

IS THERE AN AUTOIMMUNE ENCEPHALITIS-LIKE BRAIN METABOLISM PATTERN IN PATIENTS WITH BICKERSTAFF BRAINSTEM ENCEPHALITIS?

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Abstract

Background: Positron Emission Tomography (PET) utilizing 18F-fluorodeoxyglucose (18 FDG) is a valuable tool in diagnosing autoimmune encephalitis targeting post-synaptic receptors. However, there is limited understanding of metabolic alterations in other autoimmune encephalitis, such as Bickerstaff brainstem encephalitis (BBE). **Objective:** To present the case of a patient with BBE, supported by an 18 FDG PET study and to conduct a literature review on the subject. **Results:** A 20-year-old man, with no relevant medical history, presented to the emergency department due to a clinical picture of seven days of evolution, characterized by non-painful distal paresthesias in all four extremities, diplopia, gait instability and dysphagia. On the day of admission, he exhibited altered mental status. A clinical diagnosis of Bickerstaff brainstem encephalitis was established. Paraclinical evaluations, including cerebrospinal fluid analysis, were normal. The patient received treatment with human immunoglobulin (2 grams/kg) for five days. An 18 FDG PET study revealed hypermetabolism in the putamen and bilateral caudate nucleus, as well as bilateral occipital hypometabolism. **Conclusion:** Brain 18-FDG PET may serve as a surrogate marker for comprehending central nervous system involvement in BBE.

Keywords: autoimmune, Encephalitis, Bickerstaff, PET

Introduction

Bickerstaff brainstem encephalitis (BBE) is a clinical diagnosis characterized by symptoms including ophthalmoplegia, ataxia and altered consciousness. This condition is a rare clinical entity, accounting for 1.7% of Guillain-Barre syndrome (GBS) cases.^{1,2} It is associated with anti-GQ1b antibodies, which are present in 66% of patients.³ A consensus in the global medical community suggests that BBE can be regarded as a “brainstem continuum” of Miller Fisher syndrome (MF). Both entities share features of early onset, preceding infection, sensory disturbances (e.g., numbness) in distal extremities, oropharyngeal palsy, abducens palsy, and a favorable outcome and recovery.^{3,4}

The involvement of the Central Nervous System (CNS) in BBE remains controversial. In a 2016 review by Graus et al., this clinical entity was associated with a “decreased level of consciousness”.⁵ In one of the largest cohorts reported to date, Ito identified brainstem lesions through magnetic resonance imaging (MRI) in 10% of cases, with one-third of patients showing pyramidal signs and altered reflexes. Bickerstaff also made an important observation about neuropsychiatric disturbances in these patients: all of them became drowsy, being this the principal feature of the entity.⁶

Both Miller-Fisher syndrome and BBE are classified as GBS variants, sharing features such as albuminocytological dissociation and antiganglioside antibodies. However, in



BBE, not only peripheral nerves are compromised, but also certain brainstem networks, including the corticospinal pathway and the ascending reticular activating system.⁷

There have been reports on the utility of 18-FDG positron emission tomography (PET) in assessing brain metabolism alterations in patients diagnosed with autoimmune encephalitis (AE), such as that caused by antibodies against the N-methyl aspartate receptor (anti-NMDAR).⁸ However, there are few studies on brain metabolism changes specific to Bickerstaff's encephalitis. The aim of this study is to describe a case of BBE and analyze its metabolic changes utilizing 18 FDG PET, while also providing a literature review on the subject.

Case report

A 20-year-old male, with no relevant medical history, presented to our emergency department exhibiting a seven-day history of distal paresthesia affecting all four limbs. Twenty-four hours after onset of symptoms, he developed horizontal diplopia, gait instability and dysphagia.

Upon arrival, his vital signs and general examination were unremarkable. He was awake and alert, albeit with a severe flaccid dysarthria. A cranial nerve examination revealed bilateral complete ophthalmoplegia, as well as bilateral facial and soft palate weakness, and a lack of gag reflex. His strength was normal in all four limbs, but he had generalized hyporreflexia. A bilateral Babinski sign was found, and he also displayed bilateral dysmetria and ataxia. Paraclinical tests showed no abnormalities in blood cell counts, and kidney and liver function tests. Cerebrospinal fluid (CSF) analysis demonstrated normal levels of glucose (58 mg/dl), proteins (31 mg/dl) and six mononuclear cells. Initially, a Miller-Fisher syndrome was diagnosed. However, during the first hours of hospitalization, the patient developed a profound stupor, requiring mechanical ventilation. Infectious etiologies, such as aspiration pneumonia were discarded. Thus, clinical criteria of BBE were met, and a treatment of intravenous immunoglobulin (IVIg) at a dose of 2 g/day for 5 days was initiated.

