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Sporadic cerebellar ataxia associated with gluten sensitivity

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Summary

A total of 104 patients with sporadic cerebellar ataxia were tested for antigliadin and antiendomysium antibodies. Twelve individuals (11.5%) with gluten sensitivity underwent duodenal biopsy and extensive clinical, electrophysiological, neuropsychological, radiological and laboratory investigations including human leucocyte antigen (HLA) typing. Two patients showed typical changes of gluten-sensitive enteropathy with crypt hyperplasia and mucosal flattening. In five patients, the intraepithelial lymphocyte count was elevated. Sporadic ataxia with gluten sensitivity was found to be tightly linked to the HLA DQB1*0201 haplotype (70%). Neurological symptoms were not related to hypovitaminosis or inflammatory CSF changes. The clinical syndrome was dominated by progressive cerebellar ataxia with ataxia of stance and gait (100%), dysarthria (100%) and limb ataxia (97%). Oculomotor abnormalities were gaze-evoked nystagmus (66.7%), spontaneous nystagmus (33.3%), saccade slowing (25%) and upward gaze palsy (16.7%). Extracerebellar features also included deep sensory loss (58.3%), bladder dysfunction (33.3%) and reduced ankle reflexes (33.3%). In accordance with clinical findings, electrophysiological investigations revealed prominent axonal neuropathy with reduced amplitudes (50%) and abnormal evoked potentials (58.3%). On neuropsychological testing, patients presented with moderate verbal memory and executive dysfunction. All patients had evidence of cerebellar atrophy on MRI. We conclude that sporadic ataxia may be associated with positive antibodies against gliadin. Nevertheless, mucosal pathology does not represent an obligatory condition of ataxia with gluten sensitivity. The fact that the disease is strongly associated with the same HLA haplotypes found in coeliac disease not only demonstrates coeliac disease and ataxia with gluten sensitivity to be part of the same disease entity but supports the hypothesis of an immunological pathogenesis of cerebellar degeneration.

Keywords: sporadic ataxia; gluten sensitivity; antigliadin antibodies

Abbreviations: AGA = antigliadin antibodies; EA = endomysium antibodies; HLA = human leucocyte antigen; SCA = spinocerebellar ataxia

Introduction

The syndrome of gluten sensitivity is contingent upon intolerance to dietary gluten, a component of cereals such as wheat, barley and rye. The syndrome is an immunologically mediated disease strongly associated with certain human leucocyte antigen (HLA) class II alleles. The vast majority of patients with gluten sensitivity have the HLA DQ2 allele (Hadjivassiliou *et al*., 1998). Histological abnormalities range from normal, to subtotal or total villous atrophy of the small intestinal mucosa (Trier, 1991; Marsh, 1992; Hadjivassiliou *et al*., 1998). In gluten sensitivity, neurological complications may be observed in 6% of patients (Holmes, 1997), with cerebellar ataxia being the most frequent symptom (Hadjivassiliou *et al*., 1996). Patients often show circulating antibodies to gliadin (AGA) and endomysium (EA), with EA being more specific for mucosal damage but less sensitive for neurological complications (Hadjivassiliou *et al*., 1999).

The aims of the present study were: (i) to screen patients with sporadic ataxia for the presence of antibodies; (ii) to determine the frequency and severity of mucosal abnormalities by jejunal biopsy in ataxic patients with AGA and/or EA; (iii) to investigate the CSF for an inflammatory response and for the presence of AGA and EA; and (iv)

to describe the clinical, immunological, radiological, neuropsychological and electrophysiological features of sporadic cerebellar ataxia with gluten sensitivity.

Patients and methods

Patients

A total of 104 patients fulfilled the following diagnostic criteria for idiopathic cerebellar ataxia: (i) progressive cerebellar ataxia without evidence of a focal or non-focal symptomatic origin of the disease (Harding, 1981); (ii) absence of any neurodegenerative disorder in relatives and no evidence of consanguinity of parents; and (iii) negative molecular genetic testing for Friedreich's ataxia and the spinocerebellar ataxias (SCA1, SCA2, SCA3, SCA6 and SCA7) (Bürk *et al*., 1996; Campuzano *et al*., 1996; Imbert *et al*., 1996; David *et al*., 1997; Zhuchenko *et al*., 1997). All patients and control subjects used for the psychological testing gave informed consent to participate in the study, which was approved by the ethics committees of all participating institutions.

