Questions and a neurology of gl

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Practical Neurology

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.

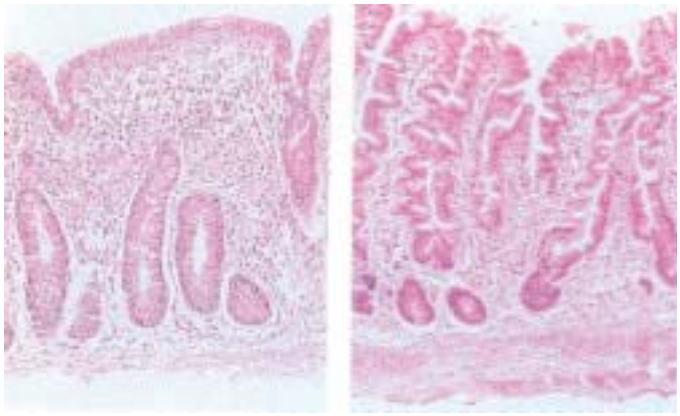

Figure 1 (a) Small bowel biopsy of a patient with untreated coeliac disease showing subtotal villous atrophy. (b) Normal small bowel biopsy after dietary treatment.

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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.

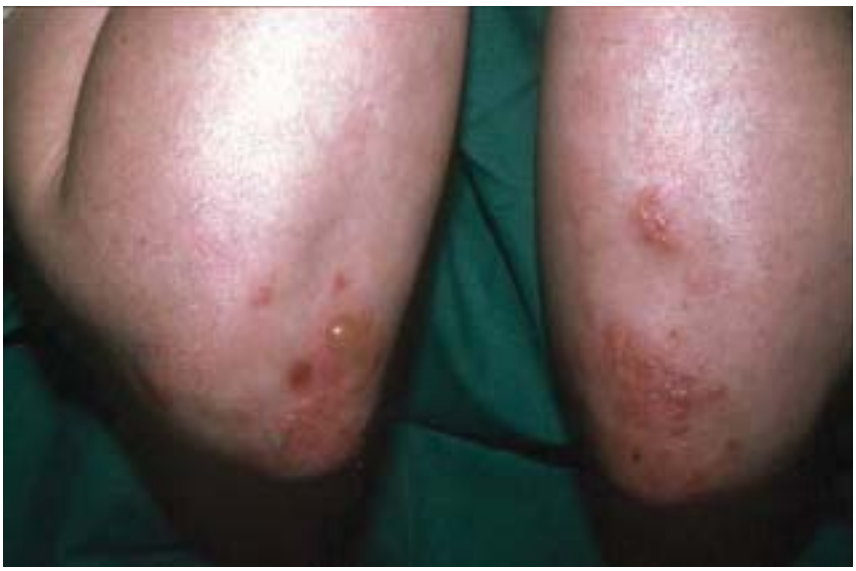

Figure 2 Blisters on the elbows of a patient with dermatitis herpetiformis. Reproduced courtesy of Professor Lionel Fry, Imperial College, London.

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-

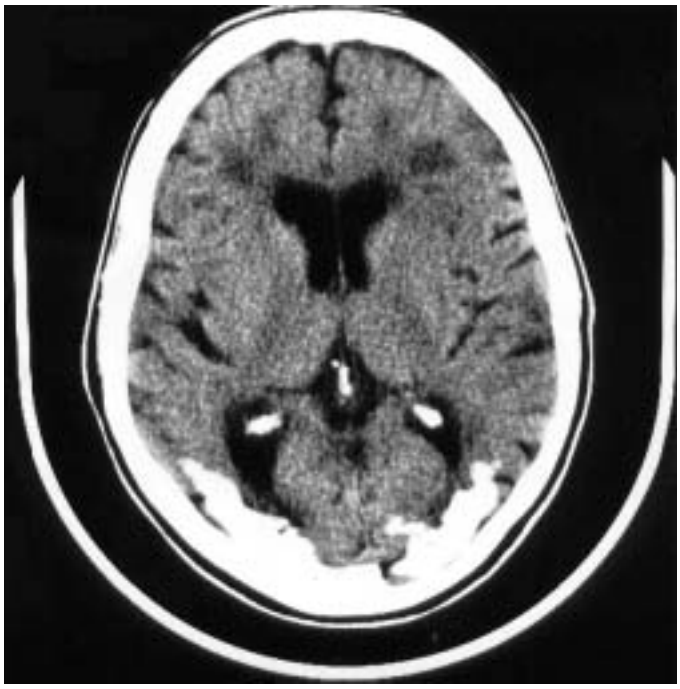

Figure 3 CT of the brain showing bilateral occipital calcifications in a patient with coeliac disease and epilepsy. Reproduced courtesy of Dr G. Plant, National Hospital for Neurology and Neurosurgery, Queen Square, London.

tients with: coeliac disease and myoclonic ataxia (Ramsay–Hunt Syndrome) (Lu *et al.* 1986; Bhatia *et al.* 1995; Chinnery *et al.* 1997); peripheral neuropathy (Simonati *et al.* 1998); CNS vasculitis (Bernier *et al.* 1976); brainstem encephalitis (Brucke *et al.* 1988); dementia (Collin *et al.* 1991); and chronic progressive leukoencephalopathy (Beyenburg *et al.* 1998). Cooke and Smith reported 16 patients with severe malabsorption complicating coeliac disease who developed a rapidly progressive neurological syndrome characterized by sensory ataxia but with no response to gluten restriction (Cooke & Smith 1966). They speculated that some trace vitamin deficiency or toxin exposure might be the cause. This hypothesis has still not been tested and we do not know whether riboflavin, niacin, thiamine or pyridoxine deficiency might be relevant.

