Opinion TRENDS in Immunology Vol.25 No.11 November 2004

The immunology of gluten sensitivity: beyond the gut

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The terms gluten sensitivity and coeliac disease (also known as gluten-sensitive enteropathy) have thus far been used synonymously to refer to a disease process affecting the small bowel and characterised by malabsorption and gastrointestinal symptoms. Yet, gluten sensitivity can exist even in the absence of an enteropathy. The systemic nature of this disease, the overwhelming evidence of an immune pathogenesis and the accumulating evidence of diverse manifestations involving organs other than the gut, such as the skin (dermatitis herpetiformis) and the nervous system (gluten ataxia, gluten neuropathy), necessitates a re-evaluation of the belief that gluten sensitivity is solely a disease of the gut. By studying the pathogenesis of these diverse manifestations we are more likely to improve our understanding of this disease entity as a whole.

When coeliac disease (CD) was first described by the ancient Greek doctor Aretaeos [1] in 100AD, the prominent gastrointestinal symptoms that characterised this disease and gave it its name (coeliac, Greek for abdominal) hinted to a pathogenesis involving the gut as the protagonist and an ingestible trigger factor as the possible aetiological agent. It took several centuries to confirm these observations, first, with the characterisation of small bowel pathology (crypt hyperplasia, villous atrophy and increased intraepithelial lymphocytes), initially on post-mortem tissue by Schein [2] in 1947 and thereafter with the introduction of peroral jejunal biopsies [3], and second, with the identification of the wheat protein gluten as the causative agent by Dicke *et al.* [4] in 1953. According to Taylor *et al.* [5] 'an obstacle to the acceptance of the immunological theory of causation in coeliac disease has been the lack of satisfactory demonstration of antibodies to the protein concerned'. Hence, in this immunological study published in 1961, he demonstrated the existence of circulating antibodies against gluten (anti-gliadin antibodies) [5].

To this day, it is difficult to understand what triggered Shuster and Marks and Marks *et al.* [6,7] to seek pathology in the gut in patients with a blistering skin condition known as dermatitis herpetiformis, particularly given the absence of any gastrointestinal symptoms. By doing this, however, they were able to identify an otherwise asymptomatic enteropathy, identical in pathological terms to CD. Crucially, they went on to demonstrate that the dermatopathy and the enteropathy were responsive to gluten withdrawal. The most important aspect of this observation should have been the realisation of the systemic nature of the immune response in the pathogenesis of gluten sensitivity. Yet, clinicians and scientists failed to capitalise on this important observation and CD was considered, almost exclusively, a disease of the gut for years to come.

Any associations of CD with other organ involvement, such as the central and peripheral nervous systems (with reports dating to as far back as 1966), were readily attributed to malabsorption and vitamin deficiencies, overlooking a possible immunological pathogenesis. This is despite the pathological evidence of an inflammatory reaction in the neural tissue involved [8] and in particular the cerebellum, which would be difficult to explain on the basis of vitamin deficiencies.

The immunology of CD has been pursued with renewed interest in the past 20 years, thanks to the work of several visionaries who were prepared to abandon dogma, and suggest that the definition of gluten sensitivity based solely on bowel involvement was outmoded. Some went as far as to suggest that gluten sensitivity is 'a state of heightened immunological responsiveness in genetically susceptible individuals', deliberately omitting any mention of the gut as a protagonist [9]. A series of elegant experiments by Marsh demonstrated a range of bowel mucosal abnormalities in patients with gluten sensitivity, ranging from histologically normal to a flat destructive lesion [10]. This implied that some patients with gluten sensitivity would have a histologically normal mucosa with the only marker of the disease being the presence of circulating antibodies against the aetiological agent.

