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Case report: stroke-like onset of Bickerstaff brainstem encephalitis with Guillain–Barré syndrome

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Case Report

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Abstract

Introduction: Bickerstaff brainstem encephalitis is a rare immune-mediated disease characterized by ophthalmoplegia, ataxia, and disturbance of consciousness; it may overlap with Guillain–Barré syndrome if there is additional limb weakness[1]. These two diseases are considered to form a continuous clinical spectrum of the same disease, and may affect the peripheral and/or central nervous systems. They have monophasic symptoms and overlapping clinical signs, and their risk of recurrence is independent and very low[2].

Case Report: This paper describes a 79-year-old man with acute dysphagia and slurred speech; his symptoms rapidly progressed to include disturbance of consciousness and the progression of lower limb paralysis. The initial diagnosis was acute cerebral infarction; however, no new cerebral infarction lesions were identified in a series of brain magnetic resonance imaging examinations. Combined with the symptoms that appeared during hospitalization, the diagnosis was considered to be overlapping Bickerstaff brainstem encephalitis and Guillain–Barré syndrome. The patient's symptoms improved after receiving treatment that included intravenous methylprednisolone.

Conclusion: This case report expands the clinical scope of this disease and provides additional directions and decision-making strategies for cases that begin with acute stroke but are not supported by imaging.

INTRODUCTION

CASE REPORT

On November 16, 2021, a 79-year-old man was admitted to the Department of Neurology of the Second Affiliated Hospital of Kunming Medical University because of dysphagia and slurred speech for 41 hours. On November 14, without any obvious inducement, the patient had suddenly developed slurred speech, dysphagia, dizziness, blurred vision, and unstable standing at around 4:00 p.m. Family members said that he had clear consciousness at that time, without confusion or lethargy. The symptoms gradually became aggravated and drowsiness appeared. On November 15, he presented to the emergency department of our hospital and underwent brain computed tomography (CT), which showed multiple lacunar cerebral infarctions in the bilateral basal ganglia and corona radiata. The patient had been ill for fewer than 48 hours before the CT examination; however, the CT examination did not show changes corresponding to acute cerebral infarction. Considering the patient's history and manifestations, he was considered to have acute cerebral infarction and was admitted to the Department of Neurology on November 16. He had previous chronic obstructive pulmonary disease for more than 10 years, prostate cancer for more than 3 years, and a history of cerebral infarction for more than 3 years without any sequelae. Before the disease, there was no history of infection (such as cold, fever, abdominal pain, or diarrhea) or vaccinations. Physical examination on admission revealed stable vital signs, drowsiness, dysarthria, ptosis of the right eye, restricted closure, shallow right frontal crease, shallow right nasolabial

groove, inability to show teeth, right tongue extension, hanging the valgus was deviated to the right, lower position of the right soft palate, swallowing dysfunction, slow bilateral gag reflexes, choking when drinking water, unstable right finger–nose test, and inaccurate right heel–knee–shin movement.

