PAPER

Neuropathy associated with gluten sensitivity

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Objectives: To prospectively study the clinical, neurophysiological and neuropathological characteristics of axonal neuropathies associated with positive antigliadin antibodies and the prevalence of such neuropathies in a cohort of patients with sporadic axonal neuropathy.
Methods: Prospective screening (using antigliadin, antiendomysium and tissue transglutaminase antibodies) of patients with peripheral neuropathy attending a neurology clinic.
Results: 215 patients with axonal neuropathy were screened. 141 patients had symmetrical sensorimotor neuropathy, 47 had mononeuropathy multiplex, 17 had motor neuropathy and 10 had small-fibre neuropathy. Despite extensive investigations of the 215 patients, 140 had idiopathic neuropathy. Positive immunoglobulin (Ig)G with or without IgA antigliadin antibodies was found in 34% (47/140) of the patients with idiopathic neuropathy. This compares with 12% prevalence of these antibodies in the healthy controls. The prevalence of coeliac disease as shown by biopsy in the idiopathic group was at least 9% as compared with 1% in the controls. The clinical features of 100 patients (47 from the prevalence study and 53 referred from elsewhere) with gluten neuropathy included a mean age at onset of 55 (range 24–77) years and a mean duration of neuropathy of 9 (range 1–33) years. Gluten-sensitive enteropathy was present in 29% of patients. The human leucocyte antigen types associated with coeliac disease were found in 80% of patients.
Conclusions: Gluten sensitivity may be aetiologically linked to a substantial number of idiopathic axonal neuropathies.

Gluten sensitivity is a state of heightened immunological responsiveness to ingested gluten in genetically susceptible people.[1] It represents a spectrum of diverse manifestations, one of which is gluten-sensitive enteropathy. The term coeliac disease should now be restricted to describe gluten-sensitive enteropathy (triad of villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes on histological examination of small-bowel mucosa). The term gluten sensitivity describes a spectrum of diseases having in common an immune response to the ingestion of gluten, but with diverse manifestations such as an enteropathy (coeliac disease), dermatopathy (dermatitis herpetiformis) and neurological disorders (eg, gluten ataxia and neuropathy).[2] Not surprisingly, the common aetiological trigger (gluten) means that these diseases overlap considerably. For example, most patients with dermatitis herpetiformis also have coeliac disease, as do a third of patients with gluten ataxia.[3] Similarly, 8% of patients with established coeliac disease develop neurological manifestations.[4]

A review of all published papers from 1964 to 2000 (single and multiple case reports) of 83 patients with coeliac disease who then develop neurological illness shows that the most common neurological entities encountered were ataxia (n = 29) and peripheral axonal neuropathy (n = 29).[5] We have previously reported that neurological manifestations can present even in the absence of an enteropathy. The most common neurological dysfunction encountered was ataxia (gluten ataxia) and peripheral axonal neuropathy.[6 7] Of 28 patients with axonal peripheral neuropathy, 13 had positive antigliadin antibodies.[6] Most neuropathies encountered were symmetrical sensorimotor axonal in type. There have since been additions to the literature on neuropathy and coeliac disease. One such study showed that among patients with established coeliac disease on a gluten-free diet, 23% had evidence of axonal peripheral neuropathy.[8] Another study found that 2.5% of all patients with neuropathy had coeliac disease.[9] The figure was higher at 8% when patients with symptoms of neuropathy but normal neurophysiological assessment were included.[9] Given that 1% of the healthy population has coeliac disease[10] with no gastrointestinal symptoms and as many as 12% may have serological evidence of gluten sensitivity, the prevalence of gluten sensitivity-related neuropathy in patients with sporadic axonal neuropathy merits more detailed investigation.

The first aim of this 10-year study was to study prospectively the prevalence of gluten sensitivity and coeliac disease (using antigliadin, antiendomysium and transglutaminase antibodies as well as duodenal biopsies) in a large number of patients with axonal neuropathies. The second aim was to characterise gluten neuropathy in clinical, neurophysiological and neuropathological terms.

