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Neurological Complications of Gastrointestinal Disease

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There is a growing interest in the extraintestinal manifestations of common pediatric gastrointestinal diseases, such as inflammatory bowel disease and celiac disease. This article specifically focuses on the neurological symptoms that manifest because of these disorders and their treatments. Many neurological symptoms have been reported in association with these diseases, including neuropathy, myopathy, ataxia, headache, and seizures, among others. It is currently believed that these neurological symptoms are largely overlooked by practitioners and could be a red flag for earlier diagnosis. However, additional research, especially in the pediatric population, is warranted to further elaborate on the causality and pathophysiology of these neurological symptoms.

Introduction

Celiac disease (CD) and inflammatory bowel disease (IBD) encompass a large percentage of luminal organic diseases diagnosed and treated by pediatric gastroenterologists. Both of them involve a genetic predisposition, environmental factors, and immune dysregulation. Traditionally, the presenting symptoms associated with these diseases have been abdominal pain, weight loss, diarrhea, and rectal bleeding. Conversely, these diseases also have extraintestinal manifestations involving other organ systems, and these too can be presenting symptoms. This article focus specifically on their neurological extraintestinal manifestations, as well as potential neurological complications of treatment.

The Neurological Complications of CD

CD is characterized by gluten sensitivity leading to enteropathy in genetically predisposed individuals (HLA class II haplotypes DQ2 or DQ8) under the correct environmental circumstances. CD occurs in 1% of the general population, making it the most common genetically based food intolerance in the world.[1]

CD typically presents with gastrointestinal symptoms such as diarrhea, abdominal distension, and failure to thrive, but there has been an increasing awareness of extraintestinal manifestations, including neurological symptoms. Initial screening tests look for autoantibodies created by the immune system in response to gluten. These tests include antitissue transglutaminase (TTG) IgA, which is the predominant screening test, as well as antiendomysial IgA and anti-deamidated gliadin (DGP)-IgA and IgG. The gold standard for diagnosis is a small bowel biopsy. The histology should reveal varying degrees of villous blunting to complete atrophy, increased intraepithelial lymphocytes, and predominant crypts.[1] The standard of care for treatment is a gluten-free diet.

As most studies have focused on the adult population, some of the information must be extrapolated from this population pending further pediatric research.

Prevalence of Neurological Symptoms in CD

Studies have shown that up to 7% of patients with CD present with neurological symptoms.[2] Neurological symptoms are more common in patients with CD compared with controls, including in pediatric patients.[3-5] Despite these findings, their prevalence in pediatric CD may be less than that in adults based on the results of a pediatric meta-analysis by Lionetti et al.[6] A small study even suggests that there may be no correlation between neurological symptoms and pediatric CD.[7]

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The most common neurological symptoms in all age groups are peripheral neuropathy and cerebellar ataxia, with headache having a high prevalence in the pediatric population.[8,9]

Cerebellar Ataxia

Biopsy proven CD has been shown in 1.9%-16% of patients with idiopathic cerebellar ataxia in some studies,[2,10-13] but others have found no incidence of CD in idiopathic cerebellar ataxia.[14] A study notes that afferent ataxia and vestibular ataxia should also be considered in patients with CD with ataxia.[15] In the few studies looking at neurological manifestations of pediatric CD, the incidence of cerebellar ataxia ranges from 2.7%-6%[3,6,16] with one study reporting an incidence rate of 0%.[5]

Although the aforementioned studies ruled out vitamin deficiencies as a cause, it is known that the malabsorption associated with CD can cause decreased levels of vitamin E, vitamin B12, and copper, all of which can cause cerebellar ataxia.[17,18] A possible explanation for cerebellar ataxia in CD is cross reactivity of antigliadin antibodies with Purkinje cells and the creation of antiPurkinje cell antibodies. Hadjivassiliou et al[19] proved this was possible through experiments on rat and human central nervous system (CNS) tissue, but antibodies have not been consistently found in patients with CD and cerebellar ataxia.[20,21]

