Gluten Sensitivity

A new condition in the spectrum of gluten-related disorders



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Background

Gluten sensitivity (GS) is defined as a non allergic and non autoimmune condition in which the consumption of gluten can lead to symptoms similar to those seen in coeliac disease (CD); clinical symptoms can overlap with CD or wheat allergy symptoms. GS is characterised by negative antibodies and grossly normal histology. The hallmark for diagnosis of this condition is the clinical improvement on a gluten-free diet in the absence of antibodies and intestinal mucosal abnormalities. It is not clear yet whether patients affected by GS might have some subtle intestinal and mucosal changes consistent with microscopic enteritis (MC). Although there are some recent studies in the literature on this topic, GS will be defined in more detail and comprehensively published in a joint paper by a panel of 14 experts participating in a consensus conference as held 11th - 12th February 2011 in Heathrow, London.

Gluten toxicity

Gluten is a protein composite found in wheat, barley and rye; it is a constituent which gives dough its elasticity, helps it rise and contributes to the texture of gluten products. Often found in staple foods like bread and pasta and added to protein deficient meals, such as imitation meats, specifically the storage proteins (prolamins) in wheat (gliadin), rye (secalin) and barley (hordein) have been shown to excert a number of toxic effects on intestinal cells in gluten sensitive people.[1-3] The toxicity of gliadin *in vitro* has been well documented by Clemente and co-workers;[4] they showed that gliadin reduces the F-actin component, inhibits cellular growth, induces apoptosis and causes a rearrangement of the cytoskeleton as well as the activation of the zonolin signaling pathway, giving rise to an increase in intestinal permeability.

Because gluten also contains the constituents prolamine and glutamine which inhibit complete enzymatic breakdown of gluten in the intestines, toxic gluten oligopeptides can accumulate in the small intestine causing an inflammatory response in subjects who cannot combat the toxic effect of gluten via intestinal defence mechanisms, including innate immunity. Sapone and co-workers highlighted in this context that the inflammatory response to gluten differs between GS and CD patients; patients with active CD showed a significant elevation of IL-17A gene expression when compared to GS patients and controls.[5] This finding, in combination with other histological differences, suggests the presence of another yet distinct type of gluten sensitivity disorder referred to as *gluten sensitivity* (GS) or *non-coeliac gluten intolerance*.

Definition of GS

Until recently the terms GS and CD were used synonymously in literature.[6] Gluten was associated only with CD and wheat allergy; therefore patients with gluten induced gastrointestinal symptoms who produced normal values of anti-tTG and IgE and showed normal histology were advised to continue integrating gluten foods into their diet, as gluten was not regarded as the cause for their condition.[7]

Meanwhile, more recent evidence suggests the classification of three gluten induced and heterogeneous conditions: CD, wheat allergy, and GS, a form of gluten intolerance that neither meets the diagnostic criteria for CD nor those for wheat allergy.[5] In an article by Verdu, *et al.* GS is defined by 'one or more of a variety of immunological, morphological, or symptomatic manifestations that may also be shared by CD and IBS'.[8]

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GS patients are unable to tolerate gluten and develop an adverse reaction when eating gluten that usually, and differently from CD, does not lead to small intestinal damage. While the gastrointestinal symptoms in GS may resemble those associated with CD, the overall clinical picture is not accompanied by the concurrence of tTG autoantibodies or autoimmune disease.

