

Gluten and the Gut: A Brief Review of Gluten-Related Gastrointestinal Disorders

Niraj James Shah* and Kumar Pallav

Department of Medicine, Division of Digestive Diseases, The University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216

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Corresponding author: Niraj James Shah, MD, Assistant Professor of Medicine, Department of Medicine, Division of Digestive Diseases, The University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, Tel: 001-601-984-4540 (extension 7915); Fax: 001-601-984-4548; E-mail: jnshah@umc.edu, nirajjames@gmail.com

Abstract

Celiac disease (CD) was the first gluten-related disorder to be described. Presently the realm of gluten-related disorders also includes non-celiac gluten sensitivity (NCGS) and wheat allergy (WA). CD is a multisystem immune mediated enteropathy observed in genetically susceptible individuals exposed to dietary gluten present in barley, rye and wheat. Although the prevalence of CD is on the rise, it still largely remains under diagnosed given that many cases can be silent, subtle or atypical. The Pathophysiology of CD includes both innate and adaptive immune response to dietary gluten. Patients present with a wide variety of intestinal and extra-intestinal symptoms and are at risk for non-Hodgkin's lymphoma and small intestinal adenocarcinoma. The cornerstone for treatment of CD is a gluten-free diet (GFD). NCGS is an emerging condition associated with gluten ingestion and the diagnosis of which is based on exclusion of CD and WA. Further evidence and studies are required to fully appreciate the clinical entity of NCGS and WA to detail its epidemiology and pathogenesis. The symptoms of NCGS and WA may overlap with CD and hence it is imperative to differentiate these clinical entities and select patients for appropriate management.

Keywords: Celiac disease, gluten related disorder, non-celiac gluten sensitivity, wheat allergy, gluten, epidemiology, clinical features, Pathophysiology, management, gluten free diet.

Core tip: CD is largely under-diagnosed while the incidence and prevalence of gluten-related disorders are on the rise. A clear understanding of the various clinical presentations of gluten-related disorders can help differentiate CD from NCGS and WA. The management for these conditions differs and hence accurate diagnosis leads to improved patient outcomes with avoidance of long-term complications as well as unnecessary testing which can be both invasive and expensive.

Materials and Methods

Literature search

We conducted online electronic searches (published manuscripts in English) of the Cochrane Library, pub med and manual searches of selected specialty journals to identify any pertinent literature. The search was conducted using the key words 'celiac disease', 'gluten related disorder', 'non celiac gluten sensitivity', 'wheat allergy', 'gluten', 'gluten free diet'. Studies not published in English or published only in the abstract form were excluded. We also conducted a focused review of available references to identify subsequent pertinent papers.

Celiac Disease

The term celiac is derived from the Greek word "koiliaks" meaning "abdominal". It was first described in the second century in modern day Turkey by a Greek physician Aretaeus of Cappadocia [1]. In 1888, Samuel Gee; a pediatrician from the United Kingdom gave the first modern-day description of the condition and associated diet to the treatment of celiac disease [1]. Later a Dutch pediatrician Dr. Willem-Karel Dicke around the 1944 Dutch famine linked wheat to the etiology of celiac disease. He noted that the scarcity of wheat contributed to clinical improvement and drop of death rate among his patients [2]. The link with the gluten component of wheat was made in 1952 in Birmingham, in England [3,4]. Villous atrophy was described by the British physician John W. Paulley in 1954 [5]. Its hereditary character was recognized in 1965 by MacDonald et al from the Washington school of Medicine [6].

Epidemiology

Celiac disease occurs in about 1% of the general population worldwide [7]. Data from the USA suggests CD to be more common in Caucasians as compared to African-Americans and Hispanics [8,9]. The initial prevalence of CD was low (1:4,000 to 1:8,000) and was based on symptomology while the recent prevalence is higher (1:70 to 1:300) and is based on serology and biopsy findings [8,10,11]. CD can occur at any age while the mortality rate due to CD after its diagnosis is low [12,13].

Pathogenesis

The estimated risk of CD in first degree relatives is between 4%-17% and up to 26% in relatives who are homozygous for HLA DQ2 [14,15]. Recently published studies indicate no association between age of gluten introduction, ongoing breast feeding and the development of CD [16,17]. Underlying viral infections triggering CD has been entertained for some time but lacks direct evidence [18-21]. A cross-sectional study from the USA suggests decreased risk of celiac disease in patients with helicobacter pylori colonization [22].

