A case report of overlapping Bickerstaff brainstem encephalitis and Guillain-Barre syndrome

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Abstract

We report a case of a 23-year-old man diagnosed with overlapping Bickerstaff brainstem encephalitis (BBE) and Guillain-Barre syndrome (GBS). The patient initially presented with fever and headache and gradually developed ataxia, disturbance of consciousness, respiratory muscle paralysis, bilateral facial paralysis and quadriplegia accompanied by significant atrophy of limb, temporalis and masseter muscles. Brain MRI revealed abnormality in the left basal ganglia, thalamus, and rightside posterior limb of the internal capsule. Electromyogram indicated neurogenic damage (mainly axonal damage) in the upper and lower limbs and bilateral facial nerve damage. Cerebrospinal fluid (CSF) collected via lumbar puncture was colorless and transparent with a pressure of 330 mm H_2O. The white blood cell count in CSF was 200×10^6/L, the protein concentration was 1.25 g/L, and Pandy's reaction was positive. Both the blood and CSF were negative for GQ1b antibody. The patient was clinically diagnosed with overlapping BBE and GBS. After treatment with ventilatorassisted breathing, hormone therapy, neurotrophic and anti-infection therapies, and symptomatic and supportive care for more than three months, spontaneous breathing was restored. By the 5-month follow-up examination, the patient had completely recovered and returned to work. Like GBS and Fisher syndrome, BBE might be an anti-GQlb IgG antibody syndrome. Although the serum GQlb IgG antibody-positive rate for BBE is only 66%, a normal brainstem MRI or GQlb lgG antibody-negative finding cannot completely rule out BBE. Therefore, identifying critical illness polyneuropathy for patients with respiratory muscle paralysis and tracheal extubation difficulties at early stages is clinically important.

CASE REPORT

INTRODUCTION

Bickerstaff brainstem encephalitis (BBE) is a rare clinical syndrome characterized by acute onset of ophthalmoplegia, ataxia, disturbance of consciousness, tendon hyperreflexia or pathological reflex. Despite severe initial symptoms, BBE usually has a good prognosis. Guillain-Barre syndrome (GBS) is a type of peripheral neuropathy with symmetrical flaccid paralysis of the limbs as its major clinical manifestation. It has been suggested that BBE and GBS may share common mechanisms of pathogenesis and exist along a spectrum of anti-GQ1b IgG antibody syndrome forms (Odaka *et*

al. 2001). Co-existence of the two syndromes results in ophthalmoplegia, ataxia, disturbance of consciousness, tendon hyperreflexia, and pathological reflexes and can lead to respiratory muscle paralysis. When critically ill patients present with general muscle weakness, loss of reflexes, and difficulty being weaned off a ventilator, it is important to check for critical illness polyneuropathy (CIP), an acute and primary axonal motor and sensory neuropathy that is caused by long-term immobilization (Hermans *et al*. 2009; Winer 2001). Here we report the case of a patient at our hospital who was diagnosed with overlapping BBE and GBS.

CASE REPORT

The patient was a 23-year-old male soldier. He had a high fever and an aggravating headache for 8 days before hospitalization, accompanied by nausea and vomiting. The cause of his fever (as high as 42 °C) and headache was not obvious. The patient had received anti-inflammatory and antipyretic treatment at his local hospital 2 days before being hospitalized, although the details of that treatment were not known. Regardless, the treatment did not significantly relieve his symptoms. The patient was sent to the emergency department of the Second Hospital of Jilin University due to the appearance of apathy and ataxia, and an inability to speak for 6 hours. At the university hospital, he was diagnosed with pneumonia based on the results of a routine blood test and lung CT scan. The patient was given traditional Chinese medicine and aspirin (doses unknown) in an attempt to alleviate his symptoms, but his symptoms persisted and he was referred to our hospital.

