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Neurological complications of gastrointestinal disorders: A review of the literature

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Abstract:

This article presents a short review of the literature concerning neurological complications of gastrointestinal disorders. These disorders include the following: inflammatory bowel diseases (ulcerative colitis, Crohn's disease), celiac disease, H. Pylori infection, hepatitis C, Wilson's disease, hepatic failure-liver transplantation, gastroenteritis. The most frequent neurological complications are peripheral neuropathy, cerebellar dysfunction, thromboembolism. The exact pathophysiologic mechanism remains unclear. In most cases neurological manifestations are the first clinical manifestation of the disease.

Keywords: neurological, complications, gastrointestinal

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Introduction

Neurological complications of gastrointestinal disorders are not of less importance. Exceptionally, they are the first clinical manifestation of the disease. The most common gastrointestinal disorders that have been correlated with neurological complications are the following: inflammatory bowel diseases (ulcerative colitis, Crohn's disease), celiac disease and hepatic failure. This article presents a short review of the literature concerning neurological complications of gastrointestinal disorders.

Inflammatory bowel diseases (ulcerative colitis, Crohn's disease)

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC) have a worldwide distribution and are common causes of gastrointestinal morbidity in Western Europe and Northern America, with prevalence approaching 400 per 100.000 [1]. The extraintestinal manifestations of IBD are not of less importance. In some cases they are the first clinical manifestation of the disease and

may precede the onset of gastrointestinal symptoms by many years. The real incidence of neurological complications is unknown with reports varying from 0.25 to 35.7% [2-5]. In some countries IBDs have an early childhood onset [6].

Neurological complications that have been reported are the following: peripheral neuropathy, drug induced neurotoxicity, cranial nerve palsies (mainly optic, facial and abducens nerve), increased risk of thromboembolism in cerebral arterial and venous circulation, multiple sclerosis (MS), myopathies. Less common symptoms of patients with IBD are migraine, tension headache, cerebellar syndrome, dystonia, urinary incontinence, Parkinson-like syndrome, organic brain syndrome, chronic fatigue syndrome, chronic back pain, vertigo, nausea [2-5,7]. Also, a rare complication of growth retardation and delayed sexual maturation due to inadequacy of hypothalamic-pituitary function in a child with Crohn's disease has been described [8].

Peripheral neuropathy (PN) is one of the most frequently reported neurological complications in IBD patients. The neuropathy may be axonal or demyelinating type [2,5]. Men with IBD may be more susceptible to the development of PN than women, but the latter may be more prone to demyelinating type. Although peripheral neuropathy is an unusual event in children with IBD, several authors report the development of sensorimotor polyneuropathy even few days before the onset of intestinal symptoms [9]. In a retrospective study of patients with PN and either CD or UC, conducted by Gondim et al., it was demonstrated that PN symptoms began earlier in the course of CD than in UC ($p < 0.05$) [10,11]. The exact mechanism of neurological complications in these patients is unclear. However, the concept that PN manifesting in IBD is probably autoimmune-induced is strongly supported by further reports, describing recovery after initiation of steroid treatment [12].

At least three different medications used in the treatment of IBD, cyclosporine A, metronidazole and sulfasalazine have been reported as causative factors for drug induced neuropathy. 25% of cyclosporine A users present with neurotoxicity. The clinical presentation of those patients includes paraesthesias, tremor, ataxia, motor deficits, altered consciousness and various degrees of visual and oculomotor disturbances. Possible mechanisms include either direct toxicity to peripheral nerves or indirect effect through thromboembolic phenomena leading to

ischemic optic neuropathy [13-15]. Peripheral neuropathy is a well-documented side effect of metronidazole, especially in daily dosages over 800 mg for long periods of time. In this case neuropathy is characterized by sensory phenomenology (with occasional sensory ataxic features) with or without resolution after discontinuation [11]. Less than 5% of treated patients with sulfasalazine present with drug induced neurotoxicity necessitating discontinuation [15].