The diversity of gluten induced conditions indicates that the immune system handles gliadin in different ways.[5] In this context, Kaukinen and co-workers reported in a study with 94 adults affected by abdominal symptoms after cereal ingestion, a prevalence of nine per cent with CD, eight per cent with latent CD and 20 per cent with cereal allergy. Sixty-three per cent of study subjects could not be classified as CD or as allergic, but were yet affected by gluten foods.[9]

CD, characterised by the presence of specific autoantibodies to tissue tranglutaminase, is considered an autoimmune and Th1-mediated disorder with strong genetic association; while all CD patients carry the genetic markers HLA-DQ2 or DQ8, only 50 per cent of GS patients, few people more than the general population, carry either HLA-DQ2 or DQ8.[5] In contrast to CD patients, GS patients do not present with histological mucosal alterations in the small intestine, show a lower increment in intraepithelial CD3 lymphocytes and are always anti-tTG-negative as well as EMA-negative. Roughly 40-50 per cent of GS patients may show IgG-type AGA or IgA-type AGA.[5, 10] Furthermore, GS patients show normal intestinal permeability and activation of the innate immunity instead of adaptive immune mechanisms when compared to CD patients.[11]

GS can present with normal or milder enteropathy like MC and may include symptoms like bloating, abdominal discomfort, pain or diarrhoea; or it may present with a variety of extraintestinal symptoms; these may include headaches and migraines, lethargy and tiredness, attention deficit syndrome and hyperactivity, autism and schizophrenia, muscular disturbances as well as bone and joint pain.[5, 12-15] See **Table One**.

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Table One: Symptoms and Associations in Gluten Sensitivity

Symptoms:
- Bloating
- Abdominal discomfort or pain
- Diarrhoea or constipations

Extra-intestinal symptoms like:
- Headaches, migraines
- Lethargy and tiredness

Associations with:
- Attention deficit syndrome
- Autism
- Muscular disturbances
- Bone, joint pain

Epidemiology

Although GS has started to gain recognition and credibility within the medical profession, it is still the most common and under-recognised form of gluten disorder. Based on the results of their cohort study investigating the mortality rates of GS and CD patients in Northern Ireland, Anderson and co-workers[16] estimate that for every person with CD there could be at least six or seven people with GS. GS may, therefore, affect six to 10 per cent of the general population, whereas CD is thought to affect one per cent. In total, all three GS disorders affect about 10 per cent of the general population.

Where immunoassays like the anti-endomysium (EMA) and anti-tissue tranglutaminase (tTG) assays are being successfully used for the diagnosis of CD, the diagnosis of GS is difficult due to the lack of diagnostic criteria.[9, 17] In the current absence of specific markers for GS, the 'gold standard' of GS testing is still the gluten elimination diet which involves strict avoidance of gluten containing foods for two to three months. Remission of symptoms upon elimination and return of symptoms upon the reintroduction of gluten are indicators for GS.

What is the relationship between CD, IBS and GS?

The association between CD and irritable bowel syndrome (IBS) was first reported in 2001.[18] We have previously investigated sequential patients presenting with IBS in secondary care (n=300) for CD. Participants were initially investigated for CD with immunoglobulins, IgA/IgG antigliadin and IgA endomysial antibodies. Any participant that had a positive IgA antigliadin antibody, IgA endomysial antibody, or IgG antigliadin antibody in the presence of IgA deficiency was offered small bowel biopsy to confirm the diagnosis of CD. We then compared our findings to a population of healthy volunteers recruited from primary care (n=1200).[19] From 1200 volunteers in primary care, there were 12 new cases of CD. The prevalence of CD in this general population sample was one per cent (95% CI 0.4-1.3%). The prevalence of CD amongst patients with IBS was 4.7 per cent (14/300, 95% CI 1.6-28). This study highlights the importance of a case-finding approach when considering patients with symptoms of IBS, where the diagnosis of CD may be missed. Since that time others have published supportive evidence/validation studies from other international cohorts.[20] Also, testing for CD in patients with IBS is now widely accepted and has been incorporated into guidelines and standard clinical practice.[21]

Furthermore, the association of CD and IBS symptoms is biologically plausible with many mechanisms being reported, for example, autonomic dysfunction, intussusception, exocrine pancreatic disease, small intestinal ulceration and associated microscopic colitis. Our own group found an increased prevalence of CD in patients referred with surgical abdominal pain, notably in those with

unexplained or non-specific abdominal pain.[22] The association between IBS and CD appears to operate in both directions, as patients with CD (on a gluten-free diet) are more likely to describe IBS symptoms (than controls).[23, 24]

