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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WHAT ARE THE MOST RELIABLE TESTS FOR GLUTEN SENSITIVE ENTHROPATHY?

Many of the signs and symptoms of coeliac disease are not specific for the diagnosis of coeliac disease or gluten sensitivity. The diagnostic yield of serological markers is unpredictable (Alvarez-Bueno et al 1998). The sensitivity and specificity of antigliadin antibodies (Alvarez-Bueno et al 1998) and antibodies to tissue transglutaminase (O’Brien et al 1999) are less than 90% (Alvarez-Bueno et al 1998). There is a high false-negative rate for IgA antigliadin antibodies and a high false-positive rate for IgG antigliadin antibodies, both of which tend to be negative in patients with coeliac disease. Therefore, serological tests should be interpreted with caution, and a gluten-free diet should be introduced only in patients with a gluten-sensitive enteropathy and positive serology (and a normal gut biopsy) in whom the serology is re-tested as negative 6 months later, even without dietary intervention. Another problem is that most patients do not have any bowel symptoms (O’Brien et al 1999) and the gluten-dependent aetiology may be missed in patients without gastrointestinal symptoms (O’Brien et al 1999). In the presence of coeliac disease, one of the most reliable tests is a marked increase in gliadin-specific IgA antibodies that persists after elimination of gluten from the diet. This increase in antibodies is also a marker for gluten sensitivity (Tengah et al 2003). 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


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