Storage proteins in wheat, rye and barley is referred to as gluten [23]. While it may be easy to avoid products directly derived from wheat, gluten contamination is universal. Hidden sources of gluten include contaminated oats, sauces (marinades, soy sauce), drug fillers,

shared food preparation equipment (pasta pot, toaster, deep fryer) and processed meats [24]. Gluten is rich in glutamines and prolamines which are incompletely digested into large peptides [25]. These peptides via transcellular and paracellular route enter into the lamina propria of the small intestinal wall, where the tissue transglutaminase (TTG) deaminates gliadin thereby increasing its immunogenicity. The deamidated gliadin peptides (DGP) undergo processing within the antigen processing cells (apcs) and are presented to the T lymphocytes in association with the HLA DQ2 or DQ8 molecules present on the surface of apcs [26,27]. The immunological cascade continues with CD4 positive T cells (specific for gliadin peptides) contributing to the production of pro-inflammatory cytokines and release of metalloproteinases leading to tissue injury [28-30]. This injury to the small intestinal Villi leads to loss of the absorptive surface area, malabsorption (of micronutrients, fat soluble vitamins, iron, vitamin B 12 and folic acid), diarrhea, weight loss along with abdominal pain and bloating [31-33]. CD has been recognized to be one of the common causes of malabsorption [34].

Diagnosis of Celiac Disease

Immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody has a high sensitivity (>95%) and specificity (>95%) and hence is the recommended screening test in patients who do not have concomitant IgA deficiency [35]. However, studies from USA and Europe indicate the prevalence of selective IgA deficiency (sigad) to be between 1.9% and 3%, which is approximately 10-15 times higher than the general population [36-39]. In patients with sigad; IgG-based testing of IgG anti-TTG or IgG DGP (deamidated gliadin peptide) should be performed [40]. IgA anti endomysial antibodies is a highly specific test (specificity approaches a 100%); but is reserved to confirm active celiac disease as it is expensive, time consuming and operator-dependent [41].

An upper endoscopy with duodenal biopsies (one or two from the duodenal bulb and at least another four biopsies from the distal duodenum) is essential for the confirmation of the diagnosis of CD [40]. The characteristic histological finding consists of > 25 intraepithelial lymphocytes (IEL) per 100 enterocytes with elongation of crypts and villous atrophy. Absence of villous atrophy in the presence of IEL is not specific for CD and other causes should be considered [40]. Despite CD is considered to be the most common etiology of villous atrophy; other possible causes of villous atrophy with absent celiac serologies can be seen in common variable immunodeficiency (CVID), autoimmune enteropathy, small intestinal bacterial over-growth, infection, intestinal lymphoma, collagenous sprue, Crohn's disease and tropical sprue [36].

Histologically duodenal biopsies are graded into 5 stages (Marsh's criteria42)

- Stage 0- Normal
- Stage 1 – increased percentage of IEL > 30%
- Stage 2- Increased presence of inflammatory cells and crypt proliferation with preserved villous architecture
- Stage 3- Mild (A), moderate (B) or subtotal (C) villous atrophy
- Stage 4- Total mucosal hypoplasia

Genetic testing for HLA-DQ2 and HLA-DQ8 has a high negative predictive value and hence a negative test helps exclude the diagnosis of CD [43-47]. HLA genetic testing is most useful in patients with discrepancy with celiac specific serology with histology, before initiating a gluten free diet and also in excluding refractory celiac. Testing for HLA-DQ2 and HLA-DQ8 has been employed in screening for family members of patients with CD and in patients with Down's syndrome.

Most histologic and serologic alterations of CD normalize on a gluten free diet [7]. Many patients get tested and evaluated with histology while on a GFD and hence have negative serology and histology but are positive for HLA-DQ2 or HLA DQ-8. These patients require a gluten challenge with a diet containing as little as 3gms of gluten per day for 6-8 weeks when a repeat serology may become positive [48,49].

Duodenal biopsies to rule out CD should be performed in all patients with dyspepsia, undergoing upper gastrointestinal endoscopy as GFD is largely helpful [31].

