

patients may not have responded. No conclusions could be reached about the ethnic response rate since the ethnic composition of the initial sample of 3500 was not known. A much larger population base with an identified ethnic distribution would be required to elucidate whether non-Caucasians are the most likely to have undiagnosed SLE.

We were disappointed by the low response rate. In future work it might be improved by translating the questionnaire into the main Asian languages, by sending repeat mailings to all non-respondents, and by telephoning those who do not come to the general practice. It is important to ascertain whether patients with undiagnosed SLE do exist in the community, since early diagnosis and treatment is likely to prevent the development of the severe disease now being seen, especially in patients from the ethnic minorities. The value of early diagnosis will need to be determined by a prospective study.

This study was supported by grants from the Arthritis and Rheumatism Council and from the West Midlands Lupus Group. We gratefully acknowledge the help and support of the general practitioners involved in the study; of the consultant rheumatologists Dr Ronald Jubb, Dr Deva Situanayake, and Dr Paul Emery; and of Dr A Silman of the Epidemiology Unit, Arthritis and Rheumatism Council, Manchester.

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Does cryptic gluten sensitivity play a part in neurological illness?

M Hadjivassiliou, A Gibson, G A B Davies-Jones, A J Lobo, T J Stephenson, A Milford-Ward

Summary

Background Antigliadin antibodies are a marker of untreated coeliac disease but can also be found in individuals with normal small-bowel mucosa. Because neurological dysfunction is a known complication of coeliac disease we have investigated the frequency of anti gliadin antibodies, as a measure of cryptic gluten sensitivity, and coeliac disease in neurological patients.

Methods Using ELISA, we estimated serum IgG and IgA anti gliadin antibodies in 147 neurological patients who were divided into two groups. There were 53 patients with neurological dysfunction of unknown cause despite full investigation (25 ataxia, 20 peripheral neuropathy, 5 mononeuritis multiplex, 4 myopathy, 3 motor neuropathy, 2 myelopathy). The remaining 94 patients were found to have a specific neurological diagnosis (16 stroke, 12 multiple sclerosis, 10 Parkinson's disease, 56 other diagnoses) and formed the neurological control group. 50 healthy blood donors formed a third group.

Findings The proportions of individuals with positive titres for anti gliadin antibodies in the three groups were 30/53, 5/94, and 6/50 respectively (57, 5, and 12%). The difference in proportion between group 1 and the combined control groups was 0.49 (95% CI 0.35-0.63). Distal duodenal biopsies in 26 out of 30 anti gliadin-positive

patients from group 1 revealed histological evidence of coeliac disease in nine (35%), non-specific duodenitis in ten (38%), and no lesion in seven (26%) individuals.

Interpretation Our data suggest that gluten sensitivity is common in patients with neurological disease of unknown cause and may have aetiological significance.

Lancet 1996; **347**: 369-71

Introduction

Many neurological manifestations are associated with coeliac disease, including ataxia, peripheral neuropathy, myelopathy, myopathy, and dementia.¹ The original cases had severe coeliac disease. The use of anti gliadin antibodies in screening has shown the frequency of coeliac disease among some symptom-free individuals to be high (1 in 256).^{2,3} Some symptom-free individuals have anti gliadin antibodies in serum, and may therefore have gluten sensitivity, but do not fulfil the histological criteria for coeliac disease. Using assay of anti gliadin antibodies, we studied the association between gluten sensitivity and neurological dysfunction in a general neurological practice.

Patients and methods

Patients

All patients attending a general neurology outpatient clinic over the three months of April to June, 1994, were enrolled in the study, provided they consented to having their serum tested for anti gliadin antibodies. During the same period, and on two separate occasions, all consenting inpatients undergoing investigation on the neurology wards at the Royal Hallamshire Hospital, Sheffield, were tested. The potential significance of a positive test was explained to all participants.

