CELIAC DISEASE WITH NEUROLOGIC MANIFESTATIONS IN CHILDREN

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CELIAC DISEASE WITH NEUROLOGIC MANIFESTATIONS IN CHILDREN (Abstract): Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals and neurologic manifestations may be one of the presentations form. The aim of this study was to report the incidence of neurologic manifestations in children with CD. Material and methods: Between 2000-2010, 48 children aged 2-18 years diagnosed with CD have been monitored. The diagnosis of CD was made by serological tests and intestinal biopsy. The study protocol included: measurement of weight and height, biological and immunological tests, histological examination, questionnaires filled out by parents about their child motor development and some neurologic signs, psychological exam, electroencephalogram, and brain CT-scan. Results: 16 of the 48 children presented one or more neurologic symptoms as the onset manifestation of CD. The neurologic signs in order of frequency were: headache/migraine, attention-deficit/hyperactivity disorder, epileptic seizures, mental retardation, cerebellar ataxia and behavior disorders. Brain CT-scan showed cerebral calcifications in 3 patients with epilepsy, and atrophy in 2 cases with cerebellar ataxia. All children received gluten free diet, but a favorable course was noticed only in the children with migraine and epilepsy, in the other patients this diet having no influence on neurologic symptoms. Conclusions: This study proved the variety of neurologic symptoms that can be included in the clinical signs of celiac disease in pediatric patients. That is why in the presence of different neurologic symptoms of unknown etiology and resistant to treatment, celiac disease must be taken into account and laboratory investigations have to include intestinal biopsy and immunological test. Keywords: CHILDREN, CELIAC DISEASE, EPILEPTIC SEIZURES, CEREBRAL CALCIFICATIONS, MIGRAINE, SCHOOL PROBLEMS.

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Its prevalence is difficult to estimate because many cases are asymptomatic or present atypical signs. The classical form of CD is characterized by gastrointestinal manifestations, including the malabsorption syndrome, steatorrhea, failure to thrive, and histopathological changes (villous atrophy, crypt hyperplasia, lymphocytic inflammatory infiltrate) found in intestinal mucosa biopsy specimens. In the past few years, the clinical spectrum of CD has been widened, atypical forms with late onset or oligosymptomatic being reported. The diagnosis of these forms is made by the identification of antigliadin (IgA-
AGA), antiendomysial (IgA-AEM) and antitissue transglutaminase IgA (IgA-ATTG) antibodies in the blood (1).

The first study on the association of neurologic manifestations in patients diagnosed with BC was published in 1966 by Cooke and Smith (2). The neurologic symptoms appear in 6-10% of the patients with CD, but it was demonstrated that a high percentage of the patients with neurologic signs of unknown cause are also sensitive to gluten (3). The most frequent neurologic symptoms described especially in adults with CD were cerebellar ataxia, epilepsy, myoclonus, neuropathy, dementia, headache, depression and multifocal leucoencephalopathy (2). These symptoms are generally chronic and progressive. At present there are not enough data on the association of neurologic symptoms with gluten sensitivity in children and adolescents.

The aim of this prospective study was to evaluate the neurological manifestations in children diagnosed with CD between 2000-2010.

MATERIAL AND METHODS

The authors conducted this prospective study with the approval of the Hospital Ethics Committee. In this study were enrolled 48 children (27 girls and 21 boys) aged 2 to 18 years who were diagnosed with CD. Informed consent was obtained from their parents. The classical onset symptoms (chronic diarrhea, anorexia, vomiting, and failure to thrive) were present in 32 patients (66% of the cases). The neurologic manifestations were the first sign of CD in 16 cases (33.33%). In all these cases the diagnosis of CD was made by increased IgA-AGA, IgA-ATTG, and IgA-AEM levels and confirmed by intestinal biopsy. IgA deficiency was excluded in all cases.

The study protocol included: physical evaluation; biological and immunological tests; intestinal biopsy with histological exam; questionnaires filled out by parents about motor development and neurologic signs (epileptic seizures, headache, gait disturbances, disorders of limb movement, school problems); neurologic exam; psychological test; electroencephalogram; cerebral CT-scan.

The diagnosis of neurobehavioral conditions, specific learning disabilities, attention-deficit/hyperactivity disorder (ADHD) was based on the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (3), the diagnosis of migraine was based on the International Headache Society Classification (4), and the diagnosis of epileptic seizures was based on the 1989 diagnostic criteria of Commission on Classification and Terminology of the International League Against Epilepsy (5).