On admission, the diagnosis was considered to be brainstem infarction; symptomatic and supportive treatment was given (dual antiplatelet, lipid-lowering, plaque stabilization, and circulation improvement). The patient's symptoms on admission did not improve on day 2 of admission, and the right upper limb shook. On day 3 of admission, the patient complained that his body shook more than before; both his right and left upper limbs shook. He also had weak lower limbs and was unable to walk. A neurological examination revealed drowsiness, dysarthria, restricted right eye closure, shallow right frontal lines, shallow right nasolabial groove, inability to show teeth, right-deviated tongue, right-deviated uvula, lower position of the right soft palate, impaired swallowing function, and slow bilateral gag reflexes. Muscle strength was grade 3 and tendon reflexes were weakened; pathological signs on both sides were negative. The finger–nose test on the right side was unstable. At the same time, relevant auxiliary examination results came back. The blood routine, blood biochemistry, electrolytes, myocardial injury markers, coagulation mechanism, serum HIV antibodies, syphilis serological, and C-reactive protein examinations showed no significant abnormalities. Serum tumor markers showed increased prostate-specific antigen (the patient had a previous history of prostate cancer). Transthoracic echocardiography revealed an increased left atrial diameter and left ventricular diastolic dysfunction. There were no obvious abnormalities in head susceptibility-weighted imaging; however, intracranial arterial angiography showed manifestations of intracranial cerebral arteriosclerosis. Cranial plain scan and magnetic resonance diffusion-weighted imaging showed white matter hyperintensities in the bilateral frontal, parietal, and temporal lobes; external capsule; and periventricular area (Fazekas grade 2) and a right basal ganglia lacunar infarction. Lumbar puncture results were as follows: pressure 190 mmH_2O; clear; cells (-); glucose 3.2 mmol/L; protein 1.6 g/L (+); chloride 123.5 mmol/L; elevated immunoglobulin IgA, IgM, and IgG; herpes virus, rubella virus, and cytomegalovirus antibodies all (-), cerebrospinal fluid smear G-diplococcus, ink staining, and acid-fast staining all (-); and bacterial culture aseptic growth (Table 1). An electroencephalogram examination showed no abnormalities. Facial muscle and limb electromyography and brainstem auditory evoked potential examinations showed the following. 1) Left and right blink: the latency of left and right stimulation of R1, R2, and R2 were significantly prolonged, indicating demyelination and multiple peripheral nerve damage. 2) Left and right facial nerve conduction studies: the compound muscle action potential amplitude of the right facial nerve was lower than that of the left. 3) Demyelination and multiple peripheral nerve damage of the extremities (both sensory and motor fibers were involved). 4) Left and right brainstem auditory evoked potential: left central damage but the right side was generally normal. After a comprehensive analysis of the patient's condition changes and auxiliary examination results, it was considered that the diagnosis was not brainstem infarction, but instead a case of Bickerstaff brainstem encephalitis (BBE) with acute stroke onset and overlapping Guillain–Barré syndrome (GBS). The treatment plan was therefore changed to an antiviral, a high-dose glucocorticoid pulse (intravenous injection of 1000 mg methylprednisolone hyaluronate, halved every 3 days), and other symptomatic and supportive treatments. On December 2, the patient

underwent a re-examination of lumbar puncture, with the following results: pressure 155 mmH2O; cells (-); glucose 4.0 mmol/L; protein 0.9 mmol/L; chloride 118.4 mmol/L; the IgA, IgM, and IgG indexes were markedly lower than before; and all other indexes were (-) (Table 1). The patient spent 20 days in hospital. At discharge, the patient was conscious, had fluent speech and a slightly shallow right frontal crease and nasolabial groove, and his swallowing function had returned to normal. The muscle strength of the left lower extremity was grade 4 + and that of the right lower extremity was grade 4, tendon reflexes were slightly weak(Table 2), and bilateral pathological signs were negative. The lateral finger–nose test remained unstable and inaccurate. On February 15, 2022, the patient returned to the hospital for a follow-up visit, and there were no positive signs of the nervous system in the physical examination (Table 2). Peripheral nerve damage without demyelination.

DISCUSSION

In 1951, Bickerstaff and Cloake first reported three cases of somnolence and ophthalmoplegia and 39 cases of ataxia, and suggested that these symptoms may be caused by midbrain damage[3,4].Six years later, Bickerstaff reported five similar cases and named the disease BBE[5]. BBE is a rare brainstem disorder that is characterized by acute ophthalmoplegia, ataxia, and altered consciousness[6]. The exact pathophysiology of the disease is unknown, but it affects both the brainstem and peripheral nervous system. Because of a lack of specific clinical criteria and biomarkers, the prevalence of BBE may be underestimated; few clinical studies have reported on large numbers of patients with BBE[7].

The etiology and pathogenesis of BBE have not yet been clarified; there are currently two main viewpoints. The first theory involves viral or bacterial infection because most patients have a history of precursor infections such as influenza, herpes simplex virus, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, Campylobacter jejuni, Listeria monocytogenes, or mycoplasma, although only a small number of BBE cases can clarify their etiology. The second theory involves a molecular mimicry mechanism between microbial antigens and the host[8]. In our case, the cerebrospinal fluid of the patient was negative for viruses (herpes simplex virus types I and II, cytomegalovirus, and rubella virus) and bacteria. Rubella virus and herpes simplex virus type I IgG antibodies in the serum were positive; however, IgG positive indicates past infection. Furthermore, the infection titer was low, which cannot provide a useful basis for the disease, so no organisms were isolated from the patient. Serum anti-GQ1b is reportedly positive in BBE patients, and new research indicates that BBE is related to GM1b and GalNAc-GD1a IgM antibodies[7]; it has also been called GQ1b IgG antibody syndrome. Unfortunately, the patient did not undergo ganglion ester antibody profiling; however, not all BBE patients are positive for anti-GQ1B antibody. It has been reported that the positive rate of serum GQ1b IgG antibody is 70% in BBE patients compared with 83% in patients with Miller Fisher syndrome[9] Antibody detection is therefore not a reliable standard for the diagnosis of BBE. In our case, the patient had symptoms of brainstem involvement, his neurophysiological conduction suggested demyelination and multiple peripheral nerve lesions, and his cerebrospinal fluid showed protein cellular dissociation. These clinical features of the patient are consistent with BBE with GBS (Table 3).