PATIENTS AND METHODS

Patient selection

All patients with clinical and neurophysiological evidence of axonal neuropathy were consecutively recruited over a period of 10 years (1994–2004) from a general neurology clinic at the Department of Clinical Neurology, The Royal Hallamshire Hospital, Sheffield, UK. The consultants running the clinic (initially GABD-J and then MH) have a particular interest in patients with chronic idiopathic axonal neuropathy, and such patients are followed up regularly. Patients with a family history of neuropathy or positive genetic testing for familial neuropathies were excluded, as were patients with demyelinating neuropathies such as Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathies with conduction block. Tertiary referrals of patients with the diagnosis of gluten sensitivity and peripheral neuropathy referred to the gluten sensitivity/neurology clinic

Abbreviation: HLA, human leucocyte antigen

by consultant neurologists from Sheffield and other UK neurology centres were not included in the prevalence part of the study, but were included for the purpose of defining the clinical characteristics. For the estimation of prevalence of antigliadin antibodies and coeliac disease in the healthy population of the region (similar demographic characteristics), a separate parallel study (1999–2001) was conducted and the results have been published.[10] The data from this study were used for the comparison of the prevalence of antigliadin antibodies and coeliac disease between healthy controls and patients with neuropathy.

Investigations of peripheral neuropathy

As part of the screening process for the aetiology of neuropathy, all patients underwent the following investigations at least once: full-blood count, erythrocyte sedimentation rate, vitamin B_{12}, red cell or serum folate, urea and electrolytes, liver function tests, thyroid function tests, random blood sugar, glycosylated haemoglobin (in selected cases, glucose tolerance test), serum angiotensin-converting enzyme, immunoglobulins and electrophoresis (with immunofixation), antinuclear antibodies, double-stranded DNA, extractable nuclear antibodies, antigliadin antibodies (IgG and IgA), IgA endomysium antibodies, IgA tissue transglutaminase antibodies (the antiendomysium and tissue transglutaminase assays became available half way through the study, which is why not all patients were tested at baseline), rheumatoid factor, antinuclear cytoplasmic antibodies and chest radiograph. Additional investigations were carried out if clinically indicated, and included borrelia serology, hepatitis B and C and HIV serology, complement levels, cryoglobulins, vitamins B_1, B_6 and E, paraneoplastic antibodies (Hu, Yo and Ri), lead levels, abdominal ultrasound scan, sural-nerve biopsy, abdominal and chest computed tomography scan, skeletal survey, bone marrow examination and positron emission tomography scan.

Additional investigations for patients with neuropathy and gluten sensitivity

All patients with positive antigliadin antibodies (IgG or IgA) irrespective of the presence of antiendomysium and tissue transglutaminase antibodies were offered duodenal biopsy. Specimens were taken from the distal duodenum using biopsy forceps, through a conventional forward-viewing endoscope (Key-Med, Southend, UK). Four biopsy specimens were taken from the third part of the duodenum. The presence of gluten-sensitive enteropathy was established by histological examination for evidence of crypt hyperplasia, villous atrophy and increase in intraepithelial lymphocyte count.[11]

Neurophysiological assessments

Nerve conduction studies and electromyography were carried out at least once in all patients where clinical evaluation suggested a diagnosis of peripheral neuropathy. All patients included in this study had evidence of axonal peripheral neuropathy on neurophysiological assessments (generalised sensory or motor peripheral neuropathy, mononeuropathy multiplex or small-fibre neuropathy). Sensory and motor nerve conduction studies and EMG were carried out using standard techniques. Nerve conduction study results were usually deemed abnormal if values fell outside 99% confidence limits, but allowance was made in interpreting values with respect to age of the patient. Where nerve conduction studies were normal and the clinical features were suspicious of small-fibre involvement, thermal threshold testing was performed. Thermal threshold results were considered to be abnormal if they fell outside 99% confidence limits obtained from age-matched healthy controls.

RESULTS

Prevalence

A total of 215 patients with axonal neuropathy participated in this study. Of these 141 had symmetrical sensorimotor axonal neuropathy, 47 had mononeuropathy multiplex, 17 had motor neuropathy and 10 had small-fibre neuropathy.