Serological test for HIV, hepatitis-B and C viruses and syphilis were negative. CSF cultures and stains were also negative. Anti-GQ1b in serum was negative. MRI showed no abnormalities, while 18F-FDG PET scans of the cerebral parenchyma indicated bilateral occipital hypometabolism in the dorsolateral cortex, bilateral temporal hypometabolism with right predominance, and hypermetabolism in the bilateral

and symmetrical striated nucleus, as well as hypermetabolism in the right thalamus (Figure 1).

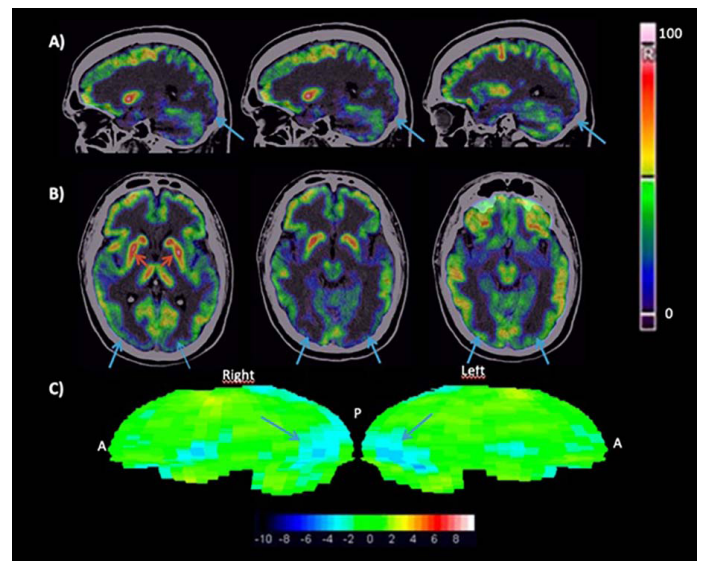


Figure 1. PET/CT imaging revealing 18F FDG metabolic pattern in Bickerstaff brainstem encephalitis. **A**) In the upper row, the sagittal cut shows occipital hypometabolism (blue arrows). **B**) In the intermediate row, axial cut exhibits hypermetabolism in the putamens and caudate nuclei (red arrows), and occipital hypometabolism (blue arrows). **C**) The Syngo Scenium image corroborates occipital hypometabolism (blue arrows).

During his evolution, the patient developed cardiovascular dysautonomia with variability in his heart rate without hemodynamic compromise. On the third day of hospitalization, withdrawal of invasive mechanical ventilation was possible due to an improvement of the wakefulness state. However, he exhibited psychomotor agitation and visual hallucinations, necessitating intravenous sedation with dexmedetomidine. The patient presented improvement in wakefulness and confusion states on the tenth day of his hospital stay, and was further discharged.

Discussion

Bickerstaff brainstem encephalitis (BBE) originates from an aberrant immune response triggered by respiratory or gastrointestinal infections, leading to the production of antibodies targeting the ganglioside GQ1b, which is detected in 66% of cases.⁷ While GBS traditionally affects the peripheral nervous system, in the case of BBE there is also involvement of the central nervous system.^{8,9} A prominent clinical feature of BBE, apart from ophthalmoplegia and ataxia, is altered

wakefulness, which is due to impaired functionality of the ascending reticular activating system within the brainstem.^{8,9} A retrospective study of five BBE patients included an analysis of electroencephalograms, revealing dysfunction and abnormalities during sleep, suggesting the involvement of the ascending reticular activating system.¹⁰ Another study involving a postmortem examination of a BBE patient reported inflammatory changes within the brainstem.⁹

The clinical presentation of BBE patients initiates with diplopia, ataxia, distal paresthesias, alteration of lower cranial nerves (VII, IX and X), and alteration in wakefulness (drowsiness, stupor or coma). Subsequently, some patients develop hyperactive delirium, usually accompanied by cardiovascular dysautonomia (fluctuations in heart rate and/or blood pressure).^{4,7} Despite the CNS involvement, paraclinical assessments focused on the blood-brain barrier and structural alterations, CSF cytochemical and MRI of the brain, typically yield normal results.⁴ This normality in ancillary tests is also observed in other models of autoimmune encephalitis (AE). One of the main AE described in recent years is directed against the NMDA receptor, where 52 % of patients exhibit non-inflammatory CSF, and up to 34.5% of patients have normal MRI findings.¹¹

