, and can also include involvement of extra-intestinal organs such as skin (with symptoms as erythema, pruritus, urticaria) and the respiratory system (with symptoms of coughing, wheezing, and rhinorrhea)⁶².

Allergen specific IgE (sIgE) antibodies to wheat typically appear within the first 2 years of life, but unlike CeD, which is life-long, most children eventually will tolerate wheat⁶³, although the allergy may persist into adolescence in a significant minority of patients⁶⁴.

A well-accepted set of criteria for the diagnosis of food allergies is lacking, though⁶³, and while detection of food-specific IgE implies sensitization it does not necessarily indicate true clinical allergy. Therefore, diagnosis requires a careful medical history, laboratory studies, and, in many cases, an oral food challenge to confirm a diagnosis⁶².

WHEAT INTOLERANCE SYNDROME (WIS)

PATHOPHYSIOLOGY & PRESENTATION

Wheat intolerance syndrome (WIS), also referred to as “non-celiac gluten sensitivity (NCGS),” describes people who report symptoms that respond to the withdrawal of wheat from the diet, return upon its reintroduction, have no mucosal injury on duodenal biopsies, and for which CeD or wheat allergy have been ruled out⁶⁵. Though NCGS continues to be used, this is an improper name given that the role of gluten is far from demonstrated and the implication of an immune involvement suggested by the term “sensitivity” is still unfounded. The most common symptoms reported with WIS include: abdominal discomfort, bloating, gassiness, diarrhea, fatigue, “foggy mind”, headache, and joint pain^{66,67}.

Despite popular belief, this is not a new disease as reports of this condition date back to 1978, when Ellis and Linaker⁶⁸ reported the case of a 43-year-old woman with these GI symptoms which improved after gluten withdrawal but relapsed upon its reintroduction in the absence of CeD and with normal duodenal biopsies both on and off gluten.

The pathophysiology remains unclear, but several hypotheses exist including increased small intestine permeability caused by gliadin^{69,70}, an adaptive immune response suggested by high anti-gliadin antibodies present in some WIS patients⁷¹⁻⁷³ or an innate immune response secondary to findings of increased small intestinal expression of TLRs, particularly TLR2 and, to a lesser extent, TLR1 and TLR4⁷⁴.

In reality, though, it still remains unclear what exact component of wheat is actually to be blamed for the clinical symptoms. While gluten is the best recognized culprit another family of wheat-associated, but not gluten-related, proteins found in wheat termed α -amylase/trypsin inhibitor [ATI]⁷⁵ could potentially also be responsible. The unproven role of immunity in this syndrome suggests that a more appropriate name for this entity may be wheat intolerance syndrome (WIS) as opposed to the currently used non-celiac gluten sensitivity (NCGS).

In the past few years, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) have gained attention for their possible role in eliciting GI symptoms in patients with self-reported WIS. Follow up studies have shown that a diet low in FODMAPs leads to greatly reduce symptoms for some⁷⁶ even with re-exposure to gluten as compared to an identical, placebo GFD⁷⁶. As many gluten-free foods are low in FODMAPs and gluten-containing foods are high in FODMAPs (Table 3)⁷⁷ this may actually suggest that the patients considered to be suffering from WIS are simply experiencing IBS-like symptoms secondary to the ingestion of FODMAPs⁷⁸, not gluten⁷⁹.

PREVALENCE

Unfortunately, given the lack of objective diagnostic parameters it is difficult to know the true prevalence of WIS. As a surrogate marker of prevalence, subjective surveys approximate prevalence rates from 13% in the UK⁸⁰ to 7.3% in Australia⁸¹ to 0.6% in the US⁸².

DIAGNOSIS

Diagnostic criteria for WIS are much harder to establish, given the present lack of any biomarkers. As stated previously, although antibodies to native gliadin have been found to occur somewhat more commonly in patients with WIS than in healthy controls, no consistent laboratory abnormalities or biomarkers have been identified⁷¹⁻⁷³. Thus, it must be emphasized that a full clinical and laboratory evaluation to exclude CeD and wheat allergy must be performed before making the diagnosis of WIS. A recently proposed diagnostic process for making this diagnosis includes adherence to a strict GFD for a period of at least 4 weeks with reintroduction of a controlled form of either gluten or placebo for a 1 week period, followed by a 1 week washout period, and then a 1 week crossover period⁸³. However, in clinical practice most patients self-reporting “gluten intolerance” are already on a GFD and unwilling to abandon it; in this case, we suggest a process outlined in the algorithm presented in Figure 2.

Confocal laser endomicroscopy (CLE) may be a promising tool for the future of WIS. A Recent work by Fritscher-Ravens et al in 2015⁸⁴ studied the impact of targeted food administration to the mucosa of the intestinal tract to assess for signs of inflammation using CLE in patients suspected of having a food intolerance leading to GI complaints. They were able to directly observe changes in the IELs, size of the intervillous space, and number of epithelial breaks after the administration of single food agents (milk, wheat, soy, or yeast) and subsequent improvements in symptoms after targeted removal of the offending food. Potentially, this may be an exciting tool for the future to better discern which patients truly do or do not have a WIS. As it stands, WIS is still an exclusion diagnosis and the only rational approach to diagnose WIS,

besides a double-blind placebo-controlled trial – ideal but difficult if not impossible to achieve in clinical practice – is to eliminate the possibilities of CeD and of wheat allergy.