Immunology, tissue typing and histology

These subjects were tested for circulating antibodies against gliadin and endomysium. Antigliadin (AGA) IgA and IgG antibodies were detected using a commercial enzyme-linked immunosorbent assay (VITA Diagnostika GmbH, Merzhausen, Germany). An immunofluorescence assay was used to screen patients' sera for EA (Stern *et al*., 1996). Twelve individuals with gluten sensitivity were personally interviewed and examined by one of us (K.B.) using a standardized examination procedure. All patients underwent HLA typing and were screened for malabsorption, hepatic disease and diabetes mellitus by determination of vitamin B12 and vitamin E levels, aspartate aminotransferase, glutamic pyruvate transaminase, red cell count and blood glucose. Lumbar CSF was subjected to the following investigations in all individuals: cell count (normal: $<6/mm^3$), quantification of albumin (normal value: 60–330 mg/l), γ-globulin (IgG) (normal value: 3–37 mg/l), IgG albumin index (normal value: 0.38–0.7), protein electrophoresis for oligoclonal bands, and AGA and EA.

Ten of 12 patients with positive antibodies underwent duodenal biopsy. Two patients refused endoscopy (see Table 1). Two to four biopsy specimens were taken from the distal duodenum through a conventional endoscope. For histological and immunohistochemical staining, the biopsy specimens were fixed in 4% buffered formalin and embedded in paraffin. For conventional histology, 5 μm sections were stained with haematoxylin and eosin and the periodic acid–Schiff reaction. For quantitative evaluation of the number of intraepithelial lymphocytes, sections were stained with an antibody against the lymphocyte common antigen (CD45; Dako, Hamburg, Germany) using the avidin–biotin–peroxidase complex method (Hsu *et al*., 1981). Gluten-sensitive enteropathy with flat mucosa was recorded in the presence of crypt hyperplasia and subtotal or total villous atrophy (Marsh, 1992).

Imaging

Cranial MRI was performed in all patients using a superconducting system operating at 1.5 T field strength (Magnetom Siemens AG, Erlangen, Germany) with a standard head coil.

Electrophysiology

Brainstem auditory, visual and cortical sensory evoked potentials after stimulation of the tibial nerve, motor nerve conduction velocity of the tibial nerve and sensory nerve conduction velocity of the sural nerve were measured following standard procedures. All patients underwent cortical sensory evoked potential and neurographic testing, while visual evoked potential and brainstem auditory evoked potentials were studied in 10 individuals. Central motor conduction time was determined using the F-wave technique in 11 patients. For the evoked potentials and nerve conduction velocities, latencies beyond the 3 SD threshold of the normative data from our laboratory were considered abnormal. Amplitudes of compound muscle potentials below 5 mV and sensory nerve action potentials below 10 μV were also considered abnormal.

Neuropsychology

Three female and five male patients with positive antibodies (mean age 49.6 ± 20.1 years, range 30–70 years; mean age of onset 33.9 ± 24.6 years, range 2–65 years; mean disease duration 13.6 ± 8.9 years, range: 5–32 years) and nine control subjects were submitted to a neuropsychological test battery comprising tests for general intellectual abilities, IQ, attention, verbal and visuospatial memory, as well as executive functions that have been described extensively elsewhere (Bürk *et al*., 1999). The control group consisted of nine volunteers recruited from advertisements or personal contact (mean age 54.3 ± 8.3 years). The control subjects were selected from a larger subject pool to ensure that their ages and IQs were comparable with those of the patients (see Results). None of the control subjects had a history of neurological disease and/or psychiatric symptoms or was taking medication at the time of testing.

Statistics

Statistical comparisons were conducted using a Student's two-tailed *t* test or a one-way analysis of variance, or repeated measures analysis of variance where appropriate with the fixed factor group. Differences were considered significant when P was <0.05. In order to achieve a global significance

Table 1 *HLA class II phenotypes of 10 patients with sporadic ataxia associated with gluten sensitivity*

Patient	HLA-DRB1	HLA-DRB3/DRB4	HLA-DQB1	Histological findings
1	*1301/*1501	B3*02x/B5*0101	*0601/*0603	IEL↑
2	*12x/*1301	B3*02x/B3*0101	*0301/*0603	
3	*1001/*1601	B5*02x	*0501/*0502	Flat mucosa
4	*0701/*1501	B5*02x/B4*01x	*0201/*0602	
5	*0701/*1301	B4*01x/B3*02x	*0201/*0603	
6	*0701/*1501	B5*0101/B4*01x	*0201/*0602	
7	*0701/*1302	nt	*0201/*0604	IEL↑
8	*0701/*1501	nt	*0201/*0501	IEL↑
9	*0301/*0401	nt	*0201/*0302	IEL↑
10	*0701/*0801	B4*01x	*0201/*0301	IEL↑

IEL = intraepithelial lymphocytes; nt = not tested.

level of 5%, the P values were corrected applying the Bonferroni–Holm adjustment.