BBE, GBS, and Miller Fisher syndrome form a series of post-infectious demyelinating diseases; BBE and GBS have overlapping manifestations in patients with lower extremity weakness and typical BBE signs. It has been suggested that the central and peripheral nervous systems are involved in combination[10]. When treated, BBE generally has a self-limiting disease course; this may be related to the binding of autoantibodies and site-specific antigens, thus resulting in functional inhibition without direct damage to nerve tissue. At present, no prospective, randomized, controlled large sample study of BBE treatments has been conducted; its treatment experience mainly comes from GBS and MFS[2,8,11], as follows. 1) Immunoglobulin therapy: high-dose, short-course intravenous drip therapy is effective and should be implemented as soon as possible. 2) Hormone therapy: widely used but remains controversial; for patients with financial difficulties, hormones are the first choice for treatment. 3) Plasma exchange therapy: can quickly remove immunoreactive substances such as antibodies from the body, shorten the course of treatment, and reduce the degree of disease; however, it lacks the support of randomized clinical trials and treatment cost is high. 4) Immunosuppressants: for patients with poor hormone effects, some scholars advocate the use of cyclophosphamide; however, its cytotoxicity means that it is generally not the first choice. 5) Other therapies: promising new treatment options include the anti-complement monoclonal antibody eculizumab (anti-C5) for GBS and rituximab (anti-CD20) for anti-myelin-associated glycoprotein neuropathy; there are currently no recommendations for new treatments for BBE. In addition, endotracheal intubation, ventilator-assisted ventilation, and symptomatic support treatment are possible. Recurrent GBS occurs in < 10% of patients; subsequent episodes appear to become more severe and occur at shorter intervals.

Our patient was an elderly man with a history of cerebral infarction. After improvement, he did not regularly use secondary prevention drugs for cerebral infarction. The present onset was in the form of acute stroke with drowsiness, right peripheral facial nerve damage, right cerebellar ataxia, and medulla oblongata dysfunction as prominent manifestations. He had no history of a cold, fever, diarrhea, or vaccination before the illness, and no new cerebral infarction in head MRI. The current diagnostic criteria of BBE states that acute-onset ophthalmoplegia, ataxia, and consciousness disturbance can be diagnosed as BBE. During the disease course, the patient developed lower extremity flaccid paralysis, muscle strength grade 3, decreased tendon reflexes, cerebrospinal fluid protein cell separation, and electromyography neurogenic damage. The clinical manifestations were consistent with BBE combined with the diagnostic criteria for GBS (ophthalmoplegia, disturbance of consciousness or pyramidal tract signs, and muscle strength ≤ grade 3); thus, the final diagnosis was BBE with GBS.

Conclusion

BBE is a rare brainstem disease, and overlapping GBS is also rare. The clinical manifestations are diverse, the etiology and pathogenesis are unclear, and clinical diagnosis is difficult. This case had a stroke-like origin of BBE combined with GBS. It is hoped that this case report will provide a reference for the future clinical diagnosis of this type of disease. The present case expands the clinical scope of this

disease and provides information that will aid in diagnostic and treatment decisions for cases with onset in the form of acute stroke without imaging support.

Declarations

Consent to Publish

Written informed consent was obtained from the patient's legally authorized representative for publication of this case report and the accompanying images.

