LETTER TO THE EDITOR

The neurology of gluten sensitivity: science vs. conviction

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EDITORIAL COMMENT
Nottingham and Sheffield are less than 50 miles apart, but clearly patients are managed very differently in the two cities when it comes to searching for the neurological complications of coeliac disease or gluten sensitivity. Whilst the observational epidemiological arguments rage backwards and forwards, the proof that patients are benefited – or not – by a gluten free diet will only come from randomised trials. After all, observational epidemiology can get the wrong answer, for example with hormone replacement therapy and the risk of stroke. However, these trials will probably have to be done by neurologists who are much less certain of their position than those in Sheffield and Nottingham who have already made up their minds to treat or not to treat.

The proliferation of publications on the neurological manifestations of gluten sensitivity reflects a surge of interest in this fascinating group of immune-mediated diseases. Thorough knowledge of the literature on the subject is essential to avoid the bias in interpretation of such studies apparent in some recent editorials, in particular the article by Pengiran Tengah and Wills in the December 2003 issue of *Practical Neurology*.

In 1996 we published a paper entitled 'Does cryptic gluten sensitivity play a part in neurological illness?' (Hadjivassiliou *et al.* 1996). On the basis of a markedly increased prevalence of circulating antigliadin antibodies in a group of patients with otherwise idiopathic neurological dysfunction, we concluded the answer was 'yes'. A follow-up paper demonstrated that the most common problem was ataxia and we introduced the term 'gluten ataxia' (Hadjivassiliou *et al.* 1998). This is no surprise. A review of all

Questions and answers about the neurology of gluten sensitivity

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In recent years there has been a plethora of articles claiming that various neurological syndromes are associated with or are caused by gluten sensitivity. However, the busy clinical neurologist needs to know the answers to just two main questions – does gluten sensitivity predispose patients to the development of various neurological complications, and should a patient with a cryptogenic neurological illness be investigated for occult gluten sensitivity (and if so how)?

WHAT IS GLUTEN SENSITIVITY?

Coeliac disease is a classic gluten sensitive enteropathy, typically presenting in childhood. It is common with a prevalence of between 1 : 80 and 1 : 300. There is characteristic small bowel villous atrophy (Fig. 1a) associated with abdominal pain, malabsorption and weight loss. A gluten-free diet rapidly reverses this atrophy (within weeks) (Fig. 1b), corrects malabsorption and leads to symptomatic improvement. In addition, patients may sometimes present with non-specific or trivial complaints and the diagnosis of coeliac disease is only suspected when haematological abnormalities develop, such as anaemia, or from the results of specific serological tests.

Dermatitis herpetiformis is rarer but is also a gluten sensitive disease manifesting as an itchy blistering skin rash (Fig. 2) and resolving (much more slowly) on a gluten-free diet. In spite of the fact that most patients do not have any bowel symptoms, they all have the gut changes characteristic of coeliac disease.

WHAT ARE THE MOST RELIABLE TESTS FOR GLUTEN SENSITIVE ENTEROPATHY?

Biopsy of skin or gut is the 'gold standard' for the diagnosis of dermatitis herpetiformis and coeliac disease, respectively. The serological tests include anti-reticulin antibodies (ARA), IgA and IgG anti-gliadin antibodies (AGA), endomysial antibodies (EMA) and tissue transglutaminase antibodies (tTG). These vary in specificity and sensitivity. EMA, ARA and tTG are better than AGA (IgA and IgG) in terms of both sensitivity and specificity (Catassi *et al* 1994; Valdimarsson *et al.* 1996). IgG AGA is probably the least reliable in identifying coeliac disease because it is found in a number of other conditions such as IgA nephropathy, and even in 10% of normal subjects. In contrast, positive ARA, tTG or EMA are all good predictors for the later development of coeliac disease, even in patients with no gut symptoms and normal small bowel histology.

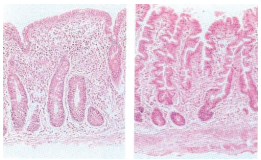

Figure 1 (a) Small bowel biopsy of a patient with untreated coeliac disease showing subtotal villous atrophy. (b) Normal small bowel biopsy after dietary treatment.

