Association of Demyelinating and Inflammatory Bowel Diseases: A Case Series and Overview of the Literature

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ABSTRACT

Neurological complications of inflammatory bowel diseases (i.e., ulcerative colitis and Crohn's disease) can be summarized as a combination of neuromuscular manifestations, cerebrovascular and demyelinating diseases that can be seen in approximately 3% of patients. In addition, asymptomatic cerebral white matter lesions may be detected in these patients. Clustering of diseases within families may be explained by the exposure to similar environmental factors, shared genes, or complex

interactions between genetic and environmental factors. Here we report an epileptic patient with Crohn's disease and cerebral white matter lesions, a family with ulcerative colitis and multiple sclerosis and two patients who have both multiple sclerosis and Crohn's disease.

Keywords: Inflammatory bowel diseases, ulcerative colitis, Crohn's disease, epilepsy partialis continua, multiple sclerosis

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are relapsing–remitting, idiopathic, inflammatory bowel diseases (IBD). At any location throughout, the gastrointestinal tract may be affected transmurally in CD. However, in UC, only the colon is affected but not transmurally (1,2). Extraintestinal manifestations can be observed in 20–40% of IBD patients. The severity of extraintestinal involvement in IBD follows a parallel course to intestinal involvement and responds to IBD treatment; however, some of the cases may follow an independent clinical course (3). Clustering of autoimmune diseases including IBD and multiple sclerosis (MS) in certain families may be explained by common genes, exposure to common environmental factors, or the combination of both (4).

CASES

Case 1

A 42-year-old female with CD for 10 years was hospitalized in the Department of Internal Medicine with complaints of diarrhea, abdominal pain and fever. Patient's medical history revealed oral aphthous ulcers for 16 years and necrotizing granuloma and ulcerative chronic inflammation with giant cells in the gingival biopsy that was performed 10 years before admission. Abdominal computed tomography (CT) scan performed three years ago revealed hepatosplenomegaly and dilatation of the portal vein. In addition, the patient's abdominal Doppler ultrasonography (USG) showed portal hypertension and her liver biopsy supported the diagnosis of granulomatous hepatitis. Contrast-enhanced abdominal CT performed during her admission revealed diffusely increased colonic-wall thickness, indicating an acute attack of CD; therefore, ciprofloxacin and metronidazole therapies were initiated. The patient's pelvic MRI showed a large rectovaginal fistula. A surgical treatment of the fistula and colectomy was planned and the patient was put on an anti-TNF- α therapy.

The patient consulted the Department of Neurology because of an epileptic seizure presenting forced rightward deviation of head and eyes followed by loss of consciousness. Next, the patient had a 2 min long generalized convulsion followed by postictal confusion lasting for 15 min. The patient's neurological examination was normal; however, her electroencephalography (EEG) showed generalized slowing of the background activity. The patient's brain MRI showed non-enhancing lesions around lateral ventricles that were hyperintense in T2 and FLAIR weighted images (Figure 1). Her cervical MRI and visual evoked potentials (VEP) were within normal limits. The patient's cerebrospinal fluid (CSF) examination revealed 552/mm³ lymphocytes that were counted by an automatic cell counter. The CSF glucose level was 55 mg/dL and simultaneous serum glucose level was 94 mg/dL. The CSF protein level was 30.5 mg/dL and CSF IgG index was 0.56. CSF oligoclonal band (OCB) examination was pattern 3. The CSF culture was sterile and the patient's serum vasculitis panel was also within normal limits. Central nervous system vasculitis rather than demyelinating disease was primarily considered in the diagnosis because the patient presented with epileptic seizures and had lymphocytic pleocytosis in the CSF, despite the OCB being pattern 3. However, the patient did not provide consent for repeating the lumbar puncture, brain MRI and conventional brain angiography during her stay in the hospital. Because of normal neurological examination, the normalisation of EEG, presence of cerebral

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Received: 26.03.2014 **Accepted:** 05.08.2014 **Available Online Date:** 07.07.2015

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Figure 1. a, b. MRI of case 1. Periventricular hyperintense lesions in FLAIR weighted axial sections

white matter lesions suggesting MS and the absence of cerebral microhemorrhages suggesting vasculitis in her brain MRI, we considered to follow up the patient and cerebral DSA, CT angiography, or brain biopsy were not considered. She was discharged from the hospital on infliximab and an antiepileptic treatment. She underwent a neurological asymptomatic course for one year.