Examinations at admission to our hospital showed a blood pressure of 137/86 mmHg, body temperature of 37.0 °C, and blood oxygen saturation level of 88%. The patient was hazy with poor body examination. His pupils were bilaterally round, equal in size with a diameter of about 2.5 mm, and sensitive to light. The patient responded to pain and retracted his limbs away from a painful stimulus. He had hyper-tense muscles, a stiff neck, and Kernig's sign was evident, though mild. He also showed a clearly positive Babinski sign on the right side and a weakly positive Babinski sign on his left side. The patient's condition deteriorated rapidly 5 hours after hospitalization: he experienced difficulty breathing and lip cyanosis; and his blood oxygen saturation level dropped to 70%. The patient was immediately given tracheal intubation surgery and ventilator-assisted breathing was initiated, supplemented with antiviral, anti-inflammatory, immunomodulatory, and dehydration treatments, with intracranial pressure-reducing therapies and symptomatic and supportive treatment.

After 20 days of medication, consciousness was restored but the ventilator could not be removed. The patient received a tracheotomy and continued to receive mechanical ventilation. Physical examinations at this time showed a heart rate of 128 beats/min, blood pressure of 126/80 mmHg, blood oxygen saturation of 98%, improved lung auscultation breath sounds, and restored consciousness. The patient's pupils were bilaterally round, equal in size with a diameter of about 2.5 mm, and sensitive to light. Eyelid closure was incomplete. He could move his left thumb and index finger. He was able to flex his right arm, but could not move his right leg. He could achieve horizontal flexion with his left leg. He

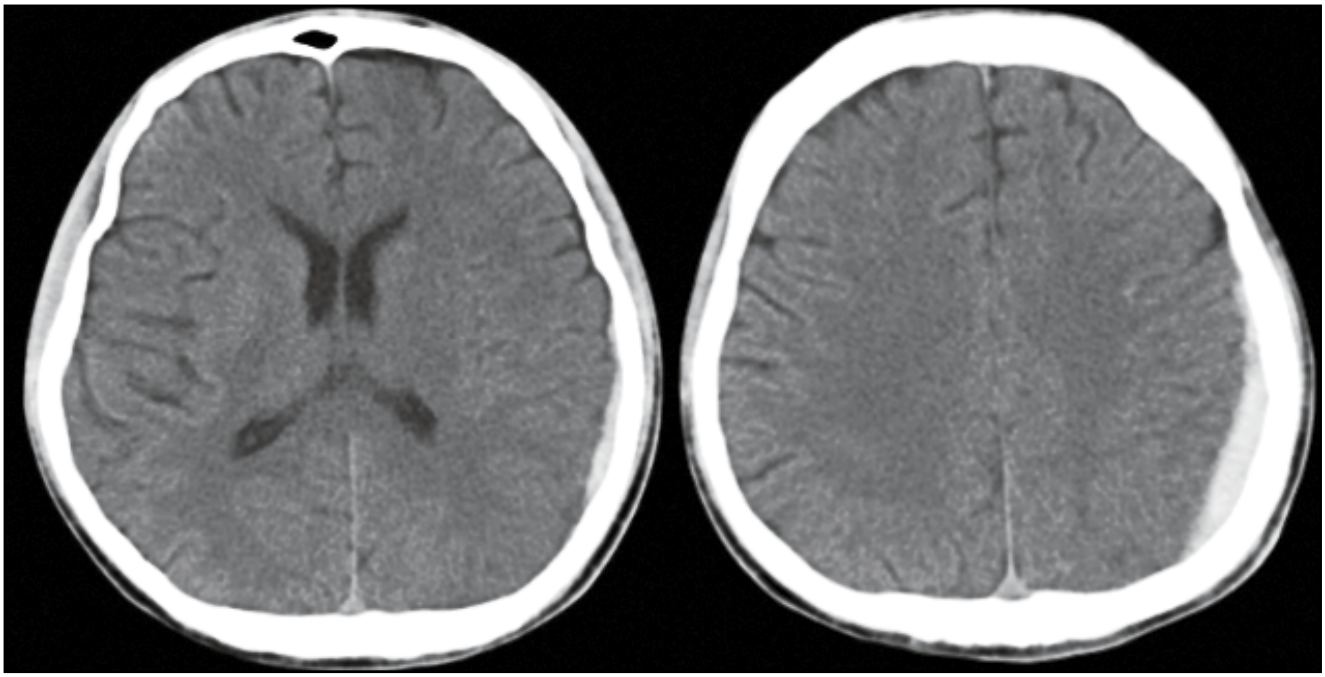

Fig. 1. Head CT scan on August 11, 2011. Arcuate high density was seen in the left frontotemporal and parietal surface areas.

