

Gluten related disorders

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ABSTRACT

Gluten associated disorders and the question around these associations has recently attracted attentions of many health professionals. This is because of high prevalence of undiagnosed gluten related disorders presenting with a multitude of symptoms and complications inside and outside small bowel. While the environmental factors associated with a complex genetics are leading to destructions of the small intestinal villi resulting in malabsorption syndrome in CD, GS is characterised by negative antibodies and grossly normal histology. The association between celiac disease and other disorders has been clearly established and there have been many reports of numerous intestinal and extra intestinal coexistent disorders with CD. But there is little information available regarding the clinical behavior of gluten sensitivity. In this review we discuss the clinical presentation of non-celiac GS and the prospect of current and the future diagnostic pathway.

Keywords: Celiac disease, Gluten sensitivity, Differentiation, Histology.

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Introduction

It is now becoming clear that, besides celiac disease (CD) and wheat allergy (WA), there are cases of gluten reactions in which neither allergic nor autoimmune mechanisms can be identified. These are generally defined as non-celiac gluten sensitivity (GS). Some individuals who experience distress when eating gluten-containing products and show improvement when following a GFD may have GS instead of CD (1, 2). Celiac disease is a specific digestive disease that results in damage to the small intestine. The disease is genetically inherited and chronic. When individuals with CD consume gluten, their bodies

have an immune response. As a result, the villi of the small intestine become damaged, which causes nutrients to pass through the digestive system without being absorbed. This leads to gastrointestinal distress and eventually, malnutrition.

Until recently the terms GS and CD were used synonymously in literature. New investigations showed that in addition to CD, there is case of gluten reactions in which neither allergic nor autoimmune mechanism is involved and this is in general defined as gluten sensitivity (GS) (3, 4). GS patients are intolerant to gluten and when eating gluten that usually, adverse reactions will develop. These reactions are different from CD and do not lead to small intestinal damages. The clinical picture of GS is generally less severe and

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is not accompanied by the positive tTG autoantibodies or autoimmune disease, while the GI symptoms in GS can lead to symptoms similar to those seen in CD (3-6).

The epidemiological study on GS patient's show that up to 6% of the general population is complains of this disorder, which means that for every person with CD there could be at least six or seven people with GS (7).

Gluten, which includes gliadin and glutenin, are the main storage proteins of wheat and comprise more than 100 species with similar amino acid sequences and biochemical properties (1). Gluten sensitivity may be defined as a state of heightened immune response to ingested gluten. Many individuals with gluten sensitivity also develop celiac disease, an inflammatory enteropathy that is characterized by villous atrophy and lymphocytic infiltration in the small intestine in genetically predisposed individuals (8, 9). Celiac disease is associated with increased reactivity to the epitopes present in deamidated forms of gluten (10) as well as to tissue transglutaminase (9) and can present at any age, most commonly in childhood or middle age (11). Most individuals with CD also have defined HLA DQ genotypes that contribute to disease pathogenesis by modulating the immune response to ingested glutens (12, 13).

Positive tests including TTG-IgA/IgG and EMA-IgA accompany by positive small intestine biopsy will define the CD. But patients with GS do not present severe enteropathy and the serology for common autoantibodies, including anti-tTG IgA, is negative. Interestingly, in almost 50% of cases AGA IgA and IgG might be positive (14).

In the recent insufficiency of precise indicators for GS, the 'gold standard' of GS testing is still elimination of gluten from the diet for two to three months. Symptoms improvement upon elimination and return of symptoms upon the re-consumption of gluten are indicators for GS.

There are plenty reports dividing CD in a range of subgroups in the current literature, but the most simple and comprehensive classification would be classical and atypical. Using the words silent, latent and potentials are overlapping and confusing the readers (1).

Symptoms of celiac disease vary with individuals and may include intestinal symptoms such as diarrhea, gas passing, bloating, vomiting, constipation, constipation alternating with diarrhea, nausea, malabsorption, and extraintestinal symptoms such as skin irritation, weight loss, anemia, chronic fatigue, weakness, muscle cramps, neurological complaints (including seizures), and possibly migraine headaches, concentration and memory problems (14). The diagnostic criteria for typical form of CD are very clear and specific but in atypical form the specialists should considered CD as one of the possible disorders. On the other hands, GS patients may be complaining from GI symptoms e.g. bloating, abdominal pain/discomfort or diarrhea, microscopic enteritis, or with extra-intestinal symptoms such as lethargy, tiredness, headaches, migraines, attention deficit syndrome, hyperactivity, autism, schizophrenia, muscular disturbances and bone/joint pain (15, 16).