Departments of Neurology (M Hadjivassiliou MRCP, A Gibson PhD, G A B Davies-Jones MD), **Gastroenterology** (A J Lobo MD), and **Histopathology** (T J Stephenson MD), **Royal Hallamshire Hospital, Sheffield, UK; and Department of Immunology** (A Milford-Ward FRCPATH), **Northern General Hospital, Sheffield**

Correspondence to: Dr M Hadjivassiliou, Department of Clinical Neurology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

| | Group 1 (no diagnosis) | Group 2 (known diagnosis) | Group 3 (blood donors) |
|--|---------------------------|------------------------------|---------------------------|
| Number | 53 | 94 | 50 |
| Mean age (range) | 56 (18-77) | 52 (19-89) | 49 (18-65) |
| Male:female ratio | 1.9:1 | 0.9:1 | 0.9:1 |
| Only IgA positive | 12 | 2 | 2 |
| Only IgG positive | 6 | 3 | 4 |
| Both positive | 12 | 0 | 0 |
| Total positive (IgA or IgG or both) | 30 (57%) | 5 (5%) | 6 (12%) |

Table 1: Participants' characteristics and antigliadin positivity

Without knowledge of the antigliadin antibody result and after all relevant neurological investigations, patients were divided into two groups: group 1 consisted of 53 patients with neurological dysfunction of unknown cause despite full investigation, and group 2 included all 94 patients with specific neurological diagnoses. The range of investigations varied according to clinical indications and included: haematological and serum biochemistry screens; assay of vitamins B12, E, thiamine, red-cell folate, ferritin, immunoglobulins, antinuclear antibodies, double-stranded DNA, rheumatoid factor, antineutrophil cytoplasmic antibodies, extractable nuclear antibodies, and complement; neuroimaging and neurophysiological studies; and examination of cerebrospinal fluid and muscle biopsy specimens. Serum from 50 anonymous blood donors was provided by the regional transfusion service and served as healthy controls (group 3).

Antigliadin measurements

IgG and IgA antigliadin antibodies were detected by ELISA. Gliadin from wheat extract (Sigma) was bound to the surface of the wells of a 96-well microtitre plate. After washing, dilutions of patients' serum, calibrants, and control serum were added to the wells and the plates were incubated at 37°C for 90 min. The plates were washed and rabbit antihuman IgG and IgA serum conjugated with alkaline phosphatase was added to the wells. After further incubation and washing, phosphatase substrate was added and colour development read on a spectrophotometer. Positive antibody responses were defined as those serum samples that demonstrated more than 0.850 optical density units of colour development. The assay was under rigid internal and external quality control with both positive and negative controls being included in each batch; the optical densities had to fall within predefined limits for acceptance of the assay.

Duodenal biopsies

All patients from groups 1 and 2 with positive IgA, IgG, or both antigliadin antibodies were offered duodenal biopsies. These were taken from the distal duodenum with biopsy forceps through a conventional forward-viewing endoscope (Key-Med). Two to four specimens were taken from the third part of the duodenum. All specimens were reviewed by a consultant histopathologist (TJS). Histological features consistent with gluten sensitive enteropathy in a duodenal biopsy included: crypt hyperplasia, villus atrophy, increase in intraepithelial lymphocytes to more than one lymphocyte per six epithelial cells, and absence of other significant pathology. Non-specific duodenitis was recorded when some, although not all, of the features of gluten-sensitive enteropathy were present. These included findings such as villus atrophy in the absence of crypt hyperplasia, or non-specific increase in inflammatory cells in the lamina propria.

Results

Table 1 shows the mean age, age range, male to female ratio, and gliadin positivity for the three groups. 30 of the patients in group 1 had antigliadin antibodies in their sera (57%). Antigliadin positivity in groups 2 and 3 was 5% and 12%, respectively. The difference in proportions between group 1 and the combined control groups was 0.49 (95% CI 0.35-0.63).

| Findings | No | Only IgA +ve | Only IgG +ve | Both +ve | Total +ve |
|------------------------|----|-----------------|-----------------|-------------|--------------|
| Ataxia | 25 | 8 | 3 | 6 | 17 |
| Peripheral neuropathy | 20 | 3 | 1 | 3 | 7 |
| Mononeuritis multiplex | 5 | 1 | 0 | 2 | 3 |
| Myopathy | 4 | 2 | 1 | 0 | 3 |
| Motor neuropathy | 3 | 0 | 1 | 2 | 3 |
| Myelopathy | 2 | 0 | 1 | 1 | 2 |

Some patients had more than one diagnosis.