Studies have reported changes in brain metabolism using 18 FDG PET in patients diagnosed with autoimmune encephalitis based on clinical criteria, including antibodies targeting surface antigens (NMDAR, VGKCc, GAD6, LGI1, etc.) among others, although patients with BBE were not included. These changes predominantly manifest as hypometabolism in several cortical and subcortical brain regions, especially in the temporal and occipital lobes.¹²

Information regarding changes in brain metabolism in patients with BBE remains limited. In a previous publication, we examined a series of cases of BBE cases, one of which involved a 60-year-old male patient who clinically presented as BEE, had normal CSF findings, an unaltered MRI, and tested positive for anti-GQ1b antibodies. In this case, an 18-FDG PET scan was performed, reporting hypometabolism in the occipital lobes.² This previously reported patient shared similar characteristics with the current case under consideration (Table 1).

Another study of by Nerrant reported the case of a 32-year-old woman diagnosed with BBE, who exhibited changes in MRI intensity due to vasogenic edema located in the cerebellum and brain stem. Additionally, the 18-FDG PET study indicated

Table 1. Baseline characteristics of our patient compared to other case reports

| | Our patient | Aguilar et al. ² | Known et al.¹⁴ | Nerrant et al.¹³ |
|------------------------------|---|---|-------------------------------------|--|
| Age (years)/gender | 20/male | 60/male | 58/male | 32/female |
| Previous infection | None | URTI | URTI | URTI |
| Wakefulness state alteration | Stupor | Stupor | Somnolence | No |
| Cranial nerve involvement | Ophthalmoplegia, VII, bulbar nerves | Ophthalmoplegia, VII, bulbar nerves | Ophthalmoplegia, VII, bulbar nerves | Diplopia (non-specified) |
| IMV requirement | (+) | (+) | (-) | (-) |
| CSF findings | No ACD | No ACD | No ACD | 1.01 gr/L of protein, 123 cells (neutrophils) |
| Treatment with IgIV | (+) | (+) | (+) | (-) |
| Antibodies | Anti-GQ1b (-) | Anti-GQ1b (+) | Anti-GQ1b (-), Anti-GM1 IgM (+) | Anti-GQ1b (-), Anti-GD1a (+) |
| MRI image | Normal | Normal | Normal | Vasogenic edema in brainstem and cerebellum white matter |
| Brain 18F-PET-FDG metabolism | Hypometabolism in the occipital and temporal lobes, hypermetabolism in striatal nuclei. | Hypometabolism in occipital lobes and cerebellum, hypermetabolism in bilateral striatum | Hypometabolism in the cerebellum. | Bilateral temporo-parieto-occipital hypometabolism |

ACD: albumin-cytologic dissociation; CSF: cerebrospinal fluid; IgIV: intravenous immunoglobulin; IMV: invasive mechanical ventilation; URTI: upper tract respiratory infection.

had bilateral temporo-parieto-occipital and cerebellar hypometabolism.¹³ Kwon et al. reported a case of BBE in a 58-year-old male patient who underwent MRI without showing any abnormalities. An 18-FDG PET scan was also performed, demonstrating bilateral cerebellar hypometabolism.¹⁴

Given the scarcity of information from previous studies, we cannot conclude that there is a characteristic pattern in 18-FDG PET findings in BBE. However, it appears that the most frequently observed finding is hypometabolism in the occipital lobes. Further research with a larger cohort of patients is still required.¹⁵

Regarding similar diseases, a meta-analysis that included 21 articles analyzing 444 patients was conducted by Bordonne et al., evaluating the most frequent sensitivity and metabolic patterns in autoimmune encephalitis. This analysis reported that in anti-NMDAR encephalitis, hypometabolism in the posterior associative cortices, particularly in the occipital lobes, demonstrated a sensitivity of 88% (74-95%), representing an early biomarker to discriminate anti-NMDAR encephalitis from other autoimmune encephalitis.⁸ This pattern may serve as an early surrogate marker for BBE.

Conclusion

Brain 18-FDG PET is useful in the diagnosis and follow-up of patients with autoimmune encephalitis. In our patient with Bickerstaff brainstem encephalitis, PET imaging revealed a pattern of brain metabolism similar to that observed in other autoimmune encephalitides, such as anti-NMDAR. This is consistent with other case reports, showing that 18-FDG PET may serve as a surrogate marker for understanding CNS compromise in BBE. However, it is important to note the limited information in the current literature, and the need for more studies on this topic.