Almost 0.12-4% of IBD patients present with cerebrovascular disorders that affect both arterial and venous circulation, occur at any age in both sexes equal and tend to correlate with disease activity. The cerebral circulation may be affected by hypercoagulability related thrombosis, vasculitis and consumption coagulopathy. It has been reported that that IBD patients, especially UC, have a three to fourfold increased risk of thromboembolism [5,16-18].

There are several reports of IBD patients who eventually developed a Multiple sclerosis-like disease as well as reports of patients diagnosed with MS who developed IBD [16,19-22]. A comorbidity between MS and CD was found by Beaugerie et al. who reported that 4 of 832 patients diagnosed with CD developed MS [23].

Myasthenia Gravis (MG) is a rare complication of IBD patients, especially those with UC. A possible mechanism could be the production of acetylcholine receptor antibodies in those patients [22,24]. A rare but well-established and serious neurological complication in patients with CD is spinal epidural abscess. Predisposing factors in these patients include both immunosuppressive treatment and the presence of intra-abdominal or retroperitoneal fistulas [25].

Celiac disease

The first reported evidence that celiac disease might present with extraintestinal manifestations was made by Shuster, Marks and Watson in 1963-65. They observed that dermatitis herpetiformis was a form of gluten-sensitive dermatopathy that shared the same small bowel pathology, but not the gastrointestinal symptoms seen in patients with celiac disease [26]. However, the first detailed descriptive study of patients with celiac disease (confirmed on jejunal biopsy) and a neurological deficit was published by Cooke and Smith in 1966. The predominant abnormality was a sensory ataxia indicative of damage to the dorsal columns in the spinal cord,

while some patients presented with cerebellar dysfunction [27]. Since then, a number of neurological disorders have been described in patients with celiac disease, the most frequent being cerebellar dysfunction, epilepsy and peripheral neuropathy.

About 10% of patients with celiac disease develop neurological complications [28]. The most common neurological manifestations include the following: cerebellar ataxia, peripheral neuropathy, epilepsy, cerebral calcifications. Less often the following neurological manifestations have been described: multifocal leukoencephalopathy, dementia, myopathy, myoclonus, myelopathy, Stiff-man syndrome, multiple sclerosis [22,29,30].

Cerebellar ataxia is the most common reported neurological complication of patients with celiac disease [28,31-33]. The exact patho-physiologic mechanism is not known. However, the increased serum levels of antigliadin antibodies (AGA) and antibodies against transglutaminase-2 (TG2) and transglutaminase-6 (TG6) are considered as the most possible causative factor [34,35]. Gluten ataxia usually presents with pure cerebellar ataxia or, rarely, ataxia in combination with myoclonus, tremor or chorea with a mean age onset of 53 years. Up to 60% of patients with celiac disease presenting with cerebellar ataxia have evidence of cerebellar atrophy on Magnetic Resonance Imaging (MRI). Also, use of proton magnetic resonance spectroscopy shows significant differences in mean N-acetyl concentrations at short echo-time and in N-acetyl aspartate to choline ratios at long echo-time between patients with gluten ataxia and healthy controls, indicative of cerebellar dysfunction [36].

The second most common complication of celiac disease is peripheral neuropathy. Up to 23% of patients with established celiac disease on a gluten-free diet have neurophysiological evidence of a peripheral neuropathy [37]. The most common type is symmetrical sensorimotor axonal peripheral neuropathy, slowly progressive with a mean age at onset of 55 years and a mean duration of neuropathy to diagnosis of gluten sensitivity of 9 years. The data available from post mortems and nerve biopsy samples are consistent with an inflammatory etiology (perivascular lymphocytic infiltration) [38].

Several reports since 1978 have suggested a link between epilepsy and celiac disease with prevalence from 1 to 5% [39-44]. The most frequently reported type of seizures is a specific type of focal epilepsy

associated with occipital calcifications, resistant to antiepileptic therapy and tends to affect young patients (mean age 16 years) [44]. More recent studies suggest a significant association between temporal lobe epilepsy with hippocampal sclerosis and celiac disease [45]. Moreover, it is remarkable the fact that some patients with celiac disease and epilepsy have a better control of seizures after the introduction of gluten-free diet [46,47].