Perhaps not surprisingly (given the often absent gastrointestinal symptoms), the realisation that CD is much more common than previously thought then followed. CD has a prevalence of one in 100 among healthy populations in Europe and the USA [11,12] and for every symptomatic patient with CD there are eight patients with CD and no gastrointestinal symptoms [13]. What of the remaining 5–10% of the 'healthy' population that have circulating anti-gliadin antibodies but no obvious classic disease manifestations (e.g. gastrointestinal symptoms)? It remains to be seen if these patients have gluten sensitivity with the potential to develop any of the manifestations encountered in this

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Available online 9 September 2004

 1471-4906/$ - see front matter doi:10.1016/j.it.2004.08.011

disease. The fact that it is out of this group that patients with latent or potential CD have been identified would suggest that all of these patients could well be gluten sensitive.

Case reports and small series of patients with CD who developed neurological dysfunction began to appear shortly after CD was diagnosable on the basis of small bowel biopsy. The largest, and one of the first, of the series, which also included pathological data, was by Cooke *et al.* in 1966 [8]. This paper not only defined the neurological phenotype (predominantly gait ataxia, often with neuropathy) but went on to show that the pathology was that of an inflammatory process primarily affecting the cerebellum and ultimately leading to Purkinje cell death. The same inflammation could, at times, also affect other parts of the brain, the spinal cord and the peripheral nerves.

Gluten sensitivity as a neurological illness

Using this information, and hence targeting patients with ataxia [14], we were able to demonstrate a high prevalence of anti-gliadin antibodies (41%) in patients with sporadic idiopathic ataxia by comparison to healthy controls (12%) and patients with familial ataxias (14%). We suggested the term 'gluten ataxia' to describe this entity [15].

Any source of dispute on the epidemiology of gluten ataxia comes predominantly from two observations. First, some epidemiological studies, although demonstrating the prevalence of anti-gliadin antibodies in sporadic ataxia to be much higher than in healthy control subjects, found the difference not to be significant. Such studies are not powerful enough to detect a significant difference. As an example, a recent study [16] demonstrated the prevalence of anti-gliadin antibodies in healthy control subjects to be 8%, and in patients with sporadic idiopathic ataxia to be 19%. A sample size of >300 subjects would have been required to have an 80% power to exclude the null hypothesis at a statistical level of $p<0.05$. Yet, the sample size in this study was 105. Only one of the studies published [14] (which confirms the association of gluten-sensitivity with ataxia) has achieved statistical power. All other smaller studies [17–20] confirm a trend in favour of a higher prevalence of anti-gliadin antibodies among idiopathic sporadic ataxias. Table 1 summarises the studies published to date.

Second, two studies [16,21] have shown the prevalence of anti-gliadin antibodies to also be high in patients with familial ataxias. Although these studies also suffer from small sample sizes, they stimulate consideration of the interaction of gluten sensitivity with familial ataxias. Gluten sensitive enteropathy is familial in ~10% of subjects with coeliac disease, which is not surprising given its strong association with HLA (human lymphocyte antigen). It is probable that gluten ataxia might have a similar familial predisposition. This observation might explain the presence of gluten sensitivity in some cases of familial ataxia. But what about those cases with a genetically characterised ataxia or even patients with Huntington's disease (a recent study suggested a high prevalence of anti-gliadin antibodies in patients with Huntington's disease [22])? Could neural-cell degeneration, resulting in antibody formation as an epiphenomenon, be the trigger to an immune response to gluten at the lamina propria of the gut? After all, the reverse has been shown to be true: anti-gliadin antibodies crossreact with epitopes on Purkinje cells [23]. If such a contention is true, the explanation might well come from the transglutaminase story (see later).