Table 2: Patients with neurological dysfunction of unknown cause (group 1)

Most (25) patients in group 1 had evidence of ataxia on clinical examination (table 2). None of them had a family history of spinocerebellar degeneration. Demyelination in this group was excluded with magnetic resonance imaging and cerebrospinal-fluid examination. Peripheral neuropathy was the second commonest finding in group 1. Four patients (included in the above figures) had ataxia and peripheral neuropathy. Five patients had neurophysiological evidence of mononeuropathy multiplex. Four patients had myopathy, two with inflammatory changes on muscle biopsy (both were also ataxic) and two had only electromyographic changes. Three patients had evidence of a pure motor neuropathy on neurophysiological testing and the final two patients had clinical evidence of a myelopathy in the absence of a structural or inflammatory lesion. None of the patients in group 1 had clinically important autoantibody titres.

Out of the 30 antigliadin-positive patients from group 1, one patient was found to have IgA deficiency (normal biopsy specimen), one patient was found to be anaemic (coeliac disease on biopsy), and one patient had low vitamin B12 (normal biopsy specimen). The remaining 27 had no clinical or laboratory evidence suggestive of malabsorption. Only three patients had complaints related to their gastrointestinal tract. All three were later found to have coeliac disease. None of the ataxic patients had low vitamin E levels. Two patients had first-degree relatives with coeliac disease (both had normal biopsy samples).

Table 3 lists the spectrum of neurological diagnoses in group 2. There were five patients with a positive antigliadin-antibody test. Two patients refused duodenal biopsy. The other three patients had normal biopsy specimens.

| Diagnosis | No | IgA+ve | IgG+ve | Biopsy |
|---------------------------------------|-----------|----------|----------|-------------|
| Stroke | 16 | 1 | 0 | Not done |
| Multiple sclerosis | 12 | 1 | 0 | Not done |
| Parkinson's disease | 10 | 0 | 0 | |
| Peripheral neuropathy (known cause) | 8 | 0 | 0 | |
| Epilepsy | 7 | 0 | 2 | Both normal |
| Myopathy (mechanical) | 7 | 0 | 0 | |
| Motor neurone disease | 6 | 0 | 1 | Normal |
| Dementia (known cause) | 5 | 0 | 0 | |
| Cerebellar degeneration (known cause) | 5 | 0 | 0 | |
| Brain tumour | 4 | 0 | 0 | |
| Polymyositis | 3 | 0 | 0 | |
| Mitochondrial cytopathy | 2 | 0 | 0 | |
| Post-infective polyradiculopathy | 2 | 0 | 0 | |
| Wernicke's encephalopathy | 2 | 0 | 0 | |
| Huntington's chorea | 1 | 0 | 0 | |
| Benign positional vertigo | 1 | 0 | 0 | |
| Gerstman-Straussler disease | 1 | 0 | 0 | |
| Bechet's disease | 1 | 0 | 0 | |
| Myasthenia gravis | 1 | 0 | 0 | |
| Total | 94 | 2 | 3 | |

Table 3: Neurological patients with specific diagnoses (group 2)

| Neurological diagnosis | Coeliac disease | Non-specific duodenitis | Normal |
|------------------------|-----------------|-------------------------|----------|
| Ataxia | 4 | 5 | 4 |
| Peripheral neuropathy | 1 | 3 | 2 |
| Myopathy | 2 | 1 | 0 |
| Myelopathy | 1 | 1 | 0 |
| Mononeuritis multiplex | 1 | 1 | 0 |
| Motor neuropathy | 2 | 0 | 1 |
| Total | 9 | 10 | 7 |

Some patients had more than one diagnosis.

