Relationship Between Neuroimmune Disorders and Inflammatory Bowel Diseases: Case Report

İnflamatuar Barsak Hastalıkları ve Nöroimmün Bozukluklar Arasındaki İlişki

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ABSTRACT Inflammatory bowel disease (IBD) and neuroimmune disorders have a close relationship to their diseases pattern and immunologic cascade with considerable morbidity and mortality. They may have common immunological pathways related with vitamin D deficiency or hygiene hypotheses and also with T cell autoimmunity. We herein report two neuroimmune disorders with low serum vitamin D levels; multiple sclerosis and acute sensory motor axonal polyneuropathy in the course of ulcerative colitis to discuss the common immunologic mechanisms. The exact incidence of neurological IBD is unknown, with reports varying from 0.25% to 35.7%. Although a reliable differentiation may clinically not always be possible, three major pathogenic entities can be differentiated: (i) cerebrovascular disease (ii) systemic and cerebral vasculitis; (iii) immune mediated neuropathy and cerebral demyelination. IBD patients should be consulted to a neurologist and examined by neuroimaging and neurophysiological studies routinely once a year, additionally serum vitamin D levels need to be assayed and replaced in these cases.

Key Words: Colitis, ulcerative; autoimmune diseases of the nervous system; multiple sclerosis; polyneuropathies

ÖZET İltihabi barsak hastalığı (İBH) ve nöroimmün bozukluklar önemli morbidite ve mortalite ile hastalık paternleri ve immünolojik kaskad açısından yakın ilişkilidir. Bu hastalıklar D vitamini eksikliği ya da hijyen hipotezi ve ayrıca T hücre otoimmünitesi ile ilgili ortak immünolojik yolaklara sahip olabilir. Biz burada düşük serum D vitamini düzeyleri ile iki nöroimmün bozukluğu; ülseratif kolit sırasında gelişen multipl skleroz ve akut duyusal motor aksonal polinöropati ortak immünolojik mekanizmaları tartışmak için rapor ettik. Nörolojik IBH'nin kesin insidansı %0.25-%35.7 arasında değişen raporlar nedeniyle net bilinmemektedir. Güvenilir bir ayırıcı tanı klinik olarak her zaman mümkün olmamasına rağmen, üç major patojenik antite ayırt edilebilir: (i)serebrovasküler hastalık; (ii) sistemik ve serebral vaskülit; (iii) immun aracılı nöropati ve serebral demiyelinizasyon. İBH olanların nörolojiye konsülte edilmesi ve nörogörüntüleme ve nörofizyolojik çalışmalar ile rutin yılda bir incelenmesi önerilmektedir, ayrıca serum D vitamini düzeylerinin de araştırılması ve eksikliğin giderilmesi gerekmektedir.

Anahtar Kelimeler: Kolit, ülseratif; sinir sisteminin otoimmün hastalıkları; multipl skleroz; polinöropatiler

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Inflammatory bowel diseases (IBD) and neuroimmune disorders have both autoimmune pattern and immunologic cascade with considerable morbidity and mortality.[1] The autoimmune diseases may be organ-specific or systemic, resulting in overlapping syndromes; more than one autoimmune disease may occur in the same patient. Different phenotypes are thought to represent a spectrum of immune dysregulation.[2] Neurologic involvement as-

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sociated with IBD is rarely reported because of the unawareness of many neurologists and gastroenterologists, although early recognition and treatment of neurologic diseases are crucial in preventing major morbidity.[3] Pathophysiologically, disorders of the peripheral and central nervous system in association with IBD can be ascribed to at least six different mechanisms, which may be present in isolation or in combination: (i) malabsorption and nutritional, particularly vitamin deficiencies, (ii) toxic metabolic agents, (iii) infections as a complication of immunosuppression, (iv) side effects of medication or therapy, (v) thromboembolism, (vi) immunological abnormalities.[4-6]

To explain the relationship between these two immune mediated diseases the hygiene and vitamin D hypotheses have been put forward. There is evidence that commensal gut bacteria may play a role in both of the diseases.[1] There are also common immunologic pathways leading to destruction of the target tissue in both diseases.[7,8]

We herein report two neuroimmune disorders with low serum vitamin D levels; multiple sclerosis (MS) and acute motor-sensory axonal polyneuropathy (AMSAN) in the course of ulcerative colitis (UC) to discuss the common immunologic mechanisms.