TREATMENT

A trial of a low FODMAP diet is recommended for any patient diagnosed with WIS who is felt to have a FODMAP sensitivity⁷⁷, see Table 3. Otherwise, eliminating all wheat-containing products is the only option. It should be noted here that eliminating the other sources of gluten (i.e. rye and barley), while anecdotally beneficial to some patients with WIS, has not been adequately proven to be necessary.

CONCLUSIONS

The spectrum of “gluten”-related disorders now encompasses celiac disease (CeD), wheat allergy and the newcomer wheat intolerance syndrome (WIS).

CeD, far from being the static, well-known entity we thought it was 20 or 30 years ago, is now evolving into an exciting field of constant flux: role of genetics being better elucidated, environmental factors (prominent among them the microbiota) being unraveled, a fast increasing prevalence to be dealt with, changing clinical features and evolving diagnostic approaches, alternative treatments and even the prospect of a cure looming at the horizon.

Interest on WIS in the meantime is exploding, with a plethora of reviews, editorials, expert opinions flourishing (though unfortunately only a small number of well-designed clinical trials so far), and an unprecedented media interest causing a worldwide wave of followers of the GFD.

While the existence of this complex entity is undeniable, much more work remains to tease out its various components and begin to understand the many possible pathogenetic mechanisms involved, their real clinical impact and objective parameters for diagnosis.

In essence: exciting times and much, much more to come!

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Figure legend:

Figure 1. – U.S. per capita wheat flour use (Ref. 60)

Current consumption of wheat per capita in the United States is roughly half of what it was in the early 1900's.

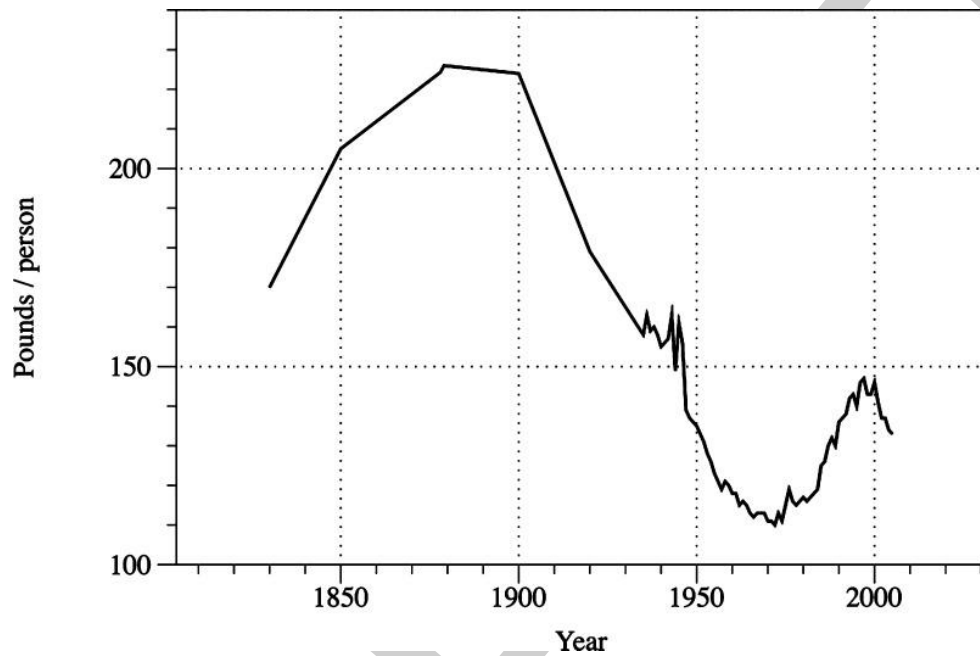


Figure 2. – Proposed algorithm for the evaluation of a patient suspect of Wheat Intolerance Syndrome

Patients already avoiding gluten intake for longer than 1 month can only be tested for HLA-DQ2, DQ8 to rule out celiac disease: then, to further define diagnostic category they must be re-exposed to gluten (amount ill-defined, probably 3-5 grams of gluten per day are adequate) for at least 2 months before being tested again.

