Case Report

Sensorineural hearing loss and status epilepticus associated with ulcerative colitis: Is there enough evidence to support immune-related mechanisms?

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ABSTRACT

Ulcerative colitis (UC) is characterized by an inflammatory disorder of the gastrointestinal tract. Immune-mediated extraintestinal manifestations of UC have increasingly attracted attention in the literature recently, for which UC is now considered as a systemic disease. Neurologic involvement associated with UC is probably under-reported because of the unawareness of many physicians, although early recognition and treatment are crucial in preventing major morbidity and sequel. In this case report is presented a patient newly diagnosed as UC, who developed both sensorineural hearing loss and intractable status epilepticus that we suggest to have resulted from immune-mediated mechanisms.

Key words: Immune-mediated mechanisms, sensorineural hearing loss, status epilepticus, ulcerative colitis

Introduction

Ulcerative colitis (UC) is characterized by an inflammatory disorder of the gastrointestinal tract. It is a chronic and debilitating disorder most often diagnosed in patients between 15 and 30 years of age, although it may present at any age. Women and men are equally affected. It has a prevalence rate of 200/100,000. In its pathogenesis, it has hypothesized abnormal or excessive responses by an inadequately regulated mucosal immune system to unknown triggers, in addition to genetic predisposition.^[1] Immune-mediated extraintestinal manifestations of UC have increasingly attracted attention in the literature recently, for which UC is now considered as a systemic disease.^[2,3]

Major target organ for UC is colon; any part may be affected. However, the most common presenting

symptoms are abdominal pain and bloody diarrhea.^[1-3] Neurologic involvement associated with UC, on the other hand, is probably under-reported because of the unawareness of many physicians. Several case presentations have reported sensorineural hearing loss as an early immune-mediated manifestation of UC,^[4-7] whereas the association of epilepsy and UC is neglected as one of the extraintestinal neurologic manifestations of UC.^[8] There are only few case reports with UC who develop epileptic seizures, which were suggested to occur in relation to structural or metabolic causes, and thus regarded secondary to a neurologic complication, but not as an immune-mediated neurologic manifestation of UC itself.^[8,9] Early recognition and treatment are crucial in preventing major morbidity and sequel.^[8,10]

In this case report, a patient newly diagnosed as UC, who developed both sensorineural hearing loss and intractable status epilepticus, which we suggest to have resulted from immune-mediated mechanisms, is presented.

Case Report

A 23-year-old woman started to have abdominal pain, recurrent vomiting, and weight loss for the previous 1 month, and she was diagnosed as having

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UC 2 weeks ago proved by colorectal biopsy. Oral methylprednisolone therapy (1 mg/kg/day) was initiated. At second week of her diagnosis, she developed bilateral hearing loss. Otologic examination revealed no abnormality in external ear canals and tympanic membranes. Pure tonal audiometry demonstrated the presence of bilateral sensorineural hearing loss (the pure tone averages for the frequencies 500, 1000, and 2000 Hz were 93dB in the left and 88 dB in the right ear). Her neurological examination was otherwise normal.

Laboratory investigations showed mild anemia, leukocytosis, hypoalbuminemia, and elevated inflammatory markers. Other detailed biochemical tests, coagulation tests, complement factors, C3 and C4 levels, and vasculitis markers were all normal. Thyroid, nuclear, cytoplasmic, and perinuclear anti-neutrophils, anti-smooth muscle antibodies, anti-gliadin and anti-*endomycium* antibodies were negative. Antibodies to *Borrelia burgdorferi* and *Treponema pallidum* were normal. The microbiological analysis of blood and stool was unremarkable.

One week later, she had a tonic-clonic generalized seizure. Electroencephalography showed generalized slowing over bilateral hemispheres (4–5/s slow-wave - delta activity). Cranial magnetic resonance (MR) imaging was normal, except bilateral peri-rolandic hyperintense signal changes compatible with postconvulsive hypoperfusion in FLAIR-weighted MR images. Cerebrospinal fluid analysis revealed that protein level was mildly elevated, cell count was normal, and oligoclonal IgG bands were negative. Detailed biochemical tests were repeated and ruled out any metabolic or electrolyte imbalance, hypovitaminosis and infections. She continued to have generalized tonic-clonic seizures in spite of high doses of intravenous valproic acid (1500 mg/day), for which she was internalized into intensive care unit and anesthetized. At the end of 1 week, she was retransferred into our neurology clinics. She was seizure-free under anti-epileptic and methylprednisolone treatment. Within 1 month, bilateral sensorineural hearing loss was increased to some extent (98 dB in the left and 91 dB in the right ear). The follow-up colonoscopy revealed complete recovery of ulcerations. After 1 month seizure-free period, antiepileptic therapy was tapered down and stopped without any seizure recurrence. She is now being followed-up in our outpatient neurology clinic for about 2 years without any complaints.