Since 2001 there are several reports of patients with celiac disease presenting with episodic headaches that mimic migraine and in some cases associated with focal neurological deficits and also white matter abnormalities in neuroimaging (gluten encephalopathy) [48-54]. It is remarkable the fact that headaches resolve with introduction of gluten-free diet in most patients, while white matter abnormalities do not resolve. The distribution of these abnormalities is more suggestive of a vascular rather than a demyelinating etiology and in some patients coexists with ataxia, neuropathy or cognitive deficits [48].

At last, a rare complication of celiac disease is dementia with remarkable memory dysfunction which did not resolve with the introduction of a gluten-free diet [55]. Other rare complications that have been reported are cognitive deficits, memory impairment, acalculia in patients with celiac disease and subsequent vitamin B12, vitamin E and folic acid deficiency. Neurological manifestations in these patients did not resolve with vitamin supplementation, however, they improved after the introduction of a gluten-free diet [56].

The initial assumption was that neurological manifestations in patients diagnosed with celiac disease were caused by vitamin deficiencies secondary to malabsorption as a result of the enteropathy. The patients were undernourished, with severe weight loss, low serum albumin, and often multiple vitamin deficiencies, mainly vitamin B1, B3, B12, E [57]. However, post-mortem data reveal an inflammatory process that primarily, but not exclusively, affect the cerebellum and other parts of central and peripheral nervous system. The few data available from post mortems and nerve biopsy samples are consistent with an inflammatory etiology revealed by the presence of perivascular lymphocytic infiltration, diffuse infiltration mainly of T lymphocytes within the cerebellar white matter as well as in dorsal root ganglia and loss of Purkinje cells throughout the cerebellar. All the above suggest

that neurological manifestations in patients with celiac disease are immune mediated [27]. The role of humoral immunity in neurological gluten sensitivity is supported by the fact that patients with celiac disease who present with neurological complications also have humoral immunity disorders. The auto-antibodies that have been mainly correlated with neurological manifestations are antibodies to transglutaminases (TG) [58,59].

H. Pylori infection

H. Pylori infection has been associated with many extra-gastrointestinal manifestations such as hematological diseases, cardiovascular disorders, metabolic disorders, skin diseases and neurological disorders. Neurological complications of H. Pylori infection include stroke, idiopathic parkinsonism, dementia, Alzheimer's disease and epilepsy [60]. Several studies have found strong association between H. Pylori infection with ischemic atherosclerotic stroke combined with greater intima-media thickness (mainly H. Pylori CagA+ strain) [61-65]. A possible explanation could be the fact that H. Pylori infection affects the instability of carotid plaque and also causes hyperhomocysteinaemia [66,67]. Moreover, there is only a small sample study reporting the association between H. Pylori infection and epilepsy, especially in patients with poor prognosis [68].

Hepatitis C virus (HCV) infection

Hepatitis C virus (HCV) infection has become a major cause of liver disease worldwide. HCV chronic infection is often associated with abnormal immunological responses that can result in several extrahepatic conditions. Neurological complications include sensory or motor peripheral neuropathy and less often central nervous system involvement (depression, cognitive impairment, cerebral vasculitis, transient ischemic attacks [69-78].

Wilson's disease

Wilson's disease is an infrequent metabolic disorder developing as the result of a dysfunction in the mechanisms regulating copper excretion into bile. Although the primary defect lies in the hepatobiliary system, it determines the accumulation of toxic levels of copper in various organs, causing different clinical manifestations. The main neurologic complication that have been reported is peripheral sensori-motor polyneuropathy with both demyelinating and axonal involvement. Other neurologic dysfunctions include tremor, abnormal movement, dysarthria, dysphagia,

dystonia and ataxia. However, most patients show improvement of neurological manifestations after liver transplantation [79,80].

