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REVIEW

US perspective on gluten-related diseases

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Abstract: The incidence of allergy and autoimmune disease in the US and other industrialized nations is increasing, and gluten-related disorders are no exception. The US has documented a profound rise in celiac disease that cannot be fully explained by improved serological techniques or better recognition by physicians. Non-celiac gluten sensitivity, a condition only recently recognized by the medical community, has become a commonly diagnosed entity. Proteins, including gluten are increasingly being identified as a source of wheat allergy. Although the gluten free diet represents a safe and effective treatment for these conditions, there is still much to be learned about the development of gluten-related disorders and the apparent increase in incidence within the US. In this article, we present a review of current knowledge on the epidemiology of gluten-related disorders within a global context, with a focus on diagnostic trends and the evaluation of potential risk factors.

Keywords: celiac disease, non-celiac gluten sensitivity, wheat allergy, risk factors, review, epidemiology

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Introduction

Celiac disease (CD), non-celiac gluten sensitivity (NCGS), and wheat allergy (WA) represent a spectrum of immune-mediated reactions to wheat and in some cases specifically gluten, a protein composite of gliadin and glutenin.[1] Once believed to be relatively rare, particularly in the US, it is now thought that gluten-related disorders affect nearly 10% of the population.[2] Although the genetic association, environmental triggers, and autoantibodies produced in CD have been identified, the pathophysiology of NCGS is unclear. The extensive clinical variability appreciated in WA further adds to the intrigue of this major food staple.

Each gluten-related disorder exhibits a unique pathophysiological response to gluten ingestion, though they may maintain considerable overlap in the clinical presentation. This overlap makes diagnosis difficult, particularly in the case of NCGS. Current research focuses on refining definitions and diagnostic criteria to better tease apart these closely linked conditions. In this review, we discuss the current understanding of the changing incidence and prevalence with a focus on CD, NCGS, and WA from the perspective of the US.

The evolution of gluten

The relative novelty of gluten-related disorders is unsurprising as gluten has not long been a part of the natural diet. The native diet of humans consisted of fruits, vegetables, and meats, with little exposure to grain.[3] However, the Neolithic Age 10,000 years ago

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brought with it revolutions in agriculture and made it possible for the first time to domesticate ancient grasses.[3,4] As these developments spread from the Fertile Crescent of the Middle East westward through Europe, symptoms concordant with CD began to be described.[2–4] The first description of CD may be traced back to the Roman Aretaeus in the late second century AD, though a full description of the disease was not published until 1888 by Samuel Gee. It was not until 1952 when WK Dick, a Dutch pediatrician, showed that children with CD improved during World War II when wheat was unavailable, that a dietary link was accepted and the gluten free diet (GFD) developed.[4]

Not all cultivars of wheat may be equally toxic. In the 10,000 years since wheat was domesticated, more than 25,000 accessions have been developed.[2,5,6] It is only in the past 500 years that the gluten content of foods containing wheat has increased.[2,4,5] Gluten helps dough rise and holds food together while maintaining a palatable texture. Gluten, which is also found in the grains rye and barley, is comprised of both gliadin and glutenin proteins. The gliadin component, which is rich in proline and glutamine cannot be degraded by intestinal enzymes and triggers an immune reaction in genetically predisposed individuals. While each type of wheat contains anywhere from a few to a few hundred gliadin and glutenin components, the toxicity of each component is unknown. In fact, each gluten protein may have a unique toxicity profile and distinct T-cell stimulatory sequences.[5] It has been posited that older varieties of wheat, such as einkorn and emmer, may be better tolerated by those with gluten-related disorders than the current strains (*Triticum aestivum*) used in food production.[4–7]

The spread of agricultural techniques, which increased the abundance and availability of wheat may explain why some areas of the world have higher rates of CD. Indeed, although gluten-related disorders were once thought of as rare in populations other than those of European origin, it is now known that this is not the case.[4] Population based screening has shown that African, South Asian, Latin American, and Middle Eastern countries have similar diagnostic rates of CD and NCGS as those in the US.[4] This may be due to the high prevalence of the related human leukocyte antigen (HLA) required for the development of CD in these regions along with an increasing influence of the western diet. [4] Regardless, experts agree that the degree to which gluten-related disorders are increasing, cannot be explained by genetic factors or increased recognition of the disease. Rather, changes of this magnitude suggest a strong role for environmental factors in the development of disease.[3]

Today, wheat remains one of the most important food sources in the world contributing 50% of calories in industrialized and developing countries. Global consumption has increased faster than any other cereal. These changes are driven by an increase in disposable income, urbanization, and transnational food corporations, as well as retail and marketing techniques.[8] Per capita, yearly wheat flour consumption is estimated at 132.5 pounds per person in the US.[9] The rising prevalence of gluten-related disorders, and their historic nonexistence, suggests the growing need to explore less allergenic grains which may be better tolerated.

