Rare disease

Bickerstaff's brainstem encephalitis associated with ulcerative colitis

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Summary

A 25-year-old Japanese man showed symptoms of common cold and digestive problems for 1 month. He later developed hypoesthesia ascending from the lower extremities and consulted the emergency outpatient department with the chief complaint of generalised dysesthesia. Because of a history of ulcerative colitis, his condition was initially treated as acute aggravation of the disease; however, after admission, his consciousness level gradually deteriorated. Physical findings showed weakened tendon reflexes, and anti-GQ1b antibodies were strongly positive in the cerebrospinal fluid. Therefore, the patient was diagnosed with Bickerstaff's brainstem encephalitis (BBE). Plasmapheresis was performed 8 times, resulting in an improvement of the symptoms; the patient was discharged 1 month later. *Campylobacter* infections are the main cause of BBE, and its incidence is high among patients with ulcerative colitis. Therefore, in cases where patients with ulcerative colitis develop disturbance in consciousness, BBE should be included in the differential diagnosis.

BACKGROUND

The Guillain-Barré syndrome (GBS) is an autoimmune peripheral nerve disease characterised by the development of acute lower-limb muscle weakness and loss or reduction in tendon reflexes following various kinds of infectious diseases. The symptoms are considered to reduce after a clinical course of several weeks, and the prognosis is generally favourable, except for one of the variants, namely, Bickerstaff's brainstem encephalitis (BBE), which is often misdiagnosed and, as a result, the initiation of treatment is often delayed.

Generally, BBE presents with central nervous system disorder, external ophthalmoplegia and cerebellar ataxia. Systemic symptoms rarely develop at the same time; however, if they are preceded by non-specific symptoms, then the diagnosis becomes difficult to determine.

CASE PRESENTATION

The patient was a 25-year-old Japanese man who experienced abdominal pain and frequent bloody stools for 1 month before hospitalisation. Later, he also developed general malaise, low-grade fever and sore throat, which prompted him to visit our hospital for outpatient consultation, 13 days before admission. The patient had a history of ulcerative colitis. Lower gastrointestinal tract endoscopy performed in an outpatient setting showed a moderate inflammation in the rectum, which led to the diagnosis of exacerbation of ulcerative colitis. Thus, treatment comprising salazosulphapyridine (SASP) and mesalazine (5-ASA) was initiated. On the day before admission, the patient noticed hypoesthesia upon awakening, which was predominantly in the lower extremities, and a feeling of light-headedness during movement. Later the same day, the hypoesthesia progressed to the upper extremities and face. He subsequently consulted our hospital because of generalised dysesthesia and inability to ingest food.

INVESTIGATIONS

His blood pressure was 96/60 mmHg; pulse, 63 beats per minute; respiratory rate, 12 per minute; body temperature, 37.4°C; Glasgow Coma Scale (GCS), E4V4M6; and physical examination showed a generalised weakness and paresthesia. Neurological findings showed a narrowing of the left palpebral fissure and reduced muscle tone in the upper and lower extremities; however, no cerebellar ataxia was observed. Other than the blood tests, which showed a slight increase in the white cell count (WBC 10,300/μl), no abnormality was found in biochemical tests, coagulation tests, cerebrospinal fluid examination, CT, MRI and EEG. Examination of the patient's stool was not performed.

DIFFERENTIAL DIAGNOSIS

1. GBS/Fisher syndrome (FS)
2. Wernicke's encephalopathy
3. Infectious diseases (*Campylobacter*, *Haemophilus influenzae*, cytomegalovirus (CMV) and mycoplasma)
4. Brain stem damage (infarction, inflammation, demyelination and tumours)
5. Myopathies (periodic paralysis, rhabdomyolysis and myositis)
6. Multiple sclerosis
7. Neuro-Behcet disease
8. Lyme disease
9. Steele-Richardson-Olszewski syndrome
10. Sarcoidosis
11. Whipple's disease
12. Listeria rhombencephalitis
13. Systemic lupus erythematosus-related vasculitis
14. Acute disseminated encephalomyelitis

TREATMENT

After admission, the patient was managed with fluid replacement. However, 3 days later (Day 3), he began

showing an agitated behaviour, but no abnormality was found in cerebrospinal fluid examination and EEG. This abnormal behaviour gradually progressed, and included violent body movements consisting of hitting the bed railings with the arms and legs. On Day 8, the patient's level of consciousness deteriorated to a GCS of E1V3M4. Therefore, EEG was performed again, which showed a mixture of slow α and θ waves of approximately 8 Hz. Meanwhile, the respiratory status of the patient remained stable. Because the physical findings on Day 10 showed diminished tendon reflexes, anti-ganglioside antibodies (anti-GQ1b-IgG antibodies) were measured and were found to be strongly positive (3+), leading to the diagnosis of BBE.

Because the patient became violently agitated on the same day as the diagnosis, he was admitted to the intensive care unit (ICU). Endotracheal intubation was performed, and plasmapheresis was performed for eight times. EEG and MRI conducted at the time of admission to the ICU showed no abnormal findings. On Day 12, the disturbance of consciousness began improving, and the generalised dysesthesia and tendon reflexes gradually improved. Therefore, the patient was extubated on Day 3 after ICU admission (Day 13). Antiganglioside antibodies were confirmed as negative immediately before the last plasmapheresis.

OUTCOME AND FOLLOW-UP

The patient was discharged approximately 1 month after admission. At the time of discharge, there was only a slight limitation of the external rotation of the right eye and sensory impairment in the distal part of the limbs.

