Coeliac Disease and Neuro-Psychiatric Disorders

Introduction

The association between coeliac disease (CD) and neuro-psychiatric disorders has long been known and has been described in both adults and children. Neurological problems can be found in association with typical signs and symptoms of CD, but they are often the only presenting symptom of gluten-sensitive enteropathy.

Epidemiology

The prevalence of the association between CD and neuro-behavioural disturbances is difficult to evaluate and is rather variable. Most reports concern the association between CD and cerebellar ataxia, sensory-motor and autonomic neuropathy, epilepsy, dementia, headache, anxiety, irritability and depression. In the past, Cooke and Smith were the first to describe a group of 16 coeliac patients with gait ataxia and peripheral neuropathy. Later, a team of British neurologists who, as early as 1996, highlighted the strong prevalence (57%) of undetected CD in subjects with neurological diseases, mostly ataxic patterns, defined this condition as gait ataxia. This is often associated with peripheral neuropathy with signs of cerebellar atrophy. In subjects affected by this disease, signs of an immune response to gluten (AGA) are increasingly observed, with autoantibodies directed against Purkinje cells, displaying positivity for CD-specific antigens of the HLA system. However, only half of the cases present with the typical histological lesions in the intestinal mucosa.

The duration of gluten exposure seems to be directly correlated to ataxia severity and indirectly correlated to the efficacy of a gluten-free diet as a treatment for symptom regression. The first evident association between coeliac disease, occipital endocranial calcifications and epilepsy, later confirmed by numerous additional studies, dates back to 1970. These are serpiginous calcifications of vascular origin. Before the syndrome was definitely recognised, some cases were classified as atypical Sturge-Weber syndrome given the similarity of the cerebral calcifications to the findings in real Sturge-Weber cases at the computed tomography (CT) examination, but without facial angioma or mental retardation. Clinically, patients present with patterns of partial occipital drug-resistant epilepsy, without clear signs of malabsorption. With regard to this relation, the autoimmune hypothesis has also been suggested. There is strong evidence showing that a gluten-free diet (GFD) can lead to a better control of seizures and a reduction in the use of antiepileptic drugs, but does not achieve a full resolution of seizures. A recent Israeli study has found that one or more common neurological disorders (such as hypotonia, retarded development, learning disorders, attention deficit/hyperactivity disorder, headache and cerebellar ataxia itself) are present in 51.4% of coeliac children, a significantly greater prevalence than that found in the control population (19.9%). The study clearly demonstrates the effectiveness of a GDF at least on hypotonia in babies and on headache. Finally, other clinical trials showed that autistic children present with histological intestinal alterations that are similar to those of CD patients, even though a direct association between autism and coeliac disease has never been proven. However, data concerning the effectiveness of a gluten-free diet in autistic children are contradictory.
Tables 1 and 2 report the main findings on the frequency of these disorders, in adult and paediatric patients respectively.

### Table 1. Prevalence of neuro-behavioural disorders in adult CD patients and vice-versa.

<table>
<thead>
<tr>
<th>Author</th>
<th>CD patients</th>
<th>Neurological Disorders (%)</th>
<th>Behavioural disorders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luostarinen L et al. (1999)</td>
<td>144</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Roche-Herrero MC et al. (2001)</td>
<td>86</td>
<td>39.5</td>
<td>10</td>
</tr>
<tr>
<td>Cicarelli G et al. (2003)</td>
<td>176</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Zeink N et al. (2004)</td>
<td>111</td>
<td>51.4</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Prevalence of CD in patients with neuro-behavioural disorders.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with neuro-behavioural disorders (n°)</th>
<th>Coeliac Disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellecchia MT et al. (1999)</td>
<td>24</td>
<td>12.5</td>
</tr>
<tr>
<td>Burk K et al., (2001)</td>
<td>104</td>
<td>1.9</td>
</tr>
<tr>
<td>Bushara KO et al. (2001)</td>
<td>50</td>
<td>37 ± 27</td>
</tr>
<tr>
<td>Gabrielli M et al. (2003)</td>
<td>90</td>
<td>4.4</td>
</tr>
<tr>
<td>Chin RL et al. (2003)</td>
<td>20</td>
<td>8</td>
</tr>
</tbody>
</table>

### Clinical aspects

The neuro-behavioural disturbances described in CD patients include rather heterogeneous clinical patterns, which vary with the type of disease and the patient’s age.

