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. 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. 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, 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.

Previous researchers have investigated the role of a GFD in the treatment of multiple sclerosis (MS) and found no benefits. 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 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 IgG 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 IgG AEA. IgA and IgG AGA were negative. A duodenal biopsy confirmed GSE, and she commenced GFD with correction of the previous borderline-low vitamin B12. 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
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. 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. Further, 70% of these seropositive cases were human leukocyte antigen (HLA) DQ2. 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 ataxic ataxia found no inflammatory changes in CSF.

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.

Acknowledgment

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References


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.
3) The CIND stroke patients at baseline had more diabetics (42%), higher use of psychotropic medications (27%), and heavy alcohol use (15%) compared to nonstroke CIND group. All of these affect cognition.3,4 Did the authors correct for these confounding variables while analyzing CIND progression in stroke patients?

Could these confounding variables have accounted for persistence of CIND 1 year later?

Meheroz Hoshang Rabadi, MD, White Plains, NY

Reply from the Authors: We thank Dr. Rabadi for his interest and comments on our manuscript.1 Our responses to the questions are as follows:

1) Our finding of persistent CIND at 12 months after stroke does not support the commonly held clinical notion of cognitive improvement in most poststroke survivors. In our cohort of first-ever stroke patients, we found that 52/99 (52.5%) were cognitively impaired 3 months after stroke. Of these, 11 (21%) progressed to dementia, four (8%) recovered completely and 6 (11%) were lost to follow-up leaving 31 (60%) with persistent impairment at 12 months. These figures are similar to those quoted by Ballard et al.2 where 87/115 (76%) had persistent or stable impairment between 3 and 15 months. These results confirm that the majority of stroke patients with early cognitive impairment after stroke will have persistent CIND at 12 or more months after stroke.

Furthermore, in our study, CIND was diagnosed using a comprehensive neuropsychological battery. Subjects without dementia scoring more than one standard deviation below age and education derived normative means on at least two cognitive domains were classified as having CIND. This method more sensitive for detecting cognitive impairment than the MMSE alone; a measure commonly adopted in clinical practice. Thus, the persistence of CIND at 1 year may not have been detected had we used this less sensitive method.

2) We agree that the poststroke cognitive state would be influenced by the prior cognitive state of the population. We have presented the data on prestroke cognitive decline using the Informant Questionnaire for Cognitive Decline in Elderly (IQCODE) among unimpaired, CIND and demented stroke patients in our supplemental data on the Neurology Web site (see table E-2 at www.neurology.org), with mean scores of 3.1 (0.5), 3.0 (0.7), and 3.8 (1.1). This suggests that those who had dementia were more likely to have prestroke cognitive decline, and that CIND patients were more likely to have been unimpaired prestroke. This was borne out in our logistic regression models.

3) In any multivariable analysis it is important to account for the possibility of confounding. The logistic regression model for risk of CIND was unchanged with the addition of vascular risk history, alcohol use, and psychotropic medication usage (results, page 790, paragraph 1). These variables consequently did not account for the persistence of CIND at 12 months.

V.K. Srikanth, PhD, Hobart, Tasmania, Australia; J.F.I. Anderson, BSc (Hons), Parkville, Victoria, Australia; G.A. Donnan, MD, Melbourne, Victoria, Australia; M.M. Saling, PhD, E. Didus, BA (DPsych), R. Alpitis, MPSych, Parkville, Victoria, Australia; H.M. Dewey, PhD, R.A.L. Macdonell, MD, A.G. Thrift, PhD, Melbourne, Victoria, Australia

Multiple sclerosis and occult gluten sensitivity

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 seenable in MS patients. Two of them also had spinal lesions. In three patients, there was neurophysiologic 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.

