

Gluten sensitivity: from gut to brain

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Gluten sensitivity is a systemic autoimmune disease with diverse manifestations. This disorder is characterised by abnormal immunological responsiveness to ingested gluten in genetically susceptible individuals. Coeliac disease, or gluten-sensitive enteropathy, is only one aspect of a range of possible manifestations of gluten sensitivity. Although neurological manifestations in patients with established coeliac disease have been reported since 1966, it was not until 30 years later that, in some individuals, gluten sensitivity was shown to manifest solely with neurological dysfunction. Furthermore, the concept of extraintestinal presentations without enteropathy has only recently become accepted. In this Personal View, we review the range of neurological manifestations of gluten sensitivity and discuss recent advances in the diagnosis and understanding of the pathophysiological mechanisms underlying neurological dysfunction related to gluten sensitivity.

Introduction

Coeliac disease was first described in 100 AD by the Greek doctor Aretaeus,¹ who used the term abdominal diathesis. When his extant works were first published in Latin in 1552, the Greek word for abdominal, *koiliaki*, was transcribed to *coeliac*. The study of coeliac disease was renewed by Gee² in 1888. His lecture on the coeliac affection described the disease according to his observations while treating children with the disease. Although clinicians began to recognise and diagnose coeliac disease, its aetiology remained obscure until 1953 when Dicke and colleagues³ reported “the presence in wheat, of a factor having a deleterious effect in cases of celiac disease”. Because gastrointestinal symptoms were dominant in patients with coeliac disease, and enteropathy was seen after enteroscopy and small bowel biopsy, it is not surprising that coeliac disease was thought to be exclusively a disease of the gut. In 1963–65, Shuster, Marks, and Watson⁴ observed that dermatitis herpetiformis was a form of gluten-sensitive dermatopathy that shared the same small bowel pathology, but not the gastrointestinal symptoms seen in patients with coeliac disease. This was the first reported evidence that coeliac disease might present with extraintestinal manifestations.

Few case reports of patients with malabsorption or steatorrhea (also referred to as sprue) and neurological manifestations^{5–7} were published before the discovery of the aetiology of coeliac disease and the introduction of jejunal biopsy, which identified the typical histological features that define coeliac disease.⁸ Such reports need to be treated with caution as a definite diagnosis of coeliac disease had not been made in patients. When the first comprehensive report of neurological manifestations in the context of histologically confirmed coeliac disease was published in 1966,⁹ the assumption was that such manifestations were caused by vitamin deficiencies secondary to malabsorption as a result of the enteropathy. The patients were undernourished, with severe weight loss, low albumin, and often multiple vitamin deficiencies. Detailed post-mortem data from the same report, however, showed an inflammatory process that primarily, but not exclusively, affected the cerebellum, and also

involved other parts of the CNS and peripheral nervous system. This finding favoured an immune-mediated pathogenesis.

Single and multiple case reports of patients with established coeliac disease who then developed neurological dysfunction continued to be published.^{10–29} The key findings from these reports were that ataxia (with and without myoclonus) and neuropathy were the most common manifestations; neurological manifestations were usually reported in the context of established coeliac disease and were almost always attributed to malabsorption of vitamins; and the effects of dietary restriction were inconsistent. A gluten-free diet did not always alleviate neurological dysfunction, although assessment of the effect of the gluten-free diet was not the main aim of these reports. None of the reports documented any attempts to monitor adherence to the diet with repeat serological testing.

In 1996, 30 years after publication of the first comprehensive case series on neurological manifestations of coeliac disease, we investigated the prevalence of gluten sensitivity in patients who presented with neurological dysfunction of unknown aetiology; most patients had ataxia either with or without neuropathy.³⁰ Presence of anti-gliadin antibodies (AGA) in these patients was common compared with controls. AGA were the only readily available serological markers of coeliac disease when the study was done (with the exception of R1-type antireticulin antibodies; endomysium antibodies were gradually introduced into clinical practice in the mid-1990s). On the basis of duodenal biopsy samples, results from this study indicated that the prevalence of coeliac disease in these patients was 16 times higher than the prevalence of coeliac disease in the healthy population. These data rekindled the interest of neurologists in a possible link between gluten sensitivity and certain neurological presentations.

Epidemiology

The prevalence of coeliac disease in the healthy population is at least 1%.^{31,32} There are no accurate estimates of the prevalence of the neurological manifestations of gluten sensitivity in the general population. A range of

10% to 22.5% for the prevalence of neurological dysfunction among patients with established coeliac disease has been reported,^{33,34} but is unlikely to be accurate because such numbers are usually derived retrospectively from gastrointestinal clinics and thus focus exclusively on patients with the classic coeliac disease presentation and also tend to include neurological dysfunctions that might be unrelated to gluten sensitivity (eg, carpal tunnel syndrome, idiopathic Parkinson's disease). Moreover, patients are unlikely to have reliably volunteered any neurological symptoms while attending a gastrointestinal clinic, and patients with neurological symptoms are more likely to present to a neurologist than to a gastroenterologist. An analogous situation is seen in patients with undiagnosed gluten sensitivity who have dermatitis herpetiformis, for which few patients will present to gastroenterology clinics as they tend not to have gastrointestinal symptoms, and instead present to a dermatologist with an itchy vesicular rash. Some estimates of prevalence can be made from patients attending the respective specialist clinics, although caution is needed when extrapolating these data as they are inevitably affected by regional referral bias. In dedicated coeliac disease and gluten sensitivity/neurology clinics in Sheffield, UK, run by two of the authors (DSS and MH, respectively), 134 patients with coeliac disease presented with neurological dysfunction and were managed in the gluten sensitivity/neurology clinic whereas 462 patients with coeliac disease presented to a gastroenterologist over the same time period. Thus, for every seven patients who present to a gastroenterologist and are then diagnosed with coeliac disease, two patients will present to a neurologist. These numbers exclude patients with neurological manifestations caused by suspected gluten sensitivity but no enteropathy (n=270), patients referred from outside the catchment area served by these clinics, and patients who presented to a gastroenterologist first before being referred to a neurologist for their symptoms.

Diagnosis of gluten sensitivity presenting with neurological manifestations

Most patients who present with neurological manifestations of gluten sensitivity have no gastrointestinal symptoms. Patients with coeliac disease might not have gastrointestinal symptoms either. Therefore, gluten sensitivity cannot be diagnosed on a clinical basis alone. Several diagnostic tests are now available that can help to decide whether patients might have coeliac disease or gluten sensitivity with extraintestinal manifestations with or without enteropathy. Figure 1 is a diagnostic flow chart we recommend to help diagnosis of neurological dysfunction related to gluten sensitivity.

