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rather than the DR53 allele may be a contributing factor in protection.

In addition to DR1, DR7,<sup>4,8,9</sup> DQw7,<sup>10</sup> and DR6<sup>4,8</sup> have been negatively associated with MS. It is of interest that in all these studies, DR2 evinced a positive association with MS. One explanation for the heterogeneous negative associations may thus be that the combined effect of HLA alleles rather than locus heterogeneity contributes in the protection, as suggested above. Therefore, our current finding may be of importance, but it needs to be confirmed in a larger population.

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## Headache and CNS white matter abnormalities associated with gluten sensitivity

**Article abstract**—The authors describe 10 patients with gluten sensitivity and abnormal MRI. All experienced episodic headache, six had unsteadiness, and four had gait ataxia. MRI abnormalities varied from confluent areas of high signal throughout the white matter to foci of high signal scattered in both hemispheres. Symptomatic response to gluten-free diet was seen in nine patients.

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Gluten sensitivity is a state of heightened immunologic responsiveness triggered by the ingestion of gluten in genetically susceptible (human lymphocyte antigen [HLA] DQ2) individuals.<sup>1</sup> Gluten sensitivity encompasses a spectrum of diverse manifestations, including gluten-sensitive enteropathy (celiac disease), dermatitis herpetiformis, and neurologic dysfunction. Neurologic manifestations and dermatitis herpetiformis can occur without histologic evidence of bowel involvement.<sup>2</sup> The commonest neurologic manifestations are cerebellar (gluten) ataxia<sup>3</sup> and gluten-related peripheral neuropathy.<sup>4</sup> MRI data from

patients with gluten sensitivity and neurologic dysfunction are limited to case reports in patients with established celiac disease who subsequently develop neurologic disease. In some, MRI showed white matter abnormalities suggestive of an inflammatory process. We present clinical and MRI data on a cohort of patients attending our gluten sensitivity/neurology clinic in whom MRI showed otherwise unexplained white matter abnormalities.

**Methods.** All 10 patients were seen at the gluten sensitivity/neurology clinic at the Royal Hallamshire Hospital, Sheffield, United Kingdom, over the last 4 years. Gluten sensitivity was defined by the presence of anti-gliadin antibodies, as well as evidence of genetic susceptibility for this disease (HLA DQ2 or DQ8). The total number of patients attending this clinic is currently 105. Forty patients with symptoms and signs of CNS dysfunction underwent MRI. Most had gluten ataxia, and their MRI results have been described elsewhere.<sup>3</sup> Selection of the 10 patients was based on the presence of CNS white matter abnormalities on MRI scan. All patients underwent medical, neurologic,

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**Table** Clinical and radiologic characteristics of the 10 patients

Age, y/sex	Presenting symptoms and signs	Intestinal symptoms/duodenal biopsy	Anti-gliadin antibodies	Vascular risks	Abnormal tests	Response to diet	Indication for MRI	MRI results
49/F	Episodic unilateral headache with visual aura and unsteadiness	N/abnormal	IgG	—	Low serum B <sub>12</sub>	Complete	Headache	Extensive confluent areas of high T2 signal in white matter of both hemispheres (figure, A)
37/M	Episodic unilateral headache and visual disturbance	Y/abnormal	IgG	—	—	Complete	Hemifacial spasm	Small foci of high T2 signal intensity in white matter of both hemispheres
42/F	Episodic unilateral headache with nausea and transient hemianopia	N/normal	IgG	Smoker	Low serum B <sub>12</sub>	Complete	Headache	Scattered foci of high T2 signal in white matter of both cerebral hemispheres
50/M	Episodic right-sided headache with nausea, confusion, unsteadiness. Right homonymous hemianopia, gait ataxia (see case report in text)	Y/abnormal	IgG, IgA	—	—	Complete	Headache	Extensive areas of high T2 signal in internal & external capsules, basal ganglia, thalamus, and pons (figure, B)
73/F	Unsteadiness, falls, and episodic unilateral headache with visual aura; gait ataxia	N/normal	IgG	Insulin-dependent diabetes mellitus	—	Complete	Ataxia	Numerous foci of high T2 signal intensity in both cerebral hemispheres
56/F	Episodic generalized headache with nausea and phonophobia; episodic dizziness, unsteadiness, and falls; painful paresthesia of feet and hands	N/abnormal	IgG	—	Abnormal thermal thresholds	Partial	Unsteadiness and headache	Numerous foci of high T2 signal intensity in both cerebral hemispheres
46/M	Episodic frontal headache, deafness left ear	N/normal	IgG	—	Abnormal audiogram left ear	Refused diet	Sensorineural deafness	Scattered small foci of high T2 signal in white matter of both hemispheres (figure, C)
61/M	Unsteadiness, episodic headache with photophobia, numbness and parasthesia right hand; gait ataxia	N/normal	IgA	—	Chronic microcytosis without anemia	Complete	Ataxia	Extensive T2 signal hyperintensities in white matter of both hemispheres (figure, D)
61/F	Episodic right-sided headache with visual aura associated with right-sided numbness and amnesia; loss of temperature sensation in feet	Y/normal	IgG	Anti-cardiolipin antibodies	Anticardiolipin antibodies, sensorimotor axonal peripheral neuropathy	Complete	Headache	Multiple T2 signal hyperintensities symmetrically distributed in white matter of both cerebral hemispheres, thalamus, and cerebellum
49/F	Tiredness, unsteadiness, falls, episodic right-sided headache with visual aura, nausea, phono- and photophobia; gait ataxia	Y/normal	IgG, IgA	—	—	Partial	Ataxia	Scattered foci of high T2 signal in white matter of both hemispheres