Marios Hadjivassiliou, MD, David S. Sanders, MRCP, Richard A. Grunewald, DPhil, Sheffield, UK

Reply from the Authors: We have read Hadjivassiliou et al.’s comments on our article 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 are AGA positive, it would appear that the detection of these antibodies 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 and Huntington disease 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 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

References

Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide

To the Editor: In the series of patients with relapsed primary CNS lymphomas (PCNSL) treated with rituximab and temozolomide, Enting et al.1 reported a 53% response rate, median overall survival of 14 months, and median progression free survival of 7.7 months. However, there was a 20 to 30% grade 3 hematologic toxicity. This high rate of hematologic toxicity could be due to dose intensification of temozolomide, ranging from 100 mg/m² to 200 mg/m² on Days 1 through 7 and 15 through 21 per 28-day cycle. This is equivalent to a dose intensity of 1,400 mg/m² to 2,800 mg/m² per cycle, a 1.4- to 2.8-fold increase in dose intensity as compared to the standard regimen of 200 mg/m² on Days 1 through 5 per cycle.

In a phase I pharmacokinetic analysis, Tolcher et al.2 reported a maximum tolerated dose (MTD) of 150 mg/m² for 7 days given every 2 weeks. However, when combined with rituximab, the MTD is probably lower than 150 mg/m². Although formal phase I dose escalation data are unavailable for combination rituximab and temozolomide, our experience with rituximab 375 mg/m² on Day 1 and temozolomide 150 to 200 mg/m² on Days 1 through 5 in 28-day cycles suggests that the MTD is probably at 150 mg/m² when combined with rituximab.

Therefore, in Enting et al.’s dose intensified schedule, temozolomide would need to be reduced to less than 150 mg/m². From an efficacy perspective, a temozolomide dose of 100 or 125 mg/m² would have equivalent efficacy for suppressing O6-alkylguanine-DNA alkyltransferase activity, and probably still synergistic for CNS lymphoma when combined with rituximab.

Another important issue is the lack of renal toxicity in rituximab and temozolomide. Although high-dose methotrexate has been the standard therapy for PCNSL, about 10% of patients in our clinical experience could not tolerate it due to renal insufficiency, cardiomyopathy preventing aggressive fluid hydration, or prior cranial irradiation.4 Furthermore, elderly patients are susceptible to delayed neurotoxicity associated with high-dose methotrexate, even without prior cranial irradiation.5 Rituximab and temozolomide, therefore, should be explored further in newly diagnosed patients.

Lastly, the efficacy of rituximab and temozolomide for leptomeningeal lymphoma is overstated in this article. The rituximab concentration in CSF is 0.1% of that in the serum6 and all of Enting et al.’s patients with positive CSF cytology received intrathecal methotrexate.

Eric T. Wong, MD, Boston, MA

Reply from the Authors: We thank Dr. Wong for his interest in our paper. As this is a retrospective report of our clinical experience with the combination of rituximab and temozolomide it is difficult to comment on the optimal doses of this combination. Both the rituximab and the temozolomide were dosed higher than the standard recommended dose in an effort to optimize CNS penetration and efficacy. In spite of this increased exposure, the toxicity experienced by our patients was acceptable and actually lower than the toxicity reported using one week on/one week off temozolomide alone (50% grade 3 and 4 toxicity).5 The tolerability of this regimen suggests that this may be a reasonable alternative for elderly patients or those with renal dysfunction that limits the use of high dose methotrexate.

However, we think that it is critical to confirm our experience with prospective data before adopting this regimen for newly diagnosed patients. Reni et al.7 have reported that single agent standard temozolomide has activity in recurrent PCNSL with a response rate of approximately 25%. The New Approaches to Brain Tumor Therapy CNS Consortium has an ongoing clinical trial investigating single agent rituximab in relapsed PCNSL. There is also an ongoing Radiation Therapy Oncology Group phase II study for newly-diagnosed PCNSL that incorporates both rituximab and temozolomide into a methotrexate-based regimen as well as a planned Cancer and Leukemia Group B study.

Lauren E. Abrey, MD, New York, NY; Roelien H. Enting, MD, Groningen, The Netherlands; Alexis Demopoulos, MD, Lisa M. DeAngelis, MD, New York, NY

References