After investigations, the aetiology of neuropathy was established in some patients as follows: diabetes mellitus was the cause of neuropathy in 24 of 215 (11%) patients (7 had type 1 and 17 had type 2 diabetes). In 16 of 215 (7%) patients, a connective tissue disease or vasculitis was confirmed to be the aetiological factor. A paraneoplastic neuropathy was diagnosed in 9 (4%) patients. Low vitamin B_{12} was found in 9 (4%) patients. Cases of monoclonal gammopathy of undetermined significance (n = 5, 2%), excessive alcohol intake (n = 4, 2%), drug related (n = 3, 2 amiodarone, 1 phenytoin, 1%) and hypothyroidism (with evidence of improvement of the neuropathy with thyroid replacement alone; n = 3, 1%) were noted. One patient was found to have low vitamin B_6 and improved with nutritional support; in another patient the neuropathy was thought to be related to sarcoidosis (confirmed by biopsy). Thus, a possible aetiology for the neuropathy was established in 75 patients, leaving 140 patients with seemingly idiopathic neuropathy. Positive serology for gluten sensitivity (IgG or IgA antigliadin antibodies) was found in 47 of 140 (34%) patients with idiopathic neuropathy. This compared with 12% prevalence of these antibodies in the control population of Sheffield.[10] The difference in prevalence of antigliadin antibodies between the two groups was significant ($p<0.001$ by χ^2 test). In addition, 7 of 75 (9%) patients with neuropathy of known aetiology (two with type 1 diabetes and five with low vitamin B_{12}) were found to have antigliadin antibodies. Of the 47 patients with gluten sensitivity, 45 underwent duodenal biopsies and 12 (27%) were found to have an enteropathy in keeping with coeliac disease. Thus, the prevalence of coeliac disease as determined by biopsy in the idiopathic group was at least 9% (12/140). This compares with 1% prevalence of coeliac disease in the controls.[9] Table 1 summarises these data.

Clinical characteristics

The clinical and immunological characteristics of the 47 patients with gluten sensitivity and otherwise idiopathic neuropathy were then combined with those of 53 patients with gluten sensitivity and neuropathy who had been referred consecutively to the gluten sensitivity/neurology clinic from other neurologists from Sheffield and elsewhere in the UK. All the additional 53 patients were investigated in a similar manner and other causes of neuropathy were excluded. Table 2 outlines the clinical features of these 100 patients.

The mean age at onset of the neuropathy was 55 (range 24–77) years, with a mean symptom duration of 9 (range 1–33) years. In all, 67 patients had a symmetrical generalised sensorimotor axonal neuropathy, 17 had mononeuropathy multiplex, 9 had pure motor neuropathy and 7 had small-fibre neuropathy. Antigliadin IgG antibodies alone were positive in 57%, antigliadin IgA alone in 16%, and both IgG and IgA were positive in the remaining 27%. Tissue transglutaminase antibodies were present in 16 of 44 (36%) patients and antiendomysium antibodies in 12 of 52 (23%) patients who underwent these additional tests. Gluten-sensitive enteropathy was present in 26 of 89 (29%) patients who underwent duodenal biopsy. The human leucocyte antigen (HLA) types associated with coeliac disease were seen in 80% (62% HLA-DQ2, 10% HLA-DQ8, 8% HLA-DR3, HLA-DR5 or HLA-DR7, without HLA-DQ2 or HLA-DQ8) of these patients. The remaining had HLA-DQ1. We found no significant differences in any of the above characteristics