Untreated patients typically have circulating antibodies to gliadin and to one or more type of transglutaminase. Except for patients with IgA deficiency, detection of IgG class antibodies has little clinical value for coeliac disease. However, this observation is organ specific and detection

of IgG type antibodies could be crucial for extraintestinal manifestations of gluten sensitivity. In patients without overt gastrointestinal involvement, serum antibodies to transglutaminase-2 (TG2) can be absent. Such patients typically have antibodies that primarily react with a different transglutaminase isozyme—TG3 in dermatitis herpetiformis and TG6 in patients with neurological manifestations. Unfortunately, tests for autoantibodies to these latter enzymes are not yet widely available. Autoantibodies to TG2 in sera samples from patients with gluten sensitivity give rise to the characteristic staining pattern on specific tissue sections (ie, referred to as reactivity with endomysial [EMA], reticulin [ARA], or jejunal [JEA] antibodies),³⁵ and such tests offer no additional information to the direct ELISAs now available for detection of TG2 IgA. Detection of antibodies to deamidated gliadin peptides (DGP) is more specific for detection of coeliac disease than are classic AGA assays.³⁶ However, unlike autoantibodies to TG2, anti-DGP antibodies can be either IgA or IgG class and not all patients have both. IgG anti-DGP has been reported to have 100% positive predictive value in adults and should therefore be included in the analysis.³⁷ At present, whether these assays are similarly sensitive for detection of neurological manifestations of gluten sensitivity is not known. Recent evidence suggests that anti-DGP antibodies might be present in only 26% of patients with gluten sensitivity who are negative for TG2 IgA.³⁸ This finding is consistent with our observation of detectable anti-DGP IgA/IgG in only 25% of patients with ataxia without enteropathy who test positive for autoantibodies to one or more transglutaminase isozymes. Table 1 details the prevalence of different types of gluten-related antibodies in patients with sporadic ataxia and in patients with gluten ataxia.

Serum IgA antibodies represent a surplus from the gut. Reaction of IgA antibodies with TG2 in the intestinal mucosa occurs before overt changes in small intestinal morphology are apparent and at least sometimes before antibodies are detectable in serum.⁴⁰ Such anti-TG2 IgA within the intestinal mucosa also seem to be present in patients with neurological disorders⁴¹ and could therefore be diagnostically useful. However, the detection of these deposits in the intestinal mucosa is not a readily available test and its interpretation requires experience. In practice, it is best to do serological tests for both IgA and IgG autoantibodies to TG2 (and, if available, anti-TG6 and anti-TG3) as well as antibodies to gliadin and DGPs (figure 1).

Limitations of conventional approach for diagnosis

Coeliac disease is characterised by the presence of an enteropathy, a practicable and mostly reliable gold standard of diagnosis. However, an enteropathy is not necessarily a prerequisite for the diagnosis of gluten sensitivity with predominantly neurological manifestations. Gluten

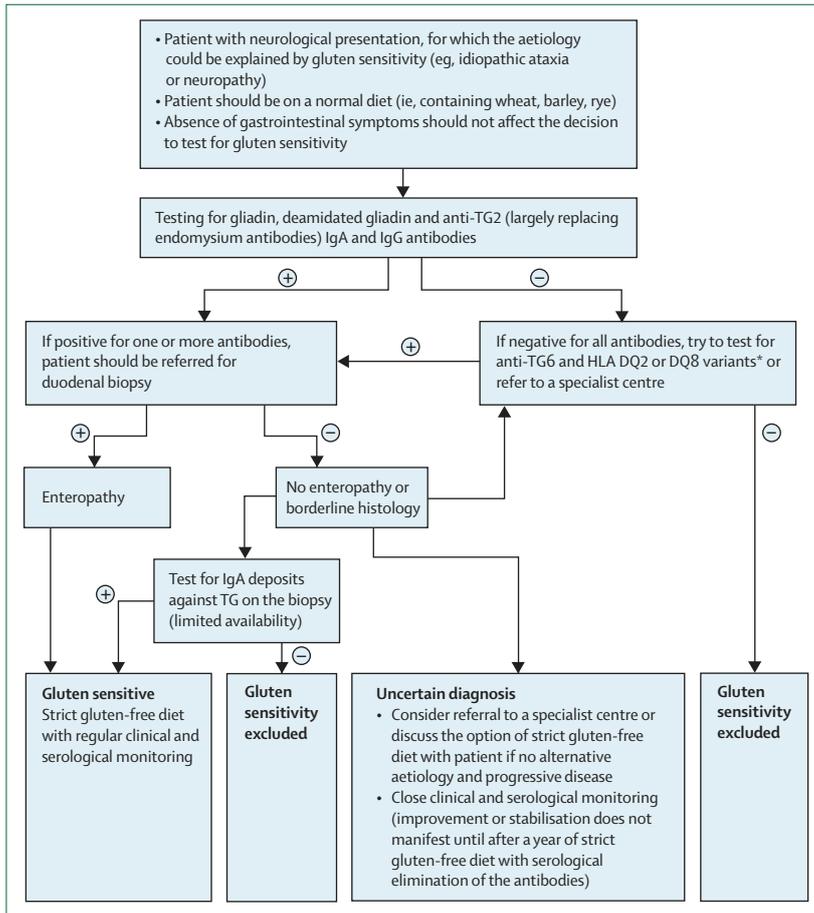


Figure 1: Flow chart of recommended approach to confirm or exclude a diagnosis of neurological dysfunction associated with gluten sensitivity

A major obstacle to accurate diagnosis is the limited availability of some of these autoantibody tests (eg, TG6). Initial serology should therefore include assessment of anti-TG2 IgA and IgG antibodies as well as antigliadin antibodies, and, if available, anti-DGP antibodies. However, for antibodies to be measurable in the serum, regular gluten ingestion is necessary. Detection of anti-TG2 IgA antibodies within the small bowel mucosa on biopsy can reveal gluten sensitivity even in patients who are seronegative. However, interpretation of this test requires specialist expertise and should be done only in specialist centres. Positive serology for antigliadin antibodies on its own is not always diagnostic of gluten sensitivity, but can be considered an indicator for further testing and for a high index of suspicion. In such cases with no enteropathy, referral to a specialised centre is advisable, particularly if access to TG6 antibody testing or testing for IgA deposits against TG on biopsy are not available (the latter requires a non-fixed fresh or frozen biopsy sample). Note that negative serology for endomysium antibodies alone cannot exclude gluten sensitivity. TG=transglutaminase. *The presence of HLA DQ2 or DQ8 variants on their own are not diagnostic of gluten sensitivity. Patients who are negative for these HLA are, however, highly unlikely to have gluten sensitivity and a negative result is thus helpful in unclear cases.

sensitivity causes a range of changes in the small bowel mucosa—from histologically normal mucosa to full-blown enteropathy to a pre-lymphomatous state. This range is categorised by the Marsh classification, which is currently accepted and used by most centres.⁴² This variety of states is a problem when defining gluten sensitivity because diagnosis currently relies on serological tests that are not 100% specific or sensitive. For example, endomysial antigen and anti-TG2 IgA antibody detection are specific for the presence of enteropathy and are excellent indicators of coeliac disease; however, these markers are often not detectable in patients with neurological manifestations,

particularly in the absence of enteropathy. Conversely, IgA and IgG AGA are not specific for coeliac disease (ie, to indicate presence of enteropathy) and are now being phased out for diagnosis of coeliac disease as more reliable tests have become available.