Clinical spectrum of Celiac disease and Gluten sensitivity

20 years ago our understanding about CD was limited to the classical presentation and the prevalence of these disorders was and is still low. By development of serological tests and advances in immuno-genetic, we also have been able to diagnose those atypical case under the water line and distinguish CD from gluten sensitivity. Some individuals who experience distress when eating gluten-containing products and show improvement when following a GFD may have GS instead of CD. The atypical forms of CD and GS comprise a range of various forms of these conditions including those with typical histology with minimal symptoms, those with minimal or normal

Table 1. Clinical spectrum of celiac disease and gluten sensitivity

	Symptoms	Serology	histology	Treatment
Typical Celiac	Malabsorption Syndrom and Diarrhoea	Positive in 99- 100%	Marsh IIIb-c rarely Marsh IIIa	Gluten free diet (GFD)
Atypical Celiac	GI and non GI symptoms	Positive only in 40-70%	Marsh 0-IIIc	Observation and or GFD
Refractory Celiac	Malabsorption Syndrom and Diarrhoea	90-100%	Marsh IIIa-IIIc	GFD and Immunomodulator
Gluten sensitivity	Typical and/or atypical symptoms	Negative	minimal or normal mucosal changes	Gluten free diet

mucosal changes with negative serology and genetic. Finally, those cases with typical mucosal changes and symptoms but non-responsive to GFD known as refractory CD (table 1).

During the last decade, several studies have identified signs and symptoms associated with non-celiac GS, particularly concerning neuropsychiatric disorders. Patients with schizophrenia have higher than expected titers of AGA that are related to CD and GS, whereas the implementation of a GFD seems to improve the behavior of a subset of children with autism spectrum disorders (ASD). However, currently there are no laboratory biomarkers specific for GS (17, 18).

Immuno-genetic of gluten sensitivity and celiac disease

Triticeae glutes are important factors in several inflammatory diseases. The immune-genetic can be subdivided into innate responses (direct stimulation of immune system), class II mediated presentation (HLA DQ), class I mediated stimulation of killer cells, and antibody recognition. The responses to gluten proteins and polypeptide regions differ according to the type of

gluten sensitivity. The response is also dependent on the genetic makeup of the human leukocyte antigen genes. In enteropathy, there are at least 3 types of recognition, innate immunity (a form of cellular immunity priming), HLA-DQ at majority, DQ8 (19) and antibody recognition of gliadin and transglutaminase (19). The three dominant sequences responsible for the antibody reaction have been identified (20, 21) with idiopathic disease only antibody recognition to gliadin has been resolved. In wheat allergy, there appears to be innate components and the response pathways are mediated through IgE against gliadin and other wheat proteins (22-24).

In the same GS patients, the up-regulation of claudin-4 was associated with an increased expression of toll like receptor-2 and a significant reduction of T-regulatory cell marker FoxP3 relative to controls and CD patients. Additionally, an increase in IELs of the classes α and β , but no increase in adaptive immunity related gut mucosal gene expression, including interleukin (IL)-6, IL-21 and interferon $-\gamma$, was detected in GS (25). These changes in GS could suggest an important role of the innate immune system without any involvement of the adaptive immune response.

The sharing of a similar HLA haplotype may partly explain the strong association between Diabetes Type I, Dawn Syndrome, IgA-Deficiency, Dermatitis herpetiformis and celiac disease. Celiac disease is a polygenic disorder and HLA is the single most important genetic factor in this condition (26).

The finding that diseases such as type I diabetes, CD and multiple sclerosis are HLA-DQ associated is not easily explained by a simple hypothesis of DQ-restricted, autoreactive T cells, considering the generally marginal role of DQ in restricting responses. Thus, both HLA-DR and -DQ polymorphism exists for hTg in autoimmune thyroiditis.

