GE J Port Gastrenterol. 2014;21(1):31–34

Jornal Português de Gastrenterologia
Portuguese Journal of Gastroenterology
www.elsevier.pt/ge

CLINICAL CASE

Acute neurologic disorder in Crohn's disease: A rare life-threatening complication

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Received 11 January 2013; accepted 25 October 2013
Available online 4 February 2014

KEYWORDS
Inflammatory bowel disease;
Crohn disease;
Thiamine deficiency;
Wernicke encephalopathy;
Deglutition disorders

Abstract Clinicians should consider and approach inflammatory bowel diseases as a multisystemic disease. Though neurologic complications related to inflammatory bowel diseases are not rare, they are frequently underdiagnosed when compared with other organ complications.

We report on a 40-year-old patient with severe Crohn's disease and an acquired demyelinating polyneurophathy, malnourished, on biological therapy, who was admitted in our institution with an opportunistic infection (esophageal candidiasis). After successful treatment of infectious complication, he maintained unexplained dysphagia and gastric stasis requiring parenteral nutrition. Some weeks later he presented with ophthalmoplegia and cognitive impairment. A clinical diagnosis of Wernicke encephalopathy was suspected despite multivitamin infusion in standard doses. After high doses of intravenous thiamine, dysphagia and gastroparesis improved substantially.

Wernicke encephalopathy is unusual in inflammatory bowel diseases patients and dysphagia is a very rare symptom of thiamine deficiency.

PALAVRAS-CHAVE
Doença inflamatória intestinal;
Doença de Crohn;
Défice de tiamina;
Encefalopatia de Wernicke;
Perturbações da deglutição

Distúrbio neurológico agudo na doença de Crohn: uma complicação grave e rara

Resumo A doença inflamatória intestinal deve ser considerada e abordada clinicamente como uma patologia multissistémica. Apesar das complicações neurológicas relacionadas com a doença inflamatória intestinal não serem raras, são frequentemente subdiagnosticadas quando comparadas com as complicações que afetam outros órgãos.

Reportamos o caso clínico de um doente de 40 anos com doença de Crohn severa e uma polineuropatia desmielinizante adquirida, subnutrido, medicado com terapêutica biológica, admitido na nossa instituição por uma infeção oportunista (candidíase esofágica). Após o tratamento eficaz da complicação infeciosa manteve disfagia e estase gástrica não explicadas, necessitando de nutrição parentérica. Algumas semanas mais tarde foram objetivadas

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0872-8178/$ – see front matter
http://dx.doi.org/10.1016/j.jpg.2013.10.006

oftalmoplegia e alterações cognitivas. Suspeitou-se, pelo quadro clínico, de encefalopatia de Wernicke, apesar da administração parentérica de suplemento multivitamínico em doses *standard*. Foi administrada, empiricamente, tiamina por via endovenosa em doses elevadas, com melhoria clínica significativa, nomeadamente, da disfagia e gastroparésia.

A encefalopatia de Wernicke é uma complicação infrequente em doentes com doença inflamatória intestinal e a disfagia relacionada com défice de tiamina é um sintoma muito raro.

Introduction

Inflammatory bowel disease (IBD), Crohn's disease (CD) and Ulcerative colitis (UC) should be approached as multisystemic diseases. Extraintestinal manifestations in IBD are widely recognized, sometimes precede intestinal symptoms or have a more severe behavior than gastrointestinal involvement. On the other hand, complications secondary to medications can involve virtually any organ or system.

Neurologic complications are not infrequent but are less recognized when compared to other organ complications. Different mechanisms are believed to be involved in the pathogenesis of central and peripheral nervous system disorders, which may present separately or in combination. Neurologic manifestations in patients with IBD can be ascribed to several pathophysiological mechanisms, one being malabsorption and nutritional deficiencies (particularly vitamin B1, B12, D, E, folic acid and nicotinamide).[1,2] In addition, unspecified neuronal influence of enteric disease onto the nervous system (and vice versa) can hypothetically play a role, based on contemporary theories considering the existence of a brain-gut axis, as well as from studies on functional neuroimaging.[3,4]