Table 1 Causes of neuropathy in 215 patients with chronic axonal neuropathy

Condition	n	Percentage
Diabetes mellitus (17 type 2, 7 type 1)	24/215	11
Vasculitis or connective tissue disease	16/215	7
Paraneoplastic	9/215	4
Low vitamin B_{12}	9/215	4
MGUS	5/215	2
Alcohol related	4/215	2
Drug related	3/215	1
Hypothyroidism	3/215	1
Low B_6	1/215	0.5
Sarcoidosis	1/215	0.5
Total with diagnosis	75	35
Idiopathic	140	65
Positive serology of gluten sensitivity (whole group)	54/215	25
Duodenal biopsy in keeping with enteropathy	14/215	7
Positive serology for gluten sensitivity (idiopathic group)	47/140	34
Duodenal biopsy in keeping with enteropathy	12/140	9
Positive serology for gluten sensitivity (diagnosis group)	7/75	9
Duodenal biopsy in keeping with enteropathy	2/75	3
Positive serology for gluten sensitivity (healthy population)	144/1200	12
Duodenal biopsy in keeping with coeliac disease	12/1200	1

MGUS, monoclonal gammopathy of undetermined significance.

between the 47 patients from the prevalence study and the 53 patients referred from elsewhere.

Neuropathological findings

Pathological data were available from three patients (sural-nerve biopsies in two patients and an autopsy in one).

A sural-nerve biopsy from a 65-year-old man (positive antigliadin antibodies, normal duodenal biopsy) with clinical and neurophysiological evidence of sensorimotor axonal neuropathy showed a focal inflammatory cell infiltrate in the epineurium and around a small endoneurial blood vessel in one fascicle (fig 1). The inflammatory cells, which included plasma cells, were closely related to the vessel wall. Resin-embedded thin sections showed a patchy loss of myelinated fibres and occasional degenerating fibres. Occasional thinly myelinated fibres were seen, but not demyelinated fibres. These appearances suggested axonal degeneration secondary to an inflammatory microvasculopathy. The patient's condition is stable while on a gluten-free diet.

Case 2 was a 49-year-old man with asymmetrical sensorimotor axonal neuropathy suggestive of mononeuropathy multiplex. He had positive antigliadin antibodies, and coeliac disease was confirmed on duodenal biopsy. He had never been strict with his gluten-free diet (persistently positive antigliadin antibodies) and the neuropathy had progressed. He underwent a fascicular sural-nerve biopsy, containing a single fascicle. This showed evidence of axonal degeneration, but no evidence of inflammatory cell infiltration.

Case 3 was a 32-year-old woman who died from a rapidly progressive neuropathy (symmetrical sensorimotor axonal neuropathy) and ataxia, whose onset coincided with the diagnosis of gluten sensitivity. She also had evidence of enteropathy on biopsy. Autopsy showed inflammatory changes in both the central and the peripheral nervous systems (represented by spinal nerve roots). Capillaries in the brain seemed prominent in some areas, with hypertrophic endothelial cells. These vascular changes were most conspicuous in white matter, including cerebral, cerebellar and brain stem white matter. However, similar changes were seen focally in grey matter areas, including the hippocampus and the inferior olivary nucleus. The capillary changes were associated with a vascular and perivascular inflammatory cell infiltrate, predominantly of histiocytes (CD68+) and a lighter population of small lymphocytes, which were mostly T cells (CD45Ro+). Occasional fragmenting nuclei, possibly representing apoptotic bodies, were seen, but there was no vascular necrosis. We observed no tissue necrosis or microinfarction, and only mild focal myelin loss. Similar changes were also seen in the spinal cord. The cerebellum showed loss of Purkinje cells (fig 2A) with increased Bergmann glia, and there was a mild patchy loss of neurones in the inferior olivary nucleus. Spinal roots of peripheral nerve showed inflammatory cell infiltrate of both lymphocytes and macrophages (fig 2B), some of which were positive for T cell markers.

Table 2 Clinical and immunological characteristics of 100 patients with gluten neuropathy

Mean age at onset of neuropathy	55 years (range 24–77)
Mean duration of disease	9 years (range 1–33)
Need walking aid	22%
Pain a prominent feature	14%
Sensorimotor axonal neuropathy	67%
Mononeuropathy multiplex	17%
Motor neuropathy	9%
Small-fibre neuropathy	7%
Only antigliadin IgG positive	57%
Only antigliadin IgA positive	16%
Both antigliadin IgG and IgA positive	27%
Tissue transglutaminase antibody positive*	16/44 (36%)
Endomysium antibody positive*	12/52 (23%)
Enteropathy on biopsy	26/89 (29%)
HLA typing in keeping with coeliac disease	80/100 (80%)

100 patients include 47 patients from the prevalence study and 53 patients with gluten neuropathy referred to the gluten sensitivity/neurology clinic from elsewhere.
HLA, human leucocyte antigen; Ig, immunoglobulin.
*The antiendomysium and tissue transglutaminase assays became available halfway through the study, which is why not all patients were tested at baseline.