Overview: defining gluten-related disorders

Celiac disease

CD is a chronic immune mediated enteropathy triggered by gluten ingestion in people who have genetic compatibility of the HLA DQ2 or DQ8 haplotype.[10] A genetic predisposition and exposure to gluten are necessary but not sufficient to develop CD. Worldwide, the disease affects approximately 1% of the general population, though this prevalence varies between countries.[7] The prevalence of CD is increasing from a global prevalence of 0.03% in the 1970s to current reports of 0.5% to 1.26% in Europe and the US.[10–14] The largest screening to date of a healthy population in the US reports a frequency of 1:105 in populations without risk factors and 1:322 in children.[14] The HLA haplotype DQ2 is carried by 90% of patients with CD, and another 5% carry HLA-DQ8.[3,4] These HLA genes are responsible for about 40% of the total genetic predisposition for CD, with over 40 different non-HLA genes contributing the remaining necessary genetics.[15,16] The importance of the genetic component of CD is further underlined by the increased prevalence seen in first-degree relatives of those with CD in the US: 8%–15%.[10,17] However, 30% of the general population carries the HLA-DQ2 allele, and yet only approximately 3% will go on to develop CD.[15]

CD is becoming increasingly difficult to recognize clinically, as it can present with a wide variety of symptoms. At this time, patients presenting with non-classical CD now exceed those with more classical symptoms of diarrhea, abdominal pain, and poor growth.[3] Although CD was once characterized as having onset in childhood, recent data shows that the loss of tolerance to gluten does not necessarily occur at the time of gluten introduction, but may occur at any point due to unknown environmental triggers.[11] As CD knowledge advances, the list of associated extra-intestinal manifestations recognized by the North American Society for Pediatric Gastroenterology and Nutrition (NASPGHAN) continues

to grow, and includes dental enamel hypoplasia of permanent teeth, osteopenia, osteoporosis, short stature, delayed puberty, and iron deficiency anemia.[18] The European Society for Pediatric Gastroenterology and Nutrition (ESPGHAN) extends this list of extra-intestinal manifestations to include amenorrhea, fatigue, recurrent aphthous stomatitis, fracture, and abnormal liver biochemistry.[19] With better recognition of these presentations, gluten-related terms that were once used interchangeably must now be defined.

The recent *Oslo definitions regarding CD and related terms*[20] help to clarify confusion surrounding current terminology. Those terms that are no longer recommended for use by the Oslo consensus group and the replacements are listed in Table 1.

Wheat allergy

WA is defined as an adverse immunologic reaction to wheat.[21] Wheat is one of the eight most common IgE-mediated food allergens in the US.[22] Worldwide, WA affects between 0.5%–9% of the population.[23] Analysis of US adults found 0.4% report an allergy to wheat diagnosed via a doctor.[24] The clinical response to wheat sensitization varies based on the route of exposure and immune response elicited. Ingestion of wheat can result in immediate or delayed onset of cutaneous, gastrointestinal, and or respiratory symptoms classically associated with food allergy.[22] Additionally, sensitization to wheat can cause food dependent exercise induced anaphylaxis (FDEIA), contact urticaria, baker's asthma, or rhinitis.[22] FDEIA is defined as an allergic reaction induced over several hours by the combination of an offending foodstuff, in this case wheat, and subsequent physical exercise. Symptoms range from urticaria to angioedema and shock.[23] Occupational asthma or specifically, baker's asthma, is an IgE-mediated response to the wheat amylase/trypsin inhibitor subunits in individuals working with wheat flour resulting in respiratory distress and rhinitis.[25]

Wheat proteins are described according to their solubility in a number of solvents. From this, they can be divided into four fractions: albumins, globulins, gliadins, and glutenins.[26] While a wide range of these four types contributes to classical food allergy, the most important described to date are the amylase/trypsin inhibitor subunits of the albumin/globulin family.[26] Gluten and high molecular weight glutenins are associated with wheat dependent exercise induced anaphylaxis, with ω-5 gliadin the most important allergen identified to date.[27]

The natural course of WA differs between children and adults. WA is more common in children with a prevalence of 0.4%–1% in the US.[28] Generally, it presents with immediate symptoms of urticaria, bronchial obstruction, nausea, or gastrointestinal complaints. Delayed hypersensitivity may present 24 hours after ingestion with gastrointestinal complaints, pruritus, or eczematous rash. The majority of wheat allergic children also suffer from atopic dermatitis and other food allergies.[26] A large pediatric study showed that resolution of WA occurred in 29% of children age four, 56% of children age eight, and 65% of children by the age of twelve.[28] Additionally, IgE levels were a useful predictor of persistent allergy and higher levels were associated with poor outcomes.[28] Adults, however, are less likely to present with symptoms of classical food allergy due to ingested wheat.[29] More likely, adults may present with FDEIA or symptoms related to inhalation of wheat products.[30]

Table 1 Oslo definition of CD and related terms

Suggested term	Definition	Related terms out of favor
Classical CD	Signs and symptoms of malabsorption; eg, diarrhea and poor growth	Typical CD
Non-classical CD	Symptoms other than malabsorption	Atypical CD
Subclinical CD	Clinical or laboratory signs of disease without symptoms sufficient to suggest clinical testing	Asymptomatic CD Silent CD
Symptomatic CD	GI or extra-intestinal symptoms occurring due to gluten ingestion	Overt CD
Potential CD	Positive serological testing with normal small bowel biopsy	Latent CD
Refractory CD	Persistent symptoms and enteropathy despite a GFD ×12 months in the absence of other causes	

Note: Data from Ludvigsson et al.[20]
Abbreviations: CD, celiac disease; GFD, gluten free diet; GI, gastrointestinal.