Funding Declaration

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Author Contribution

Y.L. collected and organized the clinical data, reviewed the literature, and drafted the manuscript. C. Liu contributed to clinical data interpretation and manuscript revision. J.Z. and J.R. assisted with data collection, literature review, and preparation of the tables. M.W. contributed to diagnostic interpretation and critically revised the manuscript. C. Li supervised the preparation of the case report and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Tables

Table 1
Comparison of cerebrospinal fluid results of two times during hospitalization

project	The results of	
	November 17, 2021	**December 2, 2021**
Brain pressure	190mmH2O	155mmH2O
White blood cells	9*10^6/L	6*10^6/L
Nucleated cells	9*10^6/L	6*10^6/L
Absolute value of mononuclear cells	7*10^6/L	5*10^6/L
Absolute value of multiple nuclear cells	2*10^6/L	1*10^6/L
Absolute value of mesenchymal cells	0*10^6/L	0*10^6/L
Percentage of mononuclear cells	77.80%	83.30%
Percentage of multiple nuclear cells	22.20%	16.70%
protein	1.60g/L ↑	0.90g/L ↑
glucose	3.20mmol/L	4.00mmol/L
chlorine	123.50mmol/L	118.40mmol/L
IgG	201.00mg/L ↑	73.40mg/L ↑
IgA	34.20mg/L ↑	9.94mg/L ↑
IgM	14.50mg/L ↑	3.93mg/L ↑
General bacterial smear	-	-
Smear for acid-fast bacilli	-	-
Smear for G- diplococcus	-	-

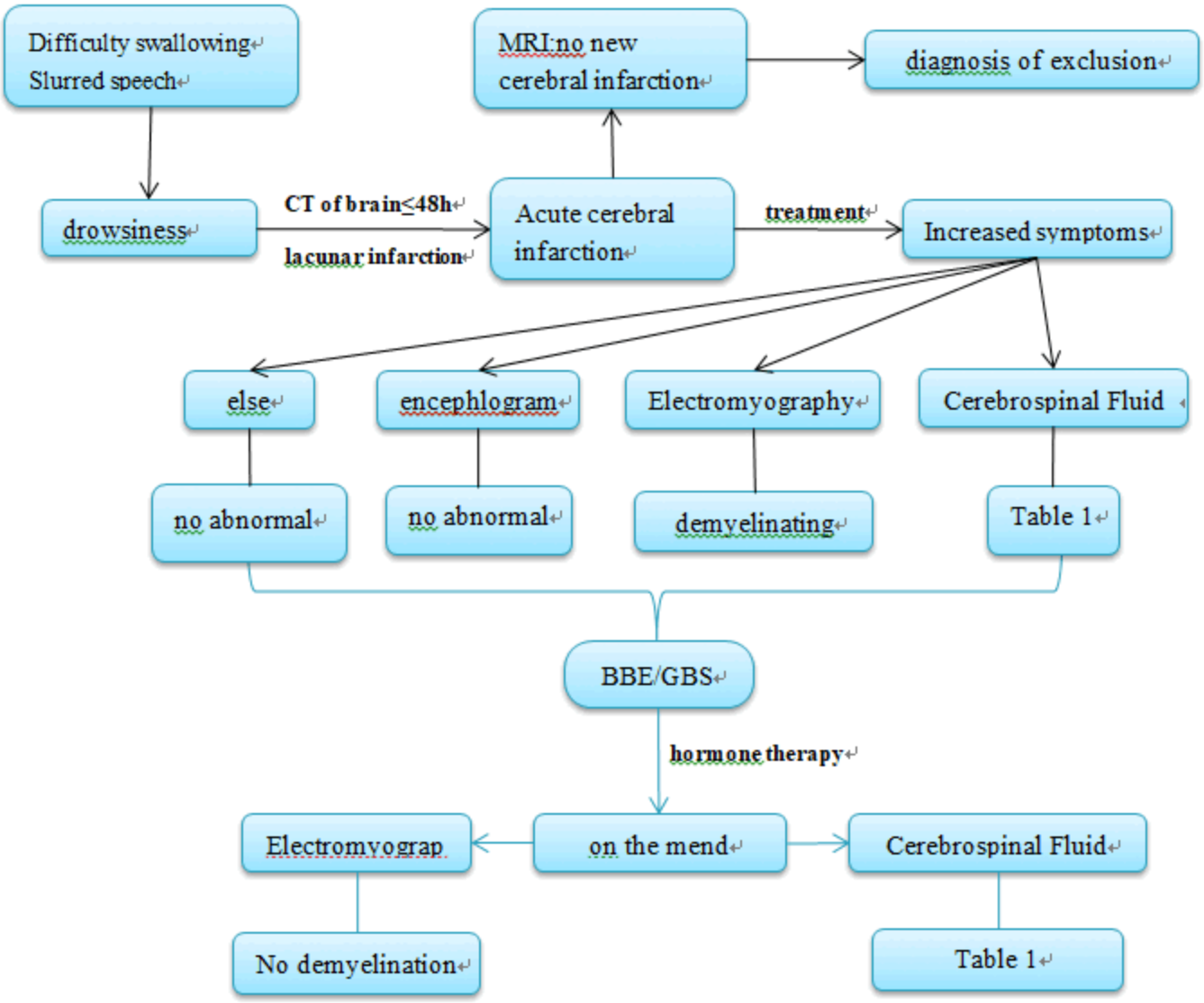
Table 2
Changes of muscle strength and muscle tone in patients