and neurophysiologic examination. Investigations included antinuclear antibodies, double-stranded DNA, antinuclear cytoplasmic antibodies, extractable nuclear antibodies, C-reactive protein, immunoglobulins, and electrophoresis, rheumatoid factor, complement levels, thrombophilia screen (anticardiolipin antibodies, lupus anticoagulant), vitamins B<sub>12</sub>, E, D, and red cell folate, full blood count, and erythrocyte sedimentation rate (ESR), urea and electro-

lytes, liver function tests, thyroid function tests, calcium, magnesium, random glucose, and angiotensin-converting enzyme levels. Endoscopy and distal duodenal biopsy was performed in all patients. Further investigations were performed if clinically indicated.

**Results.** Six women and four men had CNS white matter abnormalities on MRI (table). The mean age was 52

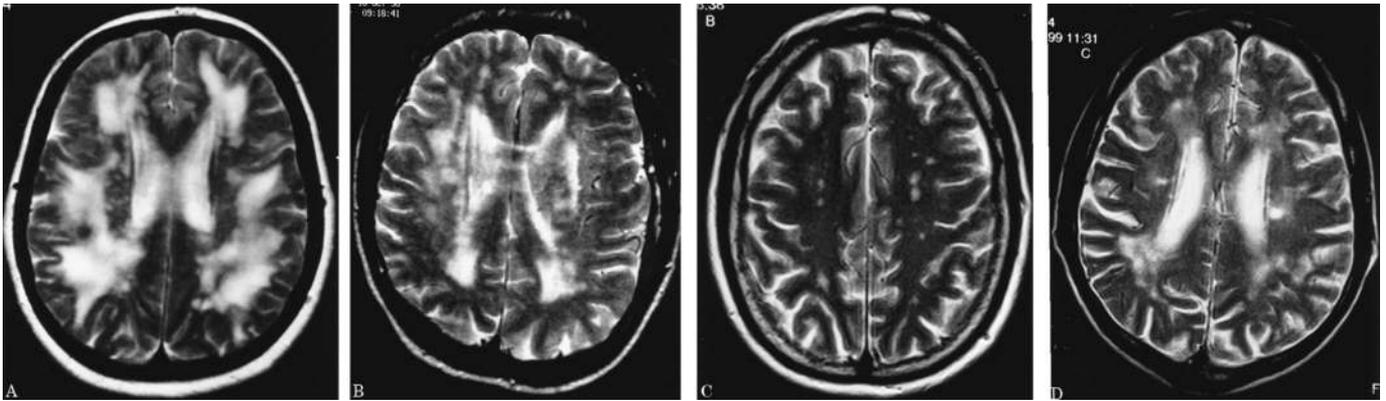


Figure. MRI from four patients, showing range of white matter abnormalities encountered.

years. All had episodic unilateral headache often associated with visual or sensory disturbance. Six reported unsteadiness when walking, and four had evidence of gait ataxia. Two also had distal sensory disturbance affecting feet and hands. All patients had the HLA DQ2. Four patients had histologic evidence of bowel inflammation on duodenal biopsy. In three, the histology was compatible with celiac disease, and in one it was compatible with Marsh type 2 lesion.<sup>1</sup> The MRI abnormalities varied from extensive confluent areas of high signal throughout the white matter to numerous foci of high signal scattered in both hemispheres. Introduction of gluten-free diet in nine patients resulted in complete resolution of the headaches in seven with partial improvement in two. One patient would not try the diet.

**Illustrative case.** A 50-year-old man developed right-sided headache and nausea associated with confusion and agitation. He had experienced episodic headache for 4 years, but more recently the attacks had become more frequent and severe. There was no family history of migraine. Neurologic examination indicated disorientation in time and place, right homonymous hemianopia, and gait ataxia. He was treated with analgesics and antiemetics and recovered fully within 24 hours.

A CT scan showed diffuse hypodensity within the white matter. Results of CSF examination and visual evoked potentials were normal. Blood tests showed positive IgG and IgA antigliadin antibodies. His MRI (figure, B) showed extensive high signal lesions in the periventricular white matter of both hemispheres with further abnormalities in the internal and external capsules, the basal ganglia, the left thalamus, and the pons.