Non-celiac gluten sensitivity

NCGS is a condition currently defined by clinical symptoms triggered by gluten ingestion in the absence of serology consistent with celiac disease, small intestine villous atrophy, and wheat allergy.[1] There may be a family history of CD and in 50% of cases the individual may have the HLA-DQ2 or DQ8 genotype.[2] Although first described approximately 30 years ago, recent work by Sapone et al defining the clinical and diagnostic features has rejuvenated this diagnosis, already popular in the general population, within the medical community.[31] NCGS is now commonly used to describe those who have a reaction to gluten without meeting the criteria for CD or WA. While powerful epidemiological studies of gluten sensitivity have not been published, it is estimated that the prevalence of gluten sensitivity is between 3%–6%.[1,32,33]

However, prevalence is difficult to estimate at this time given the lack of biomarkers available. Additionally, given the lack of confirmatory testing, many individuals are self-diagnosing the condition, likely making current estimates well below actual prevalence.

The pathogenesis of NCGS is unknown. Studies indicate that NCGS is an immune-mediated disease likely activating an innate immune response. Sapone et al compared small intestinal biopsies of patients with CD and NCGS.[34] They found that intestinal permeability was intact in patients with NCGS, unlike patients with CD. This same work showed increased intraepithelial cluster of differentiation 3+ T-cells in the biopsies of patients with NCGS. Although genes related to adaptive immunity were not upregulated in the gut mucosa, expression of Toll-like receptor-2 (TLR2), a marker of innate immunity, was increased in NCGS patients.[34] A recent study by Brottveit et al showed that NCGS patients had a higher density of intraepithelial cluster of differentiation 3+ T-cells in duodenal biopsy at baseline compared to patients with CD. Following gluten challenge, those with NCGS had a significant increase in interferon (IFN)-γ messenger ribonucleic acid (mRNA) suggesting that the adaptive immune system may play a role in NCGS.[35]

NCGS is defined by symptoms that occur soon after the ingestion of gluten. Symptoms must disappear with the withdrawal of gluten and reappear when gluten is reintroduced, preferably blindly.[1] Classically, NCGS presents with abdominal pain, bloating, diarrhea, or constipation. Extra-intestinal manifestations are common in adults and may include "foggy mind", fatigue, joint pain, paresthesias, rash, or depression.[1] In children, the most common systemic manifestation is fatigue.[36] A retrospective study at the University of Maryland between 2004 and 2010 identified 347 patients meeting criteria for NCGS. The most common complaints in these patients included abdominal pain (68%), rash (40%), headache (35%), "foggy mind" (34%), fatigue (33%), diarrhea (33%), and depression (22%).[2]

Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is a skin manifestation of CD first described in 1884.[37] It is characterized by a chronic, blistering rash and identified by pathognomonic IgA deposits in the skin. Symmetric distribution occurs on the extensor surfaces of the elbows, knees, back, buttocks, and posterior hairline.[38] This manifestation, which typically presents in the fourth decade, is most common in individuals of European descent and has a greater preponderance in men.[2] Prevalence in the US is reported as 11.2 in 100,000 individuals with an incidence of 0.98 per 100,000 yearly.[38] To date, the pathogenesis is unclear. Diagnosis is established via serum testing for tissue transglutaminase (tTG) and anti-endomysial antibodies. Small intestinal biopsy is required. Anti-epidermal transglutaminase (EtG) or transglutaminase 3 (TG3) are enzyme-linked immunosorbent assay (ELISA) tests with the highest sensitivity and specificity for diagnosing DH.[38] Additionally, 90% of patients are HLA-DQ2 or DQ8 positive. Although it is unclear how intestinal lesions and skin lesions are linked, the rash improves with gluten restriction.

