Gastroenterology and Hepatology From Bed to Bench

EDITORIAL

Non coeliac gluten sensitivity

Geoffrey Holmes
Royal Derby Hospital, Derby, UK

In the past, the terms gluten sensitivity and coeliac disease have been used synonymously but this is not acceptable since gluten sensitivity can occur in subjects who do not have coeliac disease. The entity of non coeliac gluten intolerance has been regarded as a new diagnosis (1) but it is better to consider it an old diagnosis recently rediscovered and embellished. In the late 1970s brief case reports indicated that that some patients were wheat sensitive but did not have coeliac disease (2-4). During this time 17 patients with chronic diarrhoea who had received no definitive diagnosis or effective treatment were investigated at the Birmingham General Hospital, UK (5). Of these, nine, all women, had suffered persistent diarrhoea for up to 20 years, averaging five years, which was often socially incapacitating and nocturnal and which responded to a gluten free diet. The eight remaining patients showed no such sustained benefit. Among the responders, abdominal pain, abdominal distension, malaise and lassitude were also common symptoms. Routine blood tests were normal and of six tested, none had steatorrhoea. Only three carried the HLA-B8 phenotype. Multiple jejunal biopsies taken from these nine patients generated 54 pieces of macroscopically normal jejunum although with a slight increase in cellularity. Plasma cell counts in the lamina propria and intraepithelial lymphocytes were significantly increased compared with 17 normal controls and the eight non-responders. The cell counts however, were much lower than in untreated coeliac disease (6). The response of these nine patients to a gluten free diet was dramatic. Within two weeks each noted a marked improvement in their symptoms. All of the patients elected to remain on the gluten free diet and at the time of the report had taken it for 4-6 years. Repeat jejunal biopsies revealed a return to normal of the cellular infiltrate. Gluten challenge resulted in a recurrence of symptoms within 8-12 hours and which could last as long as a week. The mucosal plasma cell numbers increased slightly (mean rise of 297 cells/mm^2) 24 hours after challenge but there were no changes in eosinophil or intraepithelial lymphocyte counts. Apart from these changes in plasma cell numbers no other immunological abnormalities were detected after gluten challenge. Of interest, in the eight patients who did not respond to the gluten free diet, the cell counts were within normal limits even after gluten challenge. It was concluded from this study that non coeliac gluten intolerance affected some patients and could be successfully treated by diet but the mechanisms responsible for producing ill-health were unknown.

This concept of non-coeliac gluten sensitivity proved controversial and at the time of publication was accompanied by an editorial which criticised the way the gluten challenges had been carried out and considered the case for the existence of this entity had not been convincingly made (7). These charges were answered in a subsequent letter to the journal by the authors who maintained that the study provided strong evidence for gluten sensitivity in patients without coeliac disease (8), a position that

still holds true. Here matters rested until fairly recently.

Perhaps because this entity was so ill-defined, there were no specific tests and symptoms overlapped with the irritable bowel syndrome, interest lapsed. The driving force that has put it back on the agenda has largely been the preoccupation of the public in recent years with "Allergy" and real or imagined reactions to ingested wheat products. The medical profession has tended to eschew all this and so have tended to lag behind public thinking and practices. Many are undoubtedly putting themselves on a gluten free diet in the absence of medical advice often with dramatic improvement in their health (9). About 20% of all Americans buy gluten free products and by 2017 it is estimated the market will be worth some 6.6 billion dollars (10). A study from New Zealand found that gluten avoidance was five times more common than medically diagnosed coeliac disease (11). It is likely that these same trends are occurring in all countries were gluten free products are available.

To better define gluten related disorders, a group of experts met in London in 2011 and proposed three forms of reactions to gluten – coeliac disease, wheat allergy and gluten sensitivity (12). Gluten sensitivity is defined as a reaction to gluten in which allergic and autoimmune mechanisms have been excluded. More specifically, patients have negative serological tests for coeliac disease (endomysial and/or tissue transglutaminase antibodies) but antigliadin antibodies may be present. The duodenal mucosa is grossly normal. Symptoms should resolve on a gluten free diet and reappear on gluten challenge. It is essentially a diagnosis of exclusion. Information on prevalence is scarce; 6% of patients seen at the clinic in Maryland, USA, fulfilled the criteria for diagnosis (12). Recent studies that are briefly reviewed have helped to characterise gluten sensitivity and delineate it from coeliac disease.