Genetics

Gluten sensitivity is strongly heritable, with about 40% of the genetic load coming from MHC class II association.⁴³ In white populations, more than 90% of patients with coeliac disease carry the HLA DQ2.5 variant (DQA1*05-DQB1*02) and most other patients carry HLA-DQ8 (DQA1*03-DQB1*0302). A few patients with coeliac disease do not belong in either of these groups but carry just one chain of the DQ2 heterodimer, either DQA1*05 (DQ7) or DQB1*02 (DQ2.2), but not both.⁴⁴ Of the two heterodimers, DQA1*05 on its own confers a low predisposition to coeliac disease. HLA genetic testing is therefore another useful tool to aid diagnosis (figure 1), particularly as, unlike other serological tests, this test is not dependent on an immunological trigger. However, the HLA DQ genotype can be used only as a test of exclusion, as the risk genotype DQ2 is common in white and Asian populations, and many carriers will never develop gluten sensitivity. We have noted an unusually high frequency of deviation from the MHC class II pattern typical for coeliac disease in patients with neurological disease due to gluten sensitivity. DQ8 was substantially more common in patients in the Sheffield neurology cohort who had no enteropathy (17% [46 of 270]) compared with patients with coeliac disease presenting to gastroenterologists (<6% [60 of 1008]).⁴⁴ Together with the finding of more variability in T-cell epitope specificity in patients carrying DQ8 compared with patients carrying DQ2,⁴⁵ this observation suggests that there are differences in disease aetiology between patients whose primary manifestation occurs in the CNS and those whose primary manifestation affects the gastrointestinal system.

Neurological manifestations of gluten sensitivity

The range of neurological manifestations of gluten sensitivity encountered in our specialist clinic over the past 15 years are listed in table 2.

Gluten ataxia

Cerebellar ataxia is one of the two most common neurological manifestations of gluten sensitivity. We defined gluten ataxia in 1996 as apparently sporadic ataxia with positive serological markers for gluten sensitivity. This definition was based on the serological tests available at the time (AGA). In a series of 500 patients with progressive ataxia evaluated over a period of 13 years in Sheffield, UK, 101 of 215 patients with idiopathic sporadic ataxia had serological evidence of gluten sensitivity.⁴⁶ The prevalence of gluten ataxia was 20% among all patients with ataxias, 25% among patients with sporadic ataxias,

	Anti-TG2 IgA	Anti-TG2 IgA/IgG	Anti-TG6 IgA/IgG	Anti-TG3 IgA/IgG	Anti-DGP IgA/IgG	Negative for DGP/TG antibodies
Gluten ataxia and enteropathy on intestinal biopsy	82% (14/17)	88% (15/17)	65% (11/17)	57% (8/14)	94% (16/17)	0% (0/17)
Gluten ataxia and no enteropathy on intestinal biopsy	11% (3/28)	43% (12/28)	50% (14/28)	32% (6/19)	14% (4/28)	39% (11/28)
All gluten ataxia	38% (17/45)	60% (27/45)	56% (25/45)	42% (14/33)	44% (20/45)	24% (11/45)
Idiopathic sporadic ataxia	6% (1/17)	24% (4/17)	18% (3/17)	..	6% (1/17)	65% (11/17)

Antibodies crossreactive between transglutaminase isozymes were found in some patients and might therefore contribute to a positive test result in more than one assay. However, inhibition studies showed that TG6 antibodies did not crossreact with TG2 in most of these patients.³⁹ ..=no data. DGP=deamidated gliadin peptide. TG=transglutaminase.

Table 1: Antibody prevalence in patients with gluten ataxia defined as idiopathic sporadic ataxia with positive antigliadin antibodies and in patients with idiopathic sporadic ataxia negative for antigliadin antibodies

and 45% among patients with idiopathic sporadic ataxias.^{46,47} By use of the same AGA assay, the prevalence of AGA-positive patients was 10% (7 of 71) in genetically confirmed ataxias, 18% (8 of 45) in familial ataxias (not genetically confirmed), and 12% (149 of 1200) in healthy volunteers. Data from several studies investigating the occurrence of AGA in ataxias have been published⁴⁸⁻⁵⁶ and are summarised in table 3. The variations in frequency might be due to the geographical differences in the prevalence of coeliac disease, referral bias, variability in the AGA assays used, selection of patients (eg, some studies categorised patients with cerebellar variant of multisystem atrophy as idiopathic sporadic ataxia⁵⁷), small study size, and absence of controls.

In all these studies, patients with sporadic ataxias had a high frequency occurrence of AGA antibodies compared with healthy controls. Gluten ataxia usually presents with pure cerebellar ataxia or, rarely, ataxia in combination with myoclonus (see below), palatal tremor,^{21,58} opsoclonus,⁵⁹ or chorea.⁶⁰ Gluten ataxia usually has an insidious onset with a mean age at onset of 53 years. Rarely, the ataxia can be rapidly progressive, mimicking paraneoplastic cerebellar degeneration. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases.⁵⁸ All patients have gait ataxia and most have limb ataxia. Less than 10% of patients with gluten ataxia will have any gastrointestinal symptoms but a third will have evidence of enteropathy on biopsy.⁵⁸ Up to 60% of patients have neurophysiological evidence of sensorimotor, length-dependent axonal neuropathy.⁵⁸ This neuropathy is usually mild and does not contribute to the ataxia. Anti-endomysium antibodies are detectable in only 22% of patients.⁵⁸ By use of ELISA, anti-TG2 IgA antibodies are present in up to 38% of patients with gluten ataxia, but often at lower titres than those seen in patients with coeliac disease. However, unlike in coeliac disease, IgG class antibodies to TG2 in patients with gluten ataxia are more common than IgA (table 1). This finding is in line with data that have provided evidence for intrathecal antibody production against TG in patients with neurological diseases.⁶¹ The high prevalence of IgG class antibodies to TG2 and TG6 in these patients is consistent with an

immune response in the CNS. Antibodies against either TG2 or TG6, or both, can be found in 85% of patients with ataxia and AGA antibodies.^{39,62} Some patients also test positive for anti-TG3 antibodies, although the frequency of such antibodies is low when compared with patients with dermatitis herpetiformis, and no patients tested positive for such antibodies in isolation. Antibodies to TG2 and TG6 can also be detected in patients with idiopathic sporadic ataxia who are negative for AGA, although at much lower frequency compared with patients with circulating antigliadin antibodies. Whether combined detection of TG2 and TG6 IgA/IgG can identify all patients with gluten sensitivity is unclear. However, detection of anti-DGP antibodies did not identify any additional patients. The discrepancy between anti-transglutaminase antibody and AGA detection is in agreement with the expected rate of false-positive results (about 12%; the frequency of AGA in the healthy population) and the sensitivity reported for coeliac disease.⁶³ The HLA type DQ2 is found in 70% of patients with ataxia who are positive for AGA (present in 90% of patients with coeliac disease and in 36% of healthy controls); the remaining 30% carry the HLA DQ8 (10%) and HLA DQ1 (20%) variants. These reported occurrences are in agreement with the results from serological testing reported in table 1 and are consistent with strict association with the HLA risk genotype of coeliac disease.

Up to 60% of patients with gluten ataxia have evidence of cerebellar atrophy on MRI. Investigation of the metabolic status of the cerebellum in 15 patients with gluten ataxia and ten controls by use of proton magnetic resonance spectroscopy showed significant differences in mean N-acetyl concentrations at short echo-time and in N-acetyl aspartate to choline ratios at long echo-time between patients with gluten ataxia and healthy controls, suggesting that cerebellar neuronal physiology is abnormal.⁶⁴ Even in patients without cerebellar atrophy, proton magnetic resonance spectroscopy of the cerebellum was abnormal.