Discussion

In this case report, a patient newly diagnosed as UC was presented, who developed both sensorineural hearing

loss and intractable status epilepticus. Upon detailed etiological work-up, we suggest that sensorineural hearing loss and status epilepticus resulted from immune-mediated extraintestinal manifestations of UC. The clinical improvement with corticosteroid therapy also supports an immune-mediated mechanism.

The mechanisms involved in the pathogenesis of extraintestinal manifestations of UC are not clear; increased bowel permeability during active disease was proposed to cause luminal antigens to be presented to systemic immune system, which in turn lead to significant inflammatory responses elsewhere in the body.^[7] Only few studies have investigated the frequency of neurologic disorders in patients with UC, but resulted to be inconsistent due to iatrogenic conditions or disease-related complications.^[8,10] Pathophysiologically, disorders of peripheral and/or central nervous system in association with UC was ascribed to six different mechanisms: (1) Malabsorption and nutritional, particularly vitamin deficiencies, (2) toxic metabolic agents, (3) infections as a complication of immunosuppression, (4) side effects of medication or therapy, (5) thromboembolism, and (6) immunological abnormalities.^[8]

Sensorineural hearing loss (SNHL) was documented to be more common in patients with UC compared with age- and gender-matched healthy controls.^[6,7] Although the pathogenesis of SNHL associated with UC is not fully understood, it is thought to be immune mediated.^[7] Humoral mechanisms were suggested due to the deposition of circulating immune complexes leading to vasculitis of vessels supplying the inner ear.^[5] A specific antibody that binds to a 68-kDa inner ear antigen, the anti-68 kDa antigen, is defined as the hallmark of inner ear autoimmune disorder; it is supposed to cause SNHL through attacking the inner ear antigen.

Epilepsy has been reported in small case series and case reports as a rare extraintestinal and neurologic manifestation of inflammatory bowel diseases.^[8,9] It has been suggested that if there was an association of epilepsy and inflammatory bowel diseases, it would preferentially be with Chron's disease, but not with UC.^[8] Epileptic seizures in UC were reported to be secondary to structural or metabolic causes and regarded as a neurologic complication rather than neurologic manifestation of UC itself.^[8,9]

In the presented case, all predisposing factors for epileptic seizures including metabolic factors have been excluded at the time she developed resistant epileptic seizures and status epilepticus. Moreover, the clinical table showed gradual improvement with corticosteroid

treatment. On this context, although not conclusively proved, we suggest that it is possible that both conditions in this patient, namely, sensorineural hearing loss and epileptic seizures, might have a common etiology in dysfunction of the immunologic system.

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Commentary

Inflammatory bowel diseases (IBDs) form a group of chronic remittent inflammatory affections of the gastrointestinal tract, among which ulcerative colitis is one of the most common. The overall IBD prevalence approximates 500-900 cases per 100,000 individuals, and has shown a marked increase during the last decades, mainly in westernized nations.^[1] Ulcerative colitis has traditionally been considered a disorder limited to the colonic mucosa. However, as it has been shown that ulcerative colitis is frequently accompanied by various extraintestinal disorders, there is increasing evidence that ulcerative colitis may also manifest in the nervous system, both in the peripheral and in the central nervous system. The nervous system is affected through three major pathogenic entities, which can be differentiated as: (i) Cerebrovascular disease as a consequence of thrombosis and thromboembolism; patients with ulcerative colitis are at an increased risk for stroke. Postmortem examinations have suggested that venous thrombosis of all sites may complicate ulcerative colitis in 39% of the cases, but only 1% of the patients are clinically affected;^[2,3] (ii) systemic and cerebral vasculitis;^[2] (iii) probably immunemediated neuropathy and cerebral demyelination, which may lead to optic neuritis or multiple sclerosis. The prevalence of general autoimmune disorders in people with ulcerative colitis is three times greater than that in the general population. Acute and chronic inflammatory

neuropathies occur more commonly than expected, and it has been postulated that *Campylobacter jejuni* may exacerbate preexisting IBD.^[2,4]

It has recently been recognized that seizures may develop in patients due to antibodies against cell-surface antigens and synaptic proteins in the brain. Although rare, this diagnosis should be considered in patients who present with seizures and status epilepticus who fail to respond to conventional therapy. Patients with seizures due to autoimmune response would become seizure free or show significant improvement in their neurological status after treatment with steroids, intravenous immunoglobulins or other immunotherapy.^[5] Moreover, the recently proved frequently co-occurrence between epilepsy and 12 autoimmune diseases: Type 1 thyroiditis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, Sjögren syndrome, myasthenia gravis and celiac disease (odds ratio, 3.8; 95% CI, 3.6-4.0; $P < 0.001$), supports that patients with either epilepsy or autoimmune disease should undergo surveillance for the other condition.^[6]

Since McCabe 1979, the autoimmune origin of sudden sensorineural hearing loss is well documented. Such linkage has been confirmed by the good response of the hearing loss to immunosuppressive therapy and detection of several antibodies in the serum of the patients, especially the