A few weeks later, he developed intermittent diarrhea and pale stools. The duodenal biopsy was abnormal. His HLA genotype was DQ2. He started a gluten-free diet in June 1996. His balance improved rapidly, and his headaches resolved completely. Two years later, he reported intermittent headaches similar to but less severe than those he experienced previously. Dietetic assessment showed his compliance with gluten-free diet to be poor. This was also confirmed by positive immunoglobulin G (IgG) antigliadin antibodies having been negative for the previous 2 years. A repeat MRI scan a year after poor compliance showed progression of the abnormalities with involvement of the right thalamus. He is currently on strict gluten-free diet and remains free of headaches.

**Discussion.** We have found 10 previous case reports of patients with celiac disease in which MRI data were provided (total of 15 patients). MRI showed involvement of the white matter in seven of 15 patients in a very similar distribution to the cases described here. These white matter abnormalities enhance with gadolinium and may respond to steroid treatment.<sup>5</sup> In two cases<sup>6,7</sup> in which autopsy results were available, histology showed evidence of vasculitis.

We describe 10 patients with gluten sensitivity and CNS white matter abnormalities without evidence of an alternative cause. A dominant symptom in all of our patients was the episodic headache. Most had a long history of episodic headache but reported increased frequency, alteration in character of the attacks, and resistance to treatment. There are anecdotal reports of migraine-like headache in patients with established celiac disease with response to gluten-free diet. Published reports, however, are rare. In a series of 388 patients with celiac disease,<sup>8</sup> the prevalence of migraine was 3.1%, which is lower than in the general population. A more recent case report<sup>9</sup> described a 45-year-old man suffering from migraine with visual aura since early childhood, whose attacks had become more severe and resistant to treatment. He was found to have celiac disease, and, after the introduction of gluten-free diet, his headaches resolved. No imaging data were available.

Such associations may be purely coincidental. However, the complete resolution of headaches in seven of the nine patients who are on gluten-free diet and partial improvement in the remaining two suggests a link between gluten sensitivity and migraine-like headaches in these cases. In the illustrative case above, relaxation of the gluten-free diet resulted in recurrence of the headaches with some progression of the white matter abnormalities on MRI. Further studies of the effect of gluten-free diet are needed to confirm these preliminary observations.

The diagnosis of gluten-related neurologic dysfunction relies on the presence of circulating anti-

gliadin antibodies. Antigliadin antibodies are the most sensitive marker of the whole spectrum of gluten sensitivity. Although antiendomysium and tissue transglutaminase antibodies are more specific in the diagnosis of gluten-sensitive enteropathy, in our experience they lack sensitivity in diagnosing gluten-related neurologic dysfunction. HLA typing can be an additional marker of gluten sensitivity, because it can confirm genetic susceptibility.

Intestinal mucosal damage in celiac disease is the result of both humoral and T-cell-mediated inflammation. Such inflammation is not, however, confined to the gut. Activated HLA-restricted gliadin-specific T cells and antigliadin antibodies are found systemically. Antigliadin antibodies are also found in the CSF. CD4 and CD8 T cells have been shown to infiltrate the cerebellum of patients with gluten ataxia.<sup>3</sup> In addition, we have found antibodies against Purkinje cells in some of our patients with gluten ataxia.<sup>10</sup> Both humoral and T-cell-mediated mechanisms are thus implicated in neural damage.

Gluten sensitivity can be primarily and at times exclusively a neurologic disease. If the results of the current study are confirmed, removal of the trigger factor by the early introduction of gluten-free diet may be a promising therapeutic intervention. Antigliadin antibodies should be part of the routine investigation of all patients with neurologic dysfunction of obscure cause, particularly patients with ataxia or peripheral neuropathy. Patients with episodic headache and un-

explained white matter lesions on MRI should be added to this list.

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## Reversible posterior leukoencephalopathy during the treatment of acute lymphoblastic leukemia

**Article abstract**—Three children with acute lymphoblastic leukemia developed altered mental status, headaches, seizures, and visual changes associated with reversible posterior cerebral changes on MRI. These clinical and radiologic findings were consistent with the reversible posterior leukoencephalopathy syndrome, which has not been widely recognized in this setting.

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In 1996, Hinchey et al. coined the term “reversible posterior leukoencephalopathy” to describe a syndrome of headaches, confusion, seizures, and visual disturbances associated with transient, predominantly posterior lesions on neuroimaging.<sup>1</sup> The re-

versible posterior leukoencephalopathy syndrome (RPLS) occurs in both children and adults in association with hypertension and/or immunosuppression.<sup>2</sup> Known triggers include acute renal failure, eclampsia (especially puerperal), and the use of cyclosporine, FK506, or interferon- $\alpha$ .<sup>1</sup> As RPLS has become better recognized, additional contributing factors have been identified. For example, reports have linked RPLS to the use of erythropoietin in end-stage renal disease, cancer treatment with cisplatin, and porphyria.<sup>3–5</sup>

We describe three children who developed RPLS during the treatment of acute lymphoblastic leukemia (ALL).

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