

Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics

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Summary

We previously have described a group of patients with gluten sensitivity presenting with ataxia (gluten ataxia) and suggested that this disease entity may account for a large number of patients with sporadic idiopathic ataxia. We have therefore investigated the prevalence of gluten sensitivity amongst a large cohort of patients with sporadic and familial ataxia and looked at possible genetic predisposition to gluten sensitivity amongst these groups. Two hundred and twenty-four patients with various causes of ataxia from North Trent (59 familial and/or positive testing for spinocerebellar ataxias 1, 2, 3, 6 and 7, and Friedreich's ataxia, 132 sporadic idiopathic and 33 clinically probable cerebellar variant of multiple system atrophy MSA-C) and 44 patients with sporadic idiopathic ataxia from The Institute of Neurology, London, were screened for the presence of anti-gliadin antibodies. A total of 1200 volunteers were screened as normal controls. The prevalence of anti-gliadin antibodies in the familial group was eight out of 59 (14%), 54 out of 132 (41%) in the sporadic idiopathic group, five out of 33 (15%) in the MSA-C group and 149 out of 1200 (12%) in the

normal controls. The prevalence in the sporadic idiopathic group from London was 14 out of 44 (32%). The difference in prevalence between the idiopathic sporadic groups and the other groups was highly significant ($P < 0.0001$ and $P < 0.003$, respectively). The clinical characteristics of 68 patients with gluten ataxia were as follows: the mean age at onset of the ataxia was 48 years (range 14–81 years) with a mean duration of the ataxia of 9.7 years (range 1–40 years). Ocular signs were observed in 84% and dysarthria in 66%. Upper limb ataxia was evident in 75%, lower limb ataxia in 90% and gait ataxia in 100% of patients. Gastrointestinal symptoms were present in only 13%. MRI revealed atrophy of the cerebellum in 79% and white matter hyperintensities in 19%. Forty-five percent of patients had neurophysiological evidence of a sensorimotor axonal neuropathy. Gluten-sensitive enteropathy was found in 24%. HLA DQ2 was present in 72% of patients. Gluten ataxia is therefore the single most common cause of sporadic idiopathic ataxia. Anti-gliadin antibody testing is essential at first presentation of patients with sporadic ataxia.

Keywords: gluten ataxia; prevalence; gluten sensitivity; coeliac disease

Abbreviations: MSA-C = cerebellar variant of multiple system atrophy; SCA = spinocerebellar ataxia

Introduction

The term 'gluten sensitivity' refers to a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals (Marsh, 1995). Gastrointestinal symptoms caused by involvement of the small bowel (coeliac disease, also known as gluten-sensitive enteropathy) have in the past been considered the most common presenting feature. Prevalence studies have shown that coeliac disease

affects up to 1% of the normal population (Fasano, 2001). It has been estimated that for every one patient with coeliac disease who presents with gastrointestinal complaints, there are seven patients with coeliac disease who have no gastrointestinal symptoms (Fasano, 2001). There is evidence to suggest that the small bowel is no longer the sole protagonist in gluten sensitivity. An itchy vesicular rash due

to skin involvement (dermatitis herpetiformis) has been recognized as a separate manifestation since 1966 (Marks *et al.*, 1966). Although neurological complications have been reported in association with established coeliac disease (Cooke and Smith, 1966), we have shown that gluten sensitivity can present solely with neurological dysfunction (Hadjivassiliou *et al.*, 1996). Ataxia (gluten ataxia) is the most common neurological manifestation of gluten sensitivity (Hadjivassiliou *et al.*, 1998). Organ-specific manifestations can occur in isolation or in combination with one another. Only a proportion of patients presenting with neurological dysfunction associated with gluten sensitivity will also have an enteropathy (Hadjivassiliou *et al.*, 1999). The remaining patients have no histological evidence of small bowel involvement but have serological markers (serum antigliadin antibodies) in keeping with gluten sensitivity, a situation analogous to dermatitis herpetiformis. Genetic susceptibility in the form of the HLA typing may play an important role in this disease. HLA DQ2 is found in up to 90% of patients with coeliac disease.