WHICH NEUROLOGICAL CONDITIONS ARE ASSOCIATED WITH COELIAC DISEASE?

Malabsorption is a well-recognized complication of coeliac disease and so it is no surprise that in a study of 35 newly diagnosed coeliac disease patients vitamin B12 deficiency was present in 13 (45%). Although none were reported to have any neurological deficit, three of these patients had presented with cold peripheries and paraesthesiae (Dahele *et al.* 1999). There are numerous case reports of coeliac disease patients with easily understandable neurological illnesses such as osteomalacic myopathy due to vitamin D malabsorption, and cerebellar ataxia complicating vitamin E deficiency, who improved with vitamin replacement and a gluten-free diet (Mauro *et al.* 1991; Battisti *et al.* 1996). However, vitamin deficiency is not always present in similar cases (Bhatia *et al.* 1995), vitamin replacement is not always helpful (Lu *et al.* 1986), and often no neurological complications occur even with severe vitamin deficiency.

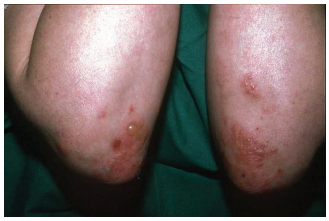

Figure 2 Blisters on the elbows of a patient with dermatitis herpetiformis. Reproduced courtesy of Professor Lionel Fry, Imperial College, London.

The association of epilepsy with coeliac disease has been suggested by a number of authors (Gobbi *et al.* 1992) but denied by others. Holmes suggested a lifetime epilepsy prevalence of 3.6% in a population of 388 patients with established coeliac disease (Holmes 1997). Italian studies have suggested a further association between coeliac disease, epilepsy and cerebral calcifications (Gobbi *et al.* 1992) (Fig. 3), although this has not been found in Irish and Finnish populations.

Three groups have shown an increased frequency of gluten sensitivity in patients with idiopathic cerebellar ataxia (Hadjivassilio *et al.* 1998; Pellecchia *et al.* 1999; Burk *et al.* 2001). However, they relied heavily on IgG AGA as a screening tool. But, AGA positivity has also been described in genetic and alcohol-induced ataxias as well as with multiple system atrophy. This suggests that AGA positivity might be an epiphenomenon associated with cerebellar damage. We have seen a patient with cerebellar degeneration associated with AGA positivity (and a normal gut biopsy) in whom the serology re-tested as negative 6 months later, even without dietary intervention. Another problem is that in the aforementioned studies, where small bowel histopathological abnormalities have been reported, the examining pathologist was not blind to the clinical status of the patients.

Other neurological associations are even less clear. There have been a few descriptions of pa-

published papers from 1964 to 2000 of 83 patients with coeliac disease who then developed a neurological illness showed that the most common were ataxia (29 patients) and peripheral neuropathy (29 patients) (Hadjivassiliou *et al.* 2002b).

The term 'coeliac disease' should now be restricted to describe gluten sensitive *enteropathy*. The term gluten sensitivity describes a spectrum of diseases that have 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 (e.g. gluten ataxia). Not surprisingly, the common aetiological trigger (gluten) means that these diseases overlap considerably. For example, the vast majority of patients with dermatitis herpetiformis also have an enteropathy, as do a third of patients with gluten ataxia (Hadjivassiliou *et al.* 2003b).

Whilst gastroenterologists now accept that gluten sensitivity can exist even in the absence of an enteropathy (Marsh 1995), some – such as Tengah and Wills – dispute the entity of gluten-related neurological dysfunction in coeliac disease, let alone in those patients without an enteropathy. Because gluten-sensitive enteropathy is often clinically silent, it follows that, if gluten sensitivity presents with neurological manifestations, symptomatic bowel involvement may be inconspicuous. Dermatitis herpetiformis (DH) makes this point because most patients complain of an itchy rash, and yet gastrointestinal symptoms are absent in the vast majority. The disorder is, however, obviously gluten-driven as it resolves with elimination of gluten from the diet. Similarly, we have recently demonstrated that a gluten-free diet is an effective treatment for gluten ataxia even in the absence of an enteropathy (Hadjivassiliou *et al.* 2003a).