had low muscle tone and weak tendon reflexes in his left arm. The rest of the body had normal muscle tone and tendon reflexes. Bilateral Babinski signs were positive, but tests on the rest of the nervous system could not be performed.

A head CT scan on August 5, 2011 showed no obvious abnormality, but a subsequent head CT scan on August 11, 2011 showed a left frontotemporal and parietal subdural hematoma (Figure 1). And a head CT on August 15, 2011 showed a left frontotemporal and parietal subdural hematoma and effusion. A head MRI on August 25, 2011 showed patchy abnormal signals in the left basal ganglia. T1-weighted imaging (T1WI) showed intermediate signal intensity, T2-weighted imaging (T2WI) showed high signal intensity, and Flair MRI showed high signal intensity. These observations suggested a left temporal subdural hematoma (Figure 2). A head MRI on September 5, 2011 (Figure 3) showed bilateral basal ganglia lesions. T1WI showed slight, low-to-intermediate signal intensity, T2WI showed high signal intensity, water- and fat-suppressed imaging showed high signal intensity, diffusion-weighted imaging (DWI) showed slightly high signal intensity in the left basal ganglia, thalamus, and right-side posterior limb of the internal capsule (PLIC), and left temporal subdural hematoma was suggested. A head MRI on October 29, 2011 (Figure 4) showed complete disappearance of the original lesions, but suspicious abnormalities in the right midbrain. A lung multidetector CT scan revealed scattered inflammation in the right upper lobe and left lower lobe.

Electromyography (EMG) and nerve conduction velocity tests on September 5, 2011 showed that the measured motor and sensory conduction velocities of

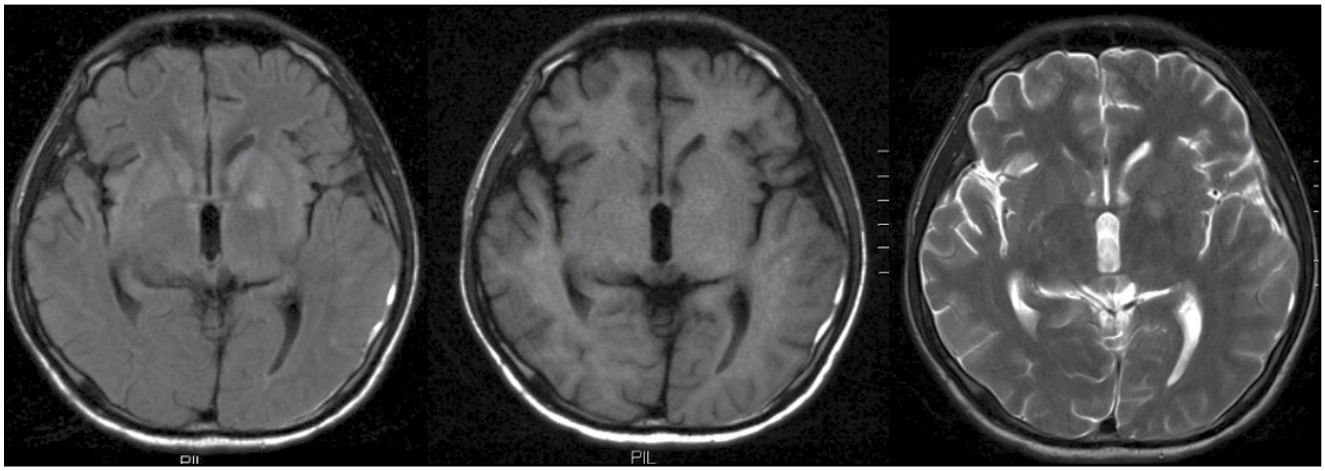

Fig. 2. Head MRI on August 25, 2011. Patchy abnormal signals were seen in the left basal ganglia. T1WI showed intermediate signal intensity, T2WI showed high signal intensity, water- and fat-suppressed imaging showed high signal intensity. This suggested left basal ganglia lesions and left temporal subdural hematoma.