Referral bias in units with an interest in genetic ataxias has produced an impression of relative rarity of idiopathic sporadic cases. One aspect of this study was to look at the prevalence of familial and sporadic ataxias in an unselected population from North Trent served by the Department of Neurology, The Royal Hallamshire, Sheffield. We have suggested that gluten ataxia may account for a large number of patients with idiopathic sporadic ataxia. We present the prevalence of gluten sensitivity amongst a large cohort of patients with sporadic and familial ataxia and investigate possible genetic predisposition to gluten sensitivity amongst these groups. In addition, we present the clinical and radiological characteristics of the largest ever reported cohort of 68 patients with gluten ataxia.

Methods

Patient selection

Over the last 8 years, we have reviewed prospectively and followed-up at 6 monthly intervals all patients with the diagnosis of cerebellar degeneration seen in a specially formed ataxia clinic based at the Department of Neurology at the Royal Hallamshire Hospital, Sheffield. The patients were identified from the disease register of the Department of Neurology, referrals from other neurology consultant colleagues based in North Trent and from the database of the regional Department of Molecular Genetics. Patients were divided into three groups. The first group consisted of patients with a family history of ataxia (autosomal recessive or dominant) and/or positive genetic testing for one of spinocerebellar ataxias (SCAs) 1, 2, 3, 6 and 7, and Friedreich's ataxia. The second group consisted of patients with sporadic idiopathic cerebellar degeneration without clinical evidence of the cerebellar variant of multiple system atrophy (MSA-C). The third group consisted of patients with

clinically probable MSA-C as defined by the consensus statement on the diagnosis of multiple system atrophy (Gilman *et al.*, 1999). Patients with a history of alcohol abuse, prolonged use of the anticonvulsant medication phenytoin, laboratory evidence of multiple sclerosis, vitamin E deficiency, paraneoplastic cerebellar degeneration and viral cerebellitis were excluded. In an attempt to eliminate possible referral bias associated with our department's involvement in research into the neurological manifestations of gluten sensitivity, we also screened a group of patients with sporadic idiopathic ataxia identified from the database of the ataxia clinic of the Institute of Neurology, Queen Square, London. All of these patients had been labelled as suffering from idiopathic late onset cerebellar ataxia, a term introduced by the late Professor Harding but now synonymous with sporadic idiopathic ataxia. Normal volunteers from the Trent region attending their primary care physician for unrelated problems (e.g. obtaining repeat prescription, accompanying relatives to their GP, common cold, etc.) were screened for the presence of IgG and/or IgA antigliadin antibodies to estimate the prevalence of such antibodies in the local population. The study was approved by the South Sheffield Ethics Committee. All patients were tested for antigliadin antibodies, and the first 169 consecutive patients (apart from the normal volunteers group) also had their HLA type determined. All patients underwent full neurological examination. Patients with gluten ataxia were referred for duodenal biopsy.

Antigliadin antibody estimation and HLA typing

IgG and IgA antigliadin antibody estimation was done using a commercially available enzyme-linked immunoassay kit (ELISA) kit (Cogent Diagnostics Ltd, Edinburgh, UK) according to the manufacturers' instructions. Briefly, 96-well microtitre plates pre-coated with purified gliadin were used. Test serum, positive and negative controls (all diluted to 1:100) or standards were added and incubated at room temperature for 30 min. Antigliadin antibodies were detected following incubation at room temperature for 15 min with mouse anti-human IgG and IgA horseradish peroxidase conjugate and subsequent development with tetra-methyl benzidine (TMB) substrate at room temperature for 15 min. Sample optical density units were converted to Cogent arbitrary units (U/ml) using the pre-calibrated standards. Concentrations of controls and standards had to fall within pre-defined limits for acceptance of assay validity.

HLA typing was performed at the regional blood transfusion unit.