In a non-randomised, prospective study of 41 patients who fulfilled the Rome II diagnostic criteria for irritable bowel syndrome but with macroscopically normal small bowel biopsies, a gastrointestinal symptom score based on abdominal pain, distension, borborygmus, bloating and fullness, decreased significantly in those treated with a gluten free diet for six months, who were positive for DQ2, IgG AGA/tTG or DQ2 and IgG AGA/tTG, than in those who were negative for these markers ($p<0.05$-<0.01) (13). Diarrhoea resolved more frequently in DQ2 positive patients with coeliac disease-associated antibodies ($p<0.05$). Individuals with positive coeliac serology but with intact duodenal villi may, in due course, develop overt coeliac disease. Such are regarded as having potential/latent coeliac disease and thus fall within the spectrum of coeliac disorders (14). This investigation has identified a subgroup of patients with diarrhoea predominant irritable bowel syndrome who are likely to respond to a gluten free diet.

The aim of a randomised, double blind, placebo-controlled re-challenge trial was to try and determine whether gluten ingestion would induce symptoms in non-coeliac patients and to explore possible mechanisms (15). Thirty-four patients with symptoms of irritable bowel syndrome fulfilling the Rome III criteria who had taken a gluten free diet for at least six weeks with benefit were recruited. Coeliac disease was excluded as a diagnosis by either the presence of a normal duodenal biopsy while on a gluten containing diet in those expressing HLA-DQ2 or DQ8 or the absence of HLA-DQ2 and DQ8. All patients were negative for tissue transglutaminase and endomysial antibodies. In the six weeks challenge phase of the study, 19 patients received gluten and 15 placebo. The gluten used was FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) negative. The primary outcome was the proportion of patients answering "No" on more than half of the symptom assessments to the question, "Over the last week were your symptoms adequately controlled?" Secondary outcomes related to changes in symptoms judged on a visual analog scale. Coeliac antibodies, C-reactive protein, intestinal permeability and faecal

lactoferrin were measured as biomarkers of any damage that the challenge might have caused. Significantly more patients (p=0.001) in the gluten group (68%) reported a "No" answer to the primary outcome question compared with those on placebo (40%). Over the study period the severity scores of pain, satisfaction with stool consistency and tiredness were significantly higher for those consuming gluten. In neither group, were any changes in the biomarkers observed and symptomatic responses did not differ in those expressing HLA-DQ2 and/or HLA-DQ8 from those who did not. It is possible that some of the patients who improved on a gluten free diet did have coeliac disease but this seems unlikely. This study indicates that gluten does trigger symptoms in individuals without coeliac disease. The gluten used in this study did not contain FODMAPs which it is speculated cause symptoms in patients with irritable bowel syndrome (16). No pointers to possible mechanisms were uncovered by the biomarkers employed but it may be that these were not sensitive enough to detect subtle abnormalities.

Of a large series of 920 patients with irritable bowel syndrome diagnosed according to the Rome II criteria, 276 were identified as having wheat sensitivity (17) as defined by the expert panel already referred to (12). Of these, 70 were found to have wheat sensitivity alone and 206, multiple food sensitivities. The subjects with wheat sensitivity alone had features more in keeping with coeliac disease. Three quarters carried the DQ2 or DQ8 haplotypes, one third produced EMA from culture of biopsies, and almost all had elevation of duodenal intraepithelial lymphocytes. Some of these may well go on to develop overt coeliac disease (18). However, wheat sensitivity also affected those who did not have coeliac disease in any form and will not develop it because the necessary HLA markers were absent. Eosinophils in the lamina propria of the duodenum and colon were also notable features and activation of the basophil activation assay may be a useful marker of wheat sensitivity. Those with multiple food sensitivity had features more in keeping with food allergy. This study has shown that patients identified as having non coeliac gluten sensitivity may have features of food allergy when further checked.

