Multiple sclerosis and occult gluten sensitivity

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Abstract—Two atypical patients with a multiple sclerosis (MS)–like illness and evidence of occult celiac disease (CD) were managed by the authors. This prompted screening of a further 49 unselected MS cases for serologic evidence of CD. IgA anti-endomysial antibody was found in one case (2%). IgG anti-gliadin antibody was found in 12% of patients and 13% of blood donors. Anti-gliadin antibody (especially IgG isotype) can be a nonspecific finding.

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Celiac disease (CD) is a gluten-sensitive enteropathy (GSE). Patients develop small bowel villous atrophy, malabsorption, and weight loss, all reversed by a strict gluten-free diet (GFD). A subgroup of patients with occult GSE with atypical or absent gut symptoms is recognized.[1]

Improved screening for IgA antibodies associated with CD (i.e., anti-reticulin [ARA], anti-gliadin [AGA], anti-endomysial [AEA], and anti-tissue transglutaminase [anti-TTG]) has improved the detection of CD in recent years. However, IgG class antibodies have poor disease specificity.[2] AGA is an anti-wheat protein antibody, which, like other food antibodies (e.g., anti-ovalbumin), especially of the IgG class, is not disease specific.

Numerous neurologic conditions, including epilepsy, sensory ataxia, and neuropathy, have a reported association with established CD. Associations between AGA positivity (as distinct from CD) and cerebellar ataxia have also been reported,[3] with speculation that the ataxia is gluten induced. Some investigators have suggested that a GFD is likely to be of benefit in idiopathic ataxic syndromes. However, AGA positivity is also seen in a number of ataxias known to have a non-gluten-sensitive pathogenesis, including autosomal dominant cerebellar ataxia and multiple-system atrophy.[4]

Previous researchers have investigated the role of a GFD in the treatment of multiple sclerosis (MS) and found no benefits.[5] The relapsing–remitting natural history of MS can make interpretations very difficult. We identified two patients with MS-like disease who were incidentally discovered to have occult CD. CD is common (around 1% of the general population), and ascertainment bias may occur. In this study, we report seropositivity for AGA, anti-TTG, and AEA in an unselected group of MS patients.

Case reports. *Patient 1.* A 24-year-old woman presented with diplopia, left retro-orbital pain, and right arm and leg weakness. Four months earlier, she had developed lumbar and buttock pain and paresthesia affecting the whole left lower limb with urinary urgency and incontinence, which resolved without treatment. On examination, she had left sixth and seventh nerve palsies, ataxia, and a mild right hemiplegia. A clinical diagnosis of MS was made. MRI of the lumbar spine was normal. MRI scan of the brain and spinal cord showed an ill-defined high signal area in the left side of the pons (figure). CSF protein, glucose, and cell count were normal. There were no oligoclonal bands in the CSF, but IgG levels were raised, suggestive of intrathecal synthesis. Subsequently, routine autoantibody screening revealed positive ARA. She was therefore screened for GSE and was found to have strongly positive IgA AEA, IgA anti-TTG, and IgG AGA in the serum. IgA AGA was negative. Interestingly, her CSF was also positive for IgA anti-TTG. A subsequent small bowel biopsy was characteristic of GSE, and she was commenced on a GFD.

Patient 2. A 26-year-old woman was admitted with gradual onset of slurred speech, clumsiness, and weakness of the right side. Examination revealed cerebellar dysarthria, right-sided weakness, and ataxia. MRI scan of the brain showed a high signal lesion in the right parietal lobe adjacent to the posterior horn of the right lateral ventricle. Antibody screening revealed strongly positive IgA ARA and IgA AEA. IgA and IgG AGA were negative. A duodenal biopsy confirmed GSE, and she commenced GFD with correction of the previous borderline-low vitamin B_{12}. She was subsequently found to have negative oligoclonal bands in her CSF. Three months later, she developed further mild right-sided weakness and subjectively altered sensation of the right-sided limbs and trunk. MRI of the cervical spine showed two high signal lesions in the cervical cord at the level of C2 to C3 and C4 to C5 on T2 weighting (see figure, B).

Both patients were acutely treated with 1 g IV of methylprednisolone daily for 3 days and had experienced no further neurologic episodes at the time of writing.

Methods. Patients were randomly recruited from general neurology and MS clinics at the Queen's Medical Centre, Nottingham, and the Derbyshire Royal Infirmary. The subjects' consent was obtained according to the Declaration of Helsinki, and ethical approval was obtained from the ethics committees of both institutions.

Forty-nine patients with MS (33 female) were recruited. Thirty-eight had relapsing–remitting disease, 10 had secondary progressive disease, and 1 had primary progressive disease. In all cases, a consultant neurologist with an interest in demyelinating disease made the diagnosis of MS. None of the patients had specific symptoms suggestive of GSE, any suggestive family history, or features suggestive of malabsorption.