Management of celiac disease

Adherence to a lifelong GFD (with avoidance of wheat, barley and rye) is the only effective treatment as we do not have any proven medications that could halt or alter gluten related mucosal injury [40]. GFD improves symptomology, reduces mucosal damage and eliminates risks for osteoporosis and bowel cancers associated with long term active CD [50-56]. All newly diagnosed patients should undergo a formal investigation for micronutrient deficiencies including serum iron, folic acid, vitamin D and vitamin B12 [40]. Nutritional assessment and counseling with a skilled registered dietician is imperative in educating patients and aids patients adhering to a GFD [57].

Absolute adherence to a GFD is difficult as gluten contamination is frequent. A persistently positive celiac serology one year after initiation of GFD may indicate gluten contamination [58] and hence requires a repeat referral to a dietician to assess for adequate knowledge and adherence to a GFD. Regular follow up for symptom review and monitoring of patients with celiac serology (IgA TTG or IgA or IgG DGP antibodies) is indicated. A repeat upper endoscopy with histology is only indicated with persistent or worsening symptoms despite confirmed adherence to a GFD.

GFD is the only intervention available. Barriers include its availability, its restriction in social situations and cost [59]. This overtime has a profound psychosocial effect on the patient's life adversely affecting his quality of life [59]. Manipulation of the mechanisms of tight junction regulators, glutenases, gluten sequestrants and immunotherapy using vaccines and nano particles are some of the novel therapeutic adjuncts to a GFD [60].

Non-responsive celiac disease (NRCD)

NRCD is defined as the persistence of clinical and laboratory abnormalities of CD even after adherence to a GFD for 6-12 months [58,61-63]. It affects 7-30% of patients on a GFD for CD [58,61,62]. The most common etiology is purposeful or hidden gluten ingestion accounting for 35% to 50% of the cases, hence a dietary referral is warranted in these cases [58,61,62]. The evaluation should also include reconfirmation of the previous diagnosis of CD and ruling out other common causes of similar

symptomology including small bowel bacterial overgrowth, food allergies, pancreatic insufficiency, irritable bowel syndrome and refractory celiac disease [58,61-65]. Since CD and microscopic colitis (MC) overlap [66,67]; MC should be considered in patients with NRCD while CD is considered in patients with unresponsive MC [68].

Refractory celiac disease (RCD)

RCD is defined as persistent clinical symptoms and signs of malabsorption with histological evidence of small bowel villous atrophy (related disorders including overt lymphoma needs to be ruled out) even after adherence to a GFD for more than 12 months [7,61,69]. It affects 1-2% of patients on a GFD for CD [64,70,71]. The clinical presentation and course of patients with RCD is much worse when compared to patients with NRCD [61,64]. The ongoing symptoms of RCD is independent of gluten-withdrawal; with only mild and transient response to gluten withdrawal and subsequent return of severe symptoms [72]. RCD is subdivided into two sub-groups:

- Type I RCD
- Histology reveals IEL with normal surface T-cell receptors and normal CD3 and CD 8 expression [71,73-75]
- Management includes avoidance of gluten exposure and repletion of nutritional deficiencies [61,64,70,71,73].
- Type II RCD
- Histology reveals IEL with loss of surface T-cell receptors and abnormal phenotypic expression and differentiation of CD3 and CD8 positive intraepithelial T cells [73-75]
- Management is similar to Type I RCD. Type II RCD is less likely to respond to treatment and carries a poorer prognosis; largely explained by its progression to enteropathy-associated T-cell lymphoma [70,71,73,76-78]

Prednisone is used in severe cases of RCD. In cases of incomplete response; other immunosuppressive agents including azathioprine, budesonide, 6-mercaptopurine, Mesalamine, cyclosporine and anti-tumor necrosis factor antibodies have been used [69-71,76,79-83].

Ulcerative jejunitis

Ulcerative jejunitis is usually seen in middle aged patients with CD refractory to steroids [84]. Monoclonal aberrant T-cell abnormality is the postulated pathogenesis [53,85]. Patients continue to experience symptoms of diarrhea, abdominal pain and malabsorption despite being on a GFD [86,87]. Workup includes an exclusion of malignancy [69,76,88,89] (EATL and small bowel adenocarcinoma) with an abdominal CT enterography or MR Enterography. Endoscopy reveals multiple benign ulcers concentrated mainly in the jejunum [70,71]; and if negative should be followed by a capsule endoscopy [90,91]. It usually carries a poor prognosis; while surgical resection of localized ulcerations and structured small bowel improves prognosis [71,76,89,92].