The response to treatment with a gluten-free diet depends on the duration of the ataxia. Loss of Purkinje cells in the cerebellum, the end result of prolonged

gluten exposure in patients with gluten ataxia, is irreversible and prompt treatment is more likely to result in improvement or stabilisation of the ataxia. Although the benefits of a gluten-free diet in the treatment of patients with coeliac disease and dermatitis herpetiformis have long been established, there are few studies, mainly case reports, of the effect of a gluten-free diet on the neurological manifestations of gluten sensitivity.^{18,22,24,28,29,65-68} Most of these reports mainly describe patients with established coeliac disease who then develop neurological symptoms. These studies suggest variable, but overall favourable, responsiveness to a gluten-free diet. A small, uncontrolled study investigated the use of intravenous immunoglobulins in the treatment of four patients with gluten ataxia without enteropathy.⁶⁹ All patients improved on the

International Co-operative Ataxia Rating Scale (ICARS). In all these reports, strict adherence to the gluten-free diet is assumed. The best marker of strict adherence to a gluten-free diet is serological evidence of elimination of circulating antibodies related to gluten sensitivity, although serum antibodies might be present for 6–12 months after the start of the diet. A systematic study of the effect of a gluten-free diet on a cohort of patients who presented with neurological dysfunction, with or without an enteropathy, has been published.⁷⁰ This study also investigated serological confirmation of adherence to the diet. 43 patients with gluten ataxia were enrolled. 26 adhered strictly to the gluten-free diet, had serological evidence of elimination of antibodies, and comprised the treatment group. 14 patients refused the diet and comprised the control group. Treatment and control groups were matched at baseline for all variables (age, duration of ataxia). There was no significant difference in the baseline performance for each ataxia test between the two groups. There was significant improvement in performance in test scores and in the subjective global clinical impression scale in the treatment group when compared with the control group. The improvement was apparent even after excluding patients with an enteropathy. A gluten-free diet could therefore be an effective treatment for gluten ataxia.

We are unaware of any published, randomised, placebo-controlled studies on the subject, perhaps indicating the practical difficulties when the intervention is dietary elimination of gluten and the ethical considerations of randomising patients with gluten ataxia who have enteropathy.

Gluten neuropathy

Peripheral neuropathy is the other most common manifestation of gluten sensitivity. Up to 23% of patients with established coeliac disease on a gluten-free diet have neurophysiological evidence of a peripheral neuropathy.⁷¹ In a large population-based study (84 000 participants) in Sweden that examined the risk of neurological disease in patients with coeliac disease, polyneuropathy was significantly associated with coeliac disease (odds ratio 5.4; 95% CI 3.6–8.2).⁷² In a UK-based study, 47 of 140 (34%) patients with idiopathic sporadic axonal neuropathy had circulating AGA.⁷³ In an Italian study, a greater proportion of patients with various types of neuropathies were positive for IgA anti-TG2 (68 of 330; 21%) compared with controls (1 of 68; 1.5%; $p < 0.0001$).⁷⁴ Finally, in a tertiary referral centre in the USA, retrospective evaluation of 400 patients with neuropathy showed the prevalence of coeliac disease to be between 2.5% and 8% (compared with 1% in the healthy population).⁷⁵

Gluten neuropathy is defined as apparently sporadic idiopathic neuropathy in the absence of an alternative aetiology and in the presence of serological evidence of gluten sensitivity. The most common type is symmetrical sensorimotor axonal peripheral neuropathy, but other

Neurological presentations	n
Ataxia (6 patients with myoclonus, 2 with palatal tremor)	184 (67)
Peripheral neuropathy	174 (46)
Sensorimotor axonal neuropathy	125
Mononeuropathy multiplex	19
Sensory neuronopathy	14
Small fibre neuropathy	8
Motor neuropathy	8
Encephalopathy	62 (36)
Myopathy	18 (10)
Myelopathy	6 (2)
Stiff-man syndrome	6 (2)
Chorea (often with ataxia)	3 (2)
Neuromyotonia	1 (1)
Epilepsy and occipital calcifications	1 (0)

The number of patients from each group that had enteropathy on biopsy is shown in brackets. Some patients had more than one type of neurological presentation.

Table 2: Neurological presentations of 424 patients with gluten sensitivity, who presented with neurological dysfunction and were seen in the gluten sensitivity/neurology clinic, in Sheffield, UK, from 1994 to 2009

	Sporadic ataxias (%)	Familial ataxias (%)	Healthy controls (%)
Numbers from the Sheffield ataxia clinic (MH)	101/215 (47%)	15/116 (13%)	149/1200 (12%)
Hadjivassiliou et al, UK ⁴⁸	59/143 (41%)	8/59 (14%)	149/1200 (12%)
Pellecchia et al, Italy ⁴⁹	3/24 (13%)	0/23 (0%)	..
Bürk et al, Germany ⁵⁰	12/104 (12%)	..	5%
Bushara et al, USA ⁵¹	7/26 (27%)	9/24 (38%)	..
Abele et al, Germany ⁵²	13/98 (13%)	1/15 (6%)	5%
Luostarinen et al, Finland ⁵³	4/24 (17%)	..	2%
Abele et al, Germany ⁵⁴	6/32 (19%)	63 (8–15%)	6/73 (8%)
Ihara et al, Japan ⁵⁵	5/14 (36%)	1/27 (4%)	1/47 (2%)
Anheim et al, France ⁵⁶	12/33 (36%)

..=not provided.

Table 3: Summary of studies on the prevalence of anti gliadin antibodies in patients with idiopathic sporadic ataxia and in controls

types of neuropathies have also been reported (asymmetrical neuropathy,⁷⁶⁻⁷⁸ sensory ganglionopathy,⁷⁹ small fibre neuropathy,⁸⁰ and, rarely, pure motor neuropathy⁷³ or autonomic neuropathy⁸¹). Gluten neuropathy is a slowly progressive disease with a mean age at onset of 55 years (range 24-77) and a mean duration of neuropathy to diagnosis of gluten sensitivity of 9 years (range 1-33). A third of patients have evidence of enteropathy on biopsy, but the presence or absence of enteropathy does not predetermine the effect of a gluten-free diet.⁸²

The few data on pathology available from post mortems and nerve biopsy samples are consistent with an inflammatory aetiology (perivascular lymphocytic infiltration).⁷³ The evidence of effectiveness of a gluten-free diet has mostly been derived from single or multiple case reports, most of which suggest improvement of the neuropathy.^{22,73,83} Data from a systematic, controlled study of the effect of a gluten-free diet on 35 patients with gluten neuropathy, with close serological monitoring of the adherence to the gluten-free diet, indicated significant improvement in the treatment group compared with the control group after 1 year ($p=0.04$ for the improvement of sural sensory action potential and $p=0.0006$ for improvement of subjective neuropathy symptom score).⁸² Benefit was defined as improvement of sural sensory action potential, the prespecified primary endpoint, and subjective improvement of the neuropathic symptoms. Subgroup analysis suggested that the capacity for recovery of the peripheral nerves might be reduced when the neuropathy is severe or that more time might be needed for such recovery to manifest. As there was a correlation between disease severity and longer disease duration, gluten neuropathy could be thought of as a progressive disease if untreated. This study also reported that neuropathy improved irrespective of the presence of enteropathy.

