Gluten sensitivity as a neurological illness

M Hadjivassiliou, R A Grünewald, G A B Davies-Jones

From gut to brain

It has taken nearly 2000 years to appreciate that a common dietary protein introduced to the human diet relatively late in evolutionary terms (some 10 000 years ago), can produce human disease not only of the gut but also the skin and the nervous system. The protein neurological manifestations of gluten sensitivity can occur without gut involvement and neurologists must therefore become familiar with the common neurological presentations and means of diagnosis of this disease.

COELIAC DISEASE THROUGH THE AGES: FROM GUT TO SKIN

"...the stomach being the digestive organ, labours in digestion, when diarrhoea..." and if in addition, the patient’s general system be debilitated by atrophy of the body, the coeliac disease of a chronic nature is formed".

This extract is from the book on chronic diseases by Areteaus the Cappadocian, one of the most distinguished ancient Greek doctors of the first century AD. This chapter, entitled “on the coeliac diathesis”, was the first description of coeliac disease (from the Greek word κοιλιακη meaning abdominal). Areteaus’ books were first published in Latin in 1500 and the new Latin word coeliac was used to translate κοιλιακη. Coeliac disease (CD) remained obscure until 1887 when Samuel Gee gave a lecture entitled On the coeliac affection at the Hospital for Sick Children, Great Ormond Street, London. In it he acknowledged Areteaus’ contribution and went on to give an accurate description of CD based on his own clinical observations.

With clinical manifestations primarily confined to the gastrointestinal tract or attributable to malabsorption, it was logical to assume that the target organ and hence the key to the pathogenesis of this disease was the gut. The first report of neurological manifestations associated with CD was by Carnegie Brown in 1908.1 In his book entitled Sprue and its treatment he mentioned two of his patients who developed “peripheral neuritis”. Elders reported the association between “sprue” and ataxia in 1925.2 The validity of these and other such reports before 1960 remains doubtful given that a precise diagnosis of CD was not possible before the introduction of small bowel biopsies. The treatment of CD remained empirical until 1940–50 when the Dutch paediatrician Willem Dicke noted the deleterious effect of wheat flour on children with CD.3 Removal of dietary products containing wheat was shown to result in complete resolution of the gastrointestinal symptoms and a resumption of normal health. The introduction of the small bowel biopsy in 1950–60 confirmed the gut as a target organ. The characteristic features of villous atrophy, crypt hyperplasia and increase in intraepithelial lymphocytes with improvement while on gluten-free diet, became the mainstays of the diagnosis of CD. In 1961 Taylor published an immunological study of CD.4 In his paper he commented that “...an obstacle to the acceptance of the immunological theory of causation has been the lack of satisfactory demonstration of antibodies to the protein concerned”. He went on to demonstrate the presence of circulating antibodies against gliadin (antigliadin antibodies), the protein responsible for CD. This provided further evidence that CD was immunologically mediated and that the immune response is not confined to the mucosa of the small bowel. Antigliadin antibodies became a useful screening tool for the diagnosis of CD.

In 1966, Marks et al demonstrated an enteropathy in nine of 12 patients with dermatitis herpetiformis,5 an itchy vesicular skin rash mainly occurring over the extensor aspect of the elbows and knees. The enteropathy had a striking similarity to that seen in CD. It was later shown that the enteropathy and the skin rash were gluten dependent but skin involvement could occur even without histological evidence of gut involvement. This was the first evidence that the gut

Table 1 Neurology of coeliac disease (based on a review of 35 papers of single or multiple case reports from 1964 to 2000)

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male to female ratio</td>
<td>44:39</td>
</tr>
<tr>
<td>Mean age</td>
<td>48</td>
</tr>
<tr>
<td>Neurological diagnosis</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>29</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>29</td>
</tr>
<tr>
<td>Myopathy</td>
<td>13</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>9</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>4</td>
</tr>
<tr>
<td>Dementia (usually with additional features)</td>
<td>6</td>
</tr>
</tbody>
</table>

A review of all such reports (with biopsy proved CD) from 1964 to date shows that ataxia and peripheral neuropathy are the commonest neurological manifestations seen in patients with established CD (table 1). Less common manifestations include inflammatory myopathies and myoclonic ataxia.6 Isolated dementia is uncommon and most cases tend to have additional neurological features (for example, ataxia or neuropathy). Patients with epilepsy associated with occipital calcifications on CT and CD have been described,7 mainly in Italy. Most present with epilepsy in

THE NEUROLOGY OF COELIAC DISEASE

In 1966 Cooke published a landmark paper on 16 patients with neurological disorders associated with adult CD.8 This was the first systematic review of the subject after the introduction of diagnostic criteria for CD. Ten of these patients had a severe progressive neuropathy. All patients had gait ataxia and some had limb ataxia. Neuropathological data from postmortem examinations showed extensive perivascular inflammatory changes affecting both the central and peripheral nervous systems. A striking feature was the loss of Purkinje cells with atrophy and gliosis of the cerebellum. All 16 patients had evidence of severe malabsorption as evidenced by anaemia and vitamin deficiencies as well as profound weight loss.