There is also confusion about the role of antigliadin antibodies as a screening tool. Given that gluten sensitivity can exist without enteropathy, it is inappropriate to estimate sensitivity and specificity of these antibodies against the presence of enteropathy as the 'gold standard'. To assert that antigliadin antibodies lack specificity based on the fact that 10% of the healthy population may have them is a misconception. It is entirely plausible that 10% of the healthy population with circulating antigliadin antibodies have gluten sensitivity without recognized manifestations. The prevalence of coeliac disease itself is now recognized to be

20 times higher than what it was thought to be 20 years ago because most cases are clinically silent. It is important to realize that amongst these 10% antigliadin antibody positive people lurks those with 'silent' gluten sensitive enteropathy. Furthermore, the high prevalence of the HLA haplotype associated with coeliac disease in those patients with circulating antigliadin antibodies but no enteropathy emphasizes that these antibodies represent more than coincidental antigenic cross-reactivity.

These observations have important implications for health care. It is ill-considered to suggest that antigliadin antibodies should not be used as a screening tool because they are found in 'healthy' individuals. Such an assertion would exclude a role for antineutrophil cytoplasmic antibodies in the diagnosis of vasculitis or of rheumatoid factor in the diagnosis of rheumatoid arthritis. It is also irresponsible to suggest that neurological patients should not be screened for coeliac disease unless additional factors are present such as unexplained anaemia or evidence of malabsorption. We have already demonstrated that gastrointestinal symptoms and occult malabsorption are rare in this patient group, even in the presence of an enteropathy (Hadjivassiliou *et al.* 1998). It is also well known that for every patient with coeliac disease presenting to the gastroenterologist there are eight without gastrointestinal symptoms (Fasano & Catassi 2001).

The evidence for the existence of gluten ataxia (sporadic ataxia with positive antigliadin antibodies) as a disease entity is now overwhelming. The syndrome is characterized by ataxia, antigliadin antibodies, the HLA haplotype associated with gluten sensitivity, Purkinje cell antibodies (Hadjivassiliou *et al.* 2002a); high chemokine IP-10 and often oligoclonal bands in the CSF (Hadjivassiliou *et al.* 2003c); inflammatory pathology of the cerebellum at postmortem (Hadjivassiliou *et al.* 1998), and the response to a gluten-free diet (Hadjivassiliou *et al.* 2003a).

The source of this dispute about the epidemiology of gluten ataxia comes mainly from two observations. Firstly, in some epidemiological studies, although the prevalence of antigliadin antibodies in sporadic ataxia was much higher than in healthy controls, the difference was not statistically significant. Such studies were under-powered to detect a significant difference. As an example, a recent study (Abele *et al.* 2003) demonstrated antigliadin antibodies in 8% of healthy controls and 19% in patients with sporadic idiopathic ataxia. A sample size of more than 300 would have been required to have 80% power to exclude the null hypothesis at $P < 0.05$. Yet the sample size in this study was 105. Only one of the studies published (Hadjivassiliou *et al.* 2003b; which confirms the association of gluten-sensitivity with ataxia) has adequate statistical power. All the other smaller studies showed a trend in favour of a higher prevalence of antigliadin antibodies amongst idiopathic sporadic ataxias (Abele *et al.* 2003; Pellecchia *et al.* 1999; Bürk *et al.* 2001; Bushara *et al.* 2001; Abele *et al.* 2002; Luostarinen *et al.* 2001). Secondly, two studies (Abele *et al.* 2003; Bushara *et al.* 2001) have shown the prevalence of antigliadin antibodies to be high in patients with familial ataxias. Whilst these studies also suffer from small sample sizes, they stimulate consideration of the interaction of gluten sensitivity with familial ataxias. Gluten sensitive enteropathy is familial in about 10% of patients with coeliac disease, not surprisingly given its strong association with HLA. It is likely therefore that gluten ataxia may have a similar familial predisposition. We have certainly encountered patients with familial gluten-related neurological dysfunction who respond to a gluten-free diet.

