

## Neurological associations of coeliac disease

### Introduction

Coeliac disease (CD) has attracted much interest in recent years because of a putative association with neurological disorders. Classically, CD is known to be an inflammatory disease of the small bowel mucosa as a result of sensitivity to gluten, a component of wheat, barley and rye. The treatment consists of a strict gluten-free diet (GFD) which results not only in symptomatic improvement but also restoration of the normal mucosal architecture. However it is increasingly recognised that CD can have atypical presentations. Cooke and Smith<sup>1</sup> first described the neurological associations of CD in 1966. Since then numerous neurological disorders have been described in association with CD predominantly epilepsy, ataxia and neuropathy. The nature and mechanism of these associations remain unclear. This review will attempt to describe some of the more commonly described neurological disorders seen with CD and the basis of an association, if indeed there is one.

### Coeliac disease

The concept of incidence and prevalence of CD has changed greatly over the years. What was once thought to be a childhood illness typically presenting with malnutrition and abdominal symptoms is now acknowledged to be a condition of all ages that may also present with atypical and often subtle symptoms. The notion of an 'iceberg' of CD has been used to describe the majority of patients with CD who remain undiagnosed because of asymptomatic, occult or latent disease<sup>2</sup>. Furthermore, population screening studies have revealed that CD is a common condition with a prevalence of at least 1:82 in certain populations<sup>3</sup>.

Patients with a genetic susceptibility to gluten may have no intestinal abnormalities on small bowel biopsy. The precise mechanism for the activation of gut inflammation by gluten is not known although it is presumed to be immunological. Immune mechanisms such as the deposition of circulating immune complexes in other organs are also thought to cause the extra-intestinal manifestations of gluten sensitivity. Dermatitis herpetiformis (DH), characterised by IgA deposition in the papillary dermis, is a blistering skin condition (See Figure 1) that exemplifies an extra-intestinal manifestation of gluten sensitivity. There is robust immuno-pathological and genetic data that DH and CD are closely related conditions. Although less than 10% of DH patients have gastrointestinal symptoms, they are all said to have gluten-sensitive enteropathy<sup>4</sup>.



Figure 1 - Blisters on the elbow of a patient with dermatitis herpetiformis.

Reproduced courtesy of Professor Lionel Fry, Imperial College, London.

### Authors



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### Serological testing

Serological testing for CD has been greatly refined in recent years. Immunological approaches now available include screening for antireticulin antibodies (ARA), IgA and IgG anti gliadin antibodies (AGA), endomysial antibodies (EMA) and tissue transglutaminase antibodies (tTG). EMA has been shown to be better than AGA in terms of both sensitivity and specificity<sup>5,6</sup>. In one study the positive predictive value of EMA was 100% compared to only 28% for IgA AGA<sup>6</sup>. Further studies have shown that IgG AGA is even less reliable than IgA AGA in identifying CD<sup>7,9</sup> with one study showing the positive predictive value of the former to be 0%<sup>10</sup>. The presence of positive coeliac antibodies with normal small bowel architecture remains problematic. Follow-up of patients with normal small bowel architecture and positive coeliac antibodies has shown that positive ARA is a good predictor for later development of the disease when compared to AGA, particularly the IgG subclass<sup>10</sup>.

### Epilepsy

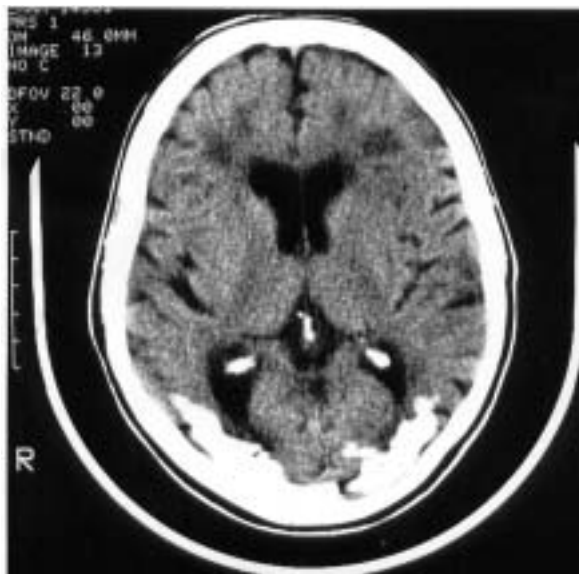
The association of epilepsy and CD has been demonstrated in a number of studies<sup>11,14</sup>. The nature of this association remains unclear. Interestingly, a number of studies, mainly in Italy, have described a further association between CD, epilepsy and cerebral calcifications<sup>13, 15-17</sup> (See Figure 2). There is no clear explanation for this finding although folic acid deficiency has been proposed<sup>16,15</sup>. Studies in Ireland<sup>11</sup> and Finland<sup>14</sup> have not shown these calcifications suggesting that this may be a geographically or ethnically restricted finding.