Several case reports followed, primarily based on patients with established CD, often with persisting troublesome gastrointestinal symptoms followed by neurological dysfunction. Data from patients with CD presenting with gastrointestinal symptoms followed up in a gastrointestinal clinic suggest that otherwise unexplained neurological dysfunction is a complication in 6% to 10% of cases.9

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childhood. Such cases are rare in the United Kingdom.

RECENT ADVANCES: PREVALENCE, SMALL BOWEL HISTOLOGY AND GENETIC SUSCEPTIBILITY

Some studies looking at normal populations have shown that the prevalence of CD is much higher than previously thought \(^{13,14}\) (approximating to 1 in 100). Most of such patients have no gastrointestinal symptoms. In addition, experimental data in patients with gluten sensitivity suggest that there is a range of mucosal abnormalities affecting the small bowel ranging from preinfiltrative (histologically normal) to infiltrative, to hyperplastic to flat destructive (seen in CD), and finally to the irreversible hypoplastic atrophic lesions. \(^{15}\) Increasing the gluten load may result in progression of the severity of the lesion. In those patients where the histology is normal, staining of the T cell subpopulations of the intraepithelial lymphocytes (increase of the \(\gamma\delta\) T cells). This finding is said to be a marker of potential CD. \(^{16}\) This procedure is only available in a very few pathology laboratories, rendering its use limited.

Finally, CD has a very strong association with the human lymphocyte antigen (HLA) of the major histocompatibility complex. Ninety per cent of patients with CD have the HLA DQ2; the rest have DQ8. These advances suggest that gastrointestinal symptoms are absent in most patients with CD, that the definition of gluten sensitivity can no longer be solely based on the presence of an enteropathy and that genetic susceptibility may be an important additional marker for gluten sensitivity. Given the knowledge of these advances and approaching gluten sensitivity from a neurological perspective we set up to address the following question: Does cryptic gluten sensitivity play a part in neurological illness?

THE NEUROLOGY OF GLUTEN SENSITIVITY

Over the past 8 years we have used antigliadin antibodies to screen patients with neurological dysfunction of unknown aetiology. Our original study concluded that gluten sensitivity played an important part in neurological illness. \(^{17}\) The evidence was statistical: Patients with neurological disease of unknown aetiology were found to have a much higher prevalence of circulating antigliadin antibodies (57%) in their blood than either healthy control subjects (12%) or those with neurological disorders of known aetiology (9%). Since then we have identified 131 patients with gluten sensitivity and neurological disorders of unknown aetiology. Table 2 shows the neurological diagnoses we have encountered. Perhaps not surprisingly the commonest manifestations are ataxia (also known as gluten ataxia)\(^ {18}\) and peripheral neuropathy. \(^{19}\)

GLUTEN ATAXIA

Systematic screening of 143 patients with so-called “idiopathic sporadic ataxia” showed that 41% had gluten sensitivity as defined by the presence of circulating antigliadin antibodies \(^{20}\) (IgG with or without IgA). The prevalence of antigliadin antibodies in 51 patients with familial ataxia did not differ from that found in normal healthy control subjects (13%). The mean age of onset of the ataxia was 54 but we have recently seen three patients with early onset (under 20 years of age) sporadic idiopathic ataxia and gluten sensitivity. Recently four patients have been described with CD presenting as gait disturbance and ataxia in infancy. \(^{21}\) Although the ataxia tends to be slowly progressive, in some cases it can take a very rapid course with the development of cerebellar atrophy within a year of the onset of the illness (fig 1). Ataxia and myoclonus is a much less common presentation (only four patients in these

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### Table 2: Neurology of gluten sensitivity

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia (four patients with myoclonus)</td>
<td>56</td>
</tr>
<tr>
<td>Sensorimotor axonal neuropathy</td>
<td>26</td>
</tr>
<tr>
<td>Motor neuropathy (three MND-like picture on NCS/EMG)</td>
<td>15</td>
</tr>
<tr>
<td>Small fibre neuropathy</td>
<td>4</td>
</tr>
<tr>
<td>Mixed demyelinating/axonal neuropathy</td>
<td>2</td>
</tr>
<tr>
<td>Myopathies</td>
<td>8</td>
</tr>
<tr>
<td>Abnormal white matter on MRI (with episodic headache)</td>
<td>19</td>
</tr>
<tr>
<td>stiff-man syndrome</td>
<td>4</td>
</tr>
<tr>
<td>Neuromyotonia</td>
<td>1</td>
</tr>
</tbody>
</table>