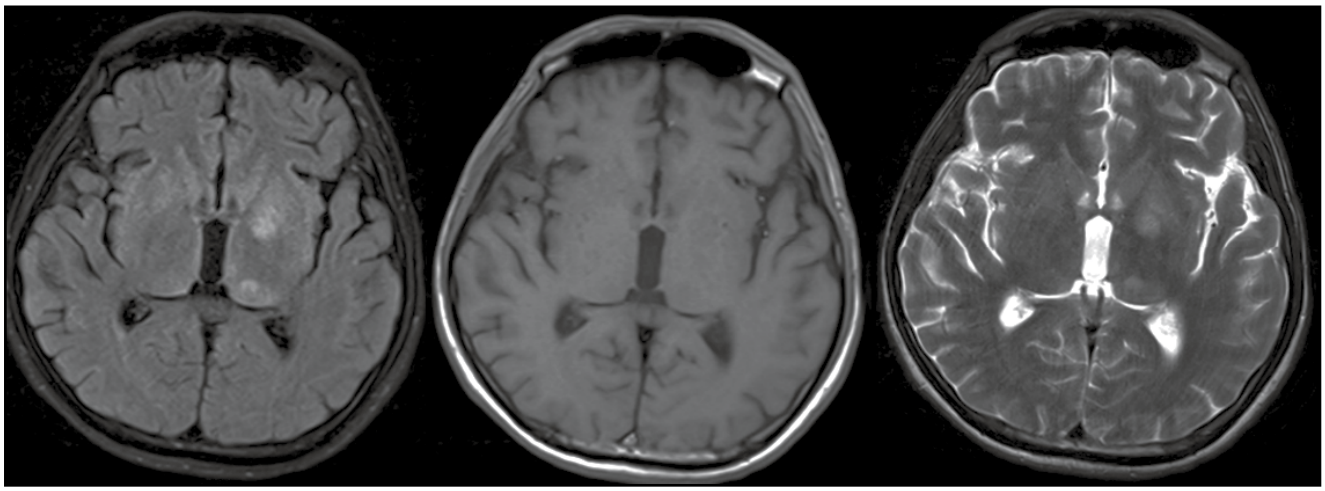

Fig. 3. Head MRI on September 5, 2011. Patchy abnormal signals were seen in the left basal ganglia. T1WI showed faint, low-to-intermediate signal, T2WI showed high signal intensity, water- and fat-suppressed imaging showed high signal intensity, and DWI showed faint high signal intensity in left basal ganglia, thalamus, and right-side PLIC. Abnormal arcuate short T1 and long T2 signals were visible under the left temporal region and fat-suppressed imaging showed high signal intensity. Bilateral basal ganglia lesions were more visible than on imaging on August 25, 2011. A left temporal subdural hematoma was seen.