Duodenal biopsies

Duodenal biopsies were taken from the distal duodenum using biopsy forceps, through a conventional forward viewing endoscope (Key-Med, Southend, UK). Four biopsies were taken from the third part of the duodenum. The presence of

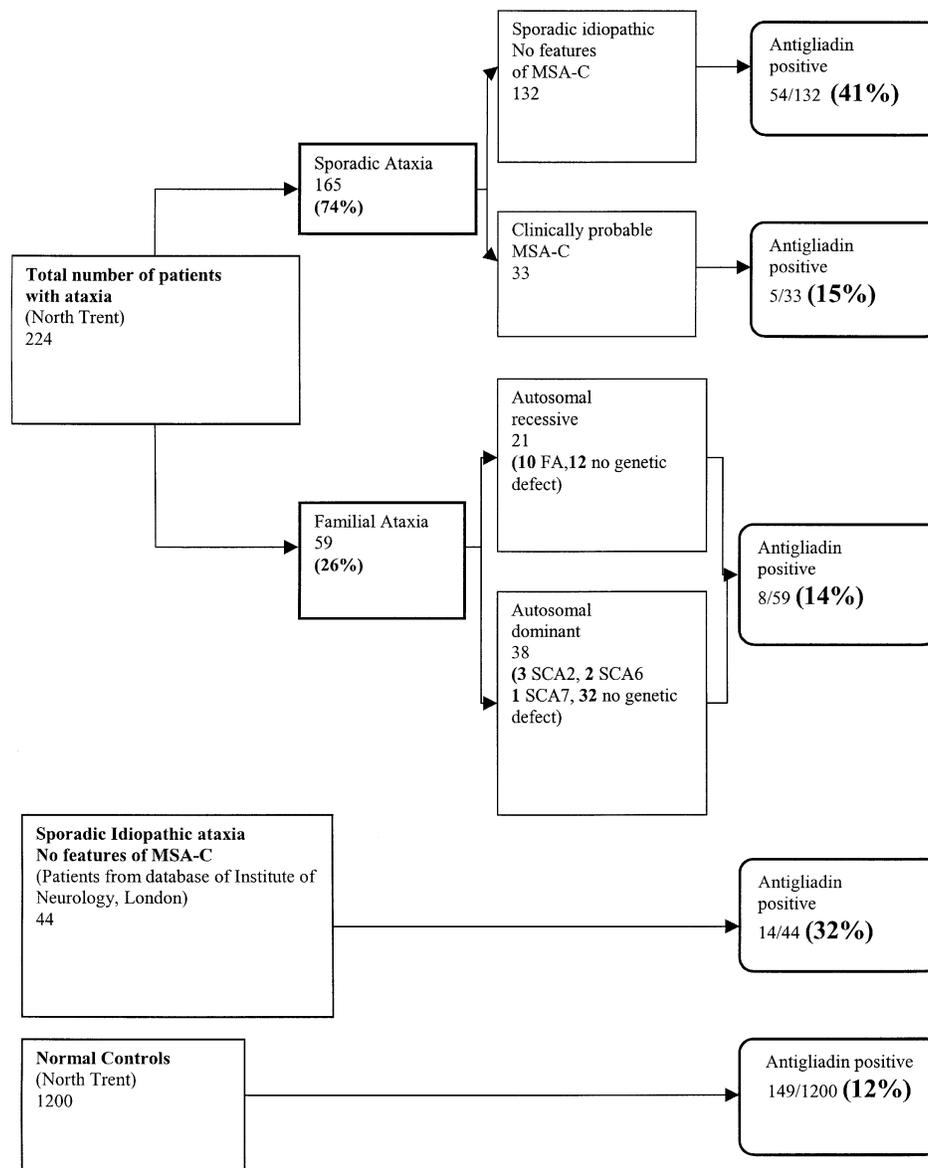


Fig. 1 The prevalence of anti-gliadin antibodies in ataxia and control groups. FA = Friedrich's ataxia; SCA = spinocerebellar ataxia, MSA-C = cerebellar variant of multiple system atrophy.

gluten-sensitive enteropathy was established by histological examination looking for evidence of crypt hyperplasia, villous atrophy and increase in intraepithelial lymphocytes.

Statistical analysis

The χ^2 test was used for comparing the prevalence of anti-gliadin antibodies in each of the groups with that of the normal controls group.