DISCUSSION

Demyelinating inflammatory neuropathies have been the focus of most research on peripheral neuropathies; yet axonal neuropathies are by far the most common type of neuropathies encountered in everyday neurological practice.[12 13] This large prospective study has attempted to identify a prevalence figure (among patients with sporadic axonal neuropathy) and clinically characterise gluten sensitivity-related neuropathy. Data on the prevalence of other causes of axonal neuropathies are also presented in this study, but are unlikely to represent the true prevalence of each aetiology in the general population because of referral bias. For example, in this study, diabetes accounted for 11% of all the neuropathies but was found to be the cause of neuropathy in >50% of patients in another study.[12] In the UK, patients with established and poorly controlled diabetes who have a neuropathy are less likely to be referred to neurology clinics, given that the aetiology and treatment of their neuropathy is apparent. In this study for most patients with non-insulin-dependent diabetes, the diagnosis of diabetes was made on the basis of the aetiology of the neuropathy. The figures of prevalence for the different aetiologies of neuropathy found in this study reflect more closely what is seen in a long-established general neurology clinic where patients with chronic axonal neuropathies are followed up long term.

The principal aim of this study was to investigate the prevalence of gluten sensitivity among patients with chronic idiopathic axonal neuropathy as defined by the presence of

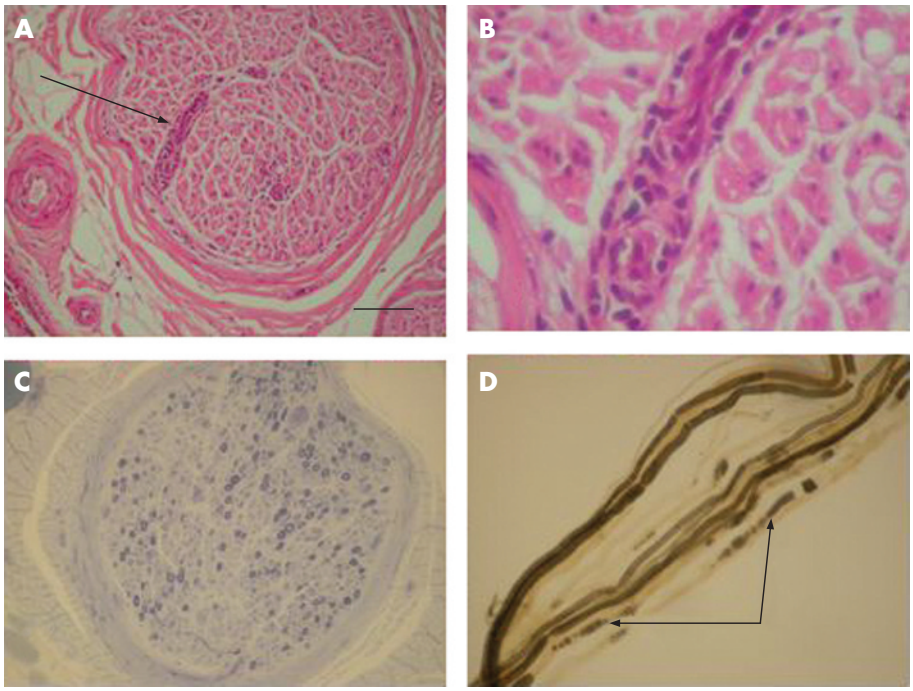

Figure 1 Sural-nerve biopsy specimen from a 65-year-old man with gluten neuropathy, showing a focal inflammatory cell infiltrate in the epineurium and around a small endoneurial blood vessel (arrow, A). The inflammatory cells were closely related to the vessel wall, but not associated with fibrinoid necrosis (A,B). Resin-embedded thin sections showed a patchy loss of myelinated fibres and occasional degenerating fibres. Demyelinated fibres were not seen (C). Teased fibre preparations showed up to 30% of the population of fibres undergoing Wallerian degeneration (arrows, D).