Sensory ganglionopathies can also be a manifestation of gluten sensitivity and might require immunosuppressive medication in addition to a strict gluten-free diet to achieve stabilisation.⁷⁹

Gluten encephalopathy

In 2001, we reported a series of ten patients with gluten sensitivity, headache, and CNS white matter abnormalities, using the term "gluten encephalopathy" to describe them.⁸⁴ The headaches are usually episodic and mimic migraine, can be associated with focal neurological deficits, and characteristically resolve with the introduction of a gluten-free diet. The white matter abnormalities (figure 2) can be diffuse or focal and do not resolve after a gluten-free diet, which simply arrests progression of these changes. The distribution of white matter abnormalities is more suggestive of a vascular rather than a demyelinating aetiology. We believe that headaches are quite common in patients with newly diagnosed coeliac disease and thus there is an overrepresentation of coeliac disease among patients with

migraine-like headaches (4.4% vs 0.4% in the control population).⁸⁵ By use of PET brain imaging, data from a study on regional cerebral perfusion showed that seven of 11 patients (73%) with coeliac disease who were not on a gluten-free diet had at least one hypoperfused brain region as compared with one of 15 healthy controls (7%) and one of 15 patients (7%) with coeliac disease who were on a gluten-free diet.⁸⁶ In another study, 20% of children with coeliac disease were shown to have white matter abnormalities.⁸⁷ A similar prevalence of AGA and TG2 antibodies was found in 86 patients with white matter lesions in the brain or spinal cord or optic neuritis compared with controls or patients with multiple sclerosis.⁸⁸

Over the past 14 years we have encountered 61 patients with gluten encephalopathy (including the initial ten patients reported in the 2001 series). Gluten encephalopathy does not always occur in isolation and patients often have additional neurological features such as ataxia, neuropathy, and cognitive deficits. A study from the Mayo Clinic emphasised the substantial cognitive deficits encountered in 13 patients with coeliac disease.⁸⁹ Another study from Finland reported five patients with coeliac disease with brain atrophy and dementia.²⁶ In a study from Italy, no higher prevalence of coeliac disease was found in patients with Alzheimer's disease compared with elderly controls,⁹⁰ perhaps emphasising that patients with gluten encephalopathy have features that distinguish them from degenerative dementias (eg, headache, abnormal MRI, response to gluten-free diet). The prevalence of enteropathy is greater in patients with gluten encephalopathy (35 of 61 compared with gluten ataxia [67 of 184] and gluten neuropathy [46 of 174]), but the age at onset is similar. The observed improvement of the headaches and arrest of progression in the MRI brain abnormalities after a gluten-free diet suggest a causal link with gluten sensitivity.^{84,91} Gluten encephalopathy has a range of clinical presentations, with episodic headaches responsive to a gluten-free diet at one end through to severe debilitating headaches associated with focal neurological deficits and abnormal white matter on MRI at the other end.

Other less common manifestations or associations

Epilepsy

Several reports have suggested a link between epilepsy and coeliac disease.⁹²⁻⁹⁴ A specific type of focal epilepsy that is associated with occipital calcifications seems to have a strong link with coeliac disease.⁹⁵⁻⁹⁷ This form is common in Italy but rare in other countries, tends to affect young patients (mean age 16 years), and the seizures are resistant to antiepileptic drugs in most patients.⁹⁷ The prevalence of epilepsy among patients with coeliac disease was 5.5% (9 of 165) according to a 1978 report;⁹² most patients had temporal lobe epilepsy. Other studies examining the frequency of coeliac disease among patients with epilepsy^{93,94} suggest a

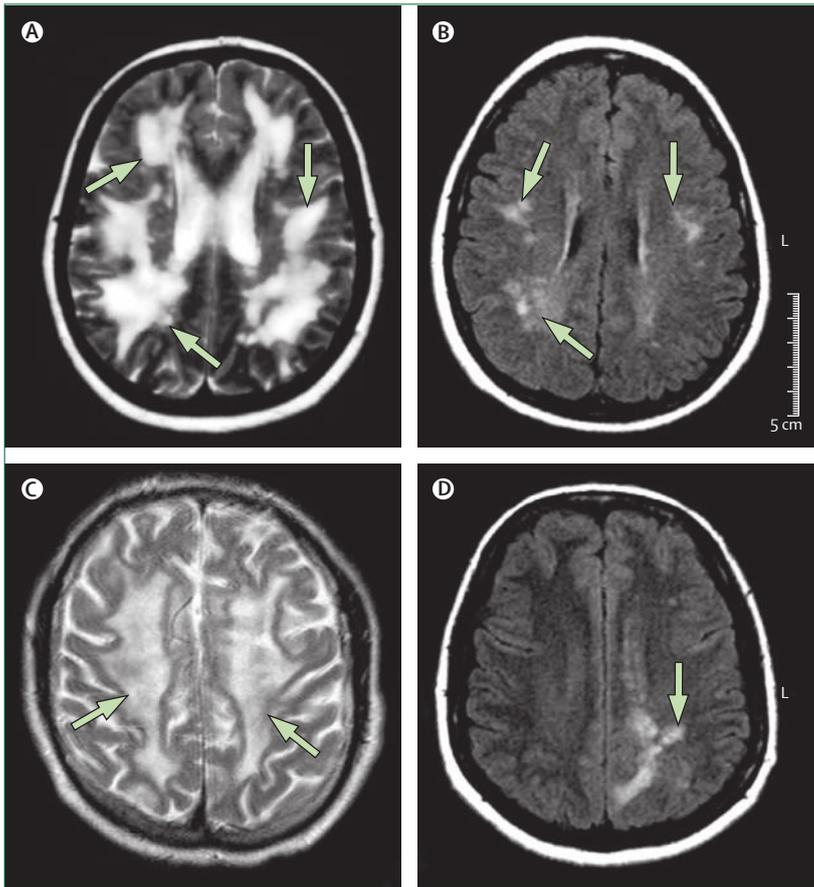


Figure 2: MRI in four patients with gluten encephalopathy

The extent and variability of white matter abnormalities caused by gluten sensitivity can be seen in these four patients (A–D). A and C show diffuse white matter changes, whereas B and D show more focal and patchy changes. Gluten-free diet results in complete resolution of the headaches but the white matter changes do not reverse. Repeat scanning while on the diet shows no progression.

prevalence of 1.2–2.3%. Larger, recent studies have not confirmed these findings.⁹⁸ However, most studies treated epilepsy as a homogeneous disorder, which is a weakness in their design. A study of the prevalence of gluten sensitivity in well characterised subgroups of patients with epilepsy found a significant association between gluten sensitivity and temporal lobe epilepsy with hippocampal sclerosis ($p < 0.0002$).⁹⁹ Of interest are some case reports on patients with coeliac disease and epilepsy, whose epilepsy improved after the introduction of a gluten-free diet.^{100,101}

Myopathy

Myopathy is a rare neurological manifestation of gluten sensitivity. In a Swedish study,¹⁰² of 76 patients with suspected polymyositis investigated at a neuromuscular unit, 17 patients had a history of gastrointestinal symptoms with evidence of malabsorption. 14 of these patients fulfilled the diagnostic criteria for polymyositis and, of those, five were diagnosed with coeliac disease. In a more recent study from Spain,¹⁰³ AGA antibodies

were present in 31% of patients with inflammatory myopathies, and there was a higher prevalence of coeliac disease in these patients when compared with healthy controls. The clinical data discussed in this section are based on 18 cases encountered by the authors over the past 14 years (13 of which have been reported previously¹⁰⁴). Enteropathy was identified in duodenal biopsy samples in ten of these patients. The mean age at onset of myopathic symptoms was 54 years. Ten patients had predominantly proximal weakness, five patients had both proximal and distal weakness, and three patients had primarily distal weakness. Two patients had ataxia and neuropathy, and one patient had just neuropathy in addition to the myopathy. Serum creatine kinase concentration ranged from normal (25–190 IU/L) to 4380 IU/L at presentation. Inflammatory myopathy was the most common finding on neuropathological examination. Six patients received immunosuppressive treatment in addition to starting a gluten-free diet, whereas the other patients were on a gluten-free diet only. Most of the patients who did not receive immunosuppressive treatment had clinical improvement of the myopathy with the gluten-free diet, suggesting that the myopathy was aetiologically linked to the gluten sensitivity. One patient developed a profound myopathy after inadvertently eating rye flour while on a gluten-free diet. He made a full recovery by re-establishing a strict gluten-free diet.