Results

Histological findings, frequency of autoantibodies and other laboratory findings

Among 104 patients with sporadic ataxia, 12 individuals (11.4%) presented with gluten sensitivity (male $n = 5$; female $n = 7$; mean age 55.5 ± 17.4 years, range 30–76 years; mean age of onset 44.8 ± 23.2 years, range 2–68 years; mean disease duration 10.7 ± 8.2 years, range 2–32 years). AGA were present in 11 individuals: IgA-AGA were found in five, IgG-AGA in two, IgA-AGA and IgA-EA in one, and IgA-AGA and IgG-AGA in three individuals. In two patients (one of whom had positive EA and IgA-AGA while the other had negative antibodies), typical flattening of small intestinal mucosa with villous atrophy was present, a finding that corresponds to the destructive (type 3) lesion of gluten-sensitive enteropathy as defined by Marsh (Marsh, 1992). The patient with negative antibodies had already been diagnosed as having gluten sensitivity prior to the manifestation of cerebellar symptoms and had been on a gluten-free diet for several years. Interestingly, both complained of weight loss, diarrhoea and flatulence. In five other patients (three with IgA-AGA, two with IgG-AGA and IgA-AGA), the number of intraepithelial lymphocytes was at least focally increased, but there were no changes in the mucosal architecture. Thus, the histological changes correspond to the infiltrative (type 1) lesion according to the classification of Marsh (Marsh, 1992).

Investigation of the CSF did not yield any abnormalities with respect to cell count, albumin, IgG content and electrophoresis. One female individual had a slightly elevated IgG albumin index (0.73) with an intact blood–brain barrier. AGA and EA could not be detected in the CSF.

HLA typing of 10 of the gluten-sensitive patients with sporadic ataxia revealed the presence of an HLA-DQB1*0201 phenotype in seven cases (Table 1), suggesting the presence of an HLA-associated susceptibility typical for coeliac disease. The other patients ($n = 3$) were negative for HLA-DRB1*04x and DQB1*0302, previously reported as other major risk alleles for coeliac disease (Hadjivassiliou *et al*., 1998). Interestingly, none of the patients showed IgA deficiency or hepatic disease. Vitamins B_{12} and E were found to be within the normal range in all patients. One male individual had moderate type II diabetes mellitus for 5 years.

Table 2 *Clinical features in sporadic ataxia with gluten sensitivity (*n *= 12); data are given in percentages*

Clinical features	Percentage
Ataxia of stance and gait	100.0
Dysarthria	100.0
Limb ataxia	91.7
Impaired smooth pursuit	91.7
Gaze-evoked nystagmus	66.7
Loss of proprioception	58.3
Dysphagia	41.7
Bladder dysfunction	33.3
Reduced/absent ankle reflexes	33.3
Spontaneous nystagmus	33.3
Saccade slowing	25.0
Double vision	16.7
Upward gaze palsy	16.7
Gastrointestinal symptoms	16.7
Fixation instability	8.3
Fasciculations	8.3
Amyotrophy	8.3

Clinical findings and imaging studies

All patients presented with predominant cerebellar ataxia of stance and gait, and dysarthria. Limb ataxia was always less pronounced (see Table 2). Ataxia of stance and gait was mild to moderate, and all patients were ambulatory. One patient with a disease duration of 14 years used a walking aid. Cerebellar oculomotor features such as impaired smooth pursuit, gaze-evoked nystagmus, spontaneous nystagmus and fixation instability were accompanied infrequently by saccade slowing, double vision and upward gaze palsy. Almost half of the patients complained of dysphagia and one-third of

bladder dysfunction. Loss of proprioception was evident in more than half of the patients, while reduced ankle reflexes, fasciculations and amyotrophy were less frequent. Other features often observed in sporadic ataxia (Harding, 1981), especially basal ganglia symptoms, pyramidal tract signs, tremor, horizontal gaze palsy and pale discs, were not part of the clinical syndrome of sporadic ataxia with gluten sensitivity. All patients had cerebellar atrophy affecting both vermis and hemispheres, while brainstem structures were normal (Fig. 1).