Because coeliac disease is so common in the general population, certain neurological 'associations' may well be coincidental. Alternatively, similar HLA haplotypes may confer an increased likelihood of autoimmune disease in general. This has been suggested as an explanation for the increased prevalence of hypothyroidism (Sategna-Guidetti *et al.* 2001) and Type 1 diabetes mellitus (Holmes 2001) in coeliac disease.

HOW SHOULD I MANAGE A PATIENT WITH KNOWN COELIAC DISEASE WHO PRESENTS WITH A NEUROLOGICAL PROBLEM?

Points to be elicited in the history should include adherence to a gluten-free diet and any symptoms indicating poor dietary compliance such as diarrhoea or abdominal pain. Serological markers (EMA/tTG/ARA) can be helpful in determining whether patients are complying with the diet because they should become negative. Gut lymphoma is a recognized complication of coeliac disease and persistent symptoms like abdominal pain, diarrhoea and weight loss refractory to diet should raise suspicion. These patients must be rapidly referred for endoscopy and small bowel biopsy. In theory, a paraneoplastic neurological disorder secondary to gut lymphoma is possible although it has never been described in association with coeliac disease. Although Shams *et al.* (2002) described a patient with a cerebellar disorder, enteropathy and positive AGA antibodies, he was actually found to have an enteropathy associated T-cell lymphoma with lymphomatous infiltration of the cerebellum.

Because coeliac disease is associated with other auto-immune conditions such as hypothyroidism and insulin-dependent diabetes mellitus, thyroid function and blood glucose should be checked. Other useful blood tests include full blood count, ferritin, B12, folate and calcium as these can be low in poorly controlled coeliac disease. Trace vitamin assays are theoretically of interest but difficult or impossible to obtain in practice.

IN WHICH NEUROLOGICAL CONDITIONS SHOULD OCCULT GLUTEN-SENSITIVITY BE SOUGHT?

It is increasingly recognized that coeliac disease is common and under-diagnosed and hence clinicians should be alert to the possibility of this diagnosis in any patient, neurological or otherwise. Despite numerous descriptions of neurological diseases in association with coeliac disease, there is still insufficient evidence for many of these associations and so most 'neurological' patients are unlikely to benefit from screening for coeliac disease.

However, epileptic patients with cerebral calcifications may benefit from serological testing because there have been reports of seizure control improving on a gluten-free diet, but this is extremely rare and has not been reported outside Italian populations. Patients with idiopathic cerebellar ataxia may have raised AGA titres but the significance of this is unclear and certainly there is no convincing published evidence for improvement on a gluten-free diet.

Any indicators of malabsorption should raise suspicion of coeliac diease. Both tetany and my-

opathy as a result of calcium deficiency have been reported in coeliac disease.

We suggest that, in general, neurological patients should not be screened for coeliac disease unless additional factors are present such as unexplained anaemia or evidence of malabsorption. Then EMA, tTG or ARA titres should be checked and, if present, specialist gastroenterological advice should be sought and a gut biopsy considered.

WHAT TREATMENT OPTIONS ARE AVAILABLE FOR PATIENTS WITH NEUROLOGICAL CONDITIONS ASSOCIATED WITH COELIAC DISEASE?

A gluten-free diet normalizes small bowel villous atrophy, reverses malabsorption and reduces the risk of small bowel lymphoma. Patients generally feel better fairly quickly, but it may take a relatively long time for the antibody titres to return to normal. However, there is very limited evidence to suggest that a gluten-free diet is helpful for any of the neurological conditions that seem to be associated with genuine gluten sensitivity. Indeed some patients have appeared to develop neurological complications even whilst strictly adhering to a gluten-free diet (Cooke & Smith 1966; Beyenburg *et al*. 1998). However, a gluten-free diet may prevent or stabilize seizures in certain forms of epilepsy (Lea *et al*. 1995). There are also case reports of improvement in peripheral neuropathy (Kaplan *et al*. 1988). There is no convincing published evidence that a gluten-free diet is likely to be of benefit in patients with cryptogenic ataxia, dementia or CNS white matter disease.

Vitamin replacement may be helpful in a select group of patients, e.g. where vitamin E or B12 deficiency complicates malabsorption. There are anecdotal reports of the use of immunosuppressive treatment in patients with coeliac disease and neurological syndromes with (Ghezzi *et al*. 1997) and without success (Beyenburg *et al*. 1998). These treatments cannot be recommended at present.

CONCLUDING REMARKS.

Occult coeliac disease is so common that it will inevitably be encountered by clinical neurologists. However, there is little evidence for the existence of true gluten–sensitive neurological syndromes. We hope that future studies will be well controlled to differentiate between the chance association of unrelated conditions and the potentially fascinating notion that gluten might be neurotoxic.

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