Results

Figure 1 summarizes the prevalence of IgG and/or IgA anti-gliadin antibodies in the various groups. A total of 268

patients with ataxia were screened, 224 from the Trent region and 44 patients with sporadic idiopathic ataxia without evidence of MSA-C taken from the ataxia database of the Institute of Neurology, London. Of the 224 patients from the Trent region, 59 had a family history (36 autosomal dominant, 23 autosomal recessive) and/or were positive on genetic testing for SCA 2 (three patients), SCA 6 (two patients), SCA 7 (one patient) and Friedrich's ataxia (10 patients). A total of 132 patients had sporadic idiopathic ataxia without any evidence of MSA-C. Thirty-three patients had clinically probable MSA-C. All 165 patients from the latter two groups tested negative for SCA 1, 2, 3, 6 and 7, and Friedrich's ataxia. Forty-four patients with sporadic idiopathic ataxia without evidence of MSA-C taken from the

database of the Institute of Neurology, London were screened for gluten sensitivity but only 31 attended for clinical examination. A total of 1200 normal volunteers were screened as controls.

The prevalence of significant titres of circulating IgG and/or IgA antigliadin antibodies amongst healthy control subjects from the Trent region was 149 out of 1200 (12%). This was not significantly different from the prevalence in patients with familial ataxia, where the antigliadin antibodies were present in eight out of 59 (14%). Of these eight patients, three had Friedreich's ataxia, one had SCA2 and one had SCA7. The remaining three had no genetic diagnosis. The prevalence in familial ataxia compares with 54 out of 132 (41%) in the group with sporadic idiopathic ataxia without features of MSA-C group from North Trent ($P < 0.0001$), five out of 33 (15%) in the group with clinically probable MSA-C

(not significant) and 14 out of 44 (32%) in the group with sporadic idiopathic ataxia from The Institute of Neurology, London ($P < 0.003$). Three of the eight antigliadin antibody-positive patients in the familial group had IgA antigliadin antibodies, but all were also IgG antigliadin positive. One of the five antigliadin antibody-positive patients in the MSA-C group was positive for IgA antigliadin antibody only. Only six out of 68 patients with gluten ataxia had IgA without IgG antigliadin antibodies.

HLA DQ2 was found in 27 out of 70 (39%) patients tested with sporadic idiopathic ataxia and in 13 of 31 patients tested (40%) with familial ataxia (not all patients from each group had HLA typing performed). The prevalence of HLA DQ2 amongst normal controls from the Trent region was 35% (data from the regional Blood Transfusion Unit); thus the prevalence of DQ2 in patients with sporadic idiopathic ataxia (without gluten sensitivity) and in those with familial ataxia was not significantly different from the control population. HLA DQ2 was present in 49 out of 68 (72%) patients with gluten ataxia (54 patients from North Trent plus 14 from The Institute of Neurology, London). Six percent had the HLA DQ8 and the remaining 22% had HLA DQ1.

Table 1 summarizes the clinical, radiological and neurophysiological characteristics of 68 patients with gluten ataxia (54 patients from North Trent plus 14 from The Institute of Neurology, London). There were 35 men and 33 women. The mean age at the onset of the ataxia was 48 years (range 14–81 years). The mean duration of the ataxia was 9.7 years (range 1–40 years). Ocular signs (spontaneous and gaze-evoked nystagmus and/or abnormal saccades) were observed in 84% of patients. Dysarthria was present in 66%. Upper limb ataxia was present in 75%, lower limb ataxia in 90% and gait ataxia in 100% of patients. Gastrointestinal symptoms (diarrhoea, abdominal bloating, weight loss) were present in only 13% of

Table 1 Characteristics of 68 patients with gluten ataxia

Male to female ratio	35 : 33
Mean age at onset of ataxia (range)	48 years (14–78 years)
Mean duration of ataxia (range)	9.7 years (1–40 years)
Ocular signs	84%
Dysarthria	66%
Upper limb ataxia	75%
Lower limb ataxia	90%
Gait ataxia	100%
Gastrointestinal symptoms	13%
Cerebellar atrophy on MRI	79%
White matter hyperintensities on MRI	19%
Sensorimotor axonal neuropathy on neurophysiology	45%
Gluten-sensitive enteropathy on biopsy	24%
HLA DQ2	72%