Electrophysiological findings

The visual evoked potential was abnormal in 30% of the patients tested and brainstem auditory evoked potentials were abnormal in 10%. Evoked potentials of the tibial nerve were abnormal in 58.3% (loss of cortical P40 responses 25%; delayed P40 33.3%), while 27.3% of the patients had an increased central motor conduction time. Neurography revealed prominent axonal neuropathy with reduced amplitudes. In 16.7% of patients, electrophysiological findings were consistent with sensorimotor axonal neuropathy. Pure sensory axonal neuropathy was found in 25% of the patients (including the patient with diabetes mellitus type II) and motor axonal neuropathy in 8.3%. While motor nerve conduction velocity was normal in all patients, additional sensory demyelinating neuropathy with reduced sensory nerve conduction velocity was diagnosed in 16.7%.

Neuropsychological testing

On the Mini-Mental State Test, none of the patients showed obvious general intellectual impairment. The cognitive deficits were more subtle, with significant verbal memory deficits on the Wechsler Memory Scale and Word Lists (see Table 3). Analysis of three verbal fluency tests yielded problems in the generation of nouns from one phonemic category and alternating semantic categories in patients with sporadic ataxia with gluten sensitivity. In accordance with the latter finding, patients attained fewer categories on the Wisconsin Card Sorting Test than controls. Both findings are consistent with executive problems although the corrected *P* values did not reach significance (Daum *et al*., 1995).

Discussion

The syndrome of gluten sensitivity is contingent upon an intolerance to the alcohol-soluble fraction of dietary gluten, i.e. the gliadin of wheat and the prolamins of rye and barley. Gluten sensitivity is an immunologically mediated disease with a strong association with certain HLA haplotypes: 90% of patients have HLA DQ2 and the remaining 10% show HLA DR4 DQ8 (Hadjivassiliou *et al*., 1998). The clinical picture of coeliac disease shows considerable variability: the classical form with childhood onset is a well-defined clinical syndrome with abdominal distension, bad appetite, vomiting,

