

Gluten sensitivity: time to move from gut to brain

In response to a recent article in the July/August ACNR by Tengab and Wills, Marios Hadjivassiliou has written this article. The issue of neurological complications in coeliac disease is a contentious one and these two articles take rather different approaches on the subject, illustrating the difficulty in proving causality in medicine rather than simply describing associations or epiphenomena. Nevertheless the neurological complications of coeliac disease remains a topic of great interest and I hope that these two articles will spur more clinicians and scientists to re-evaluate this area in terms of incidence, pathogenesis and therapy. -RB

Scepticism in the face of new ideas has long prevailed in the medical profession, and is usually healthy. Dissemination of medical advances and research now occurs rapidly and the pace of change of clinical practice has consequently increased. There is a general expectation of quicker assimilation of sound scientific observations and with it increasing demands placed on individuals to assess the scientific value and rigor of published material. The authors of review articles are in a particular position of responsibility to produce dispassionate and informed material, and reluctance to accept scientific evidence just because it does not conform to traditional thinking or because of personal bias may ultimately deprive patients of potential treatment.

An example of such reluctance is the notion that gluten sensitivity is solely a disease of the bowel. The evidence that gluten sensitivity can primarily affect other organs, with sparing of the bowel, is not new. In 1966 Marks and her colleagues demonstrated an enteropathy in 9 of 12 patients with Dermatitis Herpetiformis (DH)¹. It was later shown that the enteropathy and the skin rash were gluten dependent but skin involvement could occur without evidence of gut involvement. Moreover patients with DH characteristically have few if any gastrointestinal symptoms, in contrast to patients with coeliac disease (CD). Nowadays, dermatologists treating DH are not very interested in the state of their patients' bowel mucosa. Such patients do not routinely have a small bowel biopsy, but are treated immediately with a gluten-free diet.

In refining the pathological spectrum of the bowel mucosa in the context of gluten sensitivity Mike Marsh performed a series of elegant experiments looking at gluten load and mucosal pathology in patients with gluten sensitivity². He demonstrated that mucosal pathology correlated with gluten load, and defined a spectrum of lesions ranging from the pre-infiltrative (type 0, histologically normal mucosa) to the atrophic hypoplastic (type 4). Thus, he demonstrated that you can have gluten sensitivity but have a normal bowel mucosa. Marsh's observations were considered somewhat eccentric at the

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time, yet now most scientific papers grade gut pathology using the "Marsh classification".

Nine years ago we started working on the concept that gluten sensitivity can be principally a neurological illness. Perhaps the best characterised disorder we have studied is gluten ataxia.³ It is unscientific to suggest that neurological "associations" of gluten sensitivity such as ataxia are purely coincidental. Pathological studies and published prevalence figures confirm the contrary view. Table one summarises the published studies^{4,5,6,7,8,9} concerning the prevalence of gluten sensitivity in patients with ataxia. Although it is true that some studies are of small patient numbers with limited power and lack of adequate control populations, the more carefully executed studies with adequate controls are conclusive: there is a significantly higher prevalence of gluten sensitivity in patients with "idiopathic" sporadic ataxia than those with familial ataxia or control subjects. Variations in the prevalence between studies is likely to reflect differences in the antigliadin assay used (hence the necessity of comparison with control populations) as well as geographical variations.

Several clues to the neuropathological basis of these disorders are emerging. Neuropathological data from patients with gluten ataxia suggest an inflammatory process with T-cell infiltration primarily of the cerebellum and ultimately the loss of Purkinje cells.³ Patients with gluten ataxia have antibodies against Purkinje cells and anti-gliadin antibodies cross-react with epitopes on Purkinje cells.¹⁰ The CSF in these patients shows oligoclonal bands in more than half and upregulation of the chemokine IP-10, a T cell chemoattractant, when compared to controls.¹¹ Seventy percent of patients with gluten ataxia have the same HLA genotype¹² as found in patients with coeliac disease. There is an increased incidence of autoimmune diseases amongst patients with gluten ataxia (unpublished observation). Perhaps more compelling evidence still, comes from the results of the effect of gluten free diet in patients with gluten ataxia. Gluten free diet results in improvement of the ataxia in patients within a year of a strict gluten free diet when compared to controls.¹³ Yet the prevalence of an enteropathy in patients with gluten ataxia is only about 24%.¹²

Despite this overwhelming evidence of a gluten-driven immune pathogenesis, some continue to propose (without any corroborative scientific data) that "trace element" deficiency due to the enteropathy is a possible explanation. As only a quarter of these patients have an enteropathy, it is difficult to imagine how such a deficiency might arise, let alone what chemical might be deficient.