RESULTS

The spectrum of neurologic manifestations in the 16 patients with atypical CD onset was heterogeneous. Two or more neurologic symptoms were detected in 9 patients (tab. I). In order of frequency the neurologic and psychiatric manifestations were: headache (6 patients), learning disabilities/ADHD (5 patients), epileptic seizures (4 cases), mental retardation (4 cases), cerebellar ataxia (4 cases), and behavior problems (2 cases). All patients received gluten free diet (GFD). A favorable course was noticed only in the patients with epilepsy and headache. GFD had no influence on the neurologic symptoms in 6 children.
### Table I

**Characteristics of CD patients with neurologic manifestations**

<table>
<thead>
<tr>
<th>Case /sex /age</th>
<th>Neurologic findings</th>
<th>Other clinical symptoms</th>
<th>Delay in CD diagnosis-months</th>
<th>Serological tests/ histological findings in duodenal biopsy specimens</th>
<th>EEG findings</th>
<th>Brain CT-scan</th>
<th>Course of neurologic symptoms after GFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M 15 years</td>
<td>epilepsy seizures, pallor, failure to thrive</td>
<td>anemia, IgA-AGA, moderate villous atrophy</td>
<td>12 months</td>
<td>focal discharge</td>
<td>OC</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>2/F 11 years</td>
<td>migraine, pallor, fatigue, diarrhea</td>
<td>anemia, IgA-AGA, partial villous atrophy with crypt hyperplasia</td>
<td>10 months</td>
<td>Normal</td>
<td>normal</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>3/M 8,2 years</td>
<td>CA, learning disabilities / ADHD, ST, failure to thrive</td>
<td>anemia, IgA-EMA, villous atrophy with mononuclear submucosal infiltrates</td>
<td>24 months</td>
<td>Normal</td>
<td>cerebellar atrophy</td>
<td>no improvement</td>
<td></td>
</tr>
<tr>
<td>4/M 7,11 years</td>
<td>ADHD, pallor, chronic diarrhea</td>
<td>anemia, IgA-EMA, villous atrophy with increased IEL</td>
<td>32 months</td>
<td>Normal</td>
<td>normal</td>
<td>no improvement</td>
<td></td>
</tr>
<tr>
<td>5/F 4,3 years</td>
<td>unspecific headache, nausea, loss of appetite, diarrhea</td>
<td>IgA-AGA, villous atrophy, crypt hyperplasia and increased mitotic index in crypts</td>
<td>12 months</td>
<td>Normal</td>
<td>normal</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>6/F 14,2 years</td>
<td>migraine, short stature, diarrhea</td>
<td>IgA-AGA, villous atrophy with submucosal lymphocytic infiltrates</td>
<td>20 months</td>
<td>Normal</td>
<td>normal</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>7/M 10,4 years</td>
<td>epileptic seizures, pallor, failure to thrive</td>
<td>anemia, IgA-AGA, mild villous atrophy, crypt hyperplasia and inflammatory infiltrates in lamina propria</td>
<td>22 months</td>
<td>focal discharge</td>
<td>OC</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>8/M 7,2 years</td>
<td>MMR, behavior problems, pallor, loss of appetite, altered bowel habits</td>
<td>anemia, IgA-AGA, villous atrophy with IEL infiltrates</td>
<td>18 months</td>
<td>normal</td>
<td>normal</td>
<td>no improvement</td>
<td></td>
</tr>
<tr>
<td>9/M 16 years</td>
<td>epileptic seizures, ADHD, nausea, loss of appetite, short stature, diarrhea</td>
<td>IgA-AGA, IgA-EMA, villous atrophy, crypt hyperplasia and lymphocytic eosinophilic and basophilic infiltrates in lamina propria</td>
<td>23 months</td>
<td>generalized discharge</td>
<td>OPC</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>10/M 5,1 years</td>
<td>unspecific headache, plea</td>
<td>IgA-AGA, villous atrophy, crypt hyperplasia and IEL infiltrates</td>
<td>none reported</td>
<td>normal</td>
<td>normal</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>11/F 2,8 years</td>
<td>CA, SMR, nausea, vomiting, diarrhea</td>
<td>IgA-EMA, partial villous atrophy with increased IEL</td>
<td>12 months</td>
<td>normal</td>
<td>cerebellar atrophy</td>
<td>no improvement</td>
<td></td>
</tr>
<tr>
<td>12/F 17 years</td>
<td>migraine, behavior problems, puberty delay, failure to thrive</td>
<td>IgA-AGA, partial villous atrophy, crypt hyperplasia</td>
<td>16 months</td>
<td>normal</td>
<td>normal</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>13/F 15,9 years</td>
<td>migraine, short stature, puberty delay</td>
<td>IgA-AGA, partial villous atrophy, crypt hyperplasia</td>
<td>10 months</td>
<td>normal</td>
<td>normal</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>14/M 9,3 years</td>
<td>ADHD, loss of appetite, diarrhea, pallor</td>
<td>anemia, IgA-AGA, villous atrophy, mononuclear submucosal infiltrates</td>
<td>12 months</td>
<td>normal</td>
<td>normal</td>
<td>no improvement</td>
<td></td>
</tr>
<tr>
<td>15/F 12,8 years</td>
<td>epileptic seizures, ADHD, diarrhea, pallor</td>
<td>anemia, IgA-AGA, villous atrophy, crypt hyperplasia</td>
<td>14 months</td>
<td>generalized discharge</td>
<td>normal</td>
<td>favorable</td>
<td></td>
</tr>
<tr>
<td>16/M 4,9 years</td>
<td>CA, MMR, ST</td>
<td>IgA-EMA, IgA-AGA, villous atrophy, crypt hyperplasia</td>
<td>18 months</td>
<td>normal</td>
<td>normal</td>
<td>no improvement</td>
<td></td>
</tr>
</tbody>
</table>