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**Figure 1** Brain MRI of a patient with gluten ataxia showing rapid onset of cerebellar atrophy over a period of 15 months before the diagnosis of gluten ataxia.
series). We have encountered two pa-
tients who in addition to ataxia had evi-
dence of chorea but normal genetic test-
ing for Huntington’s disease. Gluten ataxia primarily affects the lower limbs and gait. Extrapyramidal or autonomic features are rarely apparent and these features distinguish it from the cerebel-
lar variant of multisystem atrophy (MSA). Screening of patients with clini-
cally probable MSA (cerebellar variant) for the presence of antigliadin antibodies showed the prevalence to be similar to the normal population. Brain MRI usu-
ally shows cerebellar atrophy; sometimes with evidence of white matter abnor-
malities. Up to 40% of patients also have a sensorimotor axonal peripheral neu-
ropathy that can often be subclinical. In a few cases oligoclonal bands are present
in the CSF.

PERIPHERAL NEUROPATHY
Peripheral neuropathy is the second commonest manifestation of gluten sensi-
sitivity. Prospective screening of 101 patients with idiopathic peripheral neu-
ropathy has shown the prevalence of gluten sensitivity to be 40% (unpub-
lished data). The commonest type of peripheral neuropathy we encountered is sensorimotor axonal (26) followed by mononeuropathy multiplex (15), pure motor neuropathy (10), small fibre neu-
ropathy (four) and mixed axonal and demyelinating (two). The neuropathy is
usually chronic and of gradual progres-
sion. Patients with a pure motor neu-
ropathy may progress to involvement of sensory fibres.

LESS COMMON NEUROLOGICAL MANIFESTATIONS
We encountered eight patients with myopathy and gluten sensitivity. Three had an additional neuropathy. Muscle biopsy showed inflammatory changes in five. One patient had evidence of inclu-
sion body myositis. One patient had low concentrations of vitamin D and a
predominantly proximal myopathy.

Myelopathy is rare in our series and was only seen in two patients.

We have recently identified a subgroup of patients with gluten sensitivity who
complained of episodic severe headache often with transient neurological deficit and extensive white matter abnormalities on MRL. Some of them also had ataxia or neuropathy. Their headache resolved with the introduction of a gluten free diet though the MRI abnor-
malities persisted at least for the short follow up period. We have also found a
higher incidence of gluten sensitivity in patients with systemic vasculitis and
neurological involvement, perhaps re-

tecting the autoimmune nature of glu-
ten sensitivity. There is a well known
association of CD with other auto-
immune diseases2 (for example, diabetes, thyroid disease). This may
account for the finding of the presence of antigliadin antibodies in all four of our
patients with stiff-person syndrome.

Some researchers think that pro-
longed exposure to gluten in a gluten sensitive person may be the trigger for
the development of other autoimmune disease.31

CONTENTIOUS ISSUES

"But antigliadin antibodies lack specificity"
IgG anti-gliadin antibodies have been the best diagnostic marker in the neuro-
ological population we have studied. IgG anti-gliadin antibodies have a very high
sensitivity for CD but they are said to lack specificity. In the context of a range
of mucosal abnormalities and the con-
cept of potential CD, they may be the
only available immunological marker for
the whole range of gluten sensitivity of
which CD is only a part. Further support
for our contention comes from our HLA
studies. Within the group of patients with neurological disease and gluten
sensitivity (defined by the presence of
anti-gliadin antibodies) we have found a
similar HLA association to that seen in
patients with CD: 70% of patients have
the HLA DQ2 (30% in the general popu-
lation), 9% have the HLA DQ8, and the
remainder have HLA DQ1. The finding of
an additional HLA marker (DQ1) seen in
the remaining 20% of our patients may
represent an important difference be-
tween the genetic susceptibility of pa-
tients with neurological presentation to those with gastrointestinal presentation within the range of gluten sensitivity.

"But antigliadin antibodies have been superseded by anti-endomysial and
transglutaminase antibodies"
The introduction of more CD specific
serological markers such as anti-endomysium and more recently trans-
glutaminase antibodies may have helped in diagnosing CD but their sensitivity as
markers of other manifestations of glu-
ten sensitivity (where the bowel is not
affected) is low. This certainly reflects our experience with patients with gluten
sensitivity who present with neurologi-
cal dysfunction. Endomysium and trans-
glutaminase antibodies are only positive in the majority but not in all patients
who have an enteropathy. Patients with
an enteropathy represent only a third of
patients with neurological manifesta-
tions and gluten sensitivity. Antigliadin antibodies unlike endomysium and transglutaminase antibodies are not au-
toantibodies. They are antibodies against the protein responsible for gluten sensi-
vity.