The most common presenting symptoms of cerebellar ataxia are those of abnormal stance and gait, dysarthria, and limb ataxia. Oculomotor symptoms, including gaze-evoked nystagmus, spontaneous nystagmus, saccade slowing, and upward gaze palsy have also been documented.[13] Current research has not identified a relationship between neurological symptom onset and severity of disease.[3,21]

Many studies have attempted to treat ataxia through a gluten-free diet with varying success.[3,15] Most report improvement in symptoms.[9,22,23]

It is also important to mention that there are documented cases of cerebellar ataxia in patients with positive antigliadin antibodies,[24] but with normal duodenal biopsies.[11,13] The significance of this population, which studies have termed patients with gluten sensitivity, is not yet fully understood.[11]

There is also a questionable link between both CD and gluten sensitivity and hereditary disorders of ataxia, including Friedreich ataxia and spinocerebellar ataxia.[12,24]

Epilepsy

Most pediatric studies have failed to find an increased prevalence of epilepsy in CD when compared with the general population.[4,6,16,25] A meta-analysis stated a slightly increased prevalence of epilepsy in "silent CD," asymptomatic patients with positive celiac serology.[6] Another study, which included febrile seizures in their definition of epilepsy, found an increased prevalence rate of 7.2%.[3] There has also been a study performed in all age groups, which found that patients with CD are 1.42 times more likely to develop epilepsy, with the highest risk before 20 years of age.[26] Most studies investigating the prevalence of CD in pediatric epilepsy have also found no significant difference from the prevalence in the general population.[6,7,27-29] Only a few studies have stated a prevalence slightly higher than that of the general population.[5,30,31]

The types of seizures that have been described include complex partial seizures, generalized tonic-clonic, absence, and temporal lobe seizures.[27,31] A case study found an association between CD and Lennox Gastaut syndrome.[28] Another one described a patient with celiac crisis presenting with status epilepticus and encephalopathy.[32] Febrile seizures have also been found in 0.3%-3.6% of patients with CD,[3-5] and CD has been noted in up to 8.9% of patients with febrile seizure.[33] This is representative of the prevalence in the general population.

In addition to the traditional types of seizures mentioned earlier, there is a specific syndrome identified by the literature that is characterized by bilateral occipital calcifications and seizures in patients with CD. This syndrome is relatively rare and of undetermined clinical significance.[34] Several small studies have suggested a link with folate deficiency.[35,36] It has been described as similar to Sturge-Weber syndrome, but patients lack the pathognomonic nevus flammeus and characteristic neuroimaging findings.[35,37] Most studies, including the pediatric meta-analysis by Lionetti et al,[6,29,31] have found a low incidence of cerebral calcifications in children with CD and epilepsy, on average approximately 0.2%. Smaller studies have found a higher prevalence of cerebral calcifications in patients with CD, up to 46%.[34,37] The seizures associated with cerebral calcifications have generally been described as occipito-temporal lobe in origin and refractory to antiepileptics, responding more to a gluten-free diet, and in some cases, requiring surgical resection.[34,35,37-39] Other studies have found a link between the occipital calcifications and vision loss.[27,40,41]

A gluten-free diet has not been proven to prevent seizures, but research results suggest that it may provide better control of them and allow for fewer antiepileptic medications.[8,34,42,43]

Sensorineural Hearing Loss

The association between CD and sensorineural hearing loss has recently been studied, with varying results. Although some studies indicated that there is an increased prevalence of sensorineural hearing loss in patients with CD,[44,45] others showed no significant difference in the prevalence of hearing loss in CD compared with the general population.[46-48] Sahin et al[49] did found significantly different audiometric bone conduction thresholds in patients with CD vs controls, as well as a greater difference in bone conduction threshold at later stages of disease, but not enough of a difference to diagnose clinical hearing loss. They suggested that this might represent an association between subclinical hearing loss and CD.

Based on the available data, the use of more frequent hearing screening is unclear pending further research.

Neuropathy

The most common neuropathy noted in CD is chronic, symmetric distal neuropathy, but autonomic neuropathy,