**SHORT REPORT**

Dermatitis herpetiformis and neurological dysfunction

A J Wills, B Turner, R J Lock, S L Johnston, D J Unsworth, L Fry

Dermatitis herpetiformis and coeliac disease are gluten sensitive diseases, which have common immunopathological and genetic mechanisms. Neuropsychiatric complications have been reported in up to 26% of patients with coeliac disease. This is probably an overestimate, because of the chance associations with some common neurological conditions such as epilepsy. The pathogenesis is speculative but it has been postulated that gluten is neurotoxic possibly via immune mechanisms. The frequency of neurological dysfunction in patients with dermatitis herpetiformis has not been characterised. Patients with dermatitis herpetiformis might be expected to be particularly susceptible to neuronal damage as some continue to consume gluten when their dermatological symptoms are controlled by dapsone. Thirty-five patients were recruited with dermatitis herpetiformis from dermatology clinics at St Mary’s Hospital, London and Queen’s Medical Centre, Nottingham and investigated for evidence of neurological abnormality. All patients underwent a full neurological examination and were asked about their neurological and general medical history by means of a structured questionnaire. Serum samples were taken and screened for the presence of anti-neuronal antibodies (anti-Hu and Yo) as well as anti-gliadin (IgA and G) anti-endomysial (IgA), and anti-tissue transglutaminase (IgA) antibodies. Neurophysiological tests were carried out where appropriate. Only two patients were identified with unexplained neurological abnormalities (one essential tremor, and one chorea). Two other patients had a history of migraine. The patient with chorea also had borderline/equivocally positive anti-Hu antibodies by immunofluorescence assay. All other samples were negative for anti-neuronal antibodies. Fifteen patients were positive for anti-gliadin antibodies (IgA and/or IgG), four for anti-endomysial antibodies (monkey oesophagus or umbilical cord), and six for anti-tissue transglutaminase antibodies. The presence of these antibodies did not correlate with the presence of neurological abnormalities. No cases of “gluten ataxia” were identified.

In conclusion, there was no convincing evidence for immune mediated neurological damage in this pilot study of dermatitis herpetiformis.

Dermatitis herpetiformis (DH) is a blistering skin disease characterised by IgA deposition in the papillary dermis. Patients generally respond to gluten withdrawal but dapsone provides a useful therapeutic alternative. There has been debate about the relation of DH to coeliac disease (CD) but most authorities acknowledge that they are very closely related. A gluten sensitive enteropathy underlies both conditions. The evidence for this is robust. All patients with DH have evidence of gluten sensitivity in the small intestine, although only two thirds show villous atrophy on a single biopsy. Both conditions have a 95% incidence of the HLA haplotypes DR3/DQ2. Five pairs of monozygotic twins have been described where one twin has CD and the other has DH. In addition, DH probands have an equal number of relatives with DH and CD. Anti-endomysial (AEA), anti-gliadin (AGA), anti-reticulin, and anti-tissue transglutaminase (TTG) antibodies are found in both conditions. Patients with DH differ in their response to gluten restriction in that the skin changes may take 2 years to resolve after initiation of the diet and therefore dapsone is routinely offered in addition to a gluten free diet to all patients after diagnosis.

Neurological disorders are said to occur in 10% of patients with CD. These include epilepsy, neuropathy, ataxia, and dementia. Some of these syndromes are associated with minimal or no enteric symptoms. The response to gluten restriction is unclear. Postmortem analysis of the patients with ataxia has shown Purkinje cell loss and astrocytosis.

More recently, Hadjivassiliou et al have described a syndrome which they term “gluten ataxia”. They initially made the surprising observation that 57% of patients with neurological dysfunction of unknown cause had serological evidence (AGA positivity) of gluten sensitivity. The use of AGA (especially IgG) as a screening test is questionable as AGA is commonly detected in over 10% of normal healthy controls with no apparent clinical gluten sensitivity. Subsequently, over a 4 year period they collected 28 ataxic patients, (all selected because of AGA seropositivity), and discovered that all but five had the HLA DQ2 haplotype. They postulated that these patients were gluten sensitive. Despite a “normal” duodenal biopsy in 15 cases, they concluded that gluten ataxia accounts for a significant proportion of late onset cerebellar ataxias. Analogy might be drawn with DH where subtle (gluten sensitive) abnormalities of the small bowel mucosa are associated with gluten sensitive clinical lesions (in this case a rash) remote from the gut. A suggestion was also made that some of the ataxic patients benefited on a gluten free diet, but scant supportive data were provided. The effect of gluten challenge on intraepithelial lymphocyte counts in the gut was not studied. They postulated that the central and peripheral nervous systems are susceptible to immune mediated damage mediated by gluten. Pellechia et al also identified three patients with serological and histological evidence of CD in a cohort of 24 patients with late onset idiopathic ataxia.