Case report

The patient was diagnosed with CD in 2001 at the age of 31, after surgery for intestinal obstruction at another institution, resulting in ileocaecal resection with ileocolonic anastomosis. In 2004 he was evaluated for the first time in our institution. At the initial observation, he complained of intermittent diarrhea and weigh loss. He had a body mass index (BMI) of 19.53 kg/m^2 and was medicated with steroids for a long time (steroid-dependent). After further evaluation with blood tests, endoscopic and imaging studies he began treatment with azathioprine. The following year, the disease maintained a high level of activity (abdominal pain, diarrhea and weigh loss), and anti-tumor necrosis factor (TNF) α therapy was initiated (infliximab 5 mg/kg). In 2007, during clinical remission, he was diagnosed with esophageal candidiasis. At that time azathioprine was discontinued. In 2009, he had a clinical relapse and infliximab dosage was adjusted to 10 mg/kg every 8 weeks. In February 2010, disease was still active, the patient continued to lose weight (BMI 13.47) and a biological switch to adalimumab was attempted.

In October 2010 the patient complained for the first time of progressive paraesthesias in both feet and hands and muscular weakness in upper and lower limbs. He could not specify the time of onset of the symptoms (several years) but mentioned an aggravation in the previous month. He was evaluated in the Neurology department and an acquired demyelinating polyneurophathy was diagnosed. Chronic inflammatory demyelinating polyneurophathy related to anti-TNFα therapy was suspected but, because those symptoms had been present for several years, a causal relationship was difficult to establish. We decided to stop anti-TNFα therapy and steroids were started, without clinical improvement.

Short afterwards, in November 2010, he presented with dysphagia. Endoscopic evaluation revealed lesions suggestive of severe esophageal candidiasis. Chest radiography also revealed an infiltrate in the left lung suggesting pneumonia. He began antibiotics, anti-fungic and enteral nutrition (nasogastric feeding tube).

After two weeks, upper endoscopy was repeated and no esophageal lesions were observed. The nasogastric feeding tube was removed; however, the patient maintained complaints of dysphagia and began vomiting.

In December parenteral nutrition was prescribed, adjusted to caloric requirements with multivitamin infusion and trace elements supplementation. Concomitantly, enteral nutrition (nasoenteric feeding tube) was also initiated to stimulate gut protection and function.

Three weeks later, he presented dyspnea and chest radiography revealed pneumonia in the right lung with pleural effusion. Empirical antibiotic therapy was restarted and a right thoracocentesis was performed. The following day, chest radiography revealed a right pneumothorax and a thoracic drain was placed.

One week later, respiratory complications were resolved but esophageal and gastric dysfunctions were still present. The patient was severely malnourished (BMI: 10.93 kg/m^2) with muscular atrophy and complained of visual impairment. On neurologic evaluation, diplopia and limitation of eye movements were detected.

Three days later he presented unusual behavior and disorientation. A cranial computed tomography scan was obtained and acute vascular lesions were excluded. Wernicke encephalopathy (WE) was suspected based in clinical evidence, despite multivitamin supplementation in parenteral nutrition. Laboratory tests to assess thiamine levels and Magnetic Resonance Imaging (MRI) were not promptly available. Empiric treatment with high doses of intravenous thiamine (200 mg 3 times daily) was administrated due to the low incidence of adverse effects of the treatment.

In the first 24 h of treatment, a significant improvement was observed. The patient no longer presented signs of encephalopathy. Eye movements normalized during the following week. Oral feeding was restarted, successfully, without dysphagia or vomiting. The patient was later discharged, on daily oral multivitamin supplementation and intramuscular thiamine 100 mg/day, which he maintained for several months.

In March 2011, anti-TNFα therapy was reinitiated, with clinical remission of CD and mild neurologic complaints, with a relapsing-remitting pattern.

Discussion

The case report aims at highlighting acute neurologic manifestations in a patient with severe CD.

Malnutrition and weight loss are frequently observed in patients with IBD, especially CD. This condition can result from multiple factors, including reduced food intake, malabsorption, diarrhea and oxidative stress, all of which can be worsened by disease activity.[5]

Filippi et al, evaluated 54 consecutive CD patients in clinical remission, assessing body composition, resting energy expenditure, nutrient intake, and plasma concentration. These patients were compared to 25 healthy controls. According to their results macronutrient needs are usually covered by food intake when patients are in remission; however, micronutrient deficiencies are frequent and call for specific screening and treatment.[6]

Our patient was malnourished for a long period of time, probably even before CD diagnosis, which may explain his low stature and weight. When the disease was active his nutritional status worsened despite oral nutritional supplements administration.

