

Bickerstaff Brainstem Encephalitis with Isolated Acute Bilateral Ophthalmoplegia: An Unusual Presentation

Dear Editor,

Bickerstaff brainstem encephalitis (BBE) is an immune-mediated, rare form of encephalitis traditionally characterized by progressive, relatively symmetrical *external ophthalmoplegia, ataxia, and disturbance of consciousness*. Positive anti-GQ1b antibodies are found in 66% and abnormal brain MRI in 30% of patients. We herein report our patient who unusually had external plus internal ophthalmoplegia, hyperreflexia (not altered consciousness), normal brain imaging, and negative GQ1b profile. He was still diagnosed “Possible BBE” in accordance with postulated criteria for central nervous system involvement. We, therefore, with this report, emphasize on the clear-cut diagnostic criteria defining this disorder and also on its differentials based on acute bilateral ophthalmoplegia.

We report a 22-year-old male patient who presented with acute onset double vision in all directions. There was a history of headache and fever 7 days before admission, of which fever recovered in the next 2 days. Family members had noticed diminished movement of both eyeballs in all the directions for the last 3 days. There was also a history of slight imbalance and swaying on both sides while walking for the last 2 days.

However, there was no history of altered sensorium, vision issues, drooping of eyelids, facial numbness or weakness, swallowing difficulty, sensory symptoms or limb weakness.

On examination, the patient was conscious, oriented, speech was normal, pupils were bilaterally dilated and non-reactive with restricted extraocular movements in all directions [Figure 1] [Video 1]. Other cranial nerves were normal. Muscle tone and power were tested normal. Deep tendon reflexes were brisk in both upper and lower limbs, plantar extensor bilaterally, the sensory system was normal, extrapyramidal system and peripheral nerves were normal, no signs of meningeal irritation, and no involuntary movements; ataxia was only evident on tandem gait with subtle swaying on heel shin testing.

While reviewing the causes of acute bilateral ophthalmoplegia [Table 1],^[1] possibilities of Bickerstaff encephalitis, atypical Miller–Fischer syndrome and botulism were kept. MRI brain and nerve conduction studies in all limbs were normal. Cerebrospinal fluid examination showed albumino-cytological dissociation with raised proteins (proteins 122 mg/dL, sugar 68 mg/dL, cells < 5/cumm). Patient, however, tested negative for serum IgG anti-GQ1b antibodies. Botulism was unlikely in absence of

Table 1: Enlisting common acute causes of bilateral ophthalmoplegia

Neuromuscular junction	Extra-Ocular Muscles	Central causes	Peripheral Causes	Toxic/Metabolic	Idiopathic*
Myasthenia gravis	Giant cell Arteritis	Brainstem Disease [†]	Diabetes	Botulism*	
Lambert Eaton myasthenic syndrome (rare)	* (vascular) Orbital Pseudotumor	Cavernous Sinus diseases* [†]	Miller Fischer syndrome	Organo-phosphates	
		Meningeal Disease*	Diphtheria	Neurotoxic snake bite*	
		Multiple sclerosis*	Neurosyphilis*		
		BBE*	Lymes disease		
		Wernicke’s encephalopathy			
		Whipples Disease*			

Note- * denotes diseases with associated probability of pupillary dilation. [†]acute brainstem etiologies include vascular, demyelinating, neoplastic, infective, metabolic, immune mediated and inflammatory ; acute cavernous pathologies include metastasis, infective and inflammatory

Table 2: Anti GQ1b spectrum disorders

Fischer Syndrome	Acute ataxic neuropathy (without ophthalmoplegia)	Bickerstaff brainstem encephalitis	Pharyngeal-cervical-brachial weakness	Overlap
Complete {External ophthalmoplegia, Ataxia, and Hypo/areflexia}	Ataxic Guillain–Barré syndrome	Bilateral ophthalmoplegia, ataxia, and altered consciousness/hyperreflexia	Acute Oropharyngeal and arm weakness	Fisher–Bickerstaff syndrome overlapped by pharyngeal-cervical-brachial weakness
Incomplete {External ophthalmoplegia/ptosis/mydriasis/bulbar weakness alone or combined with ataxia}	Acute sensory ataxic neuropathy			{Oropharyngeal and upper limb weakness alongwith brainstem signs}
				Fisher–Bickerstaff syndrome overlapped by Guillain–Barré syndrome
				{Oropharyngeal, upper and lower limb weakness alongwith brainstem signs}



Figure 1: Ophthalmoplegia with mydriasis in our patient

GI symptoms and bulbar affection and no incremental response seen on repetitive nerve stimulation test at >20 Hz. As patient had hyperreflexia, extensor plantars, and nerve conduction studies were normal, atypical MFS was also unlikely.