DISCUSSION

Bickerstaff and Cloake¹ reported the first case of BBE in 1951. BBE is classified as a variant of GBS, in the same manner as FS, the pure motor GBS (acute motor axonal neuropathy) and pharyngeal-cervical-brachial variant of GBS. Among these subtypes, there have been many reports of overlap syndromes with features of classic FS and BBE. The incidence of FS has been reported to occur at the rate of one in a million people,² with BBE having low incidence rates.³ In terms of physical findings, patients with FS and BBE present external ophthalmoplegia, quadriplegia and symptoms of ataxia. However, in the case of BBE, central nervous system abnormalities and tendon hyper-reflexia are present in addition to other symptoms. Typically, testing for anti-GQ1b antibodies show positive results in approximately 70% of FS and 85–90% of BBE patients.^{4–6} Furthermore, they found that the two groups were relatively similar with respect to (BBE:FS) albuminocytological dissociation (46 vs 76%), MRI abnormalities (11 vs 2%) and EEG changes (57 vs 25%).^{3–4} In most cases of BBE, the prognosis is favourable with a monophasic clinical course, which leads to an improvement of the symptoms. However, in cases showing no definitive diagnosis, the length of hospital stay may be prolonged, and death may result from complications.⁴ Steroids such as methylprednisolone, intravenous immunoglobulins and plasmapheresis are currently considered as effective treatment regimen for BBE.⁷

In this case, the patient initially presented with symptoms such as sore throat, abdominal pain and

haemorrhagic stools, and later developed symptoms such as generalised dysesthesia and ocular motility disorders. For BBE, which often begins with an antecedent infection, the initial symptoms are often non-specific, including common cold-like symptoms. When the patient has a medical history of diseases such as ulcerative colitis, similar to that observed in the case of our patient, preconceived opinions may rise and may result in a delay in the diagnosis. According to a previous report,⁴ diplopia and gait disturbance are the most common (54% and 35%, respectively) among the earliest symptoms of the disease, and are followed in subsequent order by paresthesia, disturbance of consciousness and muscular weakness of the extremities (19%, 13%, and 11%, respectively). The generalised impaired superficial sensation, which was found among the initial symptoms in this case study, has also been observed in approximately 30% of cases.⁴

Identification of the antecedent infection serves as a critical element in the diagnosis of BBE. Approximately 90% of previous cases were shown to be associated with an antecedent infection.⁴ However, the symptoms often vary, ranging from symptoms of upper respiratory infection to digestive disorders such as diarrhoea, which may be attributed to the wide variety of causative organisms involved. *Campylobacter jejuni* and *H influenzae* accounted for 23% and 6% of the cases, respectively.³ In addition, in a previous study based on the biopsy of the intestinal mucosa, the incidence of *Campylobacter* was significantly higher in patients with ulcerative colitis (33.3%) than in healthy subjects (10.8%) ($p=0.0019$).⁸ Initially, the disease was believed to occur because of a pre-existing ulcerative colitis, which is the cause of haemorrhagic stools, and therefore, sampling of stool or sputum samples for bacterial culture was not performed. *C jejuni* was not detected in stool samples collected several days after admission, but it is undeniable that if the samples had been collected at the time of outpatient consultations, there might have been a possibility that *C jejuni* could have been detected and could have led to a definitive diagnosis at an earlier stage. Thus, in cases where patients with ulcerative colitis develop disturbance in consciousness, BBE should be included in the differential diagnosis.

Learning points

- In patients who present disturbance in consciousness preceded by upper respiratory tract symptoms and gastrointestinal symptoms, Bickerstaff's brainstem encephalitis (BBE) needs to be included in the differential diagnosis.
- Antiganglioside antibody testing, examination of the cerebrospinal fluid, EEG and MRI are not 100% sensitive, whereas other tests provide a <30% sensitivity. To diagnose conditions such as BBE, detailed medical history needs to be obtained, physical examination must be conducted carefully and the test results need to be assessed in a comprehensive manner.
- Treatment comprising plasmapheresis, steroid administration and intravenous immunoglobulin should be initiated immediately after the diagnosis of BBE. The treatment can be combined or modified as needed.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Bickerstaff ER**, Cloake PC. Mesencephalitis and rhombencephalitis. *Br Med J* 1951;**2**:77–81.
2. **Arányi Z**, Kovács T, Sipos I, Bereczki D. Miller Fisher syndrome: brief overview and update with a focus on electrophysiological findings. *Eur J Neurol* 2012;**19**:15–20.
3. **Ito M**, Kuwabara S, Odaka M, *et al*. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: Clinical analysis of 581 cases. *J Neurol* 2008;**255**:674–82.
4. **Odaka M**, Yuki N, Yamada M, *et al*. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. *Brain* 2003;**126**:2279–90.
5. **Chiba A**, Kusunoki S, Obata H, *et al*. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. *Neurology* 1993;**43**:1911–17.
6. **Winer JB**. Bickerstaff's encephalitis and the Miller Fisher syndrome. *J Neurol Neurosurg Psychiatry* 2001;**71**:433–5.
7. **Roos RP**, Soliven B, Goldenberg F, *et al*. An elderly patient with Bickerstaff brainstem encephalitis and transient episodes of brainstem dysfunction. *Arch Neurol* 2008;**65**:821–4.
8. **Mukhopadhyay I**, Thomson JM, Hansen R, *et al*. Detection of *Campylobacter concisus* and other *Campylobacter* species in colonic biopsies from adults with ulcerative colitis. *PLoS One* 2011;**6**:e21490.

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