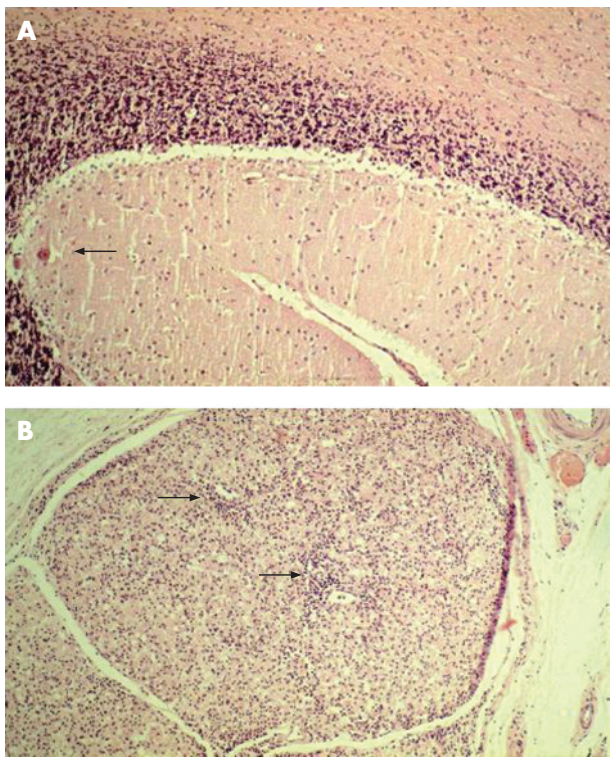

Figure 2 Cerebellum and peripheral nerve tissue obtained at autopsy from a 32-year-old woman who died from a rapidly progressive neuropathy and ataxia, the onset of which coincided with the diagnosis of gluten-sensitive enteropathy. The cerebellum (A) showed a patchy loss of Purkinje cells (arrow pointing to the only remaining Purkinje cell on this section) with increased Bergmann glia. Spinal roots of peripheral nerve (B) showed inflammatory cell infiltrate of both lymphocytes and macrophages (arrows), some of which were positive for T cell markers.

antigliadin antibodies. To avoid referral bias (in view of our interest in the neurological manifestations of gluten sensitivity), we deliberately excluded any patients referred to the gluten sensitivity/neurology clinic with an established diagnosis of gluten neuropathy. The prevalence of antigliadin antibody positivity was 34% in patients with otherwise idiopathic axonal neuropathy compared with 9% in patients with established cause of neuropathy and 12% in controls from the same region.[10] The prevalence of coeliac disease among these patients was found to be at least 9% and compares with 1% in the controls from the same region.[10] It is also possible that in those seven patients with neuropathy of known aetiology (two patients with type 1 diabetes and five patients with low vitamin B_{12}) who also had antigliadin antibodies, the aetiology of the neuropathy could be linked to gluten sensitivity rather than to diabetes or low vitamin B_{12}. We, however, found no correlation between vitamin B_{12} deficiency and the presence of enteropathy.

A previous controlled study has shown that as many as 23% of patients with established coeliac disease on a gluten-free diet showed axonal neuropathy on neurophysiological testing.[8] Given that at least 1% of the healthy population in European countries and the US has coeliac disease and up to 12% has serological evidence suggestive of gluten sensitivity, such sensitivity may well prove to be a common aetiological link to chronic idiopathic axonal neuropathy.

