Clinical Reasoning: A 35-year-old woman with diplopia, ataxia, and altered mental status

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Section 1

A 35-year-old Pacific Islander with a history of type II diabetes mellitus presented to the Emergency Department (ED) with complaints of an intermittent sense of imbalance, left-sided paresthesias of the face and extremities, and difficulty moving her eyes that had been occurring for about 1 day. She was previously in good health; however, she and other family members had had mild upper respiratory symptoms within the last 2 weeks. Due to her intermittent symptom pattern and normal neurologic examination, the patient's symptoms were initially believed to be psychogenic in nature. Over the next 24 hours, the patient developed new symptoms of horizontal diplopia, ataxia, and dysarthria. Upon her second evaluation in the ED that following day, the patient was admitted to the medical floor without a clear diagnosis. During her first hospital night, the patient gradually became obtunded and was transferred to the intensive care unit (ICU).

Upon examination in the ICU, the patient's mental status had deteriorated. She was noted to open her eyes for a short time and make incomprehensible sounds, both in response to vigorous painful stimuli. Regarding motor function, she was noted to withdraw in all 4 extremities but not localize, consistent with a Glasgow Coma Scale score of 8. Her vital signs demonstrated tachypnea, with respiratory rates in the range of 20–30 breaths per minute. There was no fever noted and she was hemodynamically stable without hypotension or abnormal heart rhythm. Her physical examination was notable for multiple neurologic abnormalities including complete external ophthalmoplegia (assessed by muted vestibulo-ocular reflex), increased upper extremity muscle tone, brisk upper and lower extremity reflexes bilaterally, and upgoing plantar reflex bilaterally. Corneal and pharyngeal reflex were intact. She was noted to have thyromegaly without discrete nodules. Her cardiopulmonary, abdominal, genitourinary, extremity, and skin examinations were otherwise unremarkable. CT of the head was negative for acute pathology.

Question for consideration:

1. What life-threatening etiologies/pathologies must be ruled out first?

GO TO SECTION 2

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Section 2

The patient's rapid decline in responsiveness was startling. Due to multiple cranial neuropathies and ataxic gait, the lesion was localized to the brainstem, specifically the midbrain to pons. Due to the acuity of her presentation, we were initially concerned for a CNS infection causing encephalitis, and she was started on broad-spectrum antibiotics empirically. Brainstem ischemia was also a concern and an MRI was ordered. MRI of the brain was normal, without evidence of ischemia or encephalitis.

Initial workup included serum laboratory studies, lumbar puncture with CSF culture, blood and urine cultures, and nasopharyngeal swab PCR culture. Complete blood count demonstrated a white blood cell (WBC) count of 13.9 and was otherwise normal. Hepatic and renal function were

normal. Blood glucose, thyroid-stimulating hormone, and ammonia were normal. CSF contained 0 WBC, 2–75 red blood cells, 44 mg/dL protein, and 103 mg/dL glucose. Blood and urine cultures were negative. Nasopharyngeal swab culture was positive for enterovirus.

EEG was performed, which displayed findings consistent with encephalopathy including diffuse global slowing and triphasic waves interweaved with temporal intermittent rhythmic delta activity.

The patient remained in a stable, comatose state.

Questions for consideration:

1. What is the differential diagnosis?
2. What further laboratory testing should be ordered?

GO TO SECTION 3

Section 3

Lack of fever and pleocytosis lowered the likelihood of CNS encephalitis. We sent tests for insidious infections such as herpes simplex virus, zoster, cytomegalovirus, West Nile, St. Louis virus, Eastern Equine virus, *Listeria*, *Mycoplasma*, and Lyme, which were negative. Ischemia had been ruled out with MRI. After considering the differential for noninfectious encephalopathy, we believed that the patient's presentation could be consistent with Hashimoto encephalopathy based on the finding of thyromegaly. Anti-NMDA and other paraneoplastic encephalitis had not been ruled out. Acute disseminated encephalomyelitis was considered; however, the patient lacked MRI findings of demyelinating lesions. A variant of Guillain-Barré syndrome was believed to be less likely at this point, due to the patient's hyperreflexia.

During the first few days of her illness, the patient developed intermittent sinus tachycardia to the 120s accompanied by diaphoresis, which would correct spontaneously after a few minutes. She also developed an anion gap metabolic acidosis requiring a bicarbonate drip to correct, possibly due to ketosis. She was persistently tachypneic and there was concern that she was not able to protect her airway. She was intubated and placed on mechanical ventilation. Enteric feeding was initiated. Levetiracetam 1,000 mg twice daily was initiated for seizure prophylaxis.

Follow-up MRI was performed on hospital day 3 and continued to demonstrate radiologically normal brain and spinal cord.

Table Antiganglioside panel results

	Result	Interpretive information
GM1 IgG	4 IV	29 IV or less: negative
GM1 IgM	6 IV	29 IV or less: negative
GD1b IgG	7 IV	29 IV or less: negative
GD1b IgM	5 IV	29 IV or less: negative
GQ1b IgG	39 IV	30–50 IV: equivocal
GQ1b IgM	4 IV	29 IV or less: negative

Abbreviations: IgG = immunoglobulin G; IgM = immunoglobulin M.