What about those cases with a genetically characterized ataxia? Could cerebellar degeneration provoke an immune response to gluten? We have demonstrated binding of antigliadin antibodies to Purkinje cells (Hadjivassiliou *et al.* 2002a). Could Purkinje cell degeneration provoke the production of antibodies to gliadin? Arguing against this is our failure to find Purkinje cell antibodies in the sera of patients with genetically characterized inherited ataxias (Hadjivassiliou *et al.* 2002a). Furthermore, cerebellar degeneration in the context of a genetically characterized inherited ataxia is not known to be associated with a pronounced inflammatory component, perhaps an important prerequisite in the production of such antibodies.

The conclusion of the article that 'there is little evidence for the existence of true gluten sensitive neurological syndromes' is dangerously misleading. Neurological manifestations of gluten sensitivity are a scientific fact, not a theological issue. Whilst the debate continues, we owe it to our patients to screen them effectively for gluten sensitivity with the simple widely available antigliadin antibody test so that we do not in the meantime deprive them of a harmless but potentially effective treatment in the form of a gluten-free diet.

It is irresponsible to suggest that neurological patients should not be screened for coeliac disease unless additional factors are present

REFERENCES

Abele M, Schols L, Schwartz S & Klockgether T (2003) Prevalence of antigliadin antibodies in ataxia patients. *Neurology*, **60**, 1674–5.

Bürk K, Bösch S & Müller CA*et al.* (2001) Sporadic cerebellar ataxia associated with gluten sensitivity. *Brain*, **124**, 1013–9.

Bushara KO, Goebel SU, Shill H, Godfarb LG & Hallett M (2001) Gluten sensitivity in sporadic and hereditary cerebellar ataxia. *Annals of Neurology*, **49**, 540–3.

Fasano A & Catassi C (2001) Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology*, **120**, 636–51.

Hadjivassiliou M, Boscolo S, Davies-Jones GAB *et al.* (2002a) The humoral response in the pathogenesis of gluten ataxia. *Neurology*, **58**, 1221–6.

Hadjivassiliou M, Davies-Jones GAB, Sanders DS & Grünewald RAG (2003a) Dietary treatment of gluten ataxia. *Journal of Neurology Neurosurgery and Psychiatry*, **74**, 1221–4.

Hadjivassiliou M, Gibson A, Davies-Jones GAB, Lobo AJ, Stephenson TJ & Milford-Ward A (1996) Does cryptic gluten sensitivity play a part in neurological illness? *Lancet*, **347**, 369–71.

Hadjivassiliou M, Grünewald RA & Chattopadhyay AK*et al.* (1998) Clinical, radiological, neurophysiological and neuropathological characteristics of gluten ataxia. *Lancet*, **352**, 1582–5.

Hadjivassiliou M, Grünewald RA & Davies-Jones GAB (2002b) Gluten sensitivity as a neurological illness. *Journal of Neurology Neurosurgery and Psychiatry*, **72**, 560–3.

Hadjivassiliou M, Grünewald RA, Sharrack B *et al.* (2003b) Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain*, **126**, 685–91.

Hadjivassiliou M, Williamson CA & Woodroofe NM (2003c) The humoral response in the pathogenesis of gluten ataxia: Reply from authors. *Neurology*, **60**, 1397–9.

Luostarinen LK, Collin PO, Paraaho MJ, Maki MJ & Pirttila TA (2001) Coeliac disease in patients with cerebellar ataxia of unknown origin. *Annals of Medicine*, **33**, 445–9.

Marsh MN (1995) The natural history of gluten sensitivity: defining, refining and re-defining. *Quarterly Journal of Medicine*, **85**, 9–13.

Pellecchia MT, Scala R, Filla A, De Michele G, Ciacci C & Barone P (1999) Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features. *Journal of Neurology, Neurosurgery and Psychiatry*, **66**, 32–5.