However, the evidence for gluten ataxia as a disease entity is now overwhelming. The disease is characterised by ataxia, the presence of anti-gliadin antibodies, the HLA haplotype (DQ2, DQ8) associated with gluten sensitivity [14], the presence of anti-Purkinje cell antibodies [23], the presence of high levels of the interferon-γ-inducible chemokine CXCL10 and often oligoclonal bands in the cerebrospinal fluid (CSF) [24] and the presence of inflammatory pathology of the cerebellum at postmortem [15]. Perhaps even more compelling is the evidence of a clinical response in the form of improvement of ataxia after a gluten-free diet, even in the absence of an enteropathy. This was demonstrated in the largest control study ever to be published [25]. The use of a gluten-free diet and immunosuppressive treatment is beneficial in smaller uncontrolled series and single case reports, predominantly in patients with established CD [26–28]. The clinical and immunological characteristics of 68 patients with gluten ataxia have been published previously [14]. Table 2 contains an update based on 100 patients with gluten ataxia regularly attending the gluten/neurology clinic at The Royal Hallamshire Hospital, Sheffield, UK.

Peripheral neuropathy is the second commonest manifestation of gluten sensitivity. Other manifestations include inflammatory myopathies, myelopathies, headache, white matter abnormalities on magnetic resonance imaging (MRI) and epilepsy with occipital calcifications.

Table 1. Studies looking at the prevalence of antigliadin antibodies in patients with sporadic ataxia and controls[a]

	Antigliadin positive/total number tested (% positive)		
Study details	**Sporadic ataxias**	**Familial ataxias**	**Controls**
Hadjivassiliou *et al.* (UK) [14]	59/143 (41%)	8/51 (14%)	149/1200 (12%)
Pellecchia *et al.* (Italy) [17][b]	3/24 (13%)	0/23 (0%)	NG
Burk *et al.* (Germany) [18]	12/104 (11.5%)	NG[c]	(5%)
Bushara *et al.* (USA) [17]	7/26 (27%)	9/24 (37%)	NG
Abele *et al.* (Germany) [19]	13/98 (13%)	1/15 (6%)	(5%)
Luostarinen *et al.* (Finland) [20][b]	44 (16.7%)	NG	(2%)
Abele *et al.* (Germany) [16]	6/32 (19%)	63 (8–15%)	6/73 (8%)

[a]Studies without controls are not included.
[b]Studies highlighted give the prevalence of enteropathy not of anti-gliadin positivity.
[c]NG: not given.

Table 2. Clinical and immunological characteristics of 100 patients with gluten ataxia

Male: female ratio	49:51
Mean age at onset of ataxia	53
Ocular signs	80%
Upper limb ataxia	70%
Lower limb ataxia	90%
Gait ataxia	100%
Atrophy of cerebellum on magnetic resonance imaging	60%
Coeliac disease on biopsy	28%
Antigliadin antibody positive	100%
Anti-endomysium antibody positive	22%
Transglutaminase antibody positive	56%
HLA (human lymphocyte antigen) DQ2	70%

What of the pathogenesis of neurological dysfunction in gluten sensitivity?

Experimental evidence suggests that there is antibody crossreactivity between antigenic epitopes on Purkinje cells and gluten peptides [23]. Thus, serum from patients with CD but no neurological symptoms demonstrate crossreactivity with epitopes on Purkinje cells (using indirect immunohistochemistry on both human and rat cerebellum). The reactivity can be abolished after adsorption of the anti-gliadin antibodies with crude gliadin. In the sera of patients with gluten ataxia, however, there is evidence of additional antibodies targeting Purkinje-cell epitopes. This is shown by the fact that removal of the anti-gliadin antibodies from sera of patients with gluten ataxia is not enough to eliminate such reactivity with Purkinje cells [23]. Determination of the cerebellar antigen targeted by these additional circulating antibodies in patients with gluten ataxia merits further investigation.

Does the pathogenesis have a humoral or cell-mediated basis?

This debate has at times been heated when addressing the pathogenesis of CD alone. Some suggest that the antibodies associated with this condition are an epiphenomenon and irrelevant to the pathogenesis of the spectrum of mucosal lesions, which are T-cell-mediated [9]. They use as evidence the existence of CD in the context of selective or total antibody-deficiency syndromes. However, this is not strong enough evidence because those cases with selective IgA deficiency, a deficiency that is ten times commoner in CD than in healthy populations [29], still have circulating IgG antibodies. IgG anti-gliadin antibodies appear to be more important in the context of a systemic immune response, such as that seen in gluten ataxia, by comparison to IgA class antibodies, which are said to originate in the bowel mucosa [30]. In those cases with total immunodeficiency, it is difficult to prove that the enteropathy is gluten sensitive, given the absence of serological markers. Indeed, the enteropathy seen in such syndromes is often not responsive to a gluten-free diet.