Tables 3 and 4 report the neurological disorders and behavioural changes most frequently observed in adults and children affected by CD.

### Table 3. Neurological disorders in CD patients.

<table>
<thead>
<tr>
<th>Adulthood</th>
<th>Childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Autism</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Migraine</td>
</tr>
<tr>
<td>Pre-senile dementia</td>
<td></td>
</tr>
<tr>
<td>Cerebellar disorders</td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Personality and behavioural changes in CD patients

<table>
<thead>
<tr>
<th>Adulthood</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Irritability</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Apathy</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
</tr>
</tbody>
</table>

Of the possible psychiatric complications, depression is the most frequent, especially in adults. Few studies have addressed this issue in childhood, as a standardised evaluation of children’s cognitive-behavioural abilities is quite complex to perform. However, the most important reported data mainly concern mood disturbances, such as irritability and apathy.
Pathogenesis
The nature of the association between CD and neurological disorders has not been clearly defined yet and several mechanisms may be involved:

Disorders of the peripheral nervous system
- Folic acid, vitamin B₁₂ and pyridoxine deficiencies caused by intestinal malabsorption.⁴⁸

Degenerative disorders of the central nervous system
- Vitamin E deficiency due to lipid malabsorption.⁴⁹

However, the results of studies addressing this issue are rather contradictory, since the symptoms related to the involvement of the cerebellar area can also be found in subjects with normal serum levels of vitamin E. Over the past ten years, an increasing number of authors have suggested that, in most patients, an ongoing immune-mediated inflammatory process, lymphocyte infiltration or vasculitis of the central nervous system can cause irreversible neuronal, glial or axonal damage.⁸

Epilepsy and cerebral calcifications
- Folic acid deficiency due to intestinal malabsorption, with subsequent alteration of lecithin metabolism (lecithins are the main constituent of myelin), and microangiopathic myelinisation of the cerebral cortex vessels and the basal nuclei, with calcific deposits in the altered organic matrix. This hypothesis is extremely interesting and would explain the cause-effect relationship between malabsorption and the origin of cerebral calcifications. However, epilepsy and cerebral calcifications can also be observed in subjects without CD and with normal folic acid serum levels.⁴¹
- Immunological hypothesis.⁴²
  
  As CD can be associated with various autoimmune disorders, it is impossible to exclude the possibility that cerebral calcifications depend on an autoimmune or inflammatory process related to the presence of immune complexes. Immune pathogenetic mechanisms have also been considered when interpreting more complex neurological disorders, such as dementia and cerebral atrophy.
- The association between CD, epilepsy and cerebral calcifications could be part of a genetically determined syndrome.²⁷

Behavioural disturbances
- Abnormal amino acid levels. Recent studies have found that both untreated and treated coeliac children show lower plasma tyrosine and tryptophan concentrations than controls.⁶

Conclusions
The association between neuro-psychiatric disorders and CD is likely to be more common than previously thought. Moreover, these disturbances are often the only presenting complaint of an untreated gluten-sensitive enteropathy. All patients, whose symptoms are suggestive of a central and/or peripheral nervous system disorder, as well as those with behavioural disturbances should be thoroughly checked for possible CD. Furthermore, special care should be given to those patients affected by seizures (epilepsy) with poor response to drugs. Although coeliac patients with neuro-behavioural disorders often present with a low-grade intensity illness, they should always be advised to follow a gluten-free diet (GFD). In most subjects affected by epilepsy, GFD can have positive effects on the evolution of the neurological disorder, as the recovery of the small intestinal mucosa is followed by an improved response to the drug therapy and, therefore, by a reduction in the frequency and intensity of seizures.

Bibliography
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