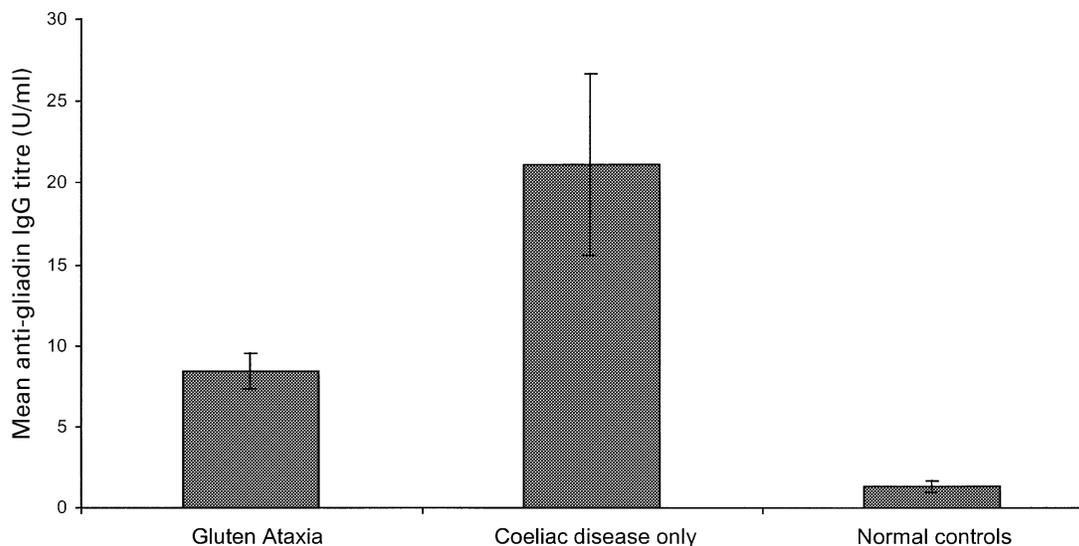


Fig. 2 Quantitative IgG antigliadin antibody titre in 30 patients with gluten ataxia, 13 patients with coeliac disease without neurological illness and 12 healthy control subjects.

patients. There was no correlation between the presence of gastrointestinal symptoms and evidence of an enteropathy on biopsy. MRI revealed atrophy of the cerebellum in 79% and white matter hyperintensities in 19% of patients. Forty-five percent of patients had neurophysiological evidence of a sensorimotor axonal neuropathy. Evidence of coeliac disease was found in 12 out of 51 (24%) patients with gluten ataxia who underwent gastroscopy and duodenal biopsy. IgG antigliadin antibody titre was higher in a cohort of 13 patients with coeliac disease and no neurological deficit when compared with a cohort of 30 patients with gluten ataxia (Fig. 2).

Discussion

In our experience of 59 patients with familial ataxia and/or positive genetic testing for SCA 1, 2, 3, 6 and 7, and Friedreich's ataxia, genetic diagnosis was only achieved in 16 (27%), leaving 73% without a genetic diagnosis. Sporadic idiopathic ataxias still account for the vast majority of patients with ataxia (74%). Of these, 20% had clinically probable MSA-C. Thus, in the majority of patients, the aetiology of ataxia still remains obscure. Our finding that gluten ataxia accounts for up to 41% of cases of sporadic idiopathic ataxia makes it the single most common cause of ataxia in this cohort of patients. This figure was slightly lower (32%) in patients with sporadic idiopathic ataxia from The Institute of Neurology in London, but the difference was not significant. The prevalence of gluten sensitivity amongst familial ataxias as well as clinically probable MSA-C from the Trent region was no different from that found in the normal population, suggesting no aetiological link between these types of ataxia and gluten sensitivity. There was, however, a small but not significant trend for the prevalence of gluten sensitivity in the MSA-C group to be higher than in the other control groups. This may reflect the fact that definite diagnosis of MSA-C on clinical grounds is impossible. Thus it is conceivable that a small number of patients with clinically probable MSA-C may prove to have gluten ataxia. This can only be determined by their response to gluten-free diet or by the pattern of progression of the disease.

Following our first publication on gluten ataxia (Hadjivassiliou *et al.*, 1998), other groups have published prevalence figures. The small number of patients screened and the lack of information on the prevalence of gluten sensitivity amongst the control population limits the value of some reports.