Recent work suggests that, even in those patients with gluten sensitivity and normal bowel mucosa (latent or potential CD), there is evidence of antibodies targeting tissue transglutaminase (the antigen recognised by anti-endomysium antibodies, the most specific marker for CD) not only in the small bowel mucosa but also at extra-intestinal sites [31]. This early antibody response supports the role of humoral immunity at an early stage.

Evidence of cell-mediated immunopathogenesis, however, is also strong (Figure 1). Virtually all patients with CD express the HLA-DQ2 or -DQ8 class II molecules. HLA class II molecules bind and present peptides derived from exogenous protein antigens to CD4 T cells. Therefore, because CD is the result of an immune response to an exogenous antigen (i.e. gliadin) and is linked to HLA DQ2/8 expression, it has been hypothesised that T cells reactive with gluten peptides have a major role in disease development [32].

Thus, like most immune-mediated diseases, there is evidence of both humoral and cell-mediated responses implicated in the pathogenesis of CD and gluten sensitivity-related neurological dysfunction.

Role of glutamic acid decarboxylase

Glutamic acid decarboxylase (GAD) is the enzyme responsible for the production of γ-aminobutyric acid (GABA), the most abundant inhibitory neurotransmitter in the central nervous system. Antibodies directed against GAD have been described in stiff person syndrome, insulin-dependent diabetes mellitus (IDDM) (the origin here is from the pancreatic β cells) and autoimmune polyendocrine syndromes, as well as in some immune mediated ataxias [33]. We have found the prevalence of these antibodies to be at least 60%, both in patients with gluten ataxia and in patients with CD and no neurological manifestations. The levels (measured by ELISA) and positivity of these anti-GAD antibodies can be significantly reduced by the introduction of a gluten-free diet in both of these patient groups [34]. Of the patients with neurological manifestations, who also have an enteropathy, the prevalence of these antibodies is 96% [34]. These observations imply that the presence of these antibodies in the context of the enteropathy might predispose individuals to the development of neurological sequelae. However, this cannot explain the entire story within the whole spectrum of gluten sensitivity because the antibodies are still present in some patients with gluten-related neurological dysfunction and no enteropathy. Patients with disease processes characterised by the presence of anti-GAD antibodies also appear to have a higher prevalence of CD (e.g. patients with IDDM [35], stiff person syndrome [36] and polyendocrine syndrome type II, where CD can be part of the syndrome). The prevalence of GAD within the nervous system (high concentrations in Purkinje cells, peripheral nerves) [37] is commensurate with the clinical presentation of ataxia and/or peripheral neuropathy being the commonest neurological manifestations of gluten sensitivity. The presence of GAD in the enteric plexus [38] could hold the key to the generation of anti-GAD antibodies in patients with CD. Perhaps GAD acts as the common antigen linking CD with neurological involvement?

Why should a common trigger factor result in such diverse manifestations?

Clues to an answer might be found in examining the role of tissue transglutaminase (of which there are several types) in the disease pathogenesis. Tissue transglutaminase