So is there a relationship between IBS and GS? We have previously reported that gliadins were present in ~12 per cent of the general population and ~17 per cent in IBS (both in the presence of a normal small bowel biopsy).[18, 19] This further supports the hypothesis of gluten sensitive IBS (see **Figure 1**).[8, 25]

Recently Wahnschaffe, *et al.* also described an association between coeliac disease-like abnormalities and a sub-group of patients with IBS. This investigating group used the presence of intestinal antibodies (to gluten) on small bowel aspirate to define an IBS sub-group (n=26).[26] These patients then agreed to commence a gluten-free diet for three to six months. During this time they reported an improvement in their symptoms. The authors have provided further work in this field suggesting that the HLA DQ2 or DQ8 pattern may be predictive of a response to a GFD.[27]

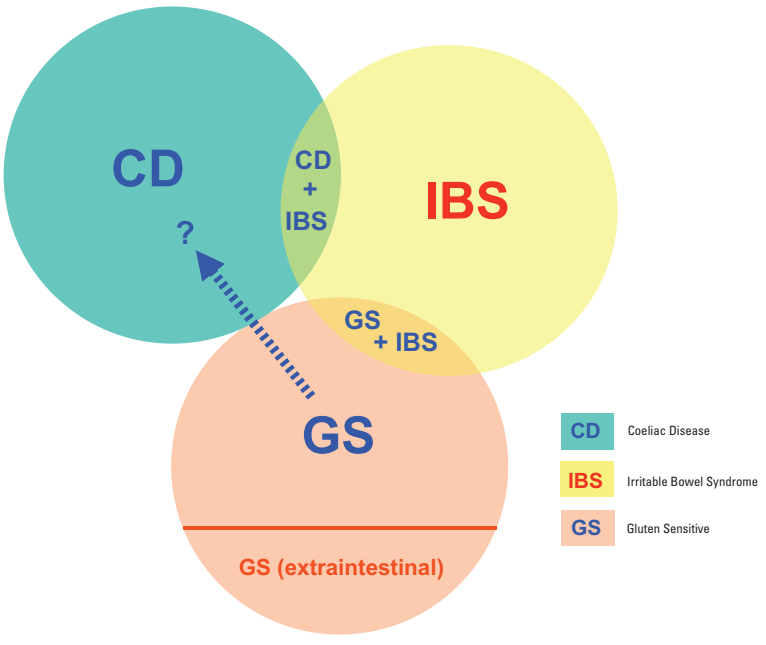
Finally, an intriguing study by an Australian group adds more to the debate.[28] The investigators undertook a double-blind, randomised, placebo-controlled rechallenge trial in patients with IBS fulfilling the Rome III criteria. CD was excluded on the basis of a normal duodenal biopsy or negative HLA DQ2 or DQ8 pattern. Patients were randomised according to a computer-generated list of random numbers held by an independent observer to either the gluten or the placebo treatment group. Over the six week study period, the severity scores of pain, satisfaction with stool consistency, and tiredness were significantly higher for those consuming the gluten diet compared to the placebo group. Despite this there was no evidence of intestinal inflammation or damage whilst being challenged with gluten (using faecal lactoferrin and intestinal permeability). Thus, these patients could not be viewed as having latent CD. This is the first study to describe a non-coeliac gluten sensitivity which may cause IBS. Based on the current data it seems clear that gluten may cause symptoms in patients with IBS. However, the two different research groups have published diametrically opposed studies. How can this be explained? Perhaps there are many mechanisms by which gluten can cause symptoms in IBS type patients? Certainly gluten sensitive IBS now appears to be part of the spectrum of gluten related disorders. See **Figure 1**.