Table 4: Findings from duodenal biopsies in group 1

| | IgA+ve only | IgG+ve only | Both +ve |
|-------------------------|-------------|-------------|----------|
| Coeliac disease | 3 | 2 | 4 |
| Non-specific duodenitis | 2 | 2 | 6 |
| Normal | 4 | 1 | 2 |
| No biopsy | 3 | 1 | 0 |

Table 5: Antigliadin antibody type and duodenal biopsy findings in group 1

Table 4 shows the results of the duodenal biopsies in relation to neurological findings in group 1. Out of 30 anti-gliadin-positive patients, 26 had duodenal biopsies (four refused). Nine patients (35%) were found to have histological features consistent with coeliac disease. Ten (38%) had non-specific duodenitis and the remaining seven patients (26%) had normal biopsy samples. In no cases did we see parasites, protozoa, or amyloidosis. The relation between the type of anti-gliadin antibody and the duodenal biopsy findings is shown in table 5.

Discussion

We found a high frequency (57%) of anti-gliadin antibodies among patients with neurological dysfunction of unknown cause. The frequency of coeliac disease within the same group was at least 16%, which is forty times higher than that in studies of symptom-free individuals.^{2,3} The male to female ratio among anti-gliadin-positive patients from group 1 was 2:1. This matches the sex ratio of the group as a whole. It is therefore unlikely that the difference in the sex ratio seen between group 1 and the two control groups influenced the difference in anti-gliadin positivity between the groups.

Most reports on coeliac disease and neurological complications are based on patients with established coeliac disease. Neurological complications are uncommon (8%) in this group.⁵ More recent studies have demonstrated that asymptomatic coeliac disease is common.^{2,3} Some individuals with serum anti-gliadin antibodies and non-specifically abnormal or even normal small-bowel mucosa may go on to develop coeliac disease.⁶ It has been suggested that gluten sensitivity should be considered as "a state of heightened immunological responsiveness (T- and B-lymphocyte based) to ingested gluten proteins in genetically predisposed individuals".⁷ This broader definition highlights the immunological nature of this disease.

The search for causes of neurological dysfunction in coeliac disease has largely ignored the immunological aspect, and has concentrated on vitamin deficiencies (B12, E, D, folic acid, pyridoxine) as a result of malabsorption. Vitamin replacement rarely improves the neurological deficit.⁵ In our anti-gliadin-positive patients only one had vitamin deficiency. Although there may be unidentified nutritional deficiencies in these patients that produce neurological disease, this is unlikely given the normal bowel mucosa in seven out of 26 patients who

underwent biopsy. Alternative hypotheses are that anti-gliadin antibodies are more directly involved in the neuropathological process, or are markers of autoimmune activity with an unidentified antibody being neurotoxic.

Our estimate of coeliac disease frequency among group 1 can only be approximate because anti-gliadin-negative patients were not examined with biopsy. The positive predictive value of anti-gliadin antibodies, an expression of the percentage of patients with positive antibody who had coeliac disease confirmed on duodenal biopsy, was 35%. Previous reports have suggested that IgG anti-gliadin antibodies are not as reliable as IgA anti-gliadin antibodies in predicting the presence of coeliac disease.^{2,8} In our study two patients with IgG anti-gliadin antibodies alone were found to have coeliac disease. None of them had IgA deficiency.

If these antibodies are directly or indirectly neurotoxic, why do patients with neurological dysfunction and on gluten-free diet not always improve? One possibility is that damaged neural tissue (eg, cerebellar Purkinje cells) does not regenerate. The second is that patients may not strictly adhere to their gluten-free diet or that the diet may be insufficient to suppress the immunological process completely, especially since patients without gastrointestinal symptoms are unlikely to adhere to a gluten-free diet.⁹

Patients with histological evidence of coeliac disease and neurological disorders should be on gluten-free diet not just from the neurological point of view but because of the well-established long-term risk of small-bowel lymphoma.^{10,11} The picture is less clear in anti-gliadin-positive patients with either a normal or a non-specifically abnormal mucosa. It is possible (though unproven) that strict adherence to gluten-free diet, with elimination of anti-gliadin antibodies, may result in stabilisation or even improvement of neurological dysfunction. Anti-gliadin antibody estimation should be part of the routine investigation of any patient with neurological dysfunction of unknown cause.

We thank R A Grünwald for reading the manuscript critically and G K T Holmes for his support. We also thank M Grundman for his enthusiasm about coeliac disease.

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