Patients with DH tend to present later than patients with CD and are therefore exposed to gluten for a longer period before the diagnosis is made. In addition, patients with DH with minimal or no enteric symptoms are less compliant with gluten restriction as their symptoms can be adequately controlled with dapsone. In this subgroup, chronic gluten toxicity might be expected to lead to an increased frequency of neurological complications in comparison with patients with CD. We set out to test this hypothesis in a group of 35 patients with DH.

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**Abbreviations:** AGA, anti-gliadin; DH, dermatitis herpetiformis; CD, coeliac disease.
METHODS
From November 1999 to April 2000 we identified 35 patients with DH attending dermatology clinics at St Mary's Hospital, London and the Queen's Medical Centre, Nottingham. All the patients had presented with a rash and the diagnosis of DH had been previously confirmed by skin biopsy showing characteristic IgA deposits in the dermoepidermal junction on direct immunofluorescence. Intestinal biopsies had previously been performed in 32 of the 35 patients. Initially, the rash was controlled with dapsone but all patients were offered a gluten free diet when the diagnosis had been confirmed. Each patient was questioned about previous and current neurological and enteric symptoms. All patients underwent a thorough neurological examination by a neurologist (BT or AJW). Nerve conduction studies were arranged where appropriate. All patients gave informed written consent.

We also took samples of fresh clotted blood for assessment of anti-neuronal antibody status. Anti-Hu and Yo were detected by indirect immunofluorescence at a dilution of 1/5, using commercial slides (The Binding Site, Birmingham, UK.) of monkey cerebrum and cerebellum as the substrate.

AGA (IgA and G) and IgA TTG antibodies were detected by enzyme linked radioimmunoassay (ELISA) as described previously with serum diluted 1/100 IgA or 1/1000 IgG respectively in phosphate buffered saline (PBS). IgA AEA antibody (using a 1/5 dilution of patient serum) was detected using monkey oesophagus/human umbilical cord as described before.

RESULTS
The mean age of the patients was 59 years (range 13–81) and mean disease duration 20 years (range 3–42, table 1). Of the 32 patients who had intestinal biopsies, 27 had villous atrophy. Only 11 of these 27 had ever reported gastrointestinal symptoms. Fourteen of the 35 patients were controlled by a gluten free diet alone, although five of these were seropositive for gluten related antibodies (table 1) suggesting poor compliance in some cases. Fifteen patients required dapsone as well as adhering to a partial gluten free diet. Six patients chose not to take a gluten free diet and the rash was controlled with dapsone alone. The clinical details are given in table 1.

Idiopathic neurological abnormalities were detected in two patients. One patient had essential tremor. The other patient had a choreiform movement disorder and was taking long term phenytoin after a single seizure in 1985 when aged 61. In addition, two patients had a history of migraine. No cases of myoclonus, ataxia, dementia, or peripheral neuropathy were identified.

One further patient had absent ankle jerks with a history of lumbar spine surgery (nerve conduction studies were normal in the upper limbs and showed only motor abnormalities in the lower limbs (lateral popliteal CMAP 0.2 mV, Sural SAP 6 µV) suggestive of a lumbar radiculopathy secondary to the previous surgery). Another had depressed upper limb reflexes, which improved clinically with reinforcement. However, nerve conduction studies were normal in this patient and the patient was judged normal.