In November 2010, when he was admitted with severe esophageal candidiasis, his nutritional condition was poor and adjusted nutritional support was provided. The infectious intercurrences related to his immunosuppressed condition were life-threatening but were successfully treated. When he presented with ophthalmoplegia and cognitive impairment, clinical diagnosis of WE was suspected, although standard parenteral multivitamin supplementation was being provided. The clinical improvement after thiamine infusion confirmed the diagnosis.

The resolution of dysphagia and gastroparesis with thiamine administration suggests that these symptoms were also related to thiamine deficiency, and in this particular case, were early symptoms.

Thiamine (vitamin B1) is a water-soluble vitamin. Thiamine diphosphate is the active form and serves as a co-factor to several enzymes involved primarily in carbohydrate catabolism. Those enzymes are important in the biosynthesis of a number of cell constituents, including neurotransmitters, and for the production of reducing equivalents used in oxidant stress defenses and in biosyntheses and for synthesis of pentoses used as nucleic acid precursors.

The major manifestations of thiamine deficiency in humans involve the cardiovascular (wet beriberi) and nervous (dry beriberi, neuropathy and Wernicke–Korsakoff syndrome) systems.[7]

WE is a devastating acute or subacute neurological disorder and remains the most important encephalopathy due to a single vitamin deficiency. The disease is rare, catastrophic in onset, clinically complex and often delayed in diagnosis. The reported prevalence of WE in autopsy studies ranges from 0.4% to 2.8%, accounting on average for 1.3% of all autopsies, and seems to be much higher in alcoholics than in non-alcoholics.[8]

The clinical diagnosis of WE requires two of the following four signs: dietary deficiencies, eye signs, cerebellar dysfunction, and either altered mental state or mild memory impairment.[8] Whenever possible, direct measurement of thiamine and its phosphate esters in human blood by high-performance liquid chromatography should be performed before thiamine administration and MRI should be used to support the diagnosis of acute WE.[8]

According to European Federation of Neurological Societies (EFNS) guidelines published in 2010, 600 cases of WE were reported in non-alcoholic patients. WE was typically associated with malignant pathologies, gastrointestinal diseases and previous surgeries, or resulting from vomiting due to hyperemesis gravidarum.[8]

There are few reports in the literature of patients with IBD developing WE. Hanh et al. reported a case of a female patient with CD that was on chronic total parenteral nutrition and developed WE after a shortage of multivitamin infusion in the United States and recovered after thiamine replacement.[9] In Larnaout et al. report, a patient with CD died due to the lack of thiamine replacement.[10] In another report, a patient with CD, submitted to intestinal resection, presented with neurological manifestations and decreased thiamine levels and a significant improvement after vitamin B1 infusion was observed.[11]

Similar to this case study, Mattioli et al. reported the occurrence of WE in a patient with complicated UC and total parenteral nutrition, despite the administration of the usually recommended doses of vitamin B1.[12]

Another unusual finding in our patient was the complaint of dysphagia and the gastric stasis that developed before other neurologic findings and recovered after thiamine infusion. Dysphagia is an unusual finding in WE, especially as presenting symptom. Karaiskos[13] described this same clinical presentation in an alcoholic man and Truedsson[14] in a non-alchoolic patient. Gastrointestinal beriberi is referred in EFNS guidelines as a manifestation of thiamine deficiency.[8]

WE is potentially lethal in a short time if not promptly recognized and treated. In severely malnourished patients, standard doses of thiamine in multivitamin infusion may not be sufficient. This diagnosis should be suspected if neurologic symptoms develop in this context. We believe that prophylactic additional supplementation of thiamine is reasonable in malnourished patients receiving enteral or parenteral nutrition in order to avoid thiamine deficiency complications.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflict of interests

The authors have not received any funding regarding this study.

Dr. Paula Ministro has participated in *advisory boards* of MSD and AbbVie. All the oher authors declare no conflicts of interest.

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