In a study from Italy (Pellecchia *et al.*, 1999), patients with sporadic ataxia were found to be more likely to have coeliac disease (three out of 24) than a group of patients with familial ataxia (zero out of 23). The authors did not quote the prevalence of antigliadin antibodies in their normal population and did not report any patients with circulating antigliadin antibodies who did not have coeliac disease. All their patients with ataxia and coeliac disease had circulating IgG antigliadin antibodies but not necessarily IgA antigliadin

or antiendomysium antibodies. Yet the last two antibodies are reported to be highly specific for gluten-sensitive enteropathy (Fasano, 2001). This observation suggests that IgA antigliadin and antiendomysium antibodies may lack sensitivity and specificity when used in a neurological population. Their observations support our contention that IgG antigliadin antibody is a better marker of the whole spectrum of gluten sensitivity irrespective of the organ involved. Possible reasons why these authors did not find patients with ataxia and circulating IgG antigliadin antibodies who did not have an enteropathy (representing 76% of our patients with gluten ataxia) include the fact that their antigliadin assay is set so as to have high specificity for coeliac disease perhaps at the expense of low sensitivity. This is what we have demonstrated by showing that the IgG antigliadin antibody titre in patients with gluten ataxia is lower than that in patients with coeliac disease without neurological illness. By increasing the antigliadin assay specificity for coeliac disease (i.e. increasing the threshold antibody titre defined as 'positive'), the sensitivity for the diagnosis of gluten ataxia will be reduced. Given that only 24% of our patients with gluten ataxia had gluten-sensitive enteropathy, potentially 76% of these patients may remain undiagnosed if such a high threshold value for positivity is adopted.

In a study from Germany (Bürk *et al.*, 2001), the prevalence of gluten ataxia amongst sporadic idiopathic ataxias was found to be 12 out of 104 (11.5%). Like us, the authors found a number of patients with positive IgG antigliadin antibodies and no enteropathy, but the appropriate HLA for coeliac disease. The prevalence of IgG antigliadin antibodies amongst normal controls was said to be 5%. This is lower than the 12% we have found in this study but again may relate to the assay. The authors did not attempt to separate those patients with clinically probable MSA-C from the idiopathic ataxia group. A more recent study from Germany (Abele *et al.*, 2002) found the prevalence of gluten sensitivity in the sporadic ataxia group to be 13% compared with 6% in patients with genetic ataxias and 5% in the normal population. The prevalence of antigliadin antibody positivity in patients with MSA-C was 9%. The authors, however, included not just patients with clinically probable MSA-C but also patients with possible MSA-C, thus potentially reducing further the accuracy of the clinical diagnosis of MSA-C.

A study from the USA (Bushara *et al.*, 2001) found a high prevalence of antigliadin antibody positivity in both sporadic (27%) and familial ataxias (37%). The numbers screened were small (26 sporadic and 24 familial). The prevalence of IgG antigliadin antibody alone, however, was higher in the sporadic ataxia group (15%) than the familial group (8%). Those authors offer no figure for the prevalence of antigliadin antibodies in the normal population for comparison.

A study from Finland (Luostarinen *et al.*, 2001) found the prevalence of coeliac disease in sporadic ataxias (44 patients) to be 16.7%, with the prevalence of coeliac disease in the normal population being ~1.6%.

A report from Spain (Combarros *et al.*, 2000) describes 32 patients with idiopathic ataxia who were screened but not found to have antigliadin antibodies. From the limited clinical data provided, 16 of these patients had features suggestive of MSA-C, leaving only 16 patients with sporadic idiopathic ataxia. The authors offer no figure for the prevalence of antigliadin antibodies in the normal population.

Finally, a much smaller study from Ireland (Lim *et al.*, 2001) reported coeliac disease in three of seven patients presenting with sporadic ataxia.

Despite possible methodological differences (e.g. antigliadin assay) and geographical variations that may contribute to differences in prevalence, all but one of these studies confirm our original findings of the existence of gluten ataxia as a disease entity. No combination of clinical features is sufficiently specific to enable a clinical diagnosis of gluten ataxia to be made with confidence, except perhaps in patients with established coeliac disease. The clinical features described in Table 1 are also seen in patients with other forms of sporadic and inherited ataxia, and this emphasizes the importance of maintaining a low threshold for suspicion of gluten sensitivity in patients presenting with ataxia.