CA= cerebellar ataxia, ADHD= attention-deficit/hyperactivity disorder, SMR=severe mental retardation, MMR=mild mental retardation, ST=steatorrhea, OC= occipital calcifications, OPC= occipito-parietal calcifications, IEL= intraepithelial lymphocytes
Celiac disease with neurologic manifestations in children

The epileptic seizures preceded the gastrointestinal manifestations in all 4 epilepsy cases. Two of them presented complex partial seizures and the remaining 2 generalized tonic-clonic seizures. Brain CT-scan revealed numerous cortico-subcortical occipital calcifications in cases number 1 (fig. 1a) and 7 (fig. 1b), and occipito-parietal calcifications in case 9 (fig. 1c). Electroencephalogram revealed generalized spike-wave complexes in occipital regions in case 1, parieto-occipital spikes with slow waves in case 7, and generalized spike-wave complexes and polyspikes with great amplitude in occipital derivations in cases 9 and 15. All patients received gluten free diet and treatment with antiepileptic drugs (oxcarbazepine in cases 1 and 7, and sodium valproate in cases 9 and 15). After antiepileptic treatment and gluten free diet these patients had a favorable course without seizures.

Cerebellar syndrome was described in 3 CD patients with a history of neuromotor development delay; one of them presented ADHD and the other two mental retardation. The neurologic exam evidenced disorders of posture (hypotonia), postural instability, gait impairment, disorders of movement coordination. CT-scan revealed cerebellar atrophy in cases number 3 and 11.

Headache was present in 6 CD cases; the diagnostic criteria for migraine were met in cases 2, 6, 12 and 13, and for unspecified headache in cases 5 and 10. In all patients both the neurologic exam and electroencephalogram were normal. CT-scan was normal in all cases. Jejunal mucosa biopsy confirmed the diagnosis of CD. Patients were fed gluten free diet associated with folic acid and B12 vitamin with favorable course. All children are still monitored, and the repetition of intestinal biopsy confirmed the mucosal recovery. Psychiatric disorders, severe enough to affect the social and occupational functioning of children, were present in 10 CD patients: ADHD/learning problems (5 cases), mental retardation (4 cases), and behavior disorders (2 cases).

DISCUSSION

The neurologic complications are a possible manifestation of CD. The central and
peripheral nervous systems are affected in different degrees (2). According to Collin et al. (6), 16% of the neurologic diseases of unknown etiology represent symptoms of undiagnosed CD.

A higher prevalence of gluten sensitivity was noticed in neuro-degenerative diseases such as hereditary spinocerebellar ataxia and Huntington disease (2). Some studies have reported the onset of CD with extra-gastrointestinal symptoms (7). In our study the neurologic signs were the first symptom of CD in 16 patients. Zelnik (1) reported neurologic complications in 51.4% of patients with CD. Briani (9) remarked the association of neurologic manifestations in 22.5% of the 71 patients with CD. On the other hand, Cakir (10) made different neuro-physiological tests in CD pediatric patients and reported subclinical neurologic signs in 11%. In our study 33.33% of children diagnosed with CD presented neurologic symptoms.

The first cases of epilepsy, and intracerebral calcifications associated with CD were described by Gobbi in 1992 (10). Even though the association between epilepsy and CD was just a coincidence, the increasing number of cases reported afterwards in the literature and a higher than expected incidence of BC in patients with epilepsy and intra-cerebral calcifications suggest a correlation. Besides, the progressive growth of intra-cerebral calcifications before the introduction of GFD and the onset of epilepsy with advancing age if CD remains undiagnosed are suggestive of a correlation between these three diseases (11). Some authors claim that the toxicity of gluten may trigger seizures in patients at high risk (1). Diaz et al. (11) believe that all patients with epilepsy and CD must be investigated for CD, even in the absence of digestive symptoms. In our study intracerebral calcifications were evidenced by CT-scan in 3 patients who also presented epileptic seizures. In all patients the association of GFD to antiepileptic medication caused the disappearance of seizures. Some authors consider that in the case of the triple association intracerebral calcifications, epilepsy and CD the favorable response to treatment is possible only if GFD is initiated early (10). Other studies report a good seizure control even if epilepsy was diagnosed after some years of gluten exposure (12).