Myelopathy

Clinical evidence of a myelopathy in the absence of vitamin and other deficiencies (particularly copper) can be a rare manifestation of coeliac disease. This myelopathy is usually associated with normal imaging of the spinal cord. However, there have been reports of patients with neuromyelitis optica (Devic's disease) and gluten sensitivity who have antibodies to aquaporin-4.^{105,106} These patients had abnormal MRI of the spinal cord, but the diagnosis of coeliac disease was only made at the time of their neurological presentation. Whether this is merely an association based on the same genetic susceptibility remains to be determined. There are few data on the effect of a gluten-free diet in such patients. Neuromyelitis optica and coeliac disease share the same HLA genetic susceptibility.

Multiple sclerosis

There is no evidence of an increase in prevalence of gluten sensitivity in patients with relapsing-remitting or secondary-progressive multiple sclerosis.^{107,108} Cases of gradually progressive neurological disease and gluten sensitivity associated with white matter lesions, both in the brain and in the spinal cord, indistinguishable from those seen in patients with multiple sclerosis, have been described.^{108,109} Such patients might also have evidence of peripheral nerve involvement, which is not seen in primary-progressive multiple sclerosis.¹⁰⁸

Stiff-man syndrome

Stiff-man syndrome is a rare autoimmune disease characterised by stiffness and positivity for anti-glutamic acid decarboxylase (GAD) antibodies. This syndrome has a strong association with other autoimmune diseases (eg, insulin-dependent diabetes mellitus and hypothyroidism). We have found a high prevalence of gluten sensitivity in patients with this disorder,¹¹⁰ more so than that expected from an association of two autoimmune diseases. The effect of a gluten-free diet on stiffness and anti-GAD titre is being studied.

Myoclonic ataxia

Myoclonic ataxia is a rare manifestation of gluten sensitivity first described in 1986.¹⁹ The myoclonus is of cortical origin but the pathology is primarily cerebellar.²⁸ In a series of patients with neurological manifestations of gluten sensitivity, five of six patients with myoclonic ataxia had evidence of enteropathy on biopsy. Despite a strict gluten-free diet, the condition of two patients progressed. Both patients were treated with mycophenolate, which resulted in stabilisation. In the remaining patients, the ataxia responded to the gluten-free diet but the myoclonus persisted.

Pathophysiology of neural damage

Neurological deficits are immune mediated

Current evidence suggests that neurological manifestations are immune mediated. Vitamin and trace element deficiencies rarely play a part, particularly as most patients with neurological manifestations have no enteropathy and are thus not prone to malabsorption and vitamin deficiencies. Post-mortem examination from patients with gluten ataxia showed patchy loss of Purkinje cells throughout the cerebellar cortex, a common finding in many end-stage diseases of the cerebellum (figure 3D).^{9,111} However, additional findings supporting an immune-mediated pathogenesis include diffuse infiltration mainly of T lymphocytes within the cerebellar white matter as well as marked perivascular cuffing with inflammatory cells (figure 3A). The peripheral nervous system also showed sparse lymphocytic infiltrates with perivascular cuffing in sural nerve biopsy samples of patients with gluten neuropathy⁷³ and in dorsal root ganglia in patients with sensory neuronopathy and patients with myopathy caused by gluten sensitivity.⁷⁹ Similar findings have been described in patients with established coeliac disease who then developed neurological dysfunction.⁹

Some experimental clues to pathogenesis

Evidence suggests there might be antibody cross-reactivity between antigenic epitopes on Purkinje cells and gluten proteins. Serum from patients with gluten ataxia and from patients with coeliac disease without neurological symptoms showed cross-reactivity with epitopes on Purkinje cells of both human and rat cerebellum.¹¹² Such reactivity can also be seen with polyclonal AGA, and the

reactivity can be eliminated by absorption with crude gliadin. When using sera from patients with gluten ataxia, there is evidence of additional antibodies targeting Purkinje cell epitopes, because elimination of AGA alone is not sufficient to remove such reactivity. Additional antibodies might be causing this reactivity, such as antibodies against one or more transglutaminase isozymes (see below). Furthermore, shared epitopes between TG2 and DGPs could provide a link between these seemingly unrelated immunological targets.¹¹³ In the case of gluten neuropathy there is evidence of antibody cross-reactivity with the neuronal protein synapsin I.¹¹⁴ Additionally, gliadin can bind to GM1 ganglioside.¹¹⁵ Ganglioside antibodies are associated with autoimmune peripheral neuropathies. Finally, sera from patients with coeliac disease and neurological manifestations also evoke a mitochondrial-dependent apoptosis *in vitro*,¹¹⁶ suggesting that neurotoxic antibodies might be present. However, the nature of these antibodies and their role in *in vivo* neurotoxicity remains to be shown.

The role of transglutaminases

TG2 belongs to a family of enzymes that covalently crosslink or modify proteins by formation of an isopeptide bond between a peptide-bound glutamine residue and a primary amine.¹¹⁷ However, in some instances, TG2 can react with water in preference over an amine, leading to the deamidation of glutamine residues.^{118,119} Gluten proteins, the immunological trigger of gluten sensitivity, are glutamine-rich donor substrates amenable to deamidation. TG2 contributes to disease development in at least two ways: first, by deamidating gluten peptides and thereby increasing their affinity for HLA-DQ2/DQ8, which potentiates the T-cell response,^{120,121} and, second, by haptenisation of self-antigens through crosslinking with gliadins.¹²² This latter activity has been implicated in autoantibody development (figure 4). Activation of TG2 and deamidation of gluten peptides seems to be central to disease development and is now well understood at a molecular level. However, events leading to the formation of the characteristic autoantibodies to TG2 are still unclear. Evidence suggests that unusually stable thioester complexes of the enzyme with the substrate peptides might have a role.¹²² Questions also remain as to the contribution of these autoantibodies to organ-specific deficits. Anti-TG2 antibodies are deposited in the small bowel mucosa of patients with gluten sensitivity, even in the absence of enteropathy.¹²⁶ Furthermore, such deposits have been found in extraintestinal sites, such as muscle and liver.¹²⁶ Widespread deposition of transglutaminase antibodies has also been found around blood vessels of the brain in patients with gluten ataxia.⁴¹ The deposition was most pronounced in the cerebellum, pons, and medulla. This finding suggests that these autoantibodies could have a role in the pathogenesis of all the manifestations seen in gluten sensitivity. However, whether these antibodies are derived from the circulation, or whether their production