“What do I do with a patient with positive anti-gliadin antibody test but normal duodenal biopsy?”
Only one third of the patients with neurological disorders associated with gluten sensitivity have villous atrophy on duodenal biopsy. Even some with bio-
chemical markers of malabsorption such as low serum vitamin B12, low red cell
folate, or vitamin D concentrations had normal conventional duodenal histology.27 These cases may illustrate the patchy nature of bowel involvement in coeliac disease and the inaccurate interpretation of duodenal biopsies by inexperienced histopathologists. Pre-
liminary data based on staining of the
subpopulation of T cells in the small
bowl epithelium suggests that these
patients have potential CD.32 There are,
however, patients where the immuno-
logical disorder is primarily directed at
the nervous system with little or no
damage to the gut. Our practice is to offer
a gluten free diet to these patients unless
the HLA genotype is not consistent with
susceptibility to gluten intolerance (that
is, other than HLA DQ2, DQ8, or DQ1). All patients are followed up and any
clinical response is documented.

“But my patient has not responded to a gluten free diet”
Reports in the literature of the effect of the gluten-free diet on neurological dys-
function are conflicting. Almost all pa-
tients reported in the literature have the diagnosis of CD before the development of neurological dysfunction. They may
represent a different group of patients
from those presenting with neurological dysfunction without bowel involvement. Additionally, improvement of gastro-
intestinal symptoms and improvement of the histological abnormalities on repeat small bowel biopsy often with measures used to assess the response to the diet. Serological evidence of response (for example, sustained elimination of antigliadin antibodies) has rarely been used as confirmation of strict adherence to the gluten-free diet. Incomplete elimi-
nation of gluten from the diet may be
enough to abolish gastrointestinal symp-
toms with recovery of the small bowel
mucosa but is insufficient to arrest the
status of heightened gastrointestinal sensi-

tiveness resulting in neuronal injury. There is a group of patients with CD “resistant” to gluten-free diet. This may
reflect hypersensitivity to the minute
amounts of gluten present in most “gluten-free” products. An analogous
situation may exist in cases of gluten
ataxia or gluten related neuropathy. The
monitoring of neurological improvement in such cases is made difficult by the slow and sometimes incomplete regen-
eration of the nervous system. In cases of gluten ataxia where the underlying pathology is loss of Purkinje cells, one

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may only expect the stabilisation of the disease without any definite clinical improvement. This is in marked contrast to the response seen in patients with florid gastrointestinal symptoms who notice almost immediate improvement after the introduction of a gluten-free diet.

"Isn’t the neurological damage nutritional?" Nutrient deficiencies (B12, folate, vitamin D, vitamin E) are rare in this neurological population. Given that two thirds of these patients have no enteroopathy this is hardly surprising. The concept of the neurological manifestations being nutritional in origin is now outdated. Intestinal mucosal damage in coeliac disease is the result of both humoral and T cell mediated inflammation. Such inflammation is not, however, confined to the gut, as activated HLA restricted gladin specific T cells and antigliadin antibodies are found systemically. Antigliadin antibodies are also found in the CSF. Postmortem findings from two of our patients with gluten ataxia has shown perivascular cuffing with both CD4 and CD8 cells. This inflammation was primarily seen 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. Our research suggests that IgG antigliadin antibodies cross react with epitopes on Purkinje cells from human cerebellum. Characterisation 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 antientomysium antibodies as a marker for coeliac disease or the anti-Yo antibody in paraneoplastic cerebellar degeneration.

FROM GUT TO BRAIN
Gluten sensitivity is best defined as a state of heightened immunological responsiveness in genetically susceptible people. This definition does not imply bowel involvement. That gluten sensitiv- ity is regarded as principally a disease of the small bowel is a historical misconception. Gluten sensitivity can be primarily and at times exclusively a neurological disease. The absence of an enteropathy should not preclude patients from treatment with a gluten-free diet. Early diagnosis and removal of the trigger factor by the introduction of gluten-free diet is a promising therapeu- tic intervention. IgG antigliadin antibodies should be part of the routine investi- gation of all patients with neurological dysfunction of obscure aetiology, particu- larly patients with ataxia and periph- eral neuropathy.

ACKNOWLEDGEMENTS
We are currently conducting a trial of the effect of gluten-free diet on patients with gluten ataxia and would welcome referrals of patients with sporadic idiopathic ataxia. We have received funds from SHS International and Ultrapharm Ltd towards a pilot study of the effect of gluten-free diet on patients with neurological dysfunction and gluten sensitiv- ity and a grant from The Friedrich's Ataxia Group for research into the immunological mechanisms of the pathogenesis of gluten ataxia.

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