Gluten ataxia

Gluten ataxia (GA) is defined as idiopathic sporadic ataxia, in the presence of positive anti-gliadin antibodies (AGA) with or without enteropathy on small intestine histology.[20] To date, large epidemiological studies evaluating this condition have not been published. Current prevalence of GA in patients with sporadic idiopathic ataxia are reported at 32% to 41% which would make gluten the most common cause of this disorder.[39] GA typically presents in the fifth decade of life or later. It is characterized by gait ataxia, limb ataxia, and gaze evoked nystagmus. Although most do not have gastrointestinal complaints, up to 33% have enteropathy on small intestinal biopsy.[2] Additionally, like CD and DH, GA is associated with HLA-DQ2 and DQ8 with 82% and 6% of 28 patients with HLA-DQ2 and HLA-DQ8, respectively.[39] Diagnosis is difficult, as antibodies used in CD and DH are not as often elevated in these patients. Recent studies have focused on transglutaminase (TG) 6 as an autoantibody primarily expressed in neural tissue that shares features with tTG and TG3 previously discussed.[2] A recent prospective study evaluating patients with ataxia, CD, and controls found a prevalence of TG6 in 32% of patients with idiopathic sporadic ataxia, 73% of patients with GA, 32% in patients with CD, and 4% of controls. Additionally, they found that TG6 decreased in response to a GFD, showing not only that TG6 is gluten dependent, but also that it may be useful as a marker in GA.[40]

Autism spectrum disorders and gluten

Autism and autism spectrum disorders (ASD) are defined by the *Diagnostic and Statistical Manual of Mental Disorders V* as persistent impairments in social interactions and social communication across multiple contexts as well as repetitive and restrictive stereotyped patterns of behavior, interests and activity.[41] According to the Center for Disease Control (CDC), ASD now affects 1 in 88 children in the US with boys affected five times more often than girls.[42] Gastrointestinal symptoms in ASD are common, but have not been shown

to be more frequent than the general public.[43] In response to rising diagnostic rates exploration into genetic susceptibility, the immune system, and environmental triggers have led to questions regarding whether gluten may play a role in this disorder. Despite limited data, family testimonials and clinical observations have continued to drive research into the relationship between gluten and autism. Historically, studies have not consistently shown a relationship between autism and serological markers of CD or specific food allergens.[44] However, Lau et al have recently shown a statistically significant elevation in IgG anti-gliadin antibodies in children with both ASD and gastrointestinal symptoms, suggesting an increased immune reactivity in children with ASD to gluten.[45] Additionally, there is evidence that children with autism have increased intestinal permeability compared to controls.[46] This finding contributes to evidence for the "opioid-excess theory" which suggests that food based peptides may cross into the blood stream causing pharmacologic effects.[47] This theory is further evaluated in studies evaluating urinary peptide levels as a surrogate marker of processes that have an opioid effect. Knivsberg et al[48] performed a randomized, blinded trial evaluating the effect of a gluten free, casein free diet on 20 children with ASD found to have elevated urinary peptide levels at baseline. This group reported improvement in autistic behavior, nonverbal cognitive levels, and motor problems, suggesting that in a subset of individuals this diet may be helpful.[48] While at this point strong, randomized trials evaluating the GFD in ASD are lacking, in the future, data may support a role for the GFD in a subset of individuals with ASD. At this time although it is not harmful, the cost and difficulty maintaining the GFD indicates a limited return on investment for most patients.

Diagnosis: gluten-related disorders

Celiac disease

The diagnostic gold standard for CD is small bowel biopsy.[18,49] Serum tests aid clinicians in selecting individuals who may benefit from biopsy. Currently diagnostic testing employs the use of IgA and IgG serum tests for tTG, EMA, AGA, and deamidated gliadin peptide antibodies (DGP). IgA EMA and IgA tTG offer sensitivity and specificity of greater than 95%.[50,51] General consensus regarding these studies is that IgA tTG is the most reliable and cost effective. Genetic testing for HLA susceptibility markers is available but limited to determining whether a patient is at increased risk of developing the disease. Approximately 40% of the population carry the HLA-DQ2 and or DQ8 markers while only 3% of individuals with these genetic predispositions go on to develop the disease.[15]

The diagnosis of CD can be quite complex when considering the patchy nature of the small intestinal damage and the expertise required by the pathologist evaluating the tissue for diagnosis. Additionally, patients are increasingly presenting with non-classical symptoms and those with family history or related disorders may be screened without gastrointestinal symptoms resulting in patients that may not fit the traditional diagnostic model. This has recently led to the development of the "4 out of 5 rule" for diagnosing CD.[52] This algorithm recognizes that not every patient with CD fulfills every finding which is commonly associated with the disease. As such, four of the following five criteria are necessary for the diagnosis of celiac disease:

1. Positive history for symptoms typically associated with celiac disease.
2. Positive serological biomarkers which are commonly associated with celiac disease, such as tTG or IgA EMA.
3. Positive genetic testing for HLA-DQ2 or DQ8 alleles.
4. Small intestinal biopsy showing blunting or absence of the villi (Marsh III) and cluster of differentiation 3+ intraepithelial lymphocytosis.
5. Improvement of symptoms with a gluten free diet.

