Miller–Fisher syndrome complicated by Bickerstaff brainstem encephalitis

A case report

Chaoyang Jing, MD, Zhuo Wang, MD, Chaojia Chu, MD, Ming Dong, PhD, Weihong Lin, PhD*

1. Introduction

In 1951, Bickerstaff and Cloake\(^1\) for the first time reported 3 cases of patients who presented with hypersomnia, ophthalmoplegia, and ataxia, and proposed that these symptoms might be caused by lesions in the midbrain. Six years later, Bickerstaff reported another 5 similar cases and named the disease Bickerstaff brainstem encephalitis (BBE).\(^2\) In 1956, Miller–Fisher reported 3 cases of another symptom plethora of ophthalmoplegia, ataxia, and hyporeflexia, which was called Miller–Fisher syndrome (MFS) in later reports.\(^3\) With more and more cases reported, more evidence indicates that BBE and MFS actually might be within the same disease spectrum. Yuki et al proposed the concept of Fisher–Bickerstaff syndrome (FBS), which includes not only BBE and MFS but also Guillain–Barre syndrome (GBS), etc.\(^4\) The incidence of GBS is 1 to 2/100,000, 5% to 10% of which is MFS.\(^5\) MFS is not commonly complicated with BBE. Herein, we report a rare case of such complication. The patient presented with normal consciousness, areflexia, positive Babinski signs, abnormal brain magnetic resonance signals, and increased GQ1b-IgG levels in both cerebrospinal fluid (CSF) and serum.

2. Case report

A 48-year-old woman was hospitalized due to blurred vision and unsteady gait lasting for 9 days, and numbness of the limbs lasting for 6 days. Nine days earlier, the patient had been admitted to her local hospital due to throat discomfort, blurred vision, diplopia, and unsteady gait. She had been treated with medicine for improving microcirculation. Her symptoms showed no improvement. Six days earlier, she started to develop numbness in her left arm, which gradually worsened and expanded to her whole body. She also presented with verbal...
clumsiness and back pain. The patient attended our outpatient unit and was hospitalized with the diagnosis of GBS.

Physical examination showed clear consciousness, normal round pupils of equal size in both eyes, normal direct and indirect pupillary light reflex, and restricted eye movement without nystagmus; bilateral flattening of forehead and nasolabial folds, positive eyelash sign, and difficulty swallowing water. Her tongue deviated to the left when protruded. The pharyngeal reflex was weaker on the left side than on the right side. She had normal muscle strength in bilateral arms, light paralysis in right leg, negative tendon reflex, bilateral Babinski signs, hypalgesia and numbness in all limbs, and positive Romberg sign. She failed the right heel–knee–tibia tests and was unable to walk in a straight line. Tonic neck reflex was negative. Kernig sign was negative.

Her brain diffusion-weighted imaging (DWI) at hospitalization showed an abnormally high circular signal in the brainstem surrounding the fourth ventricle (Fig. 1). Lumbar puncture was performed 2 days after hospitalization. Her CSF had a pressure of 120mmH2O, a protein concentration of 1.02g/L, a glucose concentration of 4.62mmol/L, a white blood cell count of 5 × 10^6/L, IgG concentration of 78.6mg/L, and was weakly positive for GQ1b-IgG. Her serum was also positive for GQ1b-IgG. Electromyography of her 4 limbs was carried out of 9 days after hospitalization and showed no abnormalities.

Starting at 2 days after hospitalization, the patient was treated with dexamethasone (intravenous infusion) at 15mg/day for 7 days, followed by 10mg/day for 3 days until discharge. During hospitalization, her vision gradually recovered with residual double vision. Her symptoms of facial nerve palsy disappeared. She could talk normally and protrude her tongue without deviation. She had symmetric pharyngeal reflex and no more back pain. She no longer felt numbness in all limbs, except in bilateral fingers. She had normal muscle strength in all limbs and less difficulty in walking. The Romberg sign was negative. DWI examination at 11 days after hospitalization showed obvious recovery of the lesions surrounding the fourth ventricle (Fig. 2A and Figure 2B). Her brainstem-evoked potential was normal. She was discharged 4 days later and was prescribed prednisolone acetate (40mg/day, po, to be reduced by 5 mg/day each week).

The patient was followed up by phone at 6 weeks after discharge. Her general condition had significantly improved compared with that at the time of discharge. Her double vision was improved to slightly blurry vision. She only felt numb in her right-hand ring finger and little finger. She had normal muscle strength and walked normally. At the 2-month follow-up, she still had slightly blurry vision. Double vision was further improved. Physical examination showed slight restriction of left eye abduction, normal muscle strength, and weak tendon reflex in all 4 limbs. Babinski signs were negative bilaterally. Sensory function was normal. She had no ataxia.