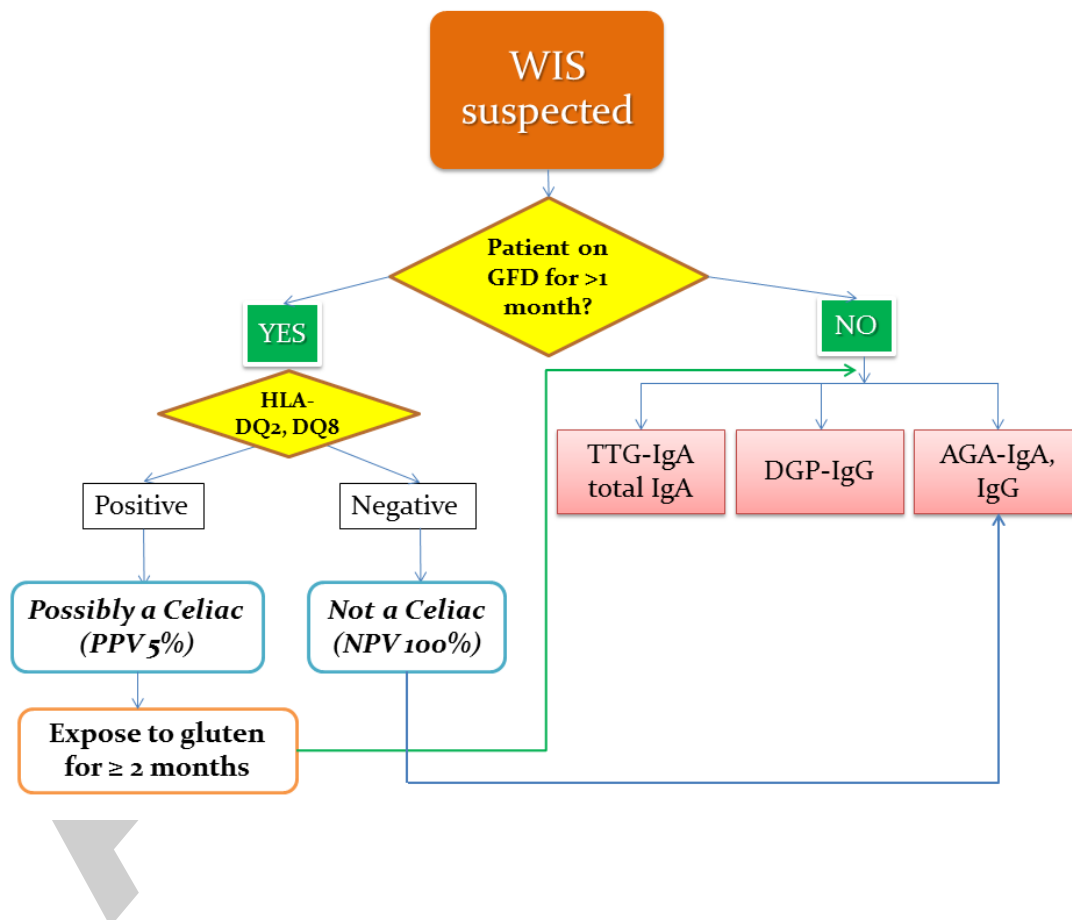


Table 1: Typical and Atypical Forms of Celiac Disease

Sign or Symptom	Age Most Commonly Involved
<i>Typical Celiac Disease</i>	
Vomiting	Infancy
Anorexia	Infancy and early childhood
Failure to thrive	Infancy and early childhood
Diarrhea	All ages
Abdominal bloating	All ages
Abdominal pain	Child to adult
Constipation	Child to adolescent
Weight loss	Child to adult
<i>Atypical Celiac Disease</i>	
Sad mood	Infancy to early childhood
Hypertransaminasemia and other liver issues	All ages
Fatigue	All ages
Delayed puberty	Adolescent
Short stature	Child to adolescent
Anemia	Adolescent to adult
Dermatitis Herpetiformis	Adolescent to adult
Dental enamel defects	Child to adult
Aphthous ulcers	Child to adult
Arthritis	Adolescent to adult
Osteopenia	Adolescent to adult
Osteoporosis	Adult
Unexplained infertility (in women)	Adult
Headaches	Adolescent to adult
Numbness/neuropathy	Adults
Idiopathic seizures	Child to adult
Psychiatric disorders	Adolescent to adult

Table 2: Individuals at Increased Risk for Celiac Disease

- Individuals presenting signs and symptoms of Table 1 not explained by another diagnosis
 - First-degree relatives of celiac patients
 - Autoimmune conditions
 - Type I diabetes
 - Autoimmune thyroiditis
 - Autoimmune hepatitis
 - Addison Disease
 - Genetic disorders
 - Down Syndrome
 - Turner Syndrome
 - William's Syndrome
 - Immunoglobulin A (IgA) Deficiency
-

Table 3: Common Sources of FODMAPs*

Food Component	Dietary Form	Common Sources
Fructose	Free monosaccharide constituent (fructose in excess of glucose)	Apple, pear, watermelon, honey, high fructose corn syrup, asparagus, artichoke
Lactose	Free disaccharide	Milk, yogurt, ice cream, soft cheese
Fructans	Fructo-oligosaccharide (FOS) and inulin	Wheat, rye, barley, garlic, leek, onion, asparagus, artichoke, peach, persimmon, watermelon, pistachio, inulin
Polyols	Sorbitol, mannitol, xylitol, maltitol, isomaltose	Apple, pear, plum, apricot, nectarine, mushroom, cauliflower, reduced calorie sweetener
Galacto-oligosaccharides	Raffinose, stachyose	Legumes, chickpeas, lentils

***FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides and polyols. From Ref (23)**