Celiac crisis

Patients with CD can present with celiac crisis; a life threatening syndrome presenting with severe diarrhea, metabolic and electrolyte derangements requiring hospitalization [93,94]. Although celiac crisis is

usually seen in children; physicians should have a high index of suspicion even in adults with CD as this would carry a high morbidity [95-99]. Hence this warrants prompt diagnosis and intervention. Limited data suggests lesser frequency of celiac crisis which has been attributed to recent improved diagnostic modalities [97]. Management includes fluid and electrolyte replacement, nutritional support and corticosteroids [100].

Non-Celiac Gluten Sensitivity (NCGS)

NCGS was first described as individual cases in the late 1970's and later as a case series in 1980 [101-103]. However, since 2010 a rapid increase in interest and case series has been published. The prevalence of NCGS is unknown and is difficult to estimate. Results from the Continuous National Health and Nutrition Examination Survey in the United States and various other surveys from the United Kingdom and other parts of Europe indicate wide range of prevalence rates with identifiable risk factors to be a young or middle aged female patient with irritable bowel syndrome (IBS) [104-107].

NCGS is a clinical entity induced by the ingestion of dietary gluten leading to intestinal and/or extra-intestinal symptoms that resolve with a GFD, and when CD and WA have been ruled out [108-111].

The pathogenesis is largely unknown. In 2011, Sapone et al suggested an innate immune response [112] with activation of toll like receptors while other studies have suggested increased intestinal permeability to be responsible [113-116]. Increased CD3 positive IELs [110,112-117] and increased interferon γ to a gluten challenge [117] suggests gut mucosal activation.

NCGS patients present with gastrointestinal symptoms (abdominal pain, bloating, altered bowel habits) and extra intestinal symptoms (fatigue, headaches, joint pain, mood disorders, eczema) [107,110,111].

Since we do not have any definite clinical, serological, endoscopic or histological criteria for NCGS; its diagnosis is mainly based on symptoms related to gluten consumption and withdrawal and the exclusion of CD and WA. Patients have a negative IgA TTG and EMA and may in up to 50% have positive IgG DGP and rarely positive IgA DGP [107,118,119]. The endoscopy is almost always normal with preserved Villi while a mild increase in IEL 119 may be observed. Up to 50% may have HLA-DQ2 and HLA-DQ8 [110].

Despite the proposed double-blind, placebo-controlled gluten-challenge trials being considered for the diagnosis of NCGS [110]; a recent meta-analysis published in March of 2017 comprising of 1312 adults from 10 trials indicated that more than 80% of the patients with suspected NCGS could not be definitely diagnosed [120]. However the proposed double blind, placebo-controlled gluten-challenge can distinguish NCGS from IBS 105. IBS-like symptoms are common in patients with NCGS. Gluten containing diets increase intestinal permeability and worsen symptoms in IBS-D subpopulation [121]. NCGS does not lead to malabsorption given lack of intestinal inflammation and for the same reason there is no risk for malignancy if left untreated. Unlike CD where the goal of treatment is complete exclusion of obvious and hidden gluten from one's diet, the treatment of NCGS revolves around symptom management.

Wheat Allergy

Since 10,000 years when humans started agriculture in Mesopotamia; wheat has become a staple diet and is the most widely grown crop [122]. Processed wheat is consumed as bread, pasta, pizza, couscous and beer [122,123].

Food allergy to wheat is typically characterized by a T helper type 2 (Th2) lymphocytic inflammation [124-128] in genetically predisposed [125,129,130] individuals. The subsequent cascade of Th2 activation could either lead to an IgE mediated (immediate response with wheat-specific IgE antibodies) or a non IgE mediated allergy (chronic cellular inflammation with presence of lymphocytes and eosinophils) [124-128].

The prevalence of ingested wheat allergy [IgE mediated anaphylaxis, wheat-dependent exercise-induced anaphylaxis (WDEIA, urticaria and angioedema is higher in children; who generally out-grow it by school-age [131-135]. Repeated exposure to wheat flour in bakers and pasta factory workers can induce an IgE mediated respiratory allergy (includes baker's asthma and baker's rhinitis) [136,137]. Non-IgE mediated wheat allergy has been postulated to lead to eosinophilic esophagitis (EOE) or eosinophilic gastritis (EG).

Patients give a history of immediate symptoms (due to release of histamine, platelet activator factors and leukotrienes) secondary to IgE mediated food allergy [138,139].