Thirty random anonymous blood donors (15 female) were used as serologic controls.

AGA (IgG and IgA) and IgA anti-TTG were detected by ELISA

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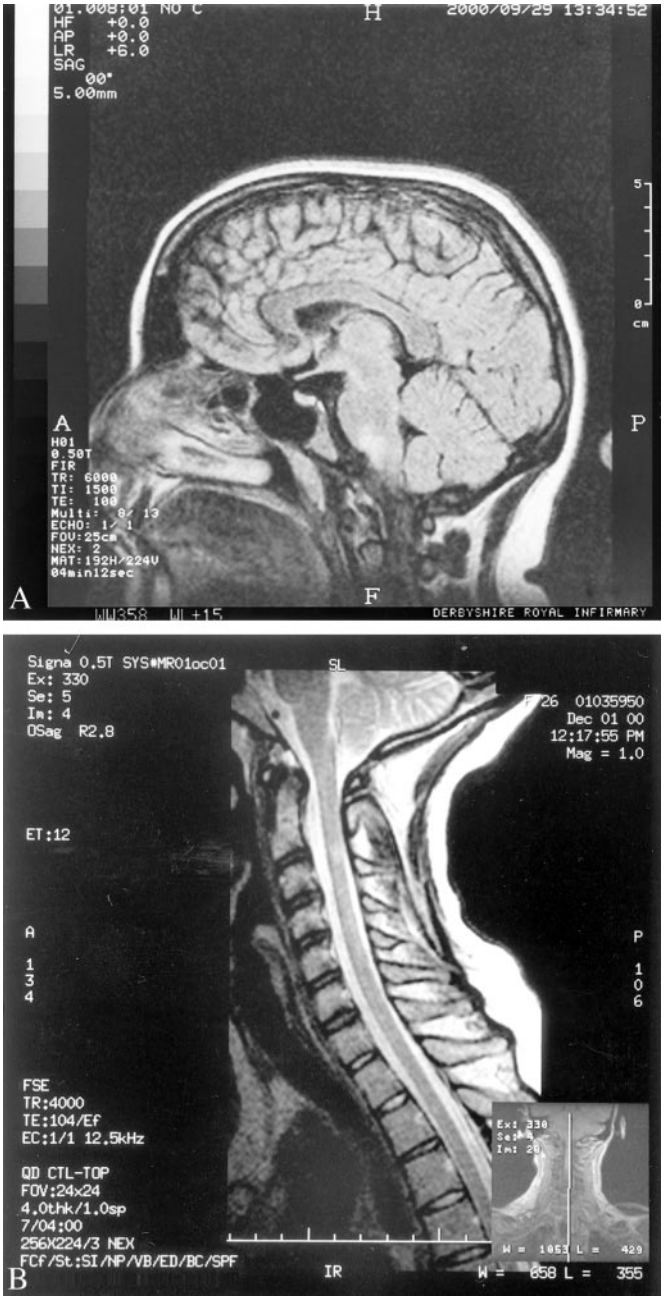

Figure. (A) T2-weighted MRI of the brain, showing high signal area in the left side of the pons. (B) T2-weighted MRI of the cervical cord, showing two high signal lesions at C2 to C3 and C4 to C5.

(Orgentec Diagnostika GmbH, Mainz, Germany). Data were analyzed by Fisher exact test to compare patients and control subjects.

Results. IgG and IgA AGA were found in 6 of 49 (12%) and 3 of 49 (6%) patients, respectively, similar to controls (13 and 7%) (p = 1.00 and 1.00). IgA anti-TTG was found in 3 of 49 patients, again similar to controls (0/30; p = 0.466). Of these, two were weakly positive and subsequently found negative for IgA AEA. Serum from one patient was strongly positive for IgG and IgA AGA and strongly positive for IgA anti-TTG and AEA, consistent with CD. This patient had no gastrointestinal symptoms and declined small bowel biopsy. One control subject was positive for IgG and IgA AGA but negative for anti-TTG and AEA.

Discussion. Historically, success with a GFD in MS has been reported, although little was known about the intestinal morphology or antibody status. Subsequently, jejunal biopsies in 14 patients with MS revealed no serologic or morphologic evidence of CD.[6]

In 1996, it was reported that 57% of patients with cryptogenic neurologic disorders were AGA seropositive (IgG or IgA or both) compared with 5% of patients with known neurologic diseases and 12% of normal control subjects.[7] Further, 70% of these seropositive cases were human leukocyte antigen (HLA) DQ2.[3] This HLA type is strongly associated with GSE but also common in the UK population (approximately 37%). A new syndrome, "gluten ataxia," was proposed, implying a gluten-mediated immunopathology. A subsequent study looking for positive gliadin antibodies in serum of patients with sporadic ataxia found no inflammatory changes in CSF.[8]

In our two patients with an MS-like illness, occult CD was suspected only following serologic clues. Interestingly, one patient had positive TTG antibodies in the CSF (not previously reported), but our studies indicate this to be secondary to leakage through a damaged blood–brain barrier. Both these patients admittedly had a slightly atypical phenotype for MS. However, we cannot exclude the possibility that these two patients have developed an inflammatory disease of the CNS associated (directly or indirectly) with gluten sensitivity.

