Case Report

Limbic Encephalitis following Guillain-Barré Syndrome Associated with *Mycoplasma* Infection

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Keywords

Limbic encephalitis · Guillain-Barré syndrome · *Mycoplasma* · Antibody to NMDA-type GluR · Anti-galactocerebroside antibody

Abstract

A 12-year-old girl was admitted to the authors' hospital due to muscle weakness, gait disturbance, dysarthria, dysphagia, and diplopia. She experienced prodromal fever 10 days before admission. On examination, deep tendon reflex was absent in the extremities, and nerve conduction velocity was decreased in the ulnar nerve. She was diagnosed with Guillain-Barré syndrome (GBS). Despite steroid pulse therapy following administration of intravenous high-dose γ -globulin, clinical manifestations remained unchanged. Therefore, plasma exchange was performed on day 10 of the illness. The titer of serum *Mycoplasma* immunoglobulin M level was increased. Immunological testing was positive for serum anti-galactocerebroside C antibody. On day 18 of the illness, however, she developed generalized convulsion. Brain magnetic resonance imaging revealed high intensity in the medial temporal lobes, including the hippocampus and thalamus on T2-weighted intensity imaging, which was consistent with limbic encephalitis. Further immunological tests revealed positivity for anti-N-methyl-D-aspartate-type glutamate receptor antibody in the cerebrospinal fluid. She was treated with additional plasma exchange; however, she exhibited residual manifestations including short-term memory

disorder, emotional incontinence, and convulsions. This article describes a notable case of limbic encephalitis following GBS associated with prodromal *Mycoplasma* infection. It is interesting that autoimmune encephalopathy is concomitant with autoimmune polyneuropathy subsequent to *Mycoplasma* infection.

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Introduction

Neurological complications associated with *Mycoplasma* infection are variable, and include meningitis, encephalitis, psychosis, cerebellar ataxia, transverse myelitis, myositis, and Guillain-Barré syndrome (GBS) [1]. The pathophysiology of these complications is considered to be the direct invasion of pathogens or autoimmune reactions. Autoimmune reactions subsequent to *Mycoplasma* infection involve several autoantibodies, including anti-galactocerebroside, which is a major glycolipid component in myelin [2, 3] and causes peripheral neuropathy.

On the other hand, an autoimmune etiology of encephalitis has been suspected among acute disseminated encephalomyelitis, multiple sclerosis, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, Rasmussen encephalitis, opsoclonus-myoclonus, and nonherpetic acute limbic encephalitis [4]. Nonherpetic acute limbic encephalitis is a rare autoimmune encephalitis, occasionally associated with antibodies to N-methyl-D-aspartate receptor (NMDAR) [5].

The present article describes a notable case involving a 12-year-old girl who experienced complications with limbic encephalitis following GBS subsequent to *Mycoplasma* infection, in which both serum anti-galactocerebroside C (Gal-C) antibody and cerebrospinal fluid anti-N-methyl-D-aspartate-type glutamate receptor (NMDA-type GluR) antibody were detected.

Case Report

A 12-year-old girl was admitted to the authors' hospital due to bilateral muscle weakness in the upper and lower extremities, gait disturbance, dysarthria, dysphagia, and diplopia. She experienced prodromal infection with fever, cough, headache, and vomiting 10 days before admission. Her state of consciousness was slightly threatening. Physical examination revealed normothermia. Tachycardia with lower heart rate variability suggested an autonomic nerve disorder. She exhibited dysarthria and dysphagia without facial palsy, which was suggestive of bulbar palsy. Her diplopia with disability in vertical eye movement suggested abducens nerve palsy. Manual muscle testing yielded a score of 1 of 5 for strength in the extremities. Neurological examinations revealed absent deep tendon reflex in the biceps muscle of the upper arm, and the patellar and Achilles tendons. She exhibited no obvious sensory disorder.

Complete blood cell count and blood chemistry were within the normal limits. Head computed tomography and cervical magnetic resonance imaging revealed no significant abnormalities. Cerebrospinal fluid examination revealed an elevated protein concentration of 55 mg/dL without pleocytosis. Nerve conduction studies revealed decreased motor nerve conduction velocity in the left ulnar and left median nerves to 24 m/s (normal, >52 m/s) and 28 m/s (normal, >54 m/s), respectively. The sizes of the compound muscle action potential of the left median nerve were 1.40 mV at the wrist and 0.74 mV at the elbow; the F wave of both nerves was not evoked (Fig. 1). Sensory nerve conduction velocity was normal in both nerves. These findings suggested demyelinating neuropathy. Serum passive hemagglutination titer to

Mycoplasma was 1:1,280, suggesting previous *Mycoplasma* infection. Further testing for anti-glycolipid antibodies were performed using an enzyme-linked immunosorbent assay (ELISA). The titer of anti-Gal-C immunoglobulin (Ig) G, which was expressed as an index value calculated as the ratio of the mean optical density (OD) of a test sample divided by the mean OD of a positive control, was 0.625 (positive if >0.4). Other anti-glycolipid antibodies were negative. She was diagnosed with GBS following *Mycoplasma* infection.