Some clinicians choose to distinguish between those patients with gluten sensitivity who have an enteropathy (coeliac disease) and those without an enteropathy but with positive serological markers for gluten sensitivity. The rationale for this is not clear, as gluten sensitivity represents a spectrum ranging from antibody-positive but normal small-bowel mucosa (often referred to as potential coeliac disease or Marsh stage 0[1]) to the presence of the classic small lesions on a biopsy sample, which define coeliac disease. The range of changes seen on examination of the small-bowel mucosa, which may relate to gluten load, has been documented in

detail and is now known as the Marsh classification.[14] Thus, in the case of our patients with peripheral neuropathy associated with gluten sensitivity, there is nothing on clinical, genetic or immunological grounds to distinguish between patients with or without enteropathy. Extraintestinal manifestations can be the presenting feature of this disease (eg, dermatitis herpetiformis, gluten ataxia), and such manifestations can be successfully treated with a gluten-free diet even in the absence of enteropathy.[15] We therefore propose the term ''gluten neuropathy'' to describe this entity. Such a term encompasses patients with positive antigliadin antibodies with or without the bowel being affected (coeliac disease) and in the absence of an alternative aetiology for the neuropathy. The HLA type may offer additional diagnostic value, given that 80% of these patients have HLA-DQ2 or HLA-DQ8. Tissue transglutaminase and antiendomysium antibodies are good markers for the presence of an enteropathy (coeliac disease) but lack sensitivity when the bowel mucosa is normal and the disease presents with extraintestinal manifestations. Some patients reported in this study probably had a neuropathy that was coincidentally rather than aetiologically linked with the presence of circulating antigliadin antibodies. This is inevitable given that as yet there are no specific serological markers for the neurological spectrum of gluten sensitivity. Antigliadin antibodies currently remain the most sensitive markers of the whole spectrum of gluten sensitivity. The prospect of an additional marker seems imminent after the recent discovery that in vivo IgA deposits against tissue transglutaminase type 2 in the small-bowel biopsy specimens of patients with diverse manifestations within the spectrum of gluten sensitivity are detected even in the absence of enteropathy. Such deposits have also been found in extraintestinal tissue, such as vessels in the cerebellum in patients with gluten ataxia. This marker seems to be highly specific for the whole spectrum of gluten sensitivity, as it was not found to be present in healthy and disease control subjects.[16]

The pathophysiology of gluten neuropathy remains unclear. Nutrient and vitamin deficiencies are unlikely to play a part, given that most of these patients have a normal nutritional status and no enteropathy. The mechanism is more likely to be immunological along the same lines as gluten ataxia.[17] The pathology is that of an inflammatory process as outlined in this study and reported previously.[7] This process can clearly affect peripheral nerves as well as the central nervous system.[18–20] More often than not, however, the biopsy findings are those of axonal degeneration without evidence of inflammation. Patients with gluten sensitivity may rarely present with a rapidly progressive neuropathy, often associated with involvement of the central nervous system, as described for case 3 in Neuropathological findings. Such cases have previously been described by Cooke and Thomas-Smith.[20] On the basis of this study and the review of published case reports, the most common neuropathy encountered in the context of gluten sensitivity is that of a chronic slowly progressive symmetrical sensorimotor axonal distally predominant peripheral neuropathy. Further evidence in support of gluten neuropathy being immune mediated comes from a report on the presence of antiganglioside antibodies in patients with coeliac disease and neuropathy.[21]

Why the same disease (gluten sensitivity) results in both symmetrical and at times asymmetrical neuropathy (mononeuropathy multiplex), or even pure motor or sensory neuropathy remains unclear. This diverse pattern of peripheral nerve involvement is also seen in other diseases such as diabetes mellitus or neuropathy associated with connective tissue diseases. In one of our patients with gluten sensitivity, we observed progression of the motor neuropathy to involvement of sensory fibres with continuous exposure to gluten.[22] It is yet unclear whether the aetiology of the mononeuropathy multiplex seen in some of these patients with gluten sensitivity is mediated through a low-grade vasculitic process.

We conclude that serological evidence of gluten sensitivity is commonly found in chronic idiopathic axonal neuropathies and may well be aetiologically linked. The effect of a gluten-free diet on the neuropathy should confirm whether or not this is another manifestation of gluten sensitivity similar to gluten ataxia, dermatitis herpediformis and gluten-sensitive enteropathy.

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