3. Discussion

The typical clinical symptoms of MFS are ophthalmoplegia, ataxia, and hyporeflexia. Patients often have a history of diarrhea with evidence of campylobacter infection or respiratory inflammation; have an acute onset and rapid progression of disease; first experience blurred and double vision and unsteady gait; then develop pupil light reflex changes and symptoms of bilateral intracranial nerve paralysis such as facial nerve paralysis, hypoglossal nerve paralysis, and bulbar paralysis; further present with muscle pain and sometimes other sensory abnormalities with a mild decrease in muscle strength in all limbs, the lower back, and even the whole body; have CSF albuminocytological dissociation; sometimes have GQ1b antibodies in both CSF and serum; and have reduced amplitudes of sensory-evoked action potentials and slower signal conduction.

Clinical symptoms of BBE mainly include ophthalmoplegia, ataxia, pyramidal signs (hyperreflexia and/or Babinski signs), and consciousness disturbances. Similar to MFS, patients often have...
histories of respiratory or gastrointestinal inflammation; have acute onset with blurred and double vision and unsteady gait; have CSF albuminocytological dissociation; and sometimes have GQ1b antibodies in both CSF and serum. BBE and MFS also have some major differences. The major differences are whether a patient has consciousness disturbances, pyramidal signs, and magnetic resonance imaging (MRI) signal abnormalities. BBE patients can develop consciousness disturbances at an earlier stage; some present with hypersonmia and pyramidal signs at onset; some have abnormal MRI signals in areas of the brainstem, thalamus, lateral ventricle, and cerebellum; electroencephalogram is often normal.

BBE and MFS also have similarities. Considering BBE and MFS have common prodromal symptoms of infection, similar clinical presentations, and CSF changes, especially same autoimmune antibodies (GQ1b), YuKi proposed in 2009 that these 2 diseases might have the same pathological mechanism, that is, infection-associated autoimmune disorder, and could be generally called “FBS.” Later, Nortina Shahrizaila and Nobuhiro YuKi proposed the concept of anti-GQ1b IgG antibody syndrome in 2013. It is possible that the differences between BBE and MFS are due to the expression of GQ1b in different locations in the 2 diseases, because BBE solely affects the central nervous system, while MFS mainly affects the peripheral nervous system.

The patient described herein presented with blurred and double vision and unsteady gait at onset. She had symptoms of multiple intracranial nerve injury and spinal nerve injury. Especially, she had areflexia. Thus, she had typical symptoms of MFS and a history of respiratory inflammation with acute onset. She also had CSF albuminocytological dissociation and GQ1b-IgG antibodies in both CSF and serum. These findings support the diagnosis of MFS. Nevertheless, the patient presented with positive Babinski signs starting from hospitalization until discharge; her brain MRI showed circular abnormal signals in the brainstem area surrounding the fourth ventricle; and she had GQ1b-IgG antibodies in both CSF and serum. These findings suggest a diagnosis of BBE. She had no obvious disturbance of consciousness, consistent with the idea that not all BBE patients present with loss of consciousness. Altogether, the case fits the diagnoses of both MFS and BBE. The condition of the patient significantly improved after the administration of dexamethasone. At discharge, she could walk independently and only suffered from slight numbness in her fingers. Her symptoms had continued to improve by the 6-week and 2-month follow-ups. These results suggest that hormone therapy is effective for this disease. Early diagnosis and timely hormone therapy are expected to improve patients’ outcomes. Further research is needed to fully understand the similarities and differences between the pathological mechanisms, treatment, and outcomes of BBE and MFS.

Acknowledgment

We thank the physicians who tested the antibodies in the CSF and provided clinical examinations. And we also wish to thank our patient and her family.

References

[1] Bickerstaff ER, Cloake PC. Mesencephalitis and rhombencephalitis. Br Med J 1951;2:77–81.
[2] Bickerstaff ER. Brain-stem encephalitis; further observations on a grave syndrome with benign prognosis. Br Med J 1957;1:1384–7.
[3] Fisher M. An unusual variant of acute idiopathic polyneuritis(syndrome of ophthalmoplegia, ataxia and areflexia). N Engl J Med 1956;255:57–65.
[4] Yuki N. Fisher syndrome and Bickerstaff brainstem encephalitis (Fisher–Bickerstaff syndrome). J Neurommunol 2009;215:1–9.
[5] Willisson HJ, O’Hanlon GM. The immunopathogenesis of Miller Fisher syndrome. J Neuroimmunol 1999;100:3–12.
[6] Matsuo M, Odaka M, Koga M, et al. Bickerstaff’s brainstem encephalitis associated with IgM antibodies to GM1b and GalNAc-GD1α. J Neurol Sci 2004;217:225.
[7] Wu L, Wu WP, Huang DH, et al. Clinical presentations and differential diagnosis of Miller–Fisher syndrome and Bickerstaff brainstem encephalitis. J Clin Neurol 2007;2082–85.
[8] Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry 2013;84:576–83.
[9] Kuwabara S. Fisher syndrome and Bickerstaff brainstem encephalitis. Brain Nerve 2015;67:1371–6.