Discussion

Although gluten induced, GS (non-coeliac gluten intolerance) differs from other gluten sensitivity disorders. While in wheat allergy and GS the immune response to the dietary component gliadin results in immunity towards it, CD involves self-directed adaptive response mechanisms leading to an auto-immune process and possibly to the onset of other autoimmune conditions.[5, 29]

CD is considered a condition which requires life-long avoidance of gliadin; GS can vary in regards to duration and gluten threshold sensitivity.[30] Yet we know very little about the pathogenic mechanism behind gluten sensitivity. At present, it is unclear if GS patients may tolerate a minimum of gluten. Furthermore, it is questionable if GS is a reversible condition and if GS patients can tolerate gluten products after an extended period of gluten avoidance.

Figure 1: A Model for the relationship between coeliac disease, IBS and gluten sensitivity?



In the light of its high prevalence and the difficulties involved with its diagnosis, there is undoubtedly a need for highly sensitive and specific serological markers alongside other markers, such as anti-tTG, already in use for CD. Therefore, it may be concluded that further research is necessary in order to better elucidate the area of GS and improve its diagnosis to support patients affected by GS in the most efficient way possible.

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This CNPD questionnaire has been kindly supported by the Dr Schär Institute, a knowledge platform for healthcare professionals providing information and support on coeliac disease and gluten sensitivity.