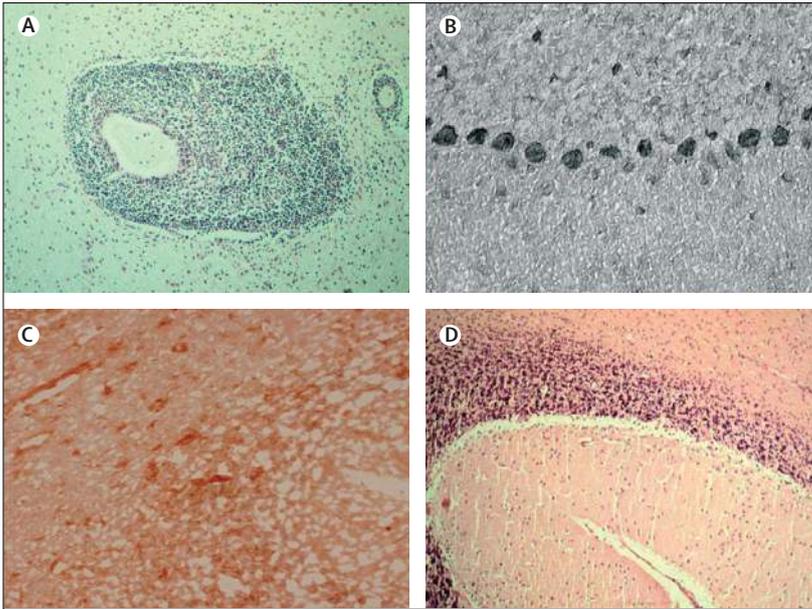


Figure 3: The immunopathology of gluten ataxia

Cerebellar tissue from a patient with gluten ataxia (A). This perivascular inflammatory infiltrate is a characteristic finding in patients with neurological manifestations of gluten sensitivity and might contribute to the loss of the integrity of the blood–brain barrier, enabling circulating antibodies to enter the CNS. Serum from patients with gluten ataxia reacts with Purkinje cell epitopes (B). Perivascular TG6 deposits are present in the cerebellum of a patient with gluten ataxia (C). The end result of these events is the loss of Purkinje cells (D) shown here in a cerebellar section from a patient with gluten ataxia showing profound loss of Purkinje cells.

is mediated within target organs after stimulation of gut-primed gliadin-reactive CD4⁺ T cells, is unclear. Such recirculating T cells have been postulated to be central to intrathecal immune responses.¹²⁷

Is the diversity of manifestations due to the type of transglutaminase targeted by the immune response?

Variations in the specificity of antibodies produced in individual patients (eg, selectivity for a particular TG2 conformation¹²⁸ or cross-reactivity between different transglutaminase isozymes) could explain the wide range of manifestations of coeliac disease. However, recent evidence suggests more fundamental differences between patients with different manifestations. While TG2 is the autoantigen in coeliac disease,¹²⁹ the epidermal TG3 seems to be the predominant autoantigen in dermatitis herpetiformis.¹³⁰ More recently, antibodies against TG6, a transglutaminase primarily expressed in the brain, were found in patients with gluten ataxia.³⁹ In gluten ataxia and dermatitis herpetiformis, IgA deposits (containing TG6 and TG3, respectively) seem to accumulate in the periphery of vessels in which the respective antigens are absent in healthy individuals (figure 3C).^{39,130} This observation could indicate either that the deposits originate from immune complexes formed elsewhere and accumulate as a consequence of enhanced vascular leaking, or that TG6 or TG3 are derived from perivascular infiltrating inflammatory cells preceding deposit formation. Perivascular cuffing with lymphocytes is a common finding in brain tissue

from patients with gluten ataxia, but is also seen in peripheral nerve and muscle in patients with gluten neuropathy or myopathy.⁷³ Furthermore, in most sera reactive to more than one transglutaminase isozyme, distinct antibody populations cause such reactivity, rather than this reactivity being a result of antibody cross-reactivity with different transglutaminase isozymes.³⁹ This finding makes shared epitopes less likely to be the cause of immune responses to other TGs and suggests that transglutaminase isozymes other than TG2 might be the primary antigen in certain patients (figure 4). Both TG6 and TG3 can deamidate gluten peptides and generate major T-cell epitopes, although there are some differences in sequence specificity of the enzymes.¹³¹

Evidence supporting a role for autoantibodies in the neurological manifestations

IgA deposition in blood vessels of the brain and the pathological finding of perivascular cuffing with inflammatory cells might indicate that vasculature-centred inflammation (driven by perivascular macrophages/dendritic cells in the choroid plexus or the subarachnoid space) could compromise the blood–brain barrier; this could expose the CNS to pathogenic antibodies and therefore trigger nervous system involvement (figure 3). TG2 is expressed by smooth muscle and endothelial cells in non-inflamed brain, and is an abundant component of the blood–brain barrier; autoantibody binding could initiate an inflammatory response. Anti-TG2 antibodies could act together with other autoantibodies (eg, AGA) to cause selective neuronal degeneration. Neuronal degeneration might also be a consequence of the repertoire of anti-transglutaminase antibodies (ie, it occurs in patients with antibodies reactive to a neuronal transglutaminase). IgG class antibodies are present in only 60% of patients with coeliac disease, whereas the occurrence was 90% in patients with gluten ataxia who were positive for anti-transglutaminase.³⁹ This shift from IgA to IgG might reflect the target organ involved (cerebellum rather than small bowel).

The development and deposition of antibodies could be coincidental rather than pathogenic. One method of showing the pathological effect of an antibody is the passive transfer of the disease through antibody injection into a naive animal. Although there is experimental evidence for only a few antibody-mediated diseases, IgG fractions of patients with anti-GAD ataxia and stiff person syndrome have been shown to compromise motor function and impair learning in rodents, an effect possibly ascribed to antibodies against GAD and amphiphysin.¹³² A common problem in such studies is to be able to show whether these specific antibodies or other autoantibodies in the IgG fraction of patient sera are the ones that cause neuronal damage. In a mouse model, sera from patients with gluten ataxia, as well as clonal monovalent anti-transglutaminase immunoglobulins obtained by phage display, caused ataxia when injected

intraventricularly.¹³³ The fact that not only immunoglobulin fractions but also monospecific single-chain variable fragments mediate functional deficits shows that there is no requirement for complement activation or for the engagement of Fc receptors on Fc receptor-bearing cells in the brain. These data therefore provide evidence that anti-transglutaminase immunoglobulins (derived from patients) compromise neuronal function in selected areas of the brain once exposed to the CNS, and suggest that this effect involves a mode of action that is independent of the immune system. However, whether this event leads to excitotoxicity of distinct neuronal cell populations remains to be shown. Nevertheless, the observed functional deficits are consistent with the selective loss of Purkinje cells in patients with ataxia and with a unique pattern of reactivity of gluten ataxia sera towards Purkinje cells when applied to brain sections. Although these data implicate anti-transglutaminase antibodies in ataxia, they do not explain the range of distinct neurological deficits currently ascribed to gluten sensitivity, nor why only a small proportion of patients with circulating anti-transglutaminase antibodies are affected.