Time	Strength				Tendon reflex
	On the left side of the		On the right side of the		
Upper limb	Lower limbs	Upper limb	Lower limbs		
2021.11.16	5	5	5	5	normal
2021.11.18	5	3	5	3	less
2021.11.22	5	4	5	4-	less
2021.11.27	5	4+	5	4	less
2021.12.07	5	4+	5	4	A little weak
2022.02.15	5	5	5	5	normal

Table 3
is based on the criteria published by Wakerley BR et al. (2014).

Clinical diagnostic criteria of Bickerstaff brain stem encephalitis (BBE) and its overlapping form with Guillain-Barre syndrome (BBE/GBS)	
For BBE	Consciousness change
	ophthalmoplegia
	ataxia
For BBE/GBS,	Consciousness change
	ophthalmoplegia
	ataxia
	Lower limb weakness
There are conditions	Exclude other diseases: vascular diseases involving the brain stem;Wernicke's encephalopathy;Botulism;Myasthenia gravis;Brain stem tumor;Pituitary apoplexy;Acute disseminated encephalomyelitis;Multiple sclerosis;Neurological diseases;Vasculitis.Lymphoma.

Figures



Flow chart of changes in patient condition

Figure 1

Legend not included with this version.

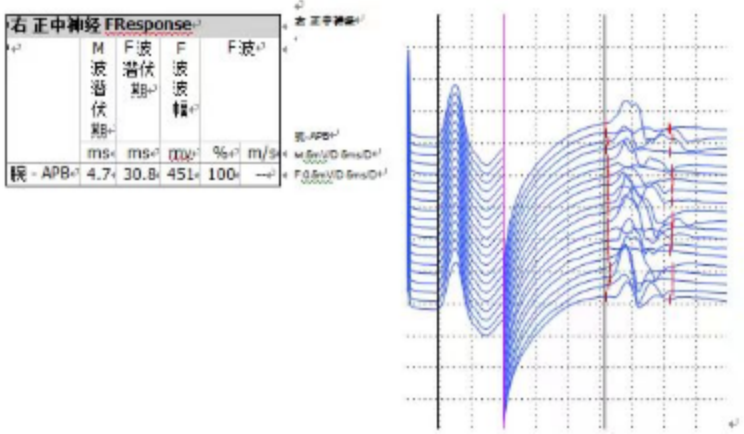


Figure 2

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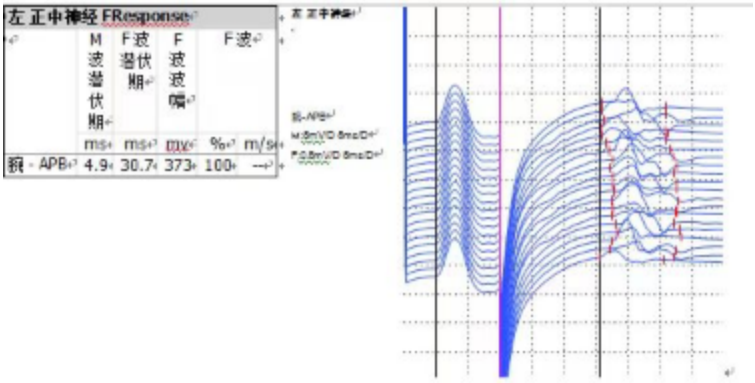


Figure 3

Legend not included with this version.