Only one patient (2%) in our study had strongly positive IgA anti-TTG and AEA, and it is likely that this patient has occult GSE. CD is common in the general population, with a prevalence rate estimated at 1% in the United Kingdom. Finding 1 patient among a cohort of 49 with occult CD is therefore likely to be a chance association. Sixteen percent of our MS patients and 17% of our blood donor controls had AGA, mainly IgG isotype, reflecting the long-established poor disease specificity for IgG AGA. IgG AGA in any neurologic case should be interpreted with caution.[9]

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To the Editor: We agree with Pengiran Tengah et al.[1] that gluten sensitivity is not etiologically linked to multiple sclerosis (MS). We screened 100 patients with relapsing-remitting, secondary progressive MS, or both, and found the prevalence of antigliadin antibodies (AGA) to be 10%; the same as in the healthy population (1,200 healthy volunteers, prevalence of 12.5%).[2] Involvement of the white matter of the brain and spinal cord in the context of gluten sensitivity has been reported.[3] However, the MRI changes in those cases were different than seen in MS, being more peripherally situated and often confluent. Pengiran Tengah et al. describe two patients with apparent "atypical" MS-like illnesses both having ataxia in addition to other neurological deficits. We encountered five patients labeled as having primary progressive or atypical MS-like illnesses who had gluten sensitivity. The predominant feature was ataxia but other focal neurologic deficits were also present. MRI of the brain showed changes confined to the white matter, indistinguishable from those seen in MS patients. Two of them also had spinal lesions. In three patients, there was neurophysiological evidence of an axonal peripheral neuropathy a finding distinguishes them from patients with MS.

The presence of oligoclonal bands cannot be used as a distinguishing feature as their presence has been reported in up to 50% of patients with gluten ataxia.[4] Gluten-free diet resulted in the stabilization of their neurology but no alteration of the MRI findings.

Gluten sensitivity may be considered as the etiology of "atypical" primary progressive MS particularly where ataxia is a prominent feature. The conclusion of Pengiran Tengah et al. that "anti-gliadin antibody (especially IgG isotype) can be a nonspecific finding" should be clarified. There is nothing in their report to support this. The existence of gluten sensitivity even in the absence of an enteropathy is now well established. The neurologic manifestations of gluten sensitivity have been shown to improve with gluten-free diet even in the absence of an enteropathy.[5]

Pengiran Tengah et al. also mention, "poor disease specificity for IgG AGA" which is meaningless given that enteropathy is not a prerequisite for the diagnosis of gluten sensitivity. One-third of patients with neurologic manifestations of gluten sensitivity have enteropathy. AGA (particularly IgG) remain the best available markers of the whole spectrum of gluten sensitivity of which enteropathy (celiac disease) is only one part.

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Reply from the Authors: We have read Hadjivassiliou et al.'s comments on our article[1] with interest. There is a fundamental difference of opinion regarding the significance of finding serum AGA (especially of IgG isotype). Given that over 10% of normals[6] are AGA positive, it would appear that positive serology of this nature has a very low positive predictive value. Assuming that the healthy seropositive subjects are not gluten sensitive, which neurology patients (patients with MS or other conditions) are gluten sensitive and which are "false" positive? Why is positive serology always significant in an ataxic case but not significant in a healthy individual? How do we know which ataxic cases are within the 10% we can ignore and which are significant? The finding of AGA in hereditary ataxias[7] and Huntington disease[8] can only be interpreted as an epiphenomenon. By way of analogy, in the investigation of suspected syphilis, the Venereal Disease Research Laboratory test is regarded as having low specificity. Better follow-up tests are necessary. In celiac disease, experts in the field regard AGA positivity (especially IgG) as so nonspecific as to require further tests (IgA antitissue transglutaminase for example).

In neurology, for patients with suspected gluten sensitivity, the AGA test is apparently 100% reliable. Our views regarding gluten

ataxia have been detailed.[9] Whether a gluten excluding diet is an effective treatment awaits further study. Our results relating to unselected idiopathic ataxia and peripheral neuropathy cases (in preparation) are very different than Dr. Hadjivassiliou's.

We have found few cases of occult celiac disease (no different to the general population) and we have had difficulty finding more than a handful of idiopathic patients in our clinics who are AGA seropositive, with HLA DQ2 or DQ8. By contrast, there seems to be an epidemic of similar cases in Dr Hadjivassiliou's series. Finally, neither of our atypical MS cases had evidence of peripheral neuropathy and one of the patients has developed further relapses since the paper was written, suggesting that she does have relapsing-remitting MS.

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