The improvement in the sensitivity and specificity of serological screening techniques, availability of genetic screening, and increased incidence of disease have also ignited a debate regarding whether an endoscopic diagnosis is necessary in every case. The most recent ESPGHAN guidelines state that a duodenal biopsy may be omitted if the individual has signs and symptoms suggestive of CD, and a tTG >10 times the upper limit of normal. The guidelines further suggest confirmatory testing with anti-endomysial antibody and genetic testing for those who will not undergo a duodenal biopsy.[19] Although biopsy is still required by current NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) guidelines it will need to be addressed in the near future as families, especially those with a strong family history, question the need for endoscopic biopsy.[19] Additionally, as the clinical acumen required in diagnosing the growing number of individuals with non-classical symptoms evolves, the debate regarding the usefulness and cost-effectiveness of universal screening in the US continues.[53,54] Current NASPGHAN guidelines recommend a case-based approach to screening with IgA tTG for children with recurrent abdominal complaints, common extra intestinal complaints, and known conditions associated

with celiac disease. Additionally, guidelines recommend that asymptomatic individuals who belong to certain high risk groups be considered for regular screening if initial serological testing is negative.[18]

Wheat allergy

The diagnostic accuracy of methods testing for WA in children and adults are imperfect. Current available tests include serum wheat specific IgE testing (RAST), skin prick tests (SPT), patch testing (PT), and oral challenge. Majamaa et al[55] compared these tests in 39 children less than 2 years of age with suspected WA. Of the 22 children testing positive for WA via oral challenge; 23% developed an immediate-type reaction. The remaining 77% developed delayed-onset reactions such as eczema or diarrhea. In patients who tested positive to oral challenge, 20% tested positive via RAST testing, 23% tested positive via SPT, and 86% tested positive via PT. Despite PT being the most sensitive measure in this age group, specificity was lacking at 35% compared to specificity of SPT and RAST at 93% and 100%, respectively.[55]

Adults are less likely than children to present with symptoms of classical food allergy due to ingested wheat; however, diagnosis remains equally problematic.[29] Scibilia et al performed a double blind placebo controlled food challenge in 27 adults and found 48% of patients tested positive for WA.[29] In patients who tested positive, 46% tested positive via SPT and 85% tested positive via wheat specific IGE. Specificity for these tests were 41% for SPT and 27% for wheat IgE.[29] Therefore, although wheat is a common allergen in both children and adults, currently available testing is unsatisfactory, and oral food challenge may be the most effective diagnostic technique.

Non-celiac gluten sensitivity

Although no biomarkers or objective diagnostic criteria have yet been identified to aid in the diagnosis of NCGS, this is currently an area of intense research.[35,56,57] Currently, NCGS remains a diagnosis of exclusion, though it has clear distinctions from both CD and WA (Table 2). Testing for CD and WA must be negative. Additionally, symptoms must occur with ingestion of gluten and symptoms must improve with a GFD. Preferably the gluten challenge would occur blindly; however, in clinical practice this is rarely feasible. Studies have suggested that testing for IgG AGA, shown to be elevated in 7.7% of individuals with NCGS, may be helpful.[57] Approximately 50% of patients with NCGS carry the HLA-DQ2 or DQ8 genotypes, slightly above the general population.[2]

Table 2 A comparison of the various reactions to gluten

	Celiac disease	Non-celiac gluten sensitivity	Wheat allergy
Onset of symptoms	Weeks to years	Hours to days	Minutes to hours
Pathophysiology	Autoimmune	Immune-mediated	Allergic
Best initial testing	tTG serology	Diagnosis of exclusion	Skin prick test
Best confirmatory testing	Small intestine biopsy	None needed	Oral challenge

Abbreviation: tTG, tissue transglutaminase.

Prevalence: high-risk groups

Celiac disease

The prevalence of CD is higher in individuals with a family history of CD. First and second-degree relatives in the US have an increased prevalence risk ratio of 1:22 and 1:39, respectively.[14] Several groups also have an increased prevalence risk ratio when compared to the general population, including individuals with Down syndrome with 1:11 and individuals with type I diabetes mellitus (T1DM) with 1:23. Studies in a US adult population found that 18% had a concurrent diagnosis of thyroid disease, 9.8% had dermatitis herpetiformis, 3.3% had T1DM, and 2% had Sjögren's syndrome.[59] Some conditions may be independently associated such as Down syndrome, Turner syndrome, William's syndrome, and IGA deficiency.[60–64] Other conditions have an increased incidence due to a shared genetic predisposition. T1DM, autoimmune thyroiditis, Addison's disease, Sjögren's syndrome, and autoimmune hepatitis are commonly associated with the HLA-DR3-DQ2 and DR4-DQ8 haplotypes.[65,66] The extent to which gluten intake is associated with these conditions is still under debate. Furthermore, the development of more than one autoimmune disease or progression of autoimmunity and whether it is related to gluten exposure, age of CD diagnosis, or whether a GFD can protect against further development of these diseases, is still unknown.