References: **1.** Edwards NM, et al (2003). Role Of Gluten And Its Components In Determining Durum Semolina Dough Viscoelastic Properties. Cereal Chemistry; 80(6): 755-763. **2.** Day L, et al (2005). Wheat-Gluten Uses And Industry Needs. Trends In Food Science & Technology; 17(2): 82-90. **3.** Hischenhuber C, et al (2006). Review Article: Safe Amounts Of Gluten For Patients With Wheat Allergy Or Coeliac Disease. Alimentary Pharmacology & Therapeutics; 23: 559–575. **4.** Clemente MG, et al (2003). Early Effects Of Gliadin On Enterocyte Intracellular Signalling Involved In Intestinal Barrier Function. Gut; 52: 218–223. **5.** Sapone A, et al (2010). Differential Mucosal IL-17 Expression In Two Gliadin-Induced Disorders: Gluten Sensitivity And The Autoimmune Enteropathy Celiac Disease. International Archives Of Allergy And Immunology; 152: 75–80. **6.** Hadjivassiliou M, Williamson CA, Woodroofe N (2004). The Immunology Of Gluten Sensitivity: Beyond The Gut. Trends In Immunology; 25(11): 578- 582. **7.** Rostami K, Villanacci V. (2009). Microscopic Enteritis: Novel Prospect In Coeliac Disease Clinical And Immuno-Histogenesis. Evolution In Diagnostic And Treatment Strategies. Digestive And Liver Disease; 41: 245-252. **8.** Verdu EF, Armstrong D, Murray JA (2009). Between Celiac Disease And Irritable Bowel Syndrome: The "No Man's Land" Of Gluten Sensitivity. The American Journal Of Gastroenterology; 104(6): 1587-1594. **9.** Kaukinen K, et al (2000). Intolerance To Cereals Is Not Specific For Celiac Disease. Scandinavian Journal Of Gastroenterology; 35: 942–946.**10.** Bizzaro N, et al (2010). Cutting-Edge Issues In Celiac Disease And In Gluten Intolerance. Clinical Reviews In Allergy And Immunology. **11.** Sapone A, et al (2009). Gluten Sensitivity Is Associated To Activation Of The Innate But Not Adaptive Immune Response To Gluten Exposure. Gastroenterology; 136(5): 413. **12.** Ford RP (2009).The Gluten Syndrome: A Neurological Disease. Medical Hypotheses; 73(3): 438-440. **13.** Elder JH, et al (2006). The Gluten-Free, Casein-Free Diet In Autism: Results Of A Preliminary Double Blind Clinical Trial. Journal Of Autism And Developmental Disorders; 36(3): 413-420. **14.** Dickerson F, et al (2010). Markers Of Gluten Sensitivity And Celiac Disease In Recent-Onset Psychosis And Multi-Episode Schizophrenia. Biological Psychiatry; 68(1): 100-104. **15.** Hadjivassiliou M, et al (2007). Myopathy Associated With Gluten Sensitivity. Muscle Nerve; 35: 443–450. **16.** Anderson LA, et al (2007). Maligancy And Mortality In A Population-Based Cohort Of Patients With Celiac Disease Or 'Gluten Sensitivity'. World Journal Of Gastroenterology; 13: 146–151. **17.** Carroccio A, et al (2002). Comparison Of Anti-Transglutaminase Elisas And An Anti- Endomysial Antibody Assay In The Diagnosis Of Celiac Disease: A Prospective Study. Clinical Chemistry; 48: 1546-1550. **18.** Sanders DS, et al (2001). Association Of Adult Coeliac Disease With Irritable Bowel Syndrome: A Case-Control Study In Patients Fulfilling ROME II Criteria Referred To Secondary Care. Lancet; 358(9292): 1504-1508. **19.** Sanders DS, et al. A Primary Care Cross-Sectional Study Of Undiagnosed Adult Coeliac Disease. European Journal Of Gastroenterology & Hepatology; 15(4): 407-413. **20.** Leeds JS, Sanders DS (2007). Is There An Association Between Coeliac Disease And IBS? Gut; 56: 1326-1327. **21.** Richey R, et al (2009). Guideline Development Group: Abuzakouk M, Burden S, Howdle P, Lister A, Macfarlane P, McGough N, O'Malley J, Sanders DS, Thomas A, Walters J, Wray D, Heath M, McAllister R, Macbeth F, Richey R, Shaw E, Stokes T, Tuvey D. Recognition And Assessment Of Coeliac Disease In Children And Adults: Summary Of NICE guidance. British Medical Journal; 338: b1684. **22.** Sanders DS, et al (2005). Association Of Adult Coeliac Disease With Surgical Abdominal Pain: A Case Control Study In Patients Referred To Secondary Care. Annals Of Surgery; 242: 201-207. **23.** O'Leary C, et al (2002). Celiac Disease And Irritable Bowel-Type Symptoms. The American Journal Of Gastroenterology; 97: 1463-1467. **24.** Barratt S, et al (2011). Reflux And Irritable Bowel Syndrome Are Negative Predictors Of Quality Of Life In Coeliac Disease And Inflammatory Bowel Disease. European Journal Of Gastroenterology & Hepatology; 23: 159-165. **25.** Ball AJ, et al (2010). Is Gluten Sensitivity A 'No Man's Land' Or A 'Fertile Crescent' For Research? The American Journal Of Gastroenterology; 105: 222-223. **26.** Wahnschaffe U, et al (2001). Celiac Disease Like Abnormalities In A Sub-Group Of Patients With Irritable Bowel Syndrome. Gastroenterology; 121: 1329-1338. **27.** Wahnschaffe U, et al (2007). Predictors Of Clinical Response In Patients Diagnosed With Diarrhea-Dominant Irritable Bowel Syndrome. Clinical Gastroenterology And Hepatology; 5: 844-850. **28.** Biesiekierski JR, et al (2011). Gluten Causes Symptoms In Subjects Without Celiac Disease: A Double Blind Randomized Placebo Controlled Trial. The American Journal Of Gastroenterology; 106: 508-514. **29.** Catassi C, Fasano A, (2008). Celiac Disease. Current Opinion In Gastroenterology; 24(6): 687-691. **30.** Catassi C, et al (2007). A Prospective, Double-Blind, Placebo-Controlled Trial To Establish A Safe Gluten Threshold For Patients With Celiac Disease. The American Journal Of Clinical Nutrition, 85: 160-166.