The patient was rehospitalized in the Department of Internal Medicine after one year due to fatigue, weight loss, melena, infection and continuous involuntary jerks in the left upper and lower extremity with preserved consciousness. Intravenous phenytoin infusion was administered with the diagnosis of epilepsia partialis continua (EPC). Maintenance treatment was first initiated with levetiracetam; however, later replaced with carbamazepine because of elevated creatinine levels. The patient's EEG examination demonstrated an active epileptogenic focus on the right temporal lobe. Her CSF protein level was 77 mg/dL without any cells and the CSF IgG index was .74. Repeated CSF OCB examination resulted as pattern 3. The first CSF cell count with 552/mm³ lymphocytes obtained a year ago was deemed retrospectively incorrect because of the previous use of an automated cell counter. The patient's brain MRI revealed right temporal signal changes that were hyperintense in FLAIR and DWI and mildly hypointense in ADC, suggesting perictal abnormalities (Figure 2). No new white matter lesions were determined when compared with the previous brain MRI. Unfortunately the patient died because of febrile neutropenia and septic shock that followed one week after the EPC.

Case 2

A 31-year-old female presented with imbalance, dizziness, nausea and vomiting. Lesions suggestive of MS were observed in her brain MRI. Intravenous high dose methylprednisolone (1000 mg/day) followed by oral maintenance therapy were administered for a month to treat an assumed brainstem attack. The patient's condition improved almost completely after two months following this treatment. She was diagnosed with MS because of the radiological features of the lesions and had no relapse under glatiramer acetate therapy. Her neurological examination a year later was within normal limits except for a mild left internuclear ophthalmoplegia that was a sequel of the initial attack and her EDSS was 2.0. The patient was a cousin of case 3 and had a sibling with ulcerative colitis (Figure 3).

Case 3

A 39-year-old female presented with right optic neuritis in 2005. She had periventricular and subcortical non-enhancing white matter lesions that were partially congruent and a lesion suggestive of MS in C3–C4 segments, as shown by cervical spinal MRI. The patient improved completely following intravenous methylprednisolone treatment. A sensory attack

Figure 2. a-c. MRI of case 1. Perictal MRI signal change in the right temporo-occipital region that is (a) hyperintense in FLAIR, (b) hyperintense in DWI and (c) hypointense in ADC images

with hand and leg paresthesia was recorded in 2007 that responded to oral methylprednisolone therapy and the patient was later put on IFN β -1b s.c. therapy. The patient did not have any other relapses since 2007 and no clinical or radiological progression was observed and her EDSS performed in 2012 was 2.0. The patient was a cousin of case 2 and had a sibling with ulcerative colitis (Figure 3).

Case 4

A 29-year-old female presented with numbness in her foot in 2005. The patient's brain and spinal MRI revealed multiple lesions in the brain, cervical and dorsal spinal cord suggestive of MS. IFN β -1b s.c. treatment was administered for 1.5 years; however, her treatment was escalated to natalizumab in 2009 because of frequent relapses and disability progression with an EDSS of 1.0–3.0. Her follow up clinical and radiological pictures remained stable; however, the natalizumab therapy was interrupted in 2010 to investigate the cause of continuously elevated serum CRP levels. After a thorough investigation, a colonic biopsy revealed Crohn's disease. The patient received methotrexate for about a year, which was stopped upon normalization of CRP levels in April 2013; furthermore, natalizum-

Figure 3. Family pedigree of cases 2 and 3 who are cousins. The patients' siblings were diagnosed with UC, a family member with breast cancer and a deceased family member with lymphoma (numbers in circles or squares refer to the number of female or male family members)

ab therapy was reinitiated to treat both MS and CD. Her last MS attack occurred in March 2013 presenting with cerebellar dysfunction in her left upper and lower extremities. The patient's EDSS was 2.0. She had no family history of any autoimmune diseases.

Case 5

A 31-year-old female patient without any family history presented with numbness in her right arm 3 years ago. The patient's medical history revealed two more attacks; one with right arm numbness and another one with right hemidysesthesia lasting for 20 days that spontaneously remitted. Her cervical spinal MRI revealed an intramedullary nonenhancing lesion in the C2–C7 spinal levels with a normal brain MRI. The patient's CSF exam showed a protein level of 66 mg/dL without any cells and a normal glucose level. The CSF's OCB test was pattern 2 and the IgG index was 1.25. Serum antiaquaporin antibody test was negative, whereas antinuclear antibody (ANA) was speckled positive, anti-ds-DNA was 52 U/mL (<25). The patient's serum test for p-ANCA was positive and ENA screening was negative. The patient was evaluated by a rheumatologist and no specific rheumatologic disease could be diagnosed. Repeat p-ANCA examination was also positive and VEP and sensory evoked potential (SEP) response latencies were bilaterally prolonged. The patient was diagnosed with MS and 1000 mg/day i.v. methylprednisolone treatment was administered for 5 days followed by 3–4 months of azathioprine 50 mg/day. Her disease modifying treatment (DMD) was switched to interferon β -1a i.m. and successively to glatiramer acetate. During her last visit she complained of diarrhea and weight loss and her MS was stable, although she was not taking any DMD for the last 6 months. The patient was evaluated in the Department of Internal Medicine and a colonoscopy was performed, revealing a cobblestone appearance with several deep ulcerations throughout the colon mucosa separated by intact areas. The patient was diagnosed with CD and her final neurological examination was normal except for gaze-evoked nystagmus and her EDSS was 1.0. The patient's brain and cervical spinal MRI did not demonstrate any new lesions.