Hepatic failure – liver transplantation

Liver dysfunction due to acute or chronic liver disease is characterized by multiple neuropsychiatric manifestations defined as hepatic encephalopathy, a condition that was first describe by Adams and Foley in 1952 [81]. Usually, hepatic encephalopathy is characterized by acute onset of altered mental status with gradual worsening that can lead to stupor or coma. Besides, encephalopathy as seen in Reye and Reye-like syndrome have been recognized in patients with hepatic failure [82]. Neurologic manifestations in hepatic failure can be divided into following groups: those due to hypoglycemia, sepsis, intracranial bleeding resulting from coagulopathies, electrolyte disturbances, renal failure, cerebral edema.

About 1/3 of patients underwent liver transplantation present with neurological complications with onset during the first month following transplantation. In general, neurological complications can be categorized into those related to the underlying disease, to the transplant procedure, to side effects of immunosuppressive drugs. Seizures are the most common neurological complication following liver transplantation. Other complications, mainly in adults, include: encephalopathy, posterior reversible leukoencephalopathy syndrome (PRES), stroke, meningitis, cerebellar dysfunction, headaches, neuropsychiatric manifestations, cognitive disorders, sleep disorders, tremor and peripheral neuropathy [83-93]. It has been presumed from several studies that metabolic derangements caused by transplantation and the alteration of blood-brain barrier, one to six months following liver transplantation in both adults and children, may be the predisposal factor in those patients [87].

PRES is clinically characterized by acute onset of neurological dysfunction in the form of seizures, headache, and visual disturbances, first described by J. Hinchev et al. in 1996. The characteristic radiological findings are symmetric bilateral subcortical/cortical hyperintensity in T2-weighted images, predominantly in the posterior regions of the cerebral hemispheres, typical of vasogenic edema. It is more common in patients receiving immunosuppressive agents (mainly cyclosporine in high doses) and can be reversed after discontinuation of reduction of the immune suppressant [93,94].

For pediatric patients with liver transplantation there are fewer references reporting an incidence of neurologic complications following transplantation from 8 to 46% [83]. In a recent retrospective study of 65 patients aged <21 years old conducted by Ghosh et al, 30.7% of patients presented with neurological complications after liver transplantation. The most common complication was seizures, while a small number of patients presented with other less common complications such as PRES, encephalopathy, headaches, peripheral neuropathy, sleep disturbances and cerebellar dysfunction. Seizures were partial or generalized, most frequently of the tonic-clonic type, caused by metabolic derangements, immunosuppressive agents, hypoxic-ischemic brain injury, cerebral structural lesions (ischemic or more commonly hemorrhagic strokes), and infections [95].

Gastroenteritis

Gastroenteritis, since 1995, has been associated with clusters of seizures even in the absence of fever. Most commonly affects children aged under 6 years old. Usually children begin to have gastrointestinal symptoms followed by clusters of seizures lasting up to 5 minutes with lethargy (with or without ataxia) and recover completely in 48 hours. The convulsions are short, symmetrical, generalized tonic-clonic, occurring in clusters. It is presumed to be a benign complication with rotavirus being the most common cause. Prognosis is always favorable and anti-convulsant therapy is not recommended [96-103]. However, more severe and life threatening complications have been reported due to infection of other pathogens rather than rotavirus (*Salmonella*, *E. Coli*) including encephalopathy, disseminated intravascular coagulation, hemolytic-uremic syndrome [104,105].

Conclusions

Neurological complications are common in patients with gastrointestinal disorders. Most references report IBD and celiac disease as the most common gastrointestinal diseases with neurological complications. The most frequently described neurological complications are peripheral neuropathy, cerebellar dysfunction, thromboembolism. The exact pathophysiologic mechanism remains unclear. However, many mechanisms have been described such as: vitamin deficiency, immunosuppression, side effects of immunosuppressive agents, thromboembolism, problems related to medical procedures. The most frequent side effects of immunosuppressive treatment

include tremor, encephalopathy, seizures and headache. Psychosis and myopathy have been reported as adverse events of corticosteroids. The acute diagnosis of patients with neurological complications is of great importance because in most cases neurological manifestations precede the onset of neurological symptoms.

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