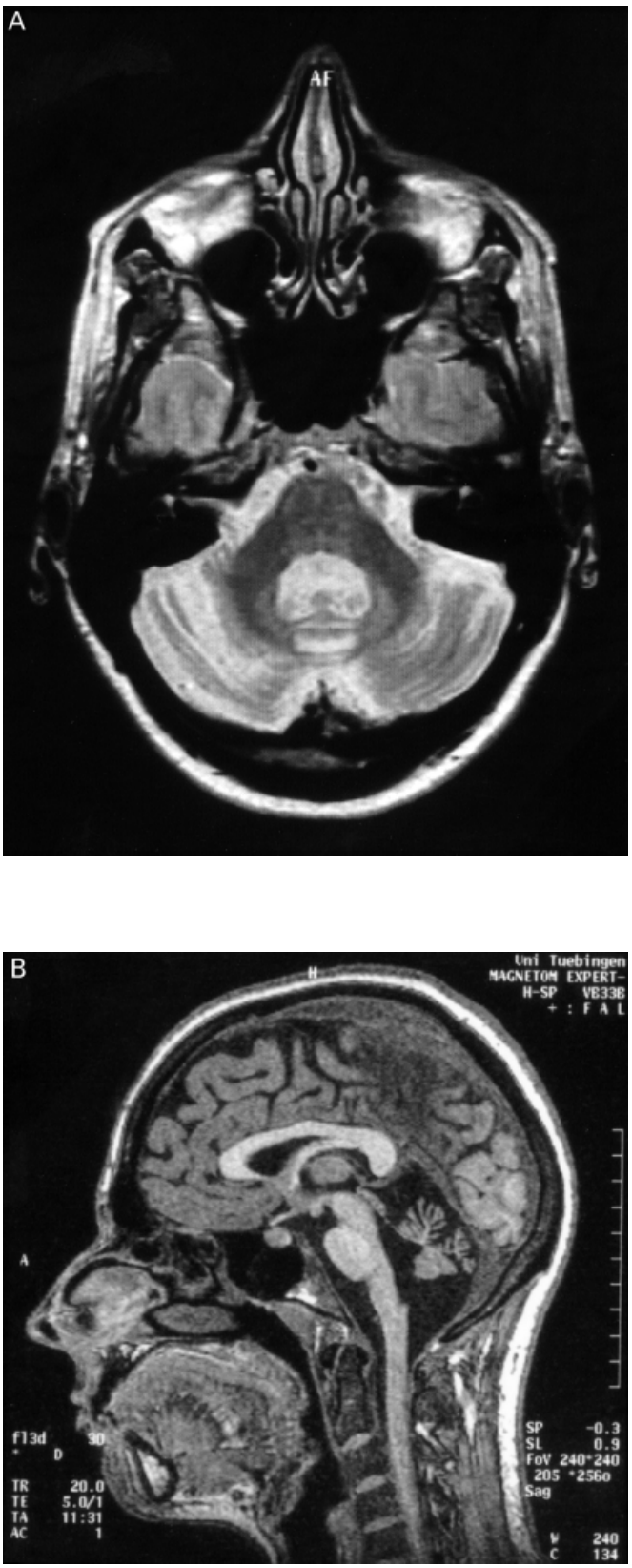

Fig. 1 (**A**) Axial T_2 and (**B**) sagittal T_1-weighted images of a 30-year-old female patient with an 8 year history of cerebellar ataxia associated with gluten sensitivity showing marked atrophy of cerebellar vermis and hemispheres. The brainstem is not affected by the atrophic process.

Table 3 *Background variables and neuropsychological test performance in eight patients with antigliadin antibodies and controls: data are given as means ± SDs*

	Controls	Patients
Number	9	8
Age (mean years)	53.4 ± 8.3	49.6 ± 20.1
Verbal IQ	119.4 ± 12.2	115.4 ± 19.3
Performance IQ	113.9 ± 10.7	114.1 ± 12.2
MMS	29.6 ± 0.7	29.4 ± 1.1
Digit span		
Forward	6.6 ± 1.2	6.6 ± 0.7
Backward	5.1 ± 1.5	5.0 ± 1.2
Wechsler Memory Scale		
Immediate recall	12.8 ± 2.6	7.8 ± 2.5***,†
Delayed recall	10.3 ± 2.6	6.5 ± 2.5**
Word lists		
Immediate recall of		
Consecutive categories list	9.8 ± 2.8	5.9 ± 1.5***,†
Randomized categories list	8.0 ± 2.2	6.3 ± 1.0
Uncategorized list	7.0 ± 1.6	3.5 ± 2.0***,†
Delayed recall of		
Consecutive categories list	4.8 ± 2.6	2.5 ± 1.5*
Randomized categories list	3.4 ± 3.4	1.6 ± 1.5*
Uncategorized list	1.7 ± 1.7	1.1 ± 1.5
Rey–Osterrieth complex figure		
Copy	46.3 ± 1.0	45.6 ± 3.0
Recall	30.0 ± 7.8	26.5 ± 12.1
Proportional recall	64.8 ± 17.1	57.7 ± 24.8
Verbal fluency		
Semantic category	26.0 ± 7.7	20.6 ± 6.3
Phonemic category	12.2 ± 2.9	8.5 ± 2.1**
Alternating semantic category	15.2 ± 2.8	12.4 ± 2.3*
Wisconsin Card Sorting Test		
Categories	5.9 ± 0.3	3.7 ± 2.4*
Random errors	3.1 ± 2.4	3.6 ± 4.4
Perseverations	0.3 ± 0.7	0.2 ± 0.4

*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$ compared with controls; †Bonferroni–Holm adjusted P values.

diarrhoea, malabsorption and weight loss. In recent years, it has become evident that the clinical spectrum of coeliac disease is much broader than originally suspected (Visakorpi and Mäki, 1994).

In peripheral blood, AGA and EA can be detected in most untreated patients with coeliac disease (Trier, 1991; Marsh, 1992; Hadjivassiliou *et al*., 1998). While IgG-AGA have been demonstrated to be very sensitive, especially in IgA deficiency, AGA of the IgA type are more specific for coeliac disease (Bodé *et al*., 1993; Bodé and Gudmand-Hoyer, 1994). EA are considered to have both high sensitivity and specificity for the presence of mucosal damage (Bürgin-Wolff *et al*., 1991). In the present study, the majority of patients had IgA-AGA, but pathognomonic villous atrophy was restricted to two subjects, one with normal antibodies who was on a gluten-free diet and the other with both EA and IgA-AGA. In two other patients, there was evidence of isolated IgG-AGA that was not related to IgA deficiency. In five patients, the histological findings corresponded to the type 1 classification of Marsh (Marsh, 1992) that may be found in early stages of coeliac disease as well as in dermatitis herpetiformis and in relatives of patients with typical coeliac disease. The existence of ataxia with gluten sensitivity, but without typical villous atrophy typical of coeliac disease had also been reported by Hadjivassiliou and colleagues (Hadjivassiliou *et al*., 1996).