While in CD there is a strong genetic association with the class II MHC haplotype, with about 95% of patients carrying HLA-DQ2 and the remaining 5% carrying HLA-DQ8, different studies have shown that only about 50% of patients with GS carry HLADQ2 and/or HLA-DQ8, a percentage slightly higher than that in the general population (21). This suggests a reduced level of involvement of MHC-dependent adaptive immune responses in GS relative to CD.

Autoimmune disorders

Obviously > 95% of autoimmune disorders associated with CD are HLA-DQ2/DQ8 positive. Thus again almost all those patients with different autoimmune disorders share the same genetic background with CD. We know that about 30% of general population are HLADQ2/8 positive. Unfortunately there is not enough evidence to show whether this group are more prone to develop autoimmune disorders compared with those who have no HLA-DQ2/DQ8.

The question is what is triggering a multiple antigenic activities in these patients as the antigen in CD is solely based on exogenous type as gluten? We know that CD's immunogenesis could be activated by infections like in tropical

sprue or other disorders not necessarily related to CD. This reality raises the question that whether untreated CD activate the autoimmune response in those susceptible individuals who coincidentally have CD? The answer to this question is yes since there are strong evidence that gluten would trigger the autoimmune process outside celiac disease in human and mouse model (27-29).

It has been shown in some studies that the prevalence of autoimmune disorders is also increased in first-degree relatives of celiac patients (30) most likely related to unrecognized and, therefore, untreated celiac disease. Fasano hypothesise that there might be linkage disequilibrium of genes predisposing for both celiac disease and the associated autoimmune disease (31) that may connect their coexistence and one lead to another. There is no doubt about disequilibrium of genes predisposing for these conditions. What we should keep in mind is the influence of environmental factors in these processes. It is clear that persistent stimulation by some pro-inflammatory cytokines such as interferon- γ and tumor necrosis factor- α can cause further processing of autoantigens and their presentation to T lymphocytes by macrophage-type immunocompetent cells (so-called antigen-presenting cells).

Prevalence of autoimmune disorders in celiac disease might be increased with increasing age at diagnosis. In a logistic regression model, age at diagnosis seems to be the only significant predictor variable of the odds of developing an autoimmune disorder (32). Interestingly, in some studies increased prevalence of autoimmune diseases in patients with a late celiac disease diagnosis does not correlate with duration of gluten intake nor does gluten withdrawal protect patients with a late diagnosis from autoimmune diseases.

Conclusion

Almost all those conditions as reported to have an association with celiac disease are or must be HLA-DQ2/DQ8 positive. That means that they all have a common characteristic sharing a similar genetic background. On the other hands only 50% characters for gluten sensitivity diagnosis is HLA-DQ2/DQ8 positive. Environmental factors play other key role in the appearance of both conditions. The proportion of contribution of the genetic and environmental factors in genesis of CD seems to be non-homorganic and variable in different subgroup. This multifactorial etiology would explain why we are unable to explain the rational for many of these associations between celiac disease and other disorders.

The theories behind this coexistence first of all bring to our attention that a good part of these associated disorders might be simple overlaps and/or coincidences as CD is quite a common and easily can overlap with GS. On the other hand the immunogenesis leading to CD is stimulated by an exogenous antigen which may have a different pathway compared to GS.

The supposedly non-specific antigliadin antibodies in gluten sensitivity provide two important pieces of information: 1) That the intestinal wall has been damaged and is permitting leakage of food proteins into the bloodstream, and; 2) That the dynamic contributing to increased autoimmunity in celiac disease may well be an important contributing factor in gluten sensitivity. In fact the most important advantage of these associations would be their possible improvement on a gluten free diet. Unfortunately, this is not the case in all patients, and we should keep in mind that a good part of associated disorders require a separate treatment in addition.

here is a need for risk stratification, a systematic workup to assign the patients to appropriate plan (amount of gluten intake etc). Patients with CD not only need to be treated for

life, but also require a very accurate treatment, as gluten traces may still be able to induce damages to their small intestinal mucosa. On the other hand, the natural history of other gluten-related disorders, particularly GS, is still unclear (33). Further studies are urgently required to clarify whether the spectrum of toxic cereals, the gluten threshold and the disease duration are the same in gluten allergy and/or sensitivity as in CD. If we can stand together in our quest for widespread recognition of the damaging impact of gluten consumption, we can all enjoy a healthier life. Our descendants will also inherit a more gluten-savvy world (33).

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