Despite immediate treatment, which consisted of intravenous administration of γ -globulin (1 g/kg) for 2 days, respiratory muscle paralysis critically worsened after admission. Respiratory support was started under administration of midazolam the day after admission. Additionally, she was treated with methylprednisolone (30 mg/kg/day) for 3 days. It was not possible to evaluate clinical manifestations, such as muscle weakness, diplopia and dysarthria, because of deep sedation. Because absent spontaneous breathing and deep tendon reflex persisted, plasma exchange was performed from day 10 of the illness for 3 subsequent days. Following these intensive treatments, clinical manifestations gradually improved, and respiratory support was discontinued on day 16 of the illness.

However, she developed generalized convulsion on day 18 of illness. Electroencephalogram displayed diffuse high amplitude with slow waves. Brain magnetic resonance imaging on day 22 of the illness revealed high-intensity lesions in the bilateral thalamus and medial temporal lobes on T2-weighted intensity and diffusion imaging (Fig. 2). These findings were consistent with limbic encephalitis. Neither obvious recurrent clinical manifestation related to GBS nor recurrent epilepsy were observed; therefore, further treatment was unnecessary. However, she developed short-term memory disorder, emotional incontinence, and sleep disturbance at discharge. Two months after discharge, she was re-admitted due to status epilepticus following eccentric vocabulary and behavior. Electroencephalogram and brain magnetic resonance imaging each revealed similar findings on day 22 of the previous admission. According to the established relationship between limbic encephalitis and anti-NMDAR antibody, further immunological evaluation of antibodies to type GluR was performed using ELISA. The titers of anti-GluN1, anti-GluN2B, and anti-GluN2D in the cerebrospinal fluid, expressed as OD, were 0.952 (reference range of disease control [rr], 0.325 ± 0.122), 0.704 (rr, 0.260 ± 0.097), and 0.913 (rr, 0.409 ± 0.107), respectively. Herpes simplex virus DNA was not detected in the cerebrospinal fluid by polymerase chain reaction testing. These findings also supported the diagnosis of nonherpetic acute limbic encephalitis. Ultrasound examination revealed no ovarian teratoma. After additional plasma exchange for 3 days, she was discharged with oral administration of valproic acid. However, she experienced short-term memory disorder, learning disorder, change in character, and recurrent convulsions in the outpatient clinic.

Discussion

We described a notable case involving a 12-year-old girl who developed limbic encephalitis following severe GBS. She developed recurrent convulsion and psychiatric disorder, which persisted over several months. The serological examination suggested a previous *Mycoplasma* infection, which may have led to both GBS and limbic encephalitis associated with both anti-Gal-C and antibodies to NMDA-type GluR.

Limbic encephalitis is characterized as autoimmune encephalitis occasionally associated with anti-NMDAR antibody [6]. Clinical manifestations of limbic encephalitis are nonspecific; however, psychiatric disturbances and schizophrenia-like symptoms are common [7]. It is

recognized as paraneoplastic syndrome and is highly associated with ovarian teratoma or lung cancer. However, younger patients with limbic encephalitis appear to be unrelated to paraneoplastic syndrome because only 20% of patients with anti-NMDAR encephalitis exhibit ovarian teratomas [8]. Gable et al. [7] reported that 50% of patients with anti-NMDAR encephalitis, in whom no ovarian tumor is detected, have positive *Mycoplasma* IgM serologies. These findings indicate that prodromal *Mycoplasma* infection causes an autoimmune response leading to limbic encephalitis especially in young children. In the present case, we speculate that limbic encephalitis was the consequence of an autoimmune reaction associated with *Mycoplasma* infection.

It is interesting that both anti-Gal-C antibody and antibodies to NMDA-type GluR were detected in our patient. Tojo et al. [9] previously described a similar case involving a 19-year-old man who developed anti-NMDAR-related limbic encephalitis following GBS. However, they were unable to detect anti-galactocerebroside antibodies in the serum and cerebrospinal fluid. Gal-C is one of major components of myelin in the peripheral and central nervous systems [10, 11]. Anti-Gal-C antibody is a well-known autoantibody subsequent to *Mycoplasma* infection [2, 12] and cross-reacts with *Mycoplasma* antigen, which elicits autoimmune demyelination and degeneration of myelinated cells, not only in the peripheral nervous system, but also in brain cells. There are several reports of acute disseminated encephalomyelitis and encephalitis with elevation of serum anti-Gal-C antibody subsequent to *Mycoplasma* infection [3, 11]. These findings suggest that anti-Gal-C antibody may cause an autoimmune reaction to brain cells mimicking the limbic encephalitis observed in the present case.

We described a notable case involving a patient with limbic encephalitis following severe GBS subsequent to *Mycoplasma* infection. It is notable that both anti-Gal-C and antibodies to NMDA-type GluR, which are related to autoimmune polyneuropathy and encephalopathy subsequent to *Mycoplasma* infection, were detected. Although the precise pathophysiology in the present case is unclear, it is interesting that autoimmune encephalopathy was concomitant with autoimmune polyneuropathy subsequent to *Mycoplasma* infection.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Fig. 1. The motor nerve conduction velocity in the left ulnar and median nerves was reduced to 24 and 28 m/s, respectively. The sizes of the compound muscle action potential of the left median nerve were 1.40 mV at the wrist and 0.74 mV at the elbow; the F wave of both nerves was not evoked.

Fig. 2. Brain magnetic resonance image on day 22 of the illness. Fluid-attenuated inversion recovery intensity (left) and diffusion-weighted (right) images reveal high-intensity lesions in the bilateral thalamus and medial temporal lobes.