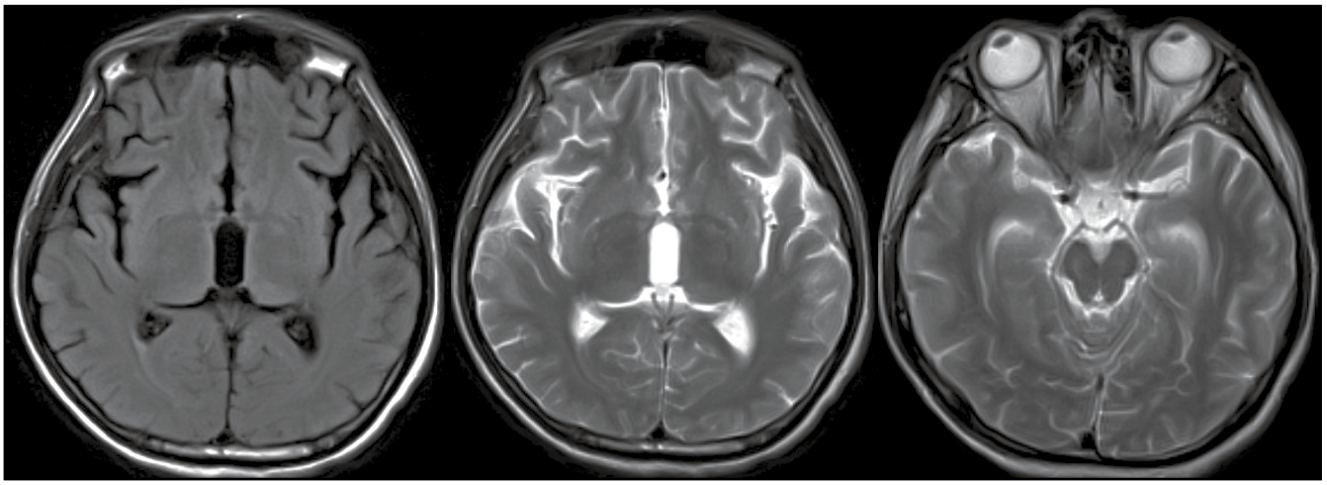

Fig. 4. Head MRI on October 29, 2011. Sulci and sylvian cisterns were slightly widened. Original lesions disappeared completely, but suspicious abnormalities appeared in the right midbrain.

the upper and lower limb nerves were generally normal. The F-wave latency of the right median nerve and ulnar nerve was slightly increased and EMG revealed a large number of spontaneous potential in the upper and lower limb muscles. The time interval of motor unit potential was approximately normal, and motor unit recruitment showed an inability to contract. There was considerable neurogenic damage (mainly axonal) in the upper and lower limbs. A facial nerve test on September 9, 2011 showed that bilateral facial nerve CMAP amplitude decreased, the bilateral blink reflex R2 latency slightly increased, and the amplitude decreased, suggesting bilateral facial nerve damage.

Electroencephalography (EEG) on September 13, 2011 showed significantly reduced background rhythm in the occipital region, with more irregular 4–7 Hz θ waves sporadically in the frontal, occipital, parietal and temporal regions. Cerebrospinal fluid (CSF) examination by lumbar puncture on August 6, 2011 showed colorless, transparent CSF with a pressure of 330 mm H_2O. Routine biochemical tests showed a protein concentration of 1.25 g/L, positive Pandy's reaction, WBC was 200×10^6 /L with 60% lymphocytes, 20% neutrophils and 10% monocytes. CSF examination on September 5, 2011 showed colorless, transparent CSF with 130 mm H_2O pressure. Protein concentration was 0.89 g/L, Pandy's reaction was positive, CSF IgG was 92.40 mg/L and all other parameters were normal. CSF examination on September 13, 2011 showed CSF pressure reduced to 110 mm H_2O. Protein concentration was 0.8 g/L, Pandy's reaction was positive, and all other parameters were normal. Blood and CSF were negative for GQ1b antibody (tested in Beijing Union Medical College Hospital). The patient was given hormone therapy, neurotrophic and anti-infection therapies, and symptomatic and supportive care after hospitalization.

After 50 days of treatment, weaning from the ventilator began and the patient eventually had fully restored spontaneous breathing, 3.5 months after disease onset. The patient's muscle strength also recovered gradually over the course of treatment. Four months after onset, limb muscle strength reached Class IV and the patient was discharged from the hospital.

DISCUSSION

In 1951 Bickerstaff and Cloake reported three cases with clinical manifestations that included drowsiness, ophthalmoplegia and ataxia. The patients were subsequently diagnosed with mesenrhombencephalitis, with midbrain lesions proposed to be responsible for the symptoms. Bickerstaff reported five additional, similar cases in 1957, with patients with increased CSF cell counts. The disease was named as Bickerstaff brainstem encephalitis.