Whilst CD, DH and gluten ataxia are all manifestations of gluten sensitivity, it is wrong to propose that DH and gluten ataxia should fall under the umbrella of CD, implying that they are all one and

Study details	sporadic ataxias	familial ataxias	normal controls
	antigliadin positive / total number tested (percentage positive)		
Hadjivassiliou et al (UK) ⁴	59/143 (41%)	8/51 (14%)	149/1200 (12%)
°Pellecchia et al (Italy) ⁵	3/24 (13%)	0/23 (0%)	N/A
Burk et al (Germany) ⁶	12/104 (11.5%)	N/A	(5%)
Bushara et al (USA) ⁷	7/26 (27%)	9/24 (37%)	N/A
Abele et al (Germany) ⁸	13/98 (13%)	1/15 (6%)	(5%)
°Luostarinen et al (Finland) ⁹	44 (16.7%)	N/A	(2%)

Table 1: A list of studies looking at the prevalence of antigliadin antibodies in patients with sporadic ataxia and controls. All but one of these studies show a significantly higher prevalence of gluten sensitivity in patients with sporadic ataxia compared to controls. Studies without controls are not included. Studies marked with ° refer to prevalence of coeliac disease. N/A: not available.

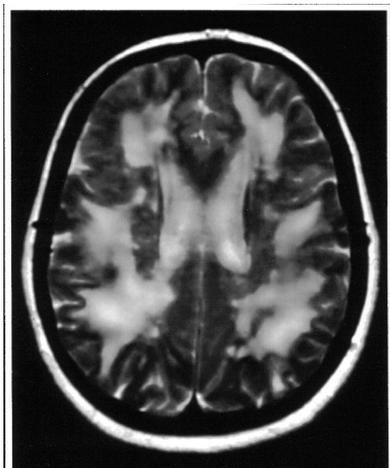


Figure 1. MRI of one of our patients with gluten sensitivity, episodic migraine-like headaches and white matter abnormalities.¹⁷ The patient remains asymptomatic 5 years after the diagnosis of gluten sensitivity and the introduction of gluten free diet. The clinical and radiological characteristics distinguish this entity from MS. The response to diet, lack of family history and absence of progression exclude CADASIL as an alternative diagnosis.

neurological dysfunction in patients with gluten sensitivity (postulated to be the case in patients with DH who may not be as strict with their diet) is unsubstantiated. If the duration of exposure to gluten was pivotal in the development of gluten related diseases, classic CD would not typically present between the age of 6 to 18 months of age. It is likely that the type and prevalence of neurological dysfunction in DH is similar to that found in patients with established CD. A recent study looking at neurological dysfunction in 35 patients with DH did not have the power to determine if the prevalence of neurological dysfunction is different in DH than in CD, but a very large difference was excluded.¹⁴ The majority of people with genetic susceptibility to gluten sensitivity (HLA DQ2) are exposed to gluten for all their lives but do not develop CD, DH or gluten ataxia. The factors responsible for the development of gluten-driven pathology are more complicated than duration of exposure.

It is of considerable interest to question why patients with gluten sensitivity manifest with such diverse organ involvement, albeit with some overlap. Clues to an answer may be found in the role of transglutaminases. Tissue transglutaminase is the antigen recognised by endomysium antibodies, the most sensitive and specific marker of gluten sensitive enteropathy (CD). Apart from crosslinking proteins, tissue transglutaminases (of which there are several types) deamidate glutamine-donor substrates, such as gliadin proteins. It has been postulated that this process may result in the creation of neoepitopes that could play a role in the immune pathogenesis of other diseases.¹⁵ A recent study reported that patients with DH have antibodies with low affinity for tissue transglutaminase but very high affinity for epidermal transglutaminase.¹⁶ This results in an immune response and clinical manifestations in the skin, the main site of epidermal transglutaminase production. An analogous situation may exist in the case of gluten ataxia where an immune response directed towards neural transglutaminases may result in clinical manifestations primarily in the brain or the peripheral nervous system and not the gut. Characterisation of the antigen recognised by Purkinje cell antibodies found in the serum of patients with gluten ataxia may contribute further in resolving the possible pathogenic mechanism.

We must advance such concepts by abandoning historical misconceptions and reviewing current literature in an analytical and disinterested way. It is time to move on from gut to brain.

the same disease. It is true that if one looked hard enough in patients with DH one would find some degree of enteropathy in most. It is also true that 8 to 10 percent of patients with CD may develop neurological dysfunction (this figure is likely to be higher if these patients underwent detailed neurological assessment). However, if these diseases are one and the same one would expect the reverse to be true: patients presenting with CD should all have DH and patients presenting with gluten ataxia should all have CD, clearly not the case.

The notion that it is the prolonged exposure to gluten that causes

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