In Bushara’s opinion headache can be an atypical manifestation of CD (2). Some authors suggest that malabsorption is not involved in the pathogenesis of headache crisis in patients with CD, but the inflammatory and autoimmune mechanism may be responsible for its occurrence (1). Roche-Herrero (14) reports the presence of migraine, tension or unspecific headache in 39.5% of children and teenagers with CD. In our study 6 of the 48 patients presented headache. In all the cases the initiation of GFD determined the disappearance of migraine and headache episodes.

Many authors reported the presence of cerebellar ataxia in CD patients (14). There are studies that report an increased incidence of CD and sensitivity to gluten in patients with idiopathic cerebellar ataxia (15). Also, some authors noticed cerebellar symptoms in patients with CD (1,14). Zelnik (1) diagnosed intracerebral calcifications in 10.25% of the patients with CD, and in our study 3 of 48 patients with CD presented signs of cerebellar ataxia.

Developmental delay is relatively frequent in the history of children with CD, in our study being found in 3 children with cerebellar ataxia and CD, probably due to
Celiac disease with neurologic manifestations in children

nutritional deficiencies and toxic effects of severe malnutrition.

Psychiatric signs may be frequent in CD patients. Rodrigo (16) claims that these symptoms may be present in about 1/3 of the cases. In the study of 111 patients with CD, Zelnik (1) noticed the learning and behavior problems in 20.7%. In our study 10 of the 48 cases presented a delay in mental development, ADHD, learning and behavior problems, these data being comparable with those reported in the literature.

The mechanism by which gluten intolerance contributes to the occurrence of neurologic manifestations remains unclear. It is supposed that the pathogenic mechanism of neurologic and psychiatric manifestations associated with CD is determined by the toxic effects of gluten or an immune reaction initiated by gluten or its metabolites in the intestinal mucosa, as well as the severe and prolonged lack of thiamine, pyridoxine, ciancobalamine (due malabsorption) and folic acid deficit (14). Some authors believe that the toxicity of gluten induces by an autoimmune mechanism irreversible lesions of vasculitis, inflammatory lesions and lymphocytic infiltrates at neuronal, glial and axonal level, reason why the clinical picture is minimally improved by GFD, and the disappearance of different antibodies in blood or cerebrospinal fluid (2).

The identification of the same phenotype HLA (DQW2DR3 and/or DR7) in patients with neurologic manifestations suggests immune system disturbances (2).

The authors who have used GFD in patients with CD and neurologic symptoms reported very different results. Siqueira stated that such a diet does not improve the neurologic symptoms (7). On the other hand, Diaz reported a favorable course after GFD in patients with CD and epilepsy (11). In our study the GFD gave good results in cases number 2, 5, 6, 10, 12 and 13 who presented migraine and headache episodes.

CONCLUSIONS

Neurologic and psychiatric symptoms may be present not only in some diseases primarily affecting the brain, but also in gastrointestinal diseases, in our case CD. That is why, CD must be considered in patients with different neurologic symptoms of unknown etiology that are resistant to treatment, because in many cases CD types are atypical, monosymptomatic or latent. In all these situations the laboratory investigations will necessarily include intestinal biopsy and immunological tests, and in patients with confirmed diagnosis GFD will be initiated, even though GFD does not always influence in a favorable way the course of neurologic symptoms.

REFERENCES


**NEWS**

**IDENTIFICATION OF PERMETHRIN RESISTANCE LOCI IN MALARIA VECTORS**

Resistance to the limited insecticides used for malaria control is a growing threat, thus, identification of the major loci responsible for resistance is in need. Witzig and co. used quantitative trait loci (QTL) mapping to identify resistance phenotypes in the major malaria vector, *Anopheles gambiae*. The study shows the results of mapping of pyrethroid resistance in 3 isofemale pedigrees established from wild *A. gambiae* and makes suggestions for future genetic mapping of insecticide resistance. Two QTL were identified on chromosomes 2L and 3R, in similar genomic sites as those previously identified in laboratory strains (Witzig C, Wondji CS, Strode C, Djouaka R, Ranson H. Identifying permethrin resistance loci in malaria vectors by genetic mapping. *Parasitology*. 2013;28:1-10). [Epub ahead of print])

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