The diagnosis of IgE mediated wheat allergy is based on a combination of patient history with specific and reproducible symptoms on exposure to wheat and immunological tests including food challenges as detailed below:

1.Skin prick test (SPT): It has a low predictive value and lacks standardization (with varied protein content) [140].

2.In vitro specific Immunoglobulin E (sige): These assays when compared to SPT are more sensitive (75%-80%) but less specific (60%) due to cross-reactivity demonstrated in wheat flour and grass pollen-sensitivity [141,142].

3.Molecular-based allergy (MA) diagnostics incorporates wheat flour extracts like omega-5 gliadin (Tri a 19), nsItp (Tri a 14), alpha-amylase/trypsin inhibitor (Tri a aa/TI) [137,143].

4.Functional assays (FA) or food challenge test: *In vitro* flow cytometry assisted basophile activation test (BAT). FA's are considered only when SPT, stge and MA are inconclusive. FA involves a double blind placebo controlled food challenge. It requires a control setting as the test has the potential to be dangerous [144,145].

Currently, the management of WA is based on avoidance of wheat. Patients should undergo dietary advice and referrals to identify relevant food allergens [146]. In the USA since 2005, Food Allergen Labeling and Consumer Protection Act of 2004 has been enacted to help with reading labels to prevent the accidental exposure to foods for eight of the most common food allergens (milk, egg, peanuts, tree nuts, fish, shellfish, soy, and wheat) [146]. Certain modalities including immunotherapy (oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT).) Are presently in the pipeline and are promising ways to treat IgE mediated reactions to wheat [147].

The clinical distinction between CD, NCGS and WA is vital in formulating a plan for management. A guide to the differential diagnosis of major gastrointestinal gluten-related disorders is detailed in (Table 1). WA may be diagnosed on the basis of a history and physical suggestive of an allergic process and confirmed with IgE based testing. On the contrary, CD and NCGS can be clinically indistinguishable. The recently published diagnostic model (Figure 1) for symptoms responsive to a GFD by Kabbani et al can be very helpful in differentiating CD from NCGS.