Conclusions and future directions

Gluten sensitivity is a common disease that can manifest in diverse ways. As screening for gluten sensitivity has become a reality in clinical practice, and as more details of the individual genetic background that leads to aberrant immune responses are being revealed,⁴³ emphasis is likely to shift towards the early identification of patients who are specifically at risk of severe, and sometimes permanent, complications (eg, T-cell lymphoma, liver failure, neurological deficits). New diagnostic tools are becoming available (eg, detection of antibodies against TG6), which will enable identification of, for example, patients with neurological manifestations. At baseline, up to 40% of patients who present to gastroenterologists and who are then diagnosed with coeliac disease also have antibodies against TG6 in addition to antibodies against TG2.³⁹ This subgroup of patients with classic coeliac disease presentation might be susceptible to the development of neurological dysfunction if they continue to consume gluten, although this association remains to be shown in longitudinal studies of large patient cohorts. The presence of gastrointestinal symptoms, however, gives this group a major potential advantage: patients who present with gastrointestinal symptoms are more likely to be diagnosed with coeliac disease, and therefore to receive treatment, than are patients who present with only extraintestinal manifestations. To improve diagnosis rates, the perception of physicians that gluten sensitivity is solely a disease of the gut must be changed. The discovery of better markers of the extraintestinal manifestations could be a good starting point in the attempt to alter this conventional but outdated thinking.

Removal of the immunological trigger (gluten) must be the basis of treatment of all manifestations and should be

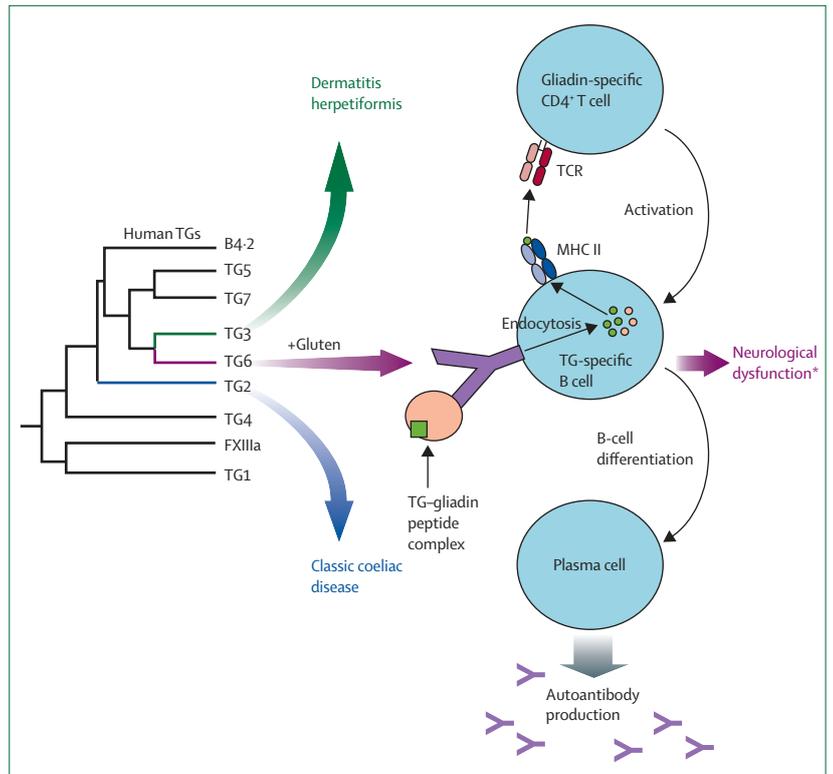


Figure 4: The role of transglutaminases in humoral immune response, which is linked to different manifestations of gluten sensitivity
 TG2, TG3, and TG6 share genetic and substantial structural similarities (phylogenetic tree of TG family is shown on the left¹²³) and have some overlap in substrate specificity, particularly in relation to pathogenic gluten epitopes. TG2 is the autoantigen in coeliac disease and TG3 the autoantigen in dermatitis herpetiformis. TG6 is primarily expressed in the CNS and antibodies against TG6 have been detected in sera from patients with gluten ataxia. A primary immune response targeting different transglutaminase isozymes might therefore explain the diverse manifestations. This is consistent with the current concept of events leading to autoantibody production and implicates the shared activity of these enzymes rather than their sequence similarity in induction of antibody production. Autocatalytic crosslinking activity of transglutaminase can result in the formation of a transglutaminase–gliadin complex. Such isopeptide bond-linked complexes, as well as potentially stable enzyme–gliadin peptide thioester complexes, are recognised by surface immunoglobulin of transglutaminase-specific B cells and are endocytosed. These B cells will then not only present peptides derived from transglutaminase but also from transglutaminase linked to gliadin. CD4⁺ T cells predominantly recognise several deamidated gliadin peptides, presented by HLA DQ2, DQ8 molecules on the cell surface of antigen-presenting cells. Such T cells can provide help to transglutaminase-specific B cells and therefore trigger expansion and antibody production.^{124,125} In the case of coeliac disease, these events occur in the gut. In dermatitis herpetiformis and in neurological manifestations, the location of these reactions is not apparent because respective enzymes are normally extremely sparse or absent in the gut. TCR=T-cell receptor. TG=transglutaminase. *As shown in figure 3.

recommended to all patients once the diagnosis is properly made. Alternative approaches to treatment are being developed and have reached clinical trial stage.¹³⁴ Such approaches principally target uptake of toxic gluten peptides by enhancing their enzymatic breakdown, by sequestering gluten proteins, or by restoring epithelial barrier function. Other approaches aim to prevent activation of gluten-specific CD4⁺ T cells by inhibiting transglutaminase and preventing deamidation or by blocking binding of gluten peptides to HLA DQ2/DQ8. Modulation of the immune system might also be possible in the future (via anticytokine therapy or vaccination to gluten epitopes). Such intervention is not without risks and therefore requires absolute certainty in the diagnosis.

It remains to be seen whether the CNS pathology associated with gluten sensitivity is the result of access of circulating antibodies that react with brain antigens after compromise of the blood–brain barrier or whether it relates to a specific T-cell subset that is involved in immune surveillance of the brain.¹³⁵ Naive T cells activated by gluten-presenting antigen-presenting cells in mesenteric lymph nodes or Peyer's patches recirculate to the target organ via the efferent lymph or thoracic duct and the systemic circulation. Gut-homing T cells can also enter the CNS and might be reactivated by resident macrophages present within the subarachnoid space. Reactivation of these antigen-specific T cells leads to cytokine-mediated activation of the endothelium and subsequent perivascular T-cell accumulation, consistent with that shown in figure 3. However, why gluten presentation should specifically occur at a site distant to the digestive system (CNS, skin) is unclear. Despite recent insights from the genome-wide association study for coeliac disease,^{43,136} which further highlighted the predominant linkage of the disease to immune regulation, much of the genetic predisposition remains unknown. Some of these additional unknown factors could add an organ-specific bias to the immune response.

Future studies should now focus on the extraintestinal manifestations of gluten sensitivity as they could provide more clues and ultimately hold the key to fully understanding the pathogenesis of gluten sensitivity.

Contributors

MH oversaw the paper and produced the first draft, did the literature search, and composed figure 2. DA and MH selected and composed the remaining figures and made major alterations to the initial draft. DSS, RAG, NW, and SB contributed comments and edited the paper.

Conflicts of interest

We have no conflicts of interest.

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