DISCUSSION

Focal cerebral white matter changes may be seen in asymptomatic IBD patients (5). These lesions can be ischemic, atherosclerotic, vasculitic or demyelinating lesions (5,6). Geissler et al. (5) observed asymptomatic cerebral

white matter lesions in 46% of UC patients, 42% of CD patients and 16% of healthy controls with an increased frequency in patients with an extraintestinal involvement. Strikingly, all of these lesions were non-enhancing lesions. In another study by Hart et al. (7), white matter lesions were observed in 12.5% of neurologically asymptomatic patients with IBD. However these lesions have been reported not to be suggestive of an active central nervous system disorder. All but one of the lesions was away from the ventricles in this study. Interestingly, case 1 presented with asymptomatic nonenhancing white matter lesions that were also located away from the ventricles.

Neurological involvement was determined in only 3% of 638 patients with IBD in a retrospective study published by Lossos et al. (8). Seventeen patients were diagnosed with a neurological disease following the initial diagnosis of IBD in 6 years on average, whereas 2 patients were diagnosed with a neurological disease along with IBD. Other extraintestinal manifestations emerged in 10 of these patients in the following years. The diagnosis was peripheral nerve disease in 6 (3 acute inflammatory demyelinating polyneuropathy, 1 brachial plexopathy and 1 mononeuritis multiplex), myelopathy in 5, cerebrovascular disease in 4, myopathy in 3 and myasthenia gravis in 1 of the patients.

Benavente et al. (9) examined 84 IBD patients with neurological manifestations in their review published in 2010 and reported neuromuscular diseases with inflammatory and axonal neuropathies, arterial or venous cerebrovascular diseases and demyelinating diseases.

A CSF examination was performed in our first case with CD because of seizures and white matter lesions in the brain MRI that showed an oligoclonal band pattern of type 3. This finding may suggest an ongoing intrathecal IgG synthesis and autoimmune demyelination. We think that this patient's seizure that occurred in the absence of anti-TNF- α therapy was related to the concurrent use of ciprofloxacin therapy (10). The use of infliximab in CD doubles the risk of severe systemic infection (11). Our patient died due to an infection and experienced EPC during the second hospitalization possibly because of the fascilitating effect of this infection.

Inflammatory bowel diseases and MS may also coexist. Studies have demonstrated that the risk of CD was increased by 1.4 fold in the first 317

degree relatives of MS patients (12) and the risk of MS was increased by 1.7 fold in IBD patients (13).

The most important genetic locus predisposing to the development of several autoimmune diseases is the MHC locus located on chromosome 6. Several autoimmune phenotypes were reported to be associated with different MHC haplotypes (14). Recently, two genes unrelated to MHC, including cytotoxic T-lymphocyte antigen-4 (CTLA4) and protein tyrosine phosphatase (PTPN22) genes, were also shown to predispose to autoimmune diseases (15). Clustering of autoimmune diseases in certain families may be explained by common genes, triggering of common environmental factors, or a combination of both (4). One study examining the familial features of autoimmune diseases demonstrated that a single nucleotide polymorphism on PTPN22 gene increased the risk of type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus and Hashimoto's thyroiditis in these families (16). Another autoimmune disease may occur in a family member of 64% of MS patients (4). The most common of these diseases are Hashimoto's thyroiditis, psoriasis, IBD and rheumatoid arthritis. This fact also supports the hypothesis that there are one or more genes that predispose to autoimmune diseases. The CTLA4 gene polymorphism is also more frequent in these families compared to healthy controls (4).

However, a Canadian epidemiological study reported that the risk of autoimmune diseases did not increase in MS patients and their first degree relatives compared to controls; furthermore, the risk of autoimmune diseases was not higher in multiple MS families compared to families with a single MS patient (17). This increased risk in MS families may develop from the selection bias of families over informed about autoimmune diseases.

A 35-year survey for the cancer risk of MS patients and their relatives reported a 10% reduction in the overall cancer risk in MS patients. However, the frequencies of some tumors such as brain or urinary tract were higher than controls. However, no difference was determined in the cancer risk of other healthy family members (18).

In summary, cerebral white matter lesions may be observed in IBD and presence of pattern 3 oligoclonal bands in the CSF may suggest a comorbid MS or an extra-intestinal manifestation of IBD. Clustering of autoimmune diseases and cancers in certain families may be incidental or triggered by certain common genes or environmental factors or a combination of both. More long-term studies examining bigger patient series should be performed to enlighten the relationship between demyelinating diseases and IBD.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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