Five of the 14 patients controlled on a “gluten free” (or gluten reduced) diet alone were seropositive for gluten associated antibodies (one IgA AGA, one AEA, two TTG). By contrast, these antibodies were commoner in the patients not attempting gluten exclusion. Thus, four of the six patients taking a normal diet had some of these antibodies and three patients had all three. Equivocally positive anti-Hu antibodies were demonstrated in one patient who also had chorea and positive IgA AGA antibodies (table 1).

DISCUSSION
This study has shown a very low prevalence of neurological abnormalities in DH. In our cohort of 35 patients, we found two patients with migraine, one with essential tremor and one with chorea. Essential tremor and migraine are sufficiently common for this to have been a chance association. The prevalence of essential tremor may be as high as 50/1000 in those older than 60 (20 patients in our study were over 60) and the 1 year prevalence of migraine in women is 25%.

Similarly, there have been isolated case reports of chorea associated with chronic phenytoin administration. In addition, there have been no previous epidemiological studies suggesting an association between essential tremor, migraine, or isolated chorea and gluten enteropathy.

This low prevalence of neurological abnormalities in DH is supported by a study of 305 patients with DH from Finland in which associated diseases were reported. That study differed from ours in that no attempt was made to specifically look for gluten exclusion. Four of the 20 patients in our study were over 60 and the 1 year prevalence of migraine in women is 25%. Similarly, there have been isolated case reports of chorea associated with chronic phenytoin administration. In addition, there have been no previous epidemiological studies suggesting an association between essential tremor, migraine, or isolated chorea and gluten enteropathy.

Some studies have reported various neurological complications in patients with CD. Chapman et al surveyed 185 patients with CD and reported nine (5.5%) with epilepsy, mainly of the complex partial type. More recently Holmes identified 388 adults with CD and found that 102 (26%) had evidence of neurological or psychiatric illness including 14 (3.6%) with epilepsy. However, the frequency of cryptogenic neurological disorders in this cohort of patients was about 10%. Axonal and demyelinating neuropathies have also been described and

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a, IgG AGA; b, IgA AGA; c, AEA; d, AEA (O); e, TG; f, Anti-Hu; ET, essential tremor; duration, disease duration.
anecdotally may respond to gluten restriction. Other neurologic syndromes such as ataxia, myoclonus, and dementia tend to be relentlessly progressive and are usually associated with minimal or no overt symptoms. The occurrence of dementia in patients with CD is intriguing especially in view of the role of transglutaminase induced bonds in paired helical filament tau in the brains of patients with Alzheimer’s disease.26

Hadjivassiliou et al have suggested that cryptic gluten sensitivity accounts for a significant proportion of idiopathic ataxias and other cryptogenic neurological syndromes.27 The mechanisms whereby gluten may cause neuronal damage are unknown but it has been suggested that AGA toxicity plays a part. AGA has been found in the CSF of one patient with myoclonic ataxia and gluten sensitive enteropathy but this may have represented leakage from the serum via a disrupted blood-brain barrier.27 In the few afatic patients with CD that have come to postmortem Purkinje cell loss and astrocytosis seem to be prominent features but Hadjivassiliou et al also demonstrated lymphocytic infiltrates in two of their patients at necropsy, suggesting immune mediated damage.27 Pellechia et al reported a single case of “gluten ataxia” where symptoms responded to gluten restriction. However, the role of disordered biotin synthesis or trace vitamin deficiencies including thiamine, niacin, and pyridoxine was not considered in that study.

We have postulated that if gluten is neurotoxic, our patients with DH with long disease duration should be at a high risk of neurological complications especially where compliance with a gluten free diet is poor. It could be argued that in those patients who continue to need dapsone for symptom control, adherence to the diet is imperfect, as found in this study. Admittedly, the numbers of patients in our study were small with only 21 on dapsone alone or in combination with a gluten free diet. It is also possible that dapsone has neuroprotective properties although this remains speculative, particularly as in high dose dapsone may cause a peripheral neuropathy. The dose of dapsone used in our cohort of patients with DH ranged from 50 mg on alternate days to 200 mg daily.

This lack of association between DH and neurological sequelae is an important finding and should be confirmed by further prospective studies of larger populations. We are attempting this as well as ascertaining the prevalence of neurological complications in patients with recent onset and established CD and confirming the previously reported high prevalence of occult gluten enteropathy in neurological populations.

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