Neurological disorders in adult celiac disease

Hugh J Freeman MD CM FRCPC FACP

Celiac disease may initially present as a neurological disorder. Alternatively, celiac disease may be complicated by neurological changes. With impaired nutrient absorption, different deficiency syndromes may occur and these may be manifested clinically with neurological changes. However, in patients with deficiency syndromes, extensive involvement of the small intestine with celiac disease is often evident. There are a number of reports of celiac disease associated with neuropathy, ataxia, dementia and seizure disorder. In these reports, there is no clear relationship with nutrient deficiency and a precise mechanism for the neurological changes has not been defined. A small number of patients have been reported to have responded to vitamin E administration, but most do not. In some, gluten antibodies have also been described, especially in those with ataxia, but a consistent response to a gluten-free diet has not been defined. Screening for celiac disease should be considered in patients with unexplained neurological disorders, including ataxia and dementia. Further studies are needed, however, to determine if a gluten-free diet will lead to improvement in the associated neurological disorder.

Key Words: Ataxia; Celiac disease; Dementia; Epilepsy; Gluten-free diet; Neurological disorders; Neopropy; Seizure disorders; Vitamin E

Les troubles neurologiques en cas de maladie cœliaque chez les adultes

La maladie cœliaque peut constituer d’abord un trouble neurologique. Elle peut aussi être compliquée par des modifications neuropathiques. En raison de la défaillance de l’absorption des nutriments, divers syndromes déficitaires peuvent survenir et se manifester cliniquement par des modifications neurologiques. Cependant, chez les patients ayant des syndromes déficitaires, une atteinte importante de l’intestin grêle touché par la maladie cœliaque est souvent évidente. Plusieurs comptes rendus associent la maladie cœliaque à une neuropathie, une ataxie, une démence ou des troubles convulsifs. Dans ces comptes rendus, il n’y a pas de relation claire avec la carence en nutriments, et on n’a pas défini de mécanisme précis pour les modifications neuropathiques. Quelques patients ont réagi à l’administration de vitamine E, mais la plupart n’y réagissent pas. Chez certains, on a également décrit des antécédents au gluten, surtout chez ceux présentant une ataxie, mais il n’existe pas de définition de réponse uniforme à un régime sans gluten. Il faudrait envisager de procéder à un test de dépistage de la maladie cœliaque chez les patients atteints de troubles neurologiques inexpliqués, y compris l’ataxie et la démence. D’autres études s’imposent, cependant, pour déterminer si un régime sans gluten favorisera une atténuation du trouble neurologique connexe.

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TABLE 1
Neurological disorders associated with vitamin deficiencies

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Associated neurological disorder(s) with deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Neuropathy, ophthalmoplegia, dementia, cerebellar ataxia, optic neuritis</td>
</tr>
<tr>
<td>B&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>Neuropathy, dementia, cerebellar ataxia, optic neuritis, myelopathy</td>
</tr>
<tr>
<td>E</td>
<td>Neuropathy, ophthalmoplegia, cerebellar ataxia, extrapyramidal disorders, myelopathy</td>
</tr>
<tr>
<td>Niacin</td>
<td>Neuropathy, dementia, cerebellar ataxia, extrapyramidal disorders, myelopathy</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Ophthalmoplegia</td>
</tr>
</tbody>
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Neuropathy may also be associated with lymphoma, thus, complicating celiac disease. This may occur directly with lymphomatous involvement of nerves or indirectly as a paraneoplastic phenomenon, similar to other malignant disorders. Interestingly, in a case of a disseminated enteropathy-type T cell lymphoma, a cauda equina syndrome was reported (22).

Ataxia

In biopsy-defined celiac disease, gait ataxia occurs, often associated with neuropathy (23). In other individuals with ataxia, cerebellar involvement may occur (24,25) with low vitamin E levels (26). In some, recognition of celiac disease may be preceded by cerebellar changes, but there are no clinical features of the ataxia that are distinctive for underlying adult celiac disease (27). In some ataxia studies (28), only serological tests were performed and celiac disease was not confirmed or biopsy-defined. Antigliadin antibodies have been noted in ataxia (28) and have also been noted in other genetically based neurodegenerative disorders (eg, spinocerebellar ataxia, Huntington's disease) (29,30).

Some have postulated that antibodies to gliadin or a peptide sequence of gliadin are neurotoxic, particularly to the cerebellum. Occasionally, biopsy-defined celiac disease is present; however, most patients have no evidence of detectable intestinal disease. In these individuals, antigliadin antibodies may simply represent an epiphenomenon with no pathogenic significance (31). In some patients, supplementation with vitamin E has apparently been useful. In others, however, normal vitamin E levels have been defined and the gait ataxia syndrome has been hypothesized to be the result of a mechanism other than a nutrient deficiency. It has also been suggested (32) that ataxia may be the result of the toxic effects of gluten per se, the so-called 'gluten-ataxia' hypothesis. To date, however, restriction of gluten alone has not been clearly shown to be an effective treatment (33-35). Claims related to the effectiveness of intravenous immunoglobulin therapy have also appeared (36).

Of note, ataxia with a pancerebellar syndrome has been associated with T cell enteropathy and lymphomatous metastases to the cerebellum (37), suggesting that this should be kept in mind for patients with celiac-related enteropathies before attributing cerebellar findings to different vitamin or other nutritional deficiencies or an associated autoimmune mechanism.

Seizure disorder

Seizure disorder (ie, epilepsy) appears to be associated with celiac disease (38,39), most often, but not exclusively, in pediatric celiac disease, rather than in adults. The effect of a gluten-free diet is not clear. Some studies (40) have reported better seizure control in children that resulted from a reduction in seizure-control medications.

A specific seizure disorder syndrome has been recorded in celiac disease with bilateral occipital calcification. This intriguing, but rare entity was first described in 1970 (41) and was later confirmed, particularly in reports from Italy (42,43). The majority of patients had complex partial seizures referable to the occipital or temporal lobes; however, generalized seizures may also occur (44,45). Calcification is generally bilateral and, pathologically, the calcifications consist of patchy pial angiomas, fibroed veins and large microcalcifications containing calcium and silica (46).

Impaired cognitive function

Dementia may occur in celiac disease, particularly in the form of memory impairment (47). In most patients, a gluten-free diet does not appear to result in an improvement of neurological disability (47). In a case series (48), the most common presenting
neurological features were amnesia, acalculia, confusion and personality changes. In subjects with a deficiency of folic acid, vitamin B12, or vitamin E, subsequent supplementation had no effect in reversing the neurological findings. However, some patients appeared to stabilize after removal of dietary gluten. Pathology studies (48) demonstrated a nonspecific gliosis. Interestingly, in a study of seven elderly celiac patients diagnosed after 60 years of age, cognitive decline attributed to Alzheimer’s dementia was evident in three cases and, in one case, neurological changes were ameliorated after initiation of a gluten-free diet (49).

Other neurological disorders
Other neurological disorders have been encountered in single case reports or case series. However, further studies are needed to determine if these disorders are directly related to adult celiac disease or represent coincidental occurrences.

CONCLUSION
Celiac disease may be initially defined after presentation with a neurological disorder. Screening for celiac disease should be considered, especially if a definitive cause for the neurological disorder is not obvious. Further studies are also needed to determine if neurological changes that have been attributed to the so-called ‘gluten-sensitivity’ in the absence of overt intestinal disease (50) can be truly reversed with a gluten-free diet.

REFERENCES