

# Inefficacy of Antipsychotics in Treatment of Delirium and Agitation in Two Cases of Bickerstaff Brainstem Encephalitis

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*The authors report two unusual cases of Bickerstaff encephalitis that presented with encephalopathy and severe agitation. Management with neuroleptics typically used for management of delirium was not effective and worsened agitation. Valproic acid was effective in treatment of agitation and well tolerated.*

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**B**ickerstaff brainstem encephalitis (BBE) is a syndrome believed to be of autoimmune origin that is characterized by acute ophthalmoplegia, ataxia, and disturbance of consciousness,<sup>1</sup> indicating CNS involvement. It is considered part of the clinical spectrum of autoimmune neuropathies, including Miller Fisher syndrome (MFS) and other variants of Guillain-Barre syndrome (GBS). Symptoms are frequently preceded by upper respiratory infection, and the most common initial symptoms are diplopia and gait disturbance.<sup>2,3</sup> In the largest case series of BBE, disturbance of consciousness is described as drowsiness.<sup>1,4</sup> To our knowledge, there are only three cases in the literature that describe delirium in BBE<sup>5,6</sup> and only two cases that describe agitation in BBE.<sup>6</sup>

In this report, we discuss two patients with BBE who experienced delirium with significant agitation. The delirium and agitation did not respond to management with neuroleptic medications.

## CASE REPORTS

### Case #1:

A 64-year-old Caucasian man with history of chronic back pain presented complaining of difficulty maintaining balance, hand swelling, numbness, and tingling. He reported experiencing symptoms of upper respiratory infection 1 week prior. He only takes meloxicam as needed, and he has no history of alcohol or substance use. Neurological examination noted up gaze deficiency, marked truncal and gait ataxia, and areflexia, but normal cranial nerves exam and normal limb strength. Both CT and MRI of the head revealed only mild chronic small vessel ischemic changes. Serum electrolytes and CBC were unremarkable. Chest X-ray showed evidence of pneumonia. CSF analysis revealed albuminocytological dissociation. Because of concern for GBS or MFS, he was started on intravenous immunoglobulin (IVIG). He received ceftriaxone and azithromycin for treatment of pneumonia. EEG revealed nonspecific diffuse slowing. Serum for anti-GQ1b antibody was sent that later came back negative. The next night, he became confused and severely agitated. Intravenous haloperidol, up to 20 mg a day was used first with no improvement, and he developed akathisia, which resolved with stopping haloperidol. Quetiapine up to 150 mg a day and olanzapine up to 10 mg a day were each tried, but the agitation didn't resolve and seemed to worsen. With the poor response to antipsychotics, valproic acid was started and titrated up to 500 mg i.v. b.i.d. Significant reduction in agitation was noted over the next 1–2 days. Clonazepam 0.5 mg p.o. q.h.s. was added for some nighttime agitation and later trazodone 100 mg p.o. q.h.s. was added for insomnia. Agitation resolved and the patient's mental status slowly returned to baseline within 3 weeks of treatment.

### Case #2:

A 56-year-old Caucasian man with a history of type 2 diabetes mellitus, hypertension, hyperlipidemia, sleep

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apnea, and alcohol abuse presented to the emergency room complaining of difficulty maintaining balance and confusion for 1 day. The only physical examination finding on admission was ataxia. Alcohol level was undetectable, and his wife confirmed his last drink was 1 week prior to admission. He had a negative urine drug screen and rapid plasma reagin. Thyrotropin (TSH), thiamine, and B12 levels were all normal. He was diagnosed with Wernicke's encephalopathy and treated with thiamine. His confusion improved, and he was discharged after 5 days. Five days later, he presented again for repeated falls, difficulty with talking, and confusion. Upon examination, he was found to have ataxia, dysarthria, slowed eye movements without nystagmus, and normal reflexes. MRI of the brain revealed slight hyperintensities in the peri-aqueductal gray matter. EEG showed diffuse slowing. CSF analysis revealed albuminocytological dissociation. A tentative diagnosis of BBE was made and plasmapheresis started. Serum anti-GQ1b antibodies were sent and later came back negative. The next day, he became more confused and agitated. Olanzapine was first given and titrated up to 20 mg daily, but his agitation continued to worsen. Olanzapine was switched to chlorpromazine and he received up to 125 mg daily, again showing little to no improvement. Lorazepam, up to 6 mg/day, was tried, but his agitation continued to worsen and he attacked a nurse. Additional EEG and a head MRI were performed and were unchanged. Given his minimal response to antipsychotics and benzodiazepines, valproic acid was attempted. A loading i.v. dose 1000 mg was given followed by 500 mg i.v. b.i.d. His agitation improved one day after starting valproic acid. He was irritable and uncooperative at times, but not aggressive. Slowly he continued to improve and later was discharged to a rehab facility on hospital day 26.