Wheat allergy

Although there are not particular disorders associated with wheat allergy, there are inherent characteristics that certainly make WA more likely in some individuals. Prospective studies have shown that a family history of allergy, male sex, and a low birth weight predispose to developing an allergy.[67] As previously discussed, those with an occupational hazard harbor the risk of developing baker's asthma through inhalation and ultimately sensitization of wheat.[25] Risk factors associated with the development of allergy have been well described and will be discussed below.

Non-celiac gluten sensitivity

NCGS has not been shown to have increased prevalence among particular groups. To date, there have been no definitive genetic links associated with NCGS. There have been trends in current epidemiological studies for an increased incidence of the HLA-DQ2 and DQ8 genotype in patients with NCGS compared to the general public. Additionally, there is evidence that this entity may be more common in those with a family history of CD.[1] At this time we cannot make statements regarding an increased prevalence among certain groups until further studies are done.

Risk factors/prevention

The pathophysiology of gluten-related disorders is currently being described, and there are no proven preventative strategies at this time. Risk factors are currently being evaluated as a promising path ultimately to prevention of these disorders.

Celiac disease

Feeding practices

Infant feeding practices have been implicated as an important risk factor in the development of CD. In Sweden, for example, the increased incidence of CD between 1984 and 1996, was found to be temporally related to changes in infant diet recommendations. This suggests that gluten load, timing of gluten introduction, and the relationship to breastfeeding affects the incidence of CD.[68,69]

An association between breastfeeding and risk of developing CD was suggested as early as the 1950s.[70] Since then, many studies have reported that breastfeeding is protective against the development of CD.[71–74] However, randomized trials are lacking and many prior studies are based on retrospective data without substantial follow-up time. Several US groups have looked at this association. D'Amico et al[75] evaluated 141 patients with biopsy confirmed celiac disease from across the US and found that exclusive breastfeeding in the first 6 months of age was associated with delayed onset of symptoms of CD by 15 months compared to formula fed infants. They concluded that exclusive breastfeeding resulted in delayed diagnosis, which they associated with a non-classical presentation of CD seen in exclusively breastfed children. They report a significantly different age at diagnosis compared to European studies with 48% of children in the US diagnosed before age 2 years compared to 75% of children in Europe.[75] The authors postulate that breastfeeding practices in the US differed from those in Europe, resulting in differences in presentation timing of CD.

Data from the Diabetes Autoimmunity Study in the Young (DAISY) study, a prospective US study evaluating the natural progression and environmental triggers associated with T1DM and CD in a genetically predisposed population, has looked at feeding practices extensively.[76] They found a greater number of participants who developed CD were breastfed while introduced to wheat, barley, or rye compared to control subjects. Additionally, subjects that developed CD were breastfed for a longer period than control subjects.[76] These findings echo results obtained by a US retrospective case control study which reported a significantly higher rate of breastfeeding and a longer duration in infants who developed CD when compared to control subjects.[77] Therefore, it may be that breastfeeding affects the clinical presentation of the disease by delaying symptom onset resulting in delayed diagnosis rather than having a protective effect.

Whether there is an optimal time to introduce gluten into an infant's diet is unknown. In the US, the DAISY study evaluated gluten introduction in genetically at risk infants.[76] Researchers found a 23-fold increase in CD in children exposed to gluten before 3 months of age compared to those exposed at age 4–6 months. They also found a four-fold increased risk in children introduced to gluten after 6 months of age compared to those exposed to gluten at 4–6 months of age. This data is based on follow-up of 4.8 years.[76] However, longitudinal prospective studies such as PREVENTCD,[69] a European, double blind, placebo controlled study and the Italian baby study, a multicenter study, evaluating infants with first-degree relatives with CD have not found that a delay in gluten introduction beyond 6 months causes an increased prevalence of CD. This data suggests that delaying gluten introduction delays, but does not prevent, the onset of CD.[69,78,79]

Infections

In addition to diet, a multitude of other environmental influences in the pre-autoimmune process have been suggested but are incompletely understood. Infections have been suggested as a mechanism of autoantibody induction and subsequent development of CD however few specific infectious etiologies have been identified. A prospective cohort study conducted in the US followed 1,931 infants at increased risk of CD and found that frequent rotavirus infection predisposed to CD.[80] Additionally, there have been several cases of rotavirus infection preceding the symptomatic presentation of CD.[81]

Microbiome

Alterations in the microbiota have been suggested as a likely factor in the pathogenesis of CD. Rod shaped bacteria have

been found in the mucosa of individuals with CD, both inactive and active, but not in controls.[82] Alterations in the composition of short chain fatty acids in fecal samples of patients with CD have also been reported.[83] Antibiotic use has been shown to be associated with biopsy proven CD, small intestine inflammation, and potential CD.[84] The development of the microbiota and its ultimate composition has also been suggested to play an active role in the pathogenesis of CD. Differences in the composition of the fecal and mucosal microbiota in individuals with CD compared to a healthy population have been described.[85–89] Infants born via cesarian section were found to have an increased risk of CD when compared with infants born vaginally. This suggests that an underlying difference in microbiota colonization of an infant's gastrointestinal tract may affect the development of autoimmunity and, specifically, CD.[76] Sellitto et al[90] prospectively characterized the microbiota and metabolome of infants at risk for CD as it relates to timing of gluten introduction and the development of autoimmunity in a proof of concept paper. This study found an overall decrease in the phylum *Bacteriodetes* and a delay in maturation of the intestinal microbiota in infants at risk for CD when compared to controls. Additionally, metabolomic analysis suggested elevations in specific metabolites, namely lactate, that may serve as a biomarker in the future to predict loss of tolerance.[90]