In an important study of 26 gluten sensitive patients, 42 with coeliac disease and 39 dyspeptic controls it was found that, much as expected, symptoms experienced by those with gluten sensitivity and coeliac disease overlapped (19). When given a gluten free diet, symptoms due to gluten sensitivity resolved within a few days and individuals remained symptom free for the duration of the study which was up to four years. 57% were HLA-DQ2 and/or DQ8 positive. This means that about half did not have coeliac disease in any of its forms because they lacked the necessary HLA profile. CD3+ intraepithelial lymphocyte numbers in the epithelium of small intestinal mucosa from gluten sensitive patients were intermediate between those with coeliac disease and controls. When assessed by the lactulose/mannitol probe, intestinal permeability in gluten sensitivity was significantly lower than in coeliac disease. Urinary recovery of lactulose appeared to implicate a paracellular mechanism to explain this and to support this view the mucosa was found to express significantly higher levels of transcripts for CLDN4 (a claudin which is said to decrease tight-junction dependent permeability) compared with controls or coeliac subjects. Of interest, 48% of gluten sensitive patients were antigliadin antibody positive indicating that gluten derivatives were still getting access to the immune system. Earlier, this group had shown that expression of the cytokine IL-17 is raised in coeliac disease (at least in a subgroup) but not in gluten sensitivity indicating that the two conditions process gluten in different ways (20). In the present study it was found that the cytokine IFN-γ is expressed in the mucosa at significantly lower levels in gluten sensitivity compared with coeliac disease while IL-6, which promotes the function of Th-17 cells is

enhanced (19). These findings indicate that in gluten sensitivity, innate immune mechanisms rather than adaptive immune responses are more importantin pathogenesis. These two studies are important because they investigate with modern techniques similar patients to those identified in Birmingham over thirty years ago.

What then can be concluded about gluten sensitivity from these studies? Clearly, gluten sensitivity exists as an entity separate from overt coeliac disease with a prevalence of about five times that of coeliac disease. It can be differentiated from coeliac disease clinically, with regard to structure and function of the small intestinal mucosa and also with respect to immunological indices. Some patients fall into the spectrum of coeliac disease, because they have the HLA markers necessary for coeliac disease to develop and also coeliac disease-associated antibodies, although a macroscopically normal small bowel mucosa and so qualify to be labelled as having potential/latent coeliac disease. About half of patients do not have coeliac disease in any of its forms because they do not have the necessary HLA profile.

What are the clinical implications? Some patients will suspect that they have an "Allergy" and begin to experiment with a gluten free diet, to which they will adhere with varying degrees of strictness and never consult a doctor or dietician especially if symptoms are improved or eliminated. Health care workers may be consulted by patients who have intractable coeliac-like symptoms who are seeking some relief from their misery and in whom overt coeliac disease and other possible diagnoses have been excluded by appropriate investigations. Under these circumstances non-coeliac gluten sensitivity should be considered a possible diagnosis. Unfortunately at present there are no tests to help establish this diagnosis so a gluten free diet, supervised by an expert dietician, should be tried to see if benefit follows. If it does, the options are either to do no more and this may be the patient's preference or to perform gluten challenge studies to try and clinch the diagnosis. Gluten challenge may also be performed in those patients who have already started a gluten free diet before seeking advice and subsequently wish to try and establish a diagnosis. Whether non-coeliac gluten intolerance is permanent once it manifests or in some cases may be transient is not known. Factors which might provoke gluten sensitivity and be self-limiting include bowel infections, changes in gluten load or stresses such as surgery or a pregnancy. Some patients may wish to test transience by adding gluten to their diet after achieving remission to see if it can be tolerated and if so, how much can be taken with impunity.

Non-coeliac gluten sensitivity has had a slow gestation but is now attracting more and more attention as a common cause of morbidity. There is still much to learn and research is likely to focus on obtaining information regarding prevalence, developing simple tests to identify patients, exploring aetiology and uncovering the damaging component of gluten and indeed if other foods contribute to ill health. Whether any long term problems arise particularly in those untreated will also require consideration. Finally, patients who have often suffered intractable symptoms for years can cured by simple dietary means and it is unfortunate when they continue unrecognised and unhelped[9].

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