CASE REPORTS

CASE 1

A 62 year-old male patient was admitted to neurology clinic with complaints of vertigo, amnesia and personality change. Cranial and cervical magnetic resonance imaging (MRI) showed, contrast enhanced demyelinating lesions in C3 level (Figure 1) and in cerebrospinal fluid oligoclonal band type 2 was positive. About 6 year ago, he had one episode of hemiparesis and sensory loss on the left side, based on these results he was accepted as definite relapsing remitting MS and treated with intravenous methylprednisolone (IVMP) 1000 mg/d for 7 days. After discharge he was referred to gastroenterology clinic with complaint of bloody diarrhea with mucous, he was diagnosed with UC after colonoscopy and intestinal biopsy characterized by ulcerous-pseudopoliposis multiple focuses and mesalazine, budenoside therapy was started. At the second time he was hospitalized with complaints of severe arthralgia and walking disability. We learned that he had diarrhea attacks and arthralgia 1-2 per year for a long time. We noted that his mother died after colon surgery. Neurological examination revealed left upper and lower extremity subtle paresis (-5/5) and bilateral negative Babinski sign. Fundus examination and eye movements were normal. Cognitive impairment in all areas was determined by neurocognitive tests. Vibration sense were delayed in lower extremities, joint position examination were normal. Lhermitte sign and Romberg test were negative. Laboratory testing in normal ranges except low vitamin D levels (6.42 ng/mL) supplemented to normal ranges (20-100 ng/mL). Vasculitis markers were negative. Cranial and cervical MRI revealed cerebral atrophy and in bilateral cerebral hemisphere and corpus callosum T2 hyper intense demyelinating lesions tend to be confluent were observed (Figure 2). Visual evoke potentials (VEP) were delayed bilaterally (p=125ms). Because of artralgia, joint swelling, redness and high Anti streptolysin O, C-reactive protein laboratory tests, the patient were consulted to rheumatology. According to clinical and laboratory assessment polyarthritis were diagnosed. Gastroenterology examined the patient and decided to continue mesalazine and added on aspirin therapy. He had no UC or MS attack during one year follow-up period.

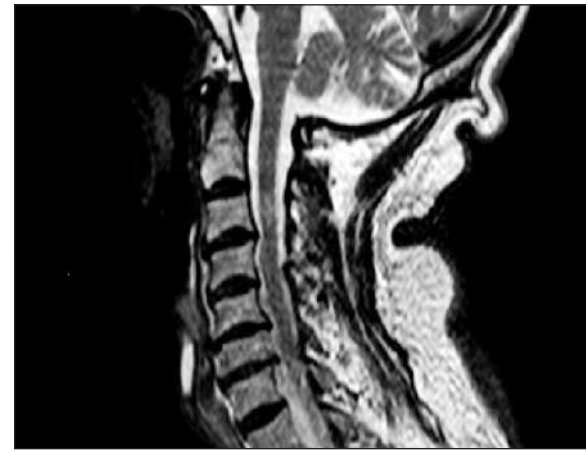

FIGURE 1: Contrast enhanced demyelinating lesion in C3 cervical spinal cord of Case 1.

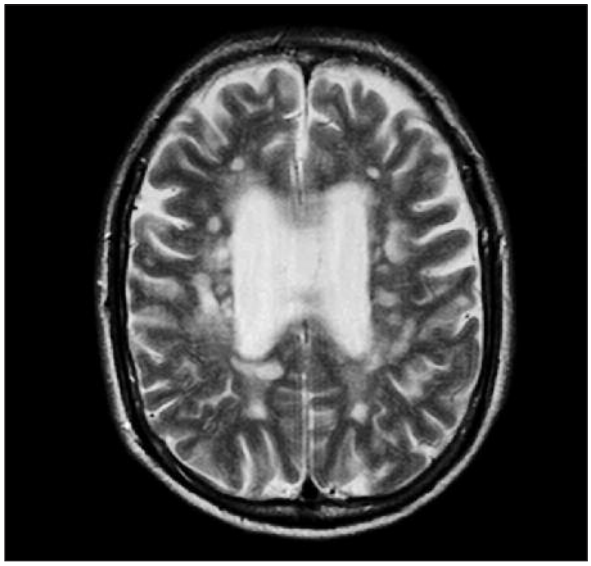

FIGURE 2: Cerebral atrophy and periventricular T2 hyperintense ovoid confluent lesions of Case 1.