Gluten exposure and risk of autoimmunity

Studies evaluating the age at which CD is diagnosed and the risk of developing subsequent autoimmune diseases once diagnosed with CD are conflicting. Ventura et al reported that children greater than 10 years of age at diagnosis were more likely to develop subsequent autoimmune diseases than younger children.[91] The authors suggested this was a result of a longer period of gluten exposure. However, Cosnes et al[92] found that a diagnosis of celiac disease after age 36 was associated with a decreased risk of developing further autoimmune disorders. They suggested that a delayed diagnosis of celiac disease in an individual may suggest a lower tendency to develop autoimmune disease overall. This study also reported a lower risk of subsequent autoimmune disorders with strict adherence to the gluten free diet.[92] Ventura et al[93] further evaluated the prevalence of T1DM related antibodies and anti-thyroid antibodies in patients with untreated CD. In this study, they found elevated T1DM related antibodies in 11.1% of untreated CD patients and elevated anti-thyroid antibodies in 14.4% of patients at diagnosis. They found that in all patients, the antibodies disappeared within 2 years of initiating a gluten free diet.[93] These studies suggest the GFD may be protective against the development of other autoimmune diseases in patients with CD.

Wheat allergy

Environmental factors are essential to the maturation of the immune system, and are responsible for the shift from a TH2 dominant response to TH1 response, thus contributing to an infant's potential to develop allergic or atopic disease.[94] Unlike CD, studies evaluating risk factors important in the development of WA are limited. However, data implicating genetics, feeding practices, and dysbiosis generally in allergy and atopic disease is well described.

Family history

Studies have shown that a family history of food allergy is a strong predictor of subsequent food allergy development in children. A prospective study of US infants born to families with a strong history found that 25% developed a food allergy by 7 years of age.[95] Despite this clear association, specific genes have not been identified.

Feeding practices

Infant feeding practices have been identified as a likely contributor to the development of food allergy, including wheat. The US prospective cohort DAISY study analyzed their data to evaluate development of WA.[96] They found a 4-fold increase in WA in patients introduced to wheat after 6 months of age compared to those introduced between 4–6 months of age.[96] A Cochrane review of breastfeeding and food allergy details only one double blinded, placebo controlled study which found that 4 months of breastfeeding did not prevent food allergy at 1-year of age.[97]

Microbiome

The microbiome is altered in children with allergic disease.[98] The colonization of the microbiome has been implicated, as infants born to mothers with allergic disease themselves have a higher risk of developing food allergy than control subjects.[98] Although WA specifically has not been evaluated, the microbiota of children with allergy have altered *Bifidobacterium* colonization when compared to controls.[100] A prospective cohort found infants with allergic disease are less frequently colonized with *Enterococci* in the first month following birth and *Bifidobacteria* during the first year when compared to healthy controls. Additionally, allergic infants had elevated Clostridia at 3 months of age, a higher proportion of *Staphylococcus aureus* at

6 months, and lower Bacteriodetes at 12 months compared to non-allergic controls.[98] Prospective studies have further shown that dysbiosis can be appreciated prior to the onset of symptoms. The stools of atopic individuals had a reduced ratio of *Bifidobacteria* to clostridia when compared to non-atopic infants and bacterial fatty acid profiles were different between 3-week old infants who were developing atopic disease and those who were not.[100] Antibiotic use in early life has been shown to have an association with increased frequency of asthma, eczema, and atopic disease, including food allergy.[101]

Exposure

Although the timing of exposure to the allergen, dose of the allergen, and route of exposure contributes greatly to allergy development, this data is limited and varies based on the food allergy. At this time there is not enough evidence to suggest maternal avoidance of a particular food, avoidance during breastfeeding, or late introduction as a means of prevention of food allergy.[102]

Non-celiac gluten sensitivity

To date there are no studies evaluating risk factors or prevention of NCGS.