Neurological manifestations such as peripheral neuropathy, progressive myoclonic ataxia, progressive multifocal leukencephalopathy, dementia and myopathy have been reported in coeliac disease (Elders, 1925; Trier, 1991; Pellecchia *et al*., 1999), but cerebellar ataxia represents the most frequently associated neurological syndrome (Hadjivassiliou *et al*., 1996). Ataxia commonly had been attributed to malabsorption of neuroprotective or neurotrophic nutrients such as vitamin E (Mauro *et al*., 1991). In the present study, none of the patients had hypovitaminosis or malabsorption, and more than half of the patients did not even show any duodenal abnormalities. Neuropathologically, there is loss of Purkinje cells and/or degeneration of the dorsal columns (Bhatia *et al*., 1995; Hadjivassiliou *et al*.,

1998) with facultative lymphocytic infiltration of the cerebellum, dorsal columns and peripheral nerves (Hadjivassiliou *et al*., 1998). In the present study, we failed to show evidence of a chronic inflammatory process in the CSF, but, irrespective of the histological findings in the gut, ataxia with gluten sensitivity was associated with the HLA DQB1*0201 haplotype in 70% of cerebellar patients. As this haplotype is present in ~40% of Caucasian control subjects (Gjertson and Lee, 1998), the association is highly significant. As coeliac disease is linked to the same haplotype (Hadjivassiliou *et al*., 1998), coeliac disease and ataxia with gluten sensitivity are not only suggested to be part of the same disease entity, but are likely to be contingent upon an immunological process despite normal CSF findings on routine examination.

Cerebellar dysfunction dominated the syndrome, with ataxia of stance and limbs, dysarthria and cerebellar oculomotor symptoms. In addition, patients had clinical and electrophysiological features suggestive of dorsal column degeneration and peripheral neuropathy prominently affecting sensory fibres. On neuropsychological testing, there was evidence of deficient verbal memory and executive dysfunction that was not related to general intellectual impairment.

The prevalence of AGA is high in British blood donors (12%) (Hadjivassiliou *et al*., 1996). In a cohort of 600 German blood donors, AGA of the IgA type were in the pathological range in 3.3% and AGA of the IgG type in 5% of the individuals tested (data provided by VITA Diagnostika GmbH, Merzhausen, Germany). Therefore, gluten sensitivity is significantly more frequent among cerebellar patients than among the general population in Germany. The present findings are also distinct from the data previously reported by Hadjivassiliou and colleagues not only in a lower prevalence of gluten sensitivity in patients with apparently idiopathic cerebellar ataxia (11.4% versus 68%) but also in the higher frequency of cerebellar atrophy (Hadjivassiliou *et al*., 1996). These discrepancies are likely to be contingent upon distinct patient characteristics. First, the study of Hadjivassiliou was based on 25 cases with idiopathic cerebellar ataxia who were part of a larger group of patients with unexplained neurological illness. Secondly, the features of ataxia with gluten sensitivity described by Hadjivassiliou with absence of cerebellar oculomotor symptoms in most patients and isolated dorsal column degeneration on post-mortem studies (Hadjivassiliou *et al*., 1998) seem rather consistent with spinal ataxia. The higher frequency of cerebellar atrophy in the present study may also be contingent upon a longer disease duration (10.7 years versus 6.4 years in the study of Hadjivassiliou), since the degree of cerebellar atrophy seems to be related to the duration of symptoms (Hadjivassiliou *et al*., 1998). In addition, the discrepancies regarding the prevalence may also result from the inclusion of patients with possible or probable multiple system atrophy in the present study (Gilman *et al*., 1999) while Hadjivassiliou had excluded all subjects with this type of cerebellar degeneration.

If villous atrophy is present, a lifelong gluten-free diet is recommended. This is of critical clinical importance not only in terms of malabsorption, but also in the light of a 40-fold increased incidence of intestinal lymphoma in untreated patients with coeliac disease (Holmes *et al*., 1989). According to these therapeutic recommendations, a gluten-free diet would not be essential in every ataxic patient with gluten sensitivity. Hadjivassiliou reported complete resolution of symptoms on a gluten-free diet in patients with prompt diagnosis (Hadjivassiliou *et al*., 1998). Regeneration in the CNS is very limited and it seems appropriate to start a gluten-free diet early in the course of the disease. Most of our patients decided to maintain a gluten-free diet in order to eliminate the triggering agent and we currently are following the therapeutic effect on the disease process.

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