In view of acute onset progressive bilateral ophthalmoplegia with pupillary involvement, brisk deep tendon reflexes in all four limbs with positive Babinski sign bilaterally, and ataxia on tandem walking, along with albuminocytological dissociation in CSF, the patient was diagnosed as “Possible BBE” and treated with Intravenous Immunoglobulin (IvIg) 0.4 mg/kg for 5 days, showing complete recovery at one month follow up. Most previous case reports of BBE have described the typical features of confusion or drowsiness as a sign of CNS involvement. However, our patient had hyperreflexia without altered consciousness, as evidence of central involvement.

Positive anti-GQ1b antibodies are known to be found in 66% and abnormal brain Magnetic Resonance Imaging (MRI) in 30% of patients,^[2,3] while our patient had neither of these; however was still clinically diagnosed and successfully treated as “Possible BBE”.

BBE initially was described by Edwin Bickerstaff in his original writings in 1951 and 1957 wherein he highlighted drowsiness as a key denominator in all eight cases.^[4,5] Common to all were also ptosis, ophthalmoplegia (mostly complete), and facial palsy. Other clinical features recorded although not always present include limb ataxia, dysarthria, and areflexia (with extensor plantars), preceded by infection.^[4,5]

The estimated annual incidence of BBE is 0.078/100000.^[2] Majority of patients see a preceding infectious illness, upper respiratory tract infection being most common (94%).^[6] Usually associated antecedent pathogens include herpes simplex virus, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, measles virus, salmonella typhi, mycoplasma pneumonia, and campylobacter jejuni enteritis.^[7] There is substantiating evidence that antiganglioside antibodies work via molecular mimicry with infectious agents.^[8]

Later, studies revealed that central nervous system manifestations included drowsiness (45%), stupor, semi-coma or coma (29%), hyperreflexia (34%), Babinski’s sign (40%) and deep sensory impairment (16%). Other common neurological features included ptosis, mydriasis, facial weakness, bulbar palsy, and nystagmus.^[9]

Along with Guillain–Barre syndrome (GBS) and Miller–Fisher syndrome, BBE forms a part of spectrum of post-infectious demyelinating diseases. The binding of GQ1b antibodies to cranial nerves and muscle spindles induces Fisher syndrome, whereas their binding to GQ1b antigen in the brainstem induces BBE, manifesting as an additional evidence of central involvement in form of altered level of consciousness (confusion, hyper-somnolence, or unconsciousness) and/or hyperreflexia differentiating BBE from these other two entities; and also from the other so-called Anti-GQ1b antibody spectrum disorders [Table 2^[9]]. These antibodies have been found in 60-70% of BBE, 83-100% of MFS,^[6] and 8% of GBS patients. Albumino-cytological dissociation in the CSF has also been seen in 25% cases of BBE and 37% cases of MFS.^[10]

MRI abnormalities in the form of T2 hyperintense lesions in the brainstem (especially midbrain), cerebellum, and thalamus have been seen in 30% of BBE patients. Over time, signal characteristics may wax and wane or regress in a descending radiologic pattern.^[9]

Besides the GQ1b variants, differential diagnoses also include Wernicke’s encephalopathy, vascular disease involving the brain stem, multiple sclerosis, botulism, and brain stem tumors.^[6,11]

Prognosis wise, ataxia improves at a median of 32 days (3–41 days after onset) and ophthalmoplegia at a median of 88 days (between 3 and 146 days).^[7] BBE is usually monophasic and self-limiting, with most patients achieving complete remission by 6 months;^[12] however, individual relapses have also been described.^[13]

A definitive treatment for BBE is yet to be found. The established treatment is the same as that used in GBS: Intravenous immunoglobulin and plasmapheresis, although more clinical trials are required to determine its effectiveness.

Henceforth, Bickerstaff encephalitis can uncommonly present with a triad of ataxia, complete ophthalmoplegia, and pyramidal signs of hyperreflexia and extensor plantar response even without evidence of impaired consciousness, neuroimaging changes, and detection of ganglioside antibodies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 03-Aug-2020 **Revised:** 13-Aug-2020 **Accepted:** 23-Aug-2020

Published: 22-Feb-2020

Video available on: www.annalsofian.org

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DOI: 10.4103/aian.AIAN_823_20