### Ataxia

The patients originally described by Cooke and Smith<sup>1</sup> in 1966 had a variety of diagnoses. Of the 16 patients described, the majority were found to have a predominantly sensory ataxia although three were also said to have a cerebellar ataxia. Since then there have been varying reports in the literature regarding the association of cerebellar (rather than sensory) ataxia and CD. Vitamin E deficiency and cerebellar ataxia has been described in CD with an improvement following vitamin E therapy<sup>18-20</sup>.

Three groups have shown an increased incidence of CD in series of patients with idiopathic cerebellar ataxia<sup>21-23</sup>. Hadjivassiliou *et al* proposed the term 'gluten ataxia' to describe a group of their patients with idiopathic ataxia, positive AGA antibodies and a HLA genotype (DQw2) appropriate for coeliac disease<sup>21</sup>. They further proposed a mechanism of immune-mediated neuronal damage triggered by gluten. In the light of their reliance on IgG AGA as a screening tool these concepts need to be interpreted with caution. The common HLA haplotype (also seen by Burk and co-workers<sup>25</sup>) is a noteworthy finding that merits further attention. Interestingly a recent study by Bushara and co-workers showed raised AGA in patients with both hereditary ataxia (9 of 24) and sporadic ataxia (7 of 26). A study by Combarros *et al* of 32 patients with idiopathic cerebellar ataxia showed no coeliac antibody positivity<sup>24</sup>.

Myoclonic ataxia (Ramsay-Hunt Syndrome) has also been described in association with coeliac disease<sup>25-28</sup>. Tijssen and co-workers<sup>29</sup> described in detail 3 patients with cortical myoclonus. Two of these had myoclonic ataxic syndrome associated with proven coeliac disease whilst the third may have had coeliac disease on the basis of a reduced vitamin B12 antemortem. They speculated Purkinje cell damage through toxins or autoantibodies in the CSF. CSF AGA was measured in 1 patient and this was negative.



**Figure 2 - CT scan of the brain showing bilateral occipital calcifications in a patient with epilepsy and coeliac disease.**

Reproduced courtesy of Dr. Gordon Plant, The National Hospital for Neurology and Neurosurgery, Queen Square, London

### Other neurological associations

There have been a few descriptions of patients with CD and peripheral neuropathy, both axonal and demyelinating, but no clear effect of gluten on the neuropathy has been established<sup>30,32</sup>. Other case reports in the medical literature have included such diverse conditions as CNS vasculitis<sup>33</sup>, brainstem encephalitis<sup>34</sup>, dementia<sup>35</sup> and chronic progressive leukoencephalopathy<sup>36</sup>. Some studies have suggested an association with migraine<sup>37</sup> whereas others have not<sup>38</sup>.

### Conclusions

There appears to be some evidence of an association between CD and certain forms of epilepsy but the basis of association with other neurological syndromes is less certain. At present, the scanty available data on neurological associations of CD is extremely heterogeneous with no universally acceptable scientific explanation for a causative effect. Given that CD is common, one possibility is that certain neurological "associations" are purely coincidental. Alternatively, similar HLA haplotypes may confer an increased likelihood of autoimmune disease as exemplified by the increased incidence of hypothyroidism<sup>39</sup> and Type 1 diabetes mellitus<sup>40</sup> in CD.

Another possible explanation is malabsorption causing vitamin and trace element deficiency as there are descriptions of patients whose neurological illnesses have improved with treatment of their CD. Besides vitamin E and folic acid deficiency as mentioned previously, tetany<sup>41</sup> and myopathy<sup>42</sup> caused by calcium deficiency have also been described. Although this does not satisfactorily explain patients in whom no vitamin deficiency is found<sup>25, 31, 43</sup> or in whom vitamin replacement has no effect<sup>26,30</sup>, this possibility should still be carefully considered in CD patients who develop neurological illness. As yet, no studies have effectively addressed the role of trace vitamin deficiency (e.g. niacin, riboflavin and thiamine) in the development of neurological complications.

Gluten neurotoxicity, as suggested by Hadjivassiliou and co-workers<sup>21</sup>, has been postulated as a mechanism to explain the apparent association of gluten sensitivity with various neurological disorders. In DH, gluten exposure is potentially greater than in CD as patients whose dermatological symptoms are controlled on dapsone may continue to consume gluten. Recent work by Wills *et al*<sup>24</sup> failed to demonstrate an increased prevalence of neurological

complications of DH.

Clearly, further more detailed investigation is required into this disease. We propose large studies looking for the prevalence of neurological conditions in CD and DH, and further investigation of the role of auto-immunity, particularly susceptible HLA groups, in neurological diseases seen with CD. However we would recommend more stringent antibody testing in neurological patients given the poor predictive value of some coeliac antibodies particularly IgG AGA.

### Acknowledgements

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