BBE is a brainstem disease of unknown etiology. It is proposed to be an autoimmune disease mediated by anti-GQ1b IgG antibody. Anti-GQlb antibody in the serum blocks acetylcholine release from motor nerve terminals. This is cytoxic to neurons and inhibits the outward growth of axons. Studies have demonstrated that patients with BBE, Fisher syndrome or GBS have the same IgG autoantibodies against GQ1b and the three syndromes might belong to the same disease spectrum. Therefore, the three diseases should be called the anti-GQlb IgG antibody syndrome to reflect the etiological relationship among these illnesses.

GQ1b antibody syndrome encompasses a group of clinical syndromes characterized by ophthalmoplegia, ataxia, disturbance of consciousness, tendon hyperreflexia, and/or pathological reflex, that have a good prognosis in most cases. The diagnostic criteria for overlapping BBE and GBS are (Susuki *et al.* 2003): (1) progressive symmetric ophthalmoplegia and ataxia in 4 weeks; (2) disturbance of consciousness or pyramidal signs; and (3) limb muscle strength Class V, limb

weakness lower than Class III, EMG showing peripheral nerve damage especially axonal damage. A patient meeting the above criteria should be diagnosed with overlapping GBS and BBE. The limb weakness symptom in BBE is considered to overlap with the motor axonal of GBS. The following diseases should be excluded: brainstem vascular disease, Wernicke encephalopathy, myasthenia gravis, acute disseminated encephalomyelitis, multiple sclerosis, Neuro-Behçet's disease and vasculitis. Of note, the positive rate for serum GQlb IgG antibody in BBE is only 66%. About one-third of BBE patients show abnormal damage in head MRI scans, such as high T2WI signal intensity in the brainstem, thalamus, cerebellum and cerebral cortex. However, some patients appear normal(Mondejar *et al.* 2002). Therefore, normal brainstem MRI or a negative result for anti-GQlb lgG cannot completely rule out a diagnosis of BBE(Winer 2001). All patients have a single-phase disease course. Although patients with overlapping BBE and GBS show disturbance of consciousness and severe nerve damage, the prognosis is usually good, and 51% of patients fully recover after 6 months. Treatment is not specific. However, combined hormone and intravenous immunoglobulin therapy has relatively good therapeutic effect.

The patient in our study clearly had a previous infection. He presented with fever and headache as initial symptoms and gradually developed ataxia, disturbance of consciousness, respiratory muscle paralysis, bilateral facial paralysis and quadriplegia. In addition, he had significant atrophy of the limb, temporalis and masseter muscles. Brain MRI revealed an abnormality in the left basal ganglia, thalamus, and right-side PLIC. EEG showed diffused slow wave activity or low volatility of θ-wave activity accompanied by altered consciousness. These signs were consistent with previous reports in the literature, and might result from damage to the upper reticular structure in the midbrain and pontine. EMG indicated facial and limb nerve damage, especially peripheral nerve damage from the overlapping axonal GBS. Although the patient was negative for GQlb IgG antibody, the clinical diagnosis was still considered to be overlapping BBE and GBS. Attempts to remove the ventilator after 50 days of hospitalization failed, with the patient experiencing extubation difficulties. The ventilator was removed more than 3 months later. BBE must be distinguished definitively from CIP. CIP often coexists with critical illness myopathy, especially in patients with severe sepsis, multiple organ failure, high blood sugar, or other conditions. The incidence of CIP and critical illness myopathy is 25% to 50%. The patient in this study had a history of brain and peripheral nerve diseases. He was infected before the onset of overlapping BBE and GBS but the infection did not progress to sepsis. In addition, the premorbid presence of ataxia was unique. This case indicated that overlapping BBE and GBS should be considered in patients with brainstem symptoms and peripheral nerve damage. Despite severe clinical manifestations at onset, most BBE patients have a good prognosis, and patients and their families should be encouraged to actively participate in treatment.

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