Treatment: gluten-associated disorders

Celiac disease

A strict GFD is the only treatment for CD. Once following a strict GFD, the majority of patients will have complete symptom resolution and normalization of antibody titers. Unfortunately, the GFD can be difficult to manage, restrictive, time consuming, and financially difficult.[103] Serological tests to follow adherence to the GFD have not been shown to be superior to a patient's interview; however, currently IgA tTG is recommended yearly for health maintenance.[104] Even with strict adherence to the diet trace amounts of gluten, via contamination, may be ingested and cause persistent symptoms and persistent mucosal damage.[105] Although studies have shown that intake of 20 ppm of gluten is safe in individuals with CD, Hollon et al reported that a subset of individuals respond to even this tiny amount of gluten resulting in continued symptoms and intestinal damage.[106,107] Individuals responding to this small amount of gluten may find relief with 3 months on the gluten contamination elimination diet, or the Fasano diet, which limits intake to only fresh fruits, vegetables, meats, and rice.[107] Once intestinal damage is resolved, additional foods, including typically gluten free products, are reintroduced.

Wheat allergy

Avoidance of wheat products is the treatment for WA. In those with wheat dependent exercise induced anaphylaxis, patients are advised to avoid exercise for 4 hours after ingestion. Additionally, these individuals should not take aspirin or other cyclooxygenase (COX)-1 inhibitors within 4 hours of consuming wheat. Patients with immediate-type reactions should carry epinephrine auto-injectors. Like all groups with gluten-related disorders, they should see a dietician to review reading food labels.[26]

Non-celiac gluten sensitivity

A GFD is the only treatment for NCGS at this time. To date, although gluten ingestion clearly causes symptoms, small intestinal mucosal damage has not been demonstrated. Therefore current recommendations include maintaining a GFD to prevent symptoms; however, no known safe or unsafe dose of gluten like that for CD has been described.[106] For that reason, until we can better define pathophysiologic alterations in NCGS a GFD is recommended. Until biomarkers are developed, pending a patient's self-reported sensitivity to gluten ingestion, they may or may not need to adhere to the same contamination free standards of a patient with CD.

Current and future trends

Ten years ago, it was unusual to find a gluten free restaurant in the US. Even choices at the grocery store were limited for those restricted to a gluten free diet. Today, however, gluten free menus and clearly labeled gluten free foods are becoming increasingly commonplace. As of 2010, the gluten free food market was worth an estimated $2.6 billion.[2,33] This market has shown a steady increase since 2008 and is predicted to continue trending upwards. While less than 2% of the population are diagnosed with CD or wheat allergy, more than 6% may suffer from NCGS. Much of the market may be due to people who simply feel better when avoiding gluten.[33] Despite limited knowledge about NCGS, much of the scientific community has accepted this diagnosis due to the undeniable clinical presentation.

The incidence of gluten-related disorders, including CD, is increasing. The profound rate of change makes environmental factors rather than changes in human genetics the likely cause. Although the GFD is the recommendation for these disorders and many believe a GFD is overall healthier, this is not always the case. Those following the diet may not

be meeting nutritional requirements as gluten free foods may not have the same dietary supplementation as gluten containing foods.[108] Evaluation of adult women on a GFD found that less than 50% were consuming recommending amounts of fiber, iron, and calcium.[109]

Despite this, a GFD will provide all the necessary nutritional requirements when using a healthy balance of fruit, vegetables, protein, and ancient grains. Although gluten is not necessary to maintain a healthy diet, the cost of sustaining a GFD if unnecessary is high. In addition to cost, navigating which processed foods are gluten free can be difficult and time consuming.[110, 111] Improvements in regulations are helping with this process. In 2004, the US Food and Drug Administration (FDA) passed the Food Allergen Labeling and Consumer Protection Act of 2004. This act required that all food products manufactured after January 1, 2006 be clearly labeled to indicate the presence of the top eight food allergens (milk, eggs, fish, shellfish, tree nuts, peanuts, soybeans, and wheat).[112] Although this act simplified label reading, until recently, there was no federal regulation defining the term "gluten free". As of August 2013, the FDA has defined the term "gluten free" for voluntary use in food labels.[113] To meet the criteria to use this term, the food must not contain a gluten-containing grain, it must not contain an ingredient that is derived from a gluten-containing grain that has not been thoroughly processed to remove gluten, it may not contain a gluten-containing grain that has been processed if it results in greater than 20 ppm or more of gluten in food, and it must not contain greater than 20 ppm of gluten based on previous studies.[106]

It is undeniable that gluten-related disorders are increasing in the US. Despite the improvement in diagnostic testing techniques for CD and a better recognition of these conditions by physicians, it is difficult to distinguish gluten-related disorders based on clinical presentation. The presentation of CD is evolving with a later age of onset and increased number of patients presenting with extra intestinal symptoms making the screening recommendations a moving target. Diagnostic tests for WA are unsatisfactory, and although no biomarkers or objective diagnostic criteria have yet been identified to aid in the diagnosis of gluten sensitivity the number of patients with complaints related to gluten ingestion without evidence of CD or WA is growing. This population along with a significant number of people who feel gluten free is healthier are contributing to the increased demand for the gluten free food market. While many people believe themselves to have gluten sensitivity, the development of objective diagnostic criteria is necessary to better evaluate the incidence and prevalence of gluten-related disorders within the US.

Disclosure

The authors report no conflicts of interest in this work.

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