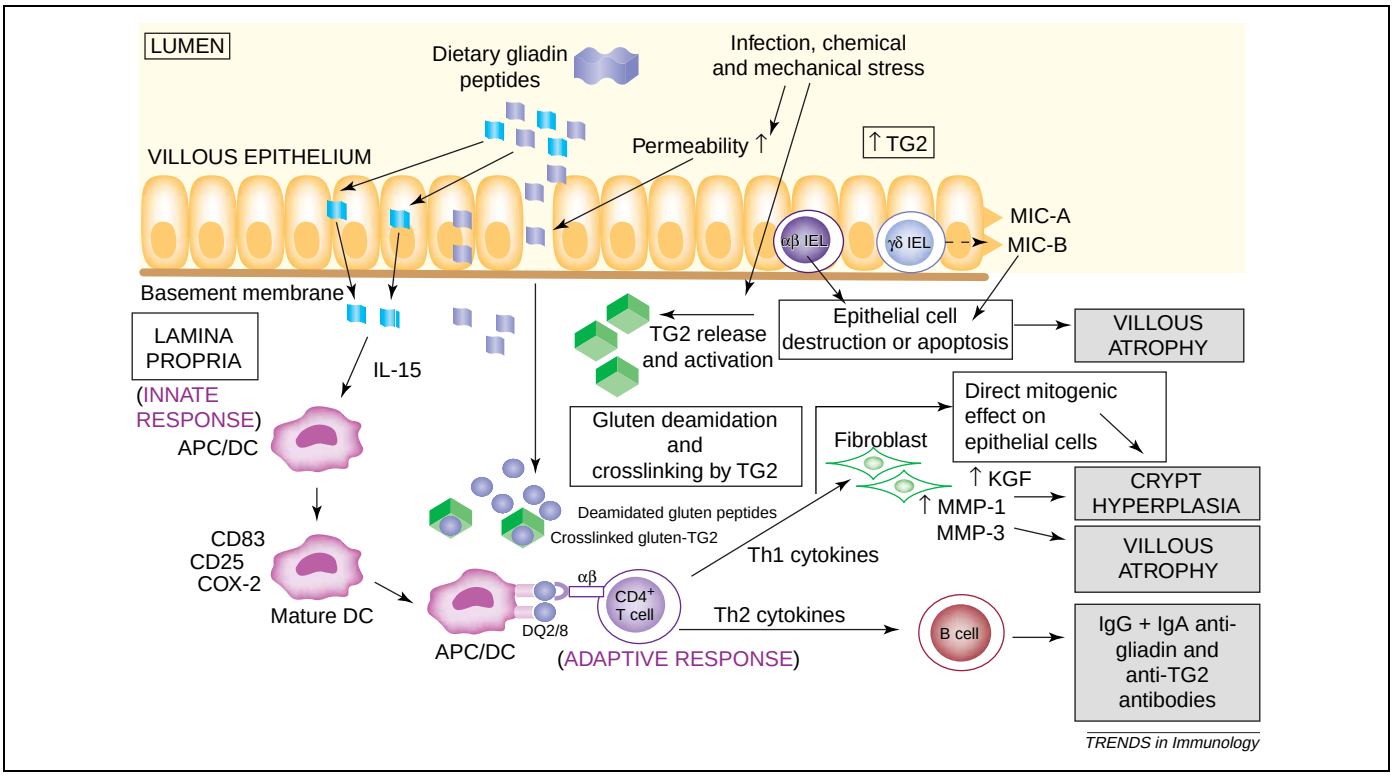

Figure 1. Summary of the molecular basis of coeliac disease. Dietary gliadin peptides reach the lamina propria. It is unclear how much of a role any impairment of mucosal integrity has (e.g. damage following intestinal infection). Gliadin deamidation by tissue transglutaminase transforms neutral glutamines from gliadin peptides to acidic, negatively charged glutamic acid residues. These fit better into the peptide binding groove of the HLA-DQ2 or -DQ8 molecules (which are coeliac disease specific) and elicit a stronger proliferative response of gliadin specific T-cell clones. APCs then drive T-cell responses towards antibody production (Th2) and/or towards inflammation and tissue remodelling (Th1). These two responses cannot occur at the same time given that antibodies against gliadin and tissue transglutaminase might precede the development of enteropathy (latent coeliac disease). Th1 cells produce TNF, which induces MMPs in intestinal fibroblasts leading to small bowel mucosal distraction (enteropathy). Th2 cells promote antibody production (antigliadin, anti-transglutaminase). Such antibodies are not confined to the lamina propria but are found systemically. Antigliadin antibodies crossreact with epitopes on cerebellar Purkinje cells and have also been found in the cerebrospinal fluid of patients with gluten ataxia. Abbreviations: APC, antigen-presenting cell; COX-2, cyclooxygenase-2; DC, dendritic cell; HLA, human lymphocyte antigen; IEL, intraepithelial lymphocyte; IL-15, interleukin-15; KGF, keratinocyte growth factor; MIC-A, MHC class I chain-related sequence-A; MMPs, matrix metalloproteinases; TG2, tissue transglutaminase; TNF, tumour necrosis factor.