## DISCUSSION

BBE was first described by Bickerstaff and Cloake in 1951.<sup>7</sup> It is considered to be the more severe clinical presentation of "anti-GQ1b antibody syndrome," whereas MFS, which typically presents with ophthalmoplegia, areflexia, and ataxia without any impairment of consciousness is the more benign presentation.<sup>8</sup> Worldwide and geographic incidence of BBE is unknown. The worldwide incidence of GBS is one to two individuals per 100,000 per year. In the Western hemisphere, 1%–7% of GBS cases are also classified as MFS, whereas

18%–19% of patients with GBS in Taiwan and 25% in Japan have MFS variant.<sup>3</sup> Both MFS and BBE are thought to be related to the GQ1b ganglioside, a cell surface component concentrated in the paranodal regions, neuromuscular junctions of the third, fourth, and sixth cranial nerves, and deep cerebellar nuclei.<sup>9</sup> It is hypothesized that after infection, neoplasm, or some other precipitating event, patients develop antiganglioside antibodies that attack the brainstem reticular formation<sup>8</sup> and lead to Schwann cell, axon, and neuromuscular junction degeneration through complement-mediated pathways.<sup>10</sup> Serum anti-GQ1gb antibodies are positive in 70% with BBE.<sup>1</sup> Other studies have also implicated anti-GalNac-GD1a and anti-GM1b antibodies as well.<sup>11</sup>

Brain MRI findings in BBE are often unremarkable but can include T2 hyper-intensities in the brainstem, thalamus, cerebrum, and/or cerebellum.<sup>1,4</sup> EEGs may show diffuse slowing in the theta and delta range.<sup>1,4</sup> CSF analysis may show albuminocytological dissociation.<sup>1,4</sup> Though laboratory tests, imaging, and neuroelectrophysiology tests can aid in a diagnosis, BBE currently remains a clinical diagnosis. According to the diagnostic criteria put forward by Odaka et al.,<sup>12</sup> BBE constitutes a clinical entity and diagnosis relies primarily on clinical presentation and physical examination.

In both of the cases presented, the diagnosis of BBE was made clinically. Other possible differential diagnosis such as seizure disorder, brainstem stroke, and Wernicke encephalopathy, were considered but ruled out with clinical assessment and focused investigations such as brain imaging and repeated EEGs. Both cases did have CSF albuminocytological dissociation and diffuse EEG slowing. Brain MRI in the second case did show some brain-stem hyper-intensities.

Anti-GQ1b antibody was negative. However, it is possible that those cases may have represented the minority of patients who do not have anti-GQ1b antibodies, or those cases may be related to other antibodies that may associate with BBE.

Both of these patients developed confusion and physical agitation so severe that it required immediate pharmacological intervention. It is important to note this aggressive presentation of BBE given its implications for treatment as well as the safety of the patients and staff. Neither patient responded to standard management of delirium with neuroleptic agents but did well with valproic acid. The exact mechanism by which valproic acid achieves these effects is not clear. There was no evidence of seizures to explain the effectiveness of valproic acid in these patients.

Valproic acid is known to present anti-inflammatory, antioxidative, and possibly neuroprotective properties.<sup>13</sup> We do not know to what extent the anti-inflammatory activity is responsible to the improvement we saw in our cases. In addition, it is possible that the delirium and agitation in BBE is not so much the result of dopamine dysregulation as opposed to other neurotransmitters that are better targeted by valproic acid. Nonetheless, valproic acid has been reported to improve delirium symptoms when utilized as an adjunctive agent<sup>14</sup> and has also proven to be effective for treatment of agitation associated with traumatic brain injury.<sup>15</sup> To our knowledge, this is the first report to discuss the treatment of hyperactive delirium in patients with BBE and to suggest that valproic acid might be an effective treatment.

## CONCLUSIONS

BBE is a rare inflammatory disorder of the CNS that might present with delirium and agitation. This case series is significant as it highlights that the delirium and agitation might not response to traditional management with neuroleptics. Furthermore, valproic acid may be effective and should be considered for treatment of agitation.

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