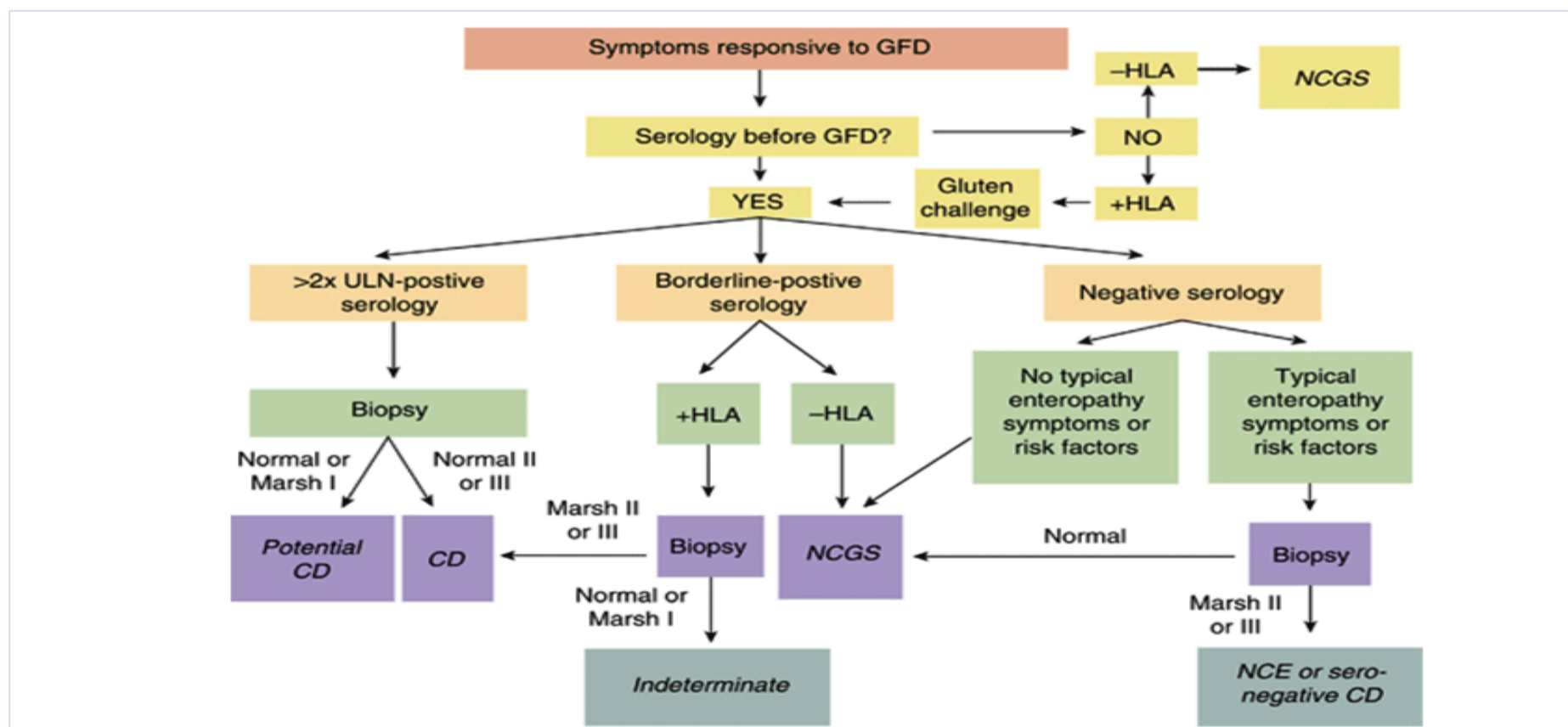


Figure 1: Diagnostic model for symptoms responsive to gluten exclusion [154]. This model can be employed to differentiate between CD and NCGS after ruling out WA with IgE assays when it is suspected based on signs of an allergic etiology such as hives, urticaria, angioedema or eczema.

Table1: Guide to differential diagnosis of CD, NCGS and WA

	Celiac disease (CD)	Non-celiac gluten sensitivity (NCGS)	Wheat allergy (WA)
Epidemiology	1% world-wide prevalence. Estimated to be higher	Largely not known. Prevalence of 0.5% in the USA (national health and nutrition examination survey report)	3% prevalence in the usa; as per the spt. Other studies indicate 0.2% - 1% of the pediatric population 148-153
Pathology	Innate and adaptive immune response. Non Th2 response	Likely innate immunity with no adaptive immune response	Food allergy, Allergic immunity, IgE mediated
Genetics HLA-DQ2 , HLA-DQ8 Testing	Negative HLA testing essentially rules out CD	Negative HLA testing does not rule out NCGS	Negative HLA testing does not rule out WA
Clinical features	Abdominal pain, altered bowel habits, fatigue, headaches, anemia, bone and joint pain, mood disorders, eczema or rash	Abdominal pain, altered bowel habits, fatigue, headaches, anemia, bone and joint pain, mood disorders, eczema or rash	Asthma, rhinitis, urticaria, angioedema,
Serology	Positive IgA TTG and EMA, IgG and IgA DGP	Negative IgA TTG and EMA, may have up to 50% positive IgG DGP and rarely positive IgA DGP	Positive IgE based assays
Histology	Partial or subtotal villous atrophy with crypt hyperplasia	Normal Villi with rare isolated intraepithelial lymphocytosis	Normal
Diagnosis based on	History, serology and histology, HLA genotyping if serological and histological discrepancy exists	Diagnosis based on exclusion of CD and WA	Skin prick test, in vitro specific IgE assays and functional assays
Management	Strict Gluten-free diet with aim of excluding any and all gluten from the diet to achieve histologic remission	Gluten avoidance to achieve symptomatic remission	Avoidance of wheat. Possible Immunotherapy in future
Complications	Osteoporosis, infertility Associated with intestinal malignancy- small bowel adenocarcinoma, esophageal cancers, B-cell and T-cell lymphomas	Not associated with malabsorption or nutritional deficiencies	No comorbidities, rare anaphylaxis
Prognosis	Excellent when recognized	Excellent	Excellent

Conclusion

Though the prevalence of gluten related gastrointestinal disorders is increasing; yet many believe this is largely an undiagnosed clinical entity. Clinicians should have a high index of suspicion for patients presenting with possible symptoms of gluten related disorders and follow the algorithm to diagnose and differentiate CD, NCGS and WA. It is essential to accurately diagnose CD, NCGS and WA as the management differs. Further research and studies will lead to enhanced understanding of gluten related disorders and facilitate better treatment selection and attainment of long-term therapeutic goals. Early and ongoing counseling with skilled celiac dietitians will aid symptom control and prevent the progression of disease reducing morbidity and improving the quality of life.

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