type 2 (TG2) is the autoantigen recognised by endomysium antibodies, the most sensitive and specific marker of gluten sensitive enteropathy [39]. The same transglutaminase has been implicated in the inclusion body formation in trinuclear expansion diseases, of which autosomal dominant ataxias and Huntington's disease are typical examples. Indeed, Cooper *et al.* [40] have demonstrated that pathological length polyglutamine repeat domains are good substrates for TG2. Apart from crosslinking such proteins, TG2 can deamidate glutamine rich donor substrates, such as gliadin proteins.

A recent study reported that patients with dermatitis herpetiformis have antibodies with low affinity for tissue TG2 but high affinity for epidermal TG [41]. This results in an immune response and clinical manifestations in the skin, the main site of epidermal TG production. We postulate that an analogous situation exists in the case of gluten ataxia, where an immune response directed towards neural TGs could result in clinical manifestations primarily in the brain or the peripheral nervous system, with minimal if any involvement of the gut.

The involvement of TG2 in the pathogenesis of trinuclear repeat neurodegenerative diseases might potentially explain the higher prevalence (as reported by Bushara *et al.*) of anti-gliadin antibodies in dominant ataxias and Huntington's disease. The generation of antibodies to TG2 or TG2–polyglutamine complex in the context of a neurodegenerative disease (probably as an epiphenomenon) might provoke an immune response at the gut level (Figure 1), where these antibodies might be exposed to ingested gluten peptides or gluten–TG complexes. If this were the case, any resulting generation of antibodies against gliadin would take place at a local level (lamina propria of the small bowel), and would thus be of the IgA type. Of interest is the observation that, in the paper by Bushara *et al.* [22], the prevalence of IgG antigliadin alone in patients with Huntigton's disease was 8%, whereas the prevalence of IgA alone was 25%. If such crossreactivity was to continue, the likelihood of developing an enteropathy (coeliac disease) will then depend on the correct genetic susceptibility (HLA DQ2, DQ8).

Concluding remarks

Gluten sensitivity is an immune-mediated systemic disease involving both humoral and cell-mediated responses. Gluten sensitivity can present with diverse manifestations. Bowel involvement in the form of gluten-sensitive enteropathy is not a prerequisite for its existence. Such contention is merely a historical misconception stemming from its original description, which was based on its common clinical manifestations (gastrointestinal symptoms and malabsorption). Unlike other autoimmune diseases, the trigger factor has been well characterised and its removal by a gluten-free diet results in resolution

of the heightened immune response with reversal, or arrest, of end organ damage. Neurological presentation can be common and usually takes the form of cerebellar ataxia and/or peripheral neuropathy. Unlike enterocytes, cerebellar Purkinje cells cannot regenerate, thus, unless the diagnosis is made and treatment instituted early, permanent damage can ensue. There are some interesting clues in explaining the diversity of manifestations but more work is needed in characterising shared antigens and crossreactivity seen in CD, gluten ataxia and dermatitis herpetiformis. Such work might involve testing for antibody affinity to novel TGs that are predominantly expressed in the central nervous system in those patients with primarily neurological manifestations, as well as the identification of antibody targets within Purkinje cells in patients with gluten ataxia, using 2D-gel electrophoresis and mass spectrometry.

Acknowledgements

We thank R.A. Grünewald, D.S. Sanders and E. Tongiori for their input into this work.

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