CASE 2

A 34-years-old woman was admitted to Neurology clinic with acute onset weakness in legs and difficulty in walking. She was referred to gastroenterology unit three months ago with the complaint of bloody diarrhea with mucous. She was diagnosed with UC after colonoscopy and intestinal biopsy and treated with mesalazine, budenoside. She had sequele right brachial plexus paralysis due to birth trauma. Her medical history was otherwise normal. Neurological examination revealed sequela 3/5 paresis in right upper extremity and hemiparesis (4/5 in left upper extremity, 2/5 in lower extremity) according to MR contrast scale, with mild sensory deficits predominantly in distal sections of all extremities. Deep tendon reflexes were absent and Babinski sign were negative bilaterally. Nerve conduction studies (NCS) and needle electromyography (EMG) showed subacute, severe, symetrical and distal axonal sensory and motor polyneuropathy, predominantly affecting the lower limbs. Antibodies against Brucella and Borrelia, serum Venereal Disease Research Laboratory (VDRL) test, anti-viral markers and vasculitic antibodies were all negative. Serum vitamin D level was low (6.11 ng/mL). Cranial and spinal MRI were normal. Cerebrospinal fluid examination was normal. Because of autoimmune pathogenesis, she was treated with high-dose IVMP 1000mg/d for 7 days, tapered with oral corticosteroids (1mg/kg/d). She continued mesalazine and budenoside given for UC. Her neurological examination after 4 weeks demonstrated mild improvement in proximal muscle strenght in lower limbs (+3/5). One year later she was able to walk without aid, with subtle weakness (5-/5) in lower extremities.

'These two cases were informed and written consent was obtained from them.'

DISCUSSION

The incidences of immune mediated diseases like neuroimmune disorders and IBD have increased in developed countries over the last 50 years.[7] Considering the pathogenesis of IBD, in addition to a genetic predisposition abnormal and excessive responses to dietary triggers, to unidentified infectious agents, and to the physiologic intestinal flora by an inadequately regulated mucosal immune system are currently being hypothesized.[4] In a large retrospective register-based study, Lossos and colleagues found neurologic involvement in 3% of the cases.[3,9] In our first case, patient had MS, UC and polyarthritis, which are immune disorders and may aggravate or initiate each other. The relationship between MS and IBD was found in the early 1980s by Rang and colleagues when they found a high incidence and prevalence of MS whilst they were studying a population who had undergone a colectomy for IBD. This relationship is supported by the role of immune mechanisms in the pathogenesis of each disorder and by the efficacy of inhibitors of the immune system that impair cell-mediated immunity in the treatment of MS and IBD. Immune-mediated or inflammatory processes have been suggested to play a role, but direct evidence is lacking.[3] Disturbances in functional T-cell subsets as well as in antigen presenting cells have been implicated. Researchers found that interferon beta (IFN-β) indeed has proinflammatory functions and aggravates the pathogenesis of T helper (Th) 17-mediated inflammatory diseases.[1,8] Especially, aberrant proinflammatory activity has been suggested as a common pathway leading to the destruction of target tissue in both diseases.[8,9] However there is

evidence that the commensal bacterial flora and other infections have environmental influences on the development of IBD and MS. The hygiene hypothesis proposes that the high rates of infection in the developing world and especially helminth infections program the immune system in a way that precludes autoimmunity. On the other hand, vitamin D levels were low in both present cases, may be due to lack of gut absorption. Vitamin D deficiency has been shown to accelerate the development of IBD and neuroimmune disorders and resulted in a decreased effectiveness of T cell immunization for delayed type hypersensitivity responses. The effects of vitamin D and 1.25 vitamin D3(1,25D3) on T cells predicts that autoimmune diseases like MS and IBD might be responsive to 1,25D3, but required adequate dietary calcium, suggesting that 1,25D3 may directly and indirectly control immune function in vivo. In addition to all vitamin D has been shown to induce anti-bacterial peptides and alter the composition of the gut microbial flora.[7] In the second case, we present acute onset axonal polyneuropathy in a UC diagnosed patient. Peripheral neuropathy is known to be related to IBD and is one of the most frequently reported neurologic complications demyelinating or axonal involvement of peripheral nerves in IBD have been described, and both neuropathies could be acute or chronic. The majority of neuropathies in UC are related to an immunologic mechanism, although non-immunologic mechanisms also have a role.[10] The pathogenesis of neuropathies is not clear, but it is probably related to a common dysimmune basis; affecting T cell mediated, humoral immunity or proinflammatory mechanisms. In addition, infection by microbial agents, namely *Campylobacter jejuni*, is linked to exacerbations of IBD and may contribute to the development of autoimmune inflammatory demyelinating polyneuropathy.[5] In a recent retrospective review, more than two-thirds of patients with IBD had axonal neuropathy, and only one third of patients with IBD developed demyelinating forms of neuropathy. Neuropathy is probably associated with an autoimmune pathogenetic mechanisms, all laboratory tests including cerebrospinal fluid are negative. Corticosteroid therapy should be chosen due to autoimmune pathology.[11] As well as MS, T cells are clearly involved in the pathogenesis of demyelinating neuropathies; however, the relationship between axonal damage and disturbances in the immune system remains obscure may suggest humoral or proinflammatory activity, but is supported by the clinical improvement after receiving immunomodulatory agents as demonstrated in our case.[3]

In our opinion, IBD patients should be consulted to a neurologist and examined by NCS and cranial MRI routinely once a year, additionally serum vitamin D levels need to be assayed and replaced in these cases.

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