IgG antigliadin antibodies by definition remain the best diagnostic marker for gluten ataxia. Although it is generally accepted that IgG antigliadin antibodies have a very high sensitivity for gluten-sensitive enteropathy, they are said by most gastroenterologists to lack specificity. In the context of a range of mucosal abnormalities seen in this disease, ranging from normal to irreversible hypoplastic atrophic lesions (Marsh, 1995), and the concept of potential coeliac disease (Maki *et al.*, 1991), meaning a histologically normal mucosa but altered T-cell subpopulations, IgG antigliadin antibodies may be the only available immunological marker for the whole spectrum of gluten sensitivity, of which gluten-sensitive enteropathy is only a part. Further support for our contention comes from our HLA studies. Within the group of patients with gluten ataxia (defined by the presence of IgG antigliadin antibodies), we have found an HLA association similar to that seen in patients with coeliac disease: 72% of patients have the HLA DQ2 (35% in the general population), 6% have the HLA DQ8 and the remainder have HLA DQ1.

We have looked at the prevalence of HLA DQ2 in both familial and sporadic idiopathic ataxia in an attempt to clarify whether the high prevalence of gluten ataxia in sporadic idiopathic ataxias may be related to a high prevalence of this HLA type within this group. Our results show no significant differences of the prevalence of this HLA type amongst normal controls, familial or sporadic idiopathic ataxias. The high prevalence of gluten ataxia in the group of patients with sporadic idiopathic ataxias cannot simply be explained on the grounds of the prevalence of HLA DQ2 within this group. It is likely, however, that the prevalence of HLA DQ2 in the general population may have some influence on the prevalence of gluten-related diseases. It would be interesting to study the prevalence of gluten ataxia in Japan where the prevalence of HLA DQ2 is only 1%.

The introduction of more coeliac disease-specific serological markers such as endomysium and, more recently, tissue transglutaminase antibodies may have helped in diagnosing gluten-sensitive enteropathy, but their sensitivity as markers of other manifestations of gluten sensitivity (where the bowel is not affected) is, by definition, low. This reflects our findings with patients with gluten ataxia. Endomysium and tissue transglutaminase antibodies are positive in the majority but not necessarily all of the gluten ataxia patients with an enteropathy. Patients with an enteropathy represent only a small proportion of patients with gluten ataxia (24%).

Intestinal mucosal damage in gluten-sensitive enteropathy is both humoral and T cell mediated. Such inflammation is not, however, confined to the gut, as activated HLA-restricted gliadin-specific T cells and antigliadin antibodies are found systemically (Sollid and Thorsby, 1993; Jensen *et al.*, 1995). Antigliadin antibodies are also found in the CSF (Chinnery *et al.*, 1997). Post-mortem findings from two of our patients with gluten ataxia has shown perivascular cuffing with both CD4 and CD8 cells. This inflammation was seen primarily in the white matter of the cerebellum. There was also marked but patchy Purkinje cell loss. We have also found antibodies against Purkinje cells in patients with gluten ataxia (Hadjivassiliou *et al.*, 2002b). Our research suggests that antigliadin antibodies cross-react with epitopes on Purkinje cells from human and rat cerebellum. Characterization of the anti-Purkinje cell antibodies by immunoblotting may provide a useful marker for the diagnosis of gluten ataxia in a manner analogous to the use of antiendomysium antibodies as a marker for coeliac disease, or the anti-Yo and other antibodies in paraneoplastic cerebellar degeneration. This will eliminate the potential problem of overdiagnosing gluten ataxia by 12% given that antigliadin antibodies are found in 12% of the normal population. What is unclear at present (due to lack of definition) is whether the prevalence of gluten sensitivity (with or without an enteropathy) in the general population could be as high as 12%.

Evidence is emerging that a gluten-free diet may be beneficial in the treatment of gluten ataxia in terms of both the symptoms of ataxia and the neurophysiological assessment of the peripheral neuropathy (Hadjivassiliou *et al.*, 2002a). The timing of the diagnosis and treatment of these patients appears to be crucial because of the loss of Purkinje cells which is irreversible. Thus, antigliadin antibodies should be an essential part of the investigation of patients with sporadic idiopathic ataxia at first presentation, and a gluten-free diet should be advised even in the absence of an enteropathy.

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