The patient was treated empirically for suspected Hashimoto encephalopathy with methylprednisolone at 1,000 mg daily for 3 days. Corticosteroids were only initiated after infectious etiologies had been ruled out. Steroid treatment was administered with subtle improvement in the patient's hyperreflexia, and no improvement in her overall level of consciousness.

Paraneoplastic panel (Anti-NMDA, anti-Hu, anti-La, amphiphysin antibodies) was negative. Serum antiganglioside panel results are shown in the table.

Question for consideration:

1. What is the diagnosis?

GO TO SECTION 4

Section 4

After elevation of anti-GQ1b immunoglobulin G (IgG) was noted, the favored diagnosis was Bickerstaff brainstem encephalitis (BBE).

BBE was first described by Bickerstaff and Cloake¹ in 1951 and has since been grouped with Miller Fisher syndrome (MFS), acute ataxic neuropathy without ophthalmoplegia, and acute ophthalmoparesis (AO) without ataxia. There is mounting case analysis evidence to suggest that these syndromes have overlap and may be phenotypes of the same pathogenic process known as anti-GQ1b antibody syndrome.^{2–12} GQ1b is a ganglioside found to be highly expressed in the oculomotor, trochlear, and abducens nerves, muscle spindles in the limbs, and probably reticular formation in the brainstem.³ Acute ataxic neuropathy and AO are considered incomplete forms of MFS. MFS and BBE are defined by ophthalmoplegia and ataxia; however, only BBE demonstrates CNS involvement with variable hyperreflexia or hyporeflexia and cognitive depression. The spectrum of cognitive depression seen in BBE varies from drowsiness, to stupor, to coma. A minority of patients (34%) will require intensive supportive care including mechanical ventilation.⁴ Postmortem studies in patients with BBE have demonstrated definite inflammation in the brainstem, with perivascular

lymphocytic infiltration and edema.⁴ It is postulated that BBE occurs when a breakdown in the blood–brain barrier occurs (possibly via the area postrema), and the reticular formation becomes involved with anti-GQ1b-IgG related inflammation.⁴ MRI abnormalities are rarely seen (11%–30% in BBE, 1% in MFS), but have included T2 hyperintensities in the pons, thalamus, or other areas.^{4,5}

Similar to Guillain-Barré syndrome (GBS), antecedent illness is repeatedly demonstrated in cases of MFS and BBE and is believed to cause a molecular mimicry type reaction producing the anti-GQ1b antibody. This type of immunologic reaction manifests in approximately 10–14 days.⁶ Upper respiratory infectious symptoms are more commonly seen preceding MFS and BBE (60%–76%), vs diarrhea (25%–29%).⁴ Specific respiratory viruses, including *Enterovirus* spp, have been implicated as commonly causative in cases of GBS.⁷ While comprehensive viral testing has not generally been done in recorded cases of BBE, we did isolate *Enterovirus* in our patient, and future research may be able to define more causative viruses with comprehensive PCR testing.

Questions for consideration:

1. How should the patient be treated?
2. What is the patient's prognosis?

GO TO SECTION 5

Section 5

IV immunoglobulin (IVIg), plasmapheresis, and glucocorticoids have historically been applied as treatment for MFS and BBE. Study of treatment effectiveness is limited to retrospective research in a small number of patients, which has not demonstrated a benefit to any treatment with respect to overall neurologic recovery time.³ One retrospective study demonstrated a small improvement in time to amelioration of ophthalmoplegia and ataxia with IVIg therapy.⁸ Regardless of whether or not immunotherapy is applied, nearly all patients will recover full neurologic function by 6 months from the onset of their illness.³

After initially treating with high-dose corticosteroids, we administered IVIg at a dose of 0.4g/kg daily for 5 consecutive days (hospital days 8–12). After the IVIg treatment, the patient was observed to have an increased frequency of spontaneous movements and increased responsiveness to stimuli. After 14 days in a comatose state, the patient began to open her eyes spontaneously and respond to commands. The patient was transferred to a tertiary care hospital and continued to recover her neurologic function. Her most recent documented follow-up is 3 months since the onset of her initial illness and she has made nearly a complete recovery.

Discussion

BBE is a rare neuroinflammatory disorder. The diagnostic approach relies on recognition of unique clinical findings including complete external ophthalmoplegia, ataxia, and depressed cognition. BBE usually occurs in the setting of a recent upper respiratory or diarrheal illness. Serum anti-GQ1b IgG antibody is often (66%–68%) but not always positive, thus the laboratory finding should not be considered necessary for diagnosis.^{4,5} Variable findings of autonomic dysfunction, sensory disturbances, and limb weakness may indicate an overlap with weakness-predominant GBS and can confuse the clinical picture.^{3,9} The differential diagnosis includes brainstem ischemia, infectious rhomboencephalitis,

multiple sclerosis, toxic encephalopathy, and Wernicke encephalopathy, which should be ruled out.³

The prognosis for MFS/BBE patients is excellent, and spontaneous recovery is expected. Current expert recommendations only support trial of IVIg or plasmapheresis in cases wherein the patient is at clear risk for complications, such as severe BBE.^{3,4,8}

Author contributions

Z. Bauer: primary manuscript author. K.S. Eum: content contributions and manuscript editing. J. Ji: content contributions and manuscript editing. J. Bunin: content contributions and manuscript editing. J. Sherratt: content contributions and manuscript editing.

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Disclosure

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