Data Availability Statement (DAS)

The data that support the findings of this study are available upon request from the corresponding author, (JCLH).

References

1. Wakerley BR, Uncini A, Yuki N. Guillain-Barré and Miller Fisher syndromes - new diagnostic classification. *Nat Rev Neurol.* 2014;10(9):537-44. doi: [10.1038/nrneurol.2014.138](https://doi.org/10.1038/nrneurol.2014.138)
2. Aguilar-Parra LG, Rodríguez-Jiménez KV, de-Saráchaga AJ, Bazán-Rodríguez AL, Martínez-Jiménez E, Galnares-Olalde JA, et al. Frequency, clinical, and paraclinical characteristics of patients with Bickerstaff brainstem encephalitis in a tertiary-referral neurological center. *Rev Mex Neurocienc.* 2022;23(2):57-62. doi: [10.24875/rmn.21000050](https://doi.org/10.24875/rmn.21000050)
3. Koga M, Kusunoki S, Kaida K, Uehara R, Nakamura Y, Kohriyama T, et al. Nationwide survey of patients in Japan with Bickerstaff brainstem encephalitis: epidemiological and clinical characteristics. *J Neurol Neurosurg Psychiatry.* 2012;83(12):1210-5. doi: [10.1136/jnnp-2012-303060](https://doi.org/10.1136/jnnp-2012-303060)
4. Ito M, Kuwabara S, Odaka M, Misawa S, Koga M, Hirata K, et al. Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. *J Neurol.* 2008;255(5):674-82. doi: [10.1007/s00415-008-0775-0](https://doi.org/10.1007/s00415-008-0775-0)
5. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016;15(4):391-404. doi: [10.1016/S1474-4422\(15\)00401-9](https://doi.org/10.1016/S1474-4422(15)00401-9)
6. Bickerstaff ER. Brain-stem encephalitis; further observations on a grave syndrome with benign prognosis. *Br Med J.* 1957;1(5032):1384-7. doi: [10.1136/bmj.1.5032.1384](https://doi.org/10.1136/bmj.1.5032.1384)
7. Shahrizaila N, Yuki N. Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. *J Neurol Neurosurg Psychiatry.* 2013;84(5):576-83. doi: [10.1136/jnnp-2012-302824](https://doi.org/10.1136/jnnp-2012-302824)
8. Bordonne M, Chawki MB, Doyen M, et al. Brain 18F-FDG PET for the diagnosis of autoimmune encephalitis: a systematic review and a meta-analysis. *Eur J Nucl Med Mol Imaging.* 2021;48(12):3847-58. doi: [10.1007/s00259-021-05299-y](https://doi.org/10.1007/s00259-021-05299-y)
9. Odaka M, Yuki N, Yamada M, Koga M, Takemi T, Hirata K, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. *Brain.* 2003;126(Pt 10):2279-90. doi: [10.1093/brain/awg233](https://doi.org/10.1093/brain/awg233)
10. Yoshimura H, Togo M, Ishii J, Ishiyama H, Tamura R, Kimura M, et al. Electroencephalographic findings in Bickerstaff's brainstem encephalitis: a possible reflection of the dysfunction of the ascending reticular activating system. *Clin Neurophysiol Pract.* 2021;6:29-35. doi: [10.1016/j.cnp.2020.11.004](https://doi.org/10.1016/j.cnp.2020.11.004)
11. Espinola-Nadurille M, Bautista-Gomez P, Flores J, Rivas-Alonso V, Perez-Esparza R, Solís-Vivanco R, et al. Non-inflammatory cerebrospinal fluid delays the diagnosis and start of immunotherapy in anti-NMDAR encephalitis. *Arq Neuropsiquiatr.* 2018;76(1):2-5. doi: [10.1590/0004-282X20170179](https://doi.org/10.1590/0004-282X20170179)
12. Probasco JC, Solnes L, Nalluri A, Cohen J, Jones KM, Zan E, et al. Abnormal brain metabolism on FDG-PET/CT is a common early finding in autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm.* 2017;4(4):e352. doi: [10.1212/NXI.0000000000000352](https://doi.org/10.1212/NXI.0000000000000352)
13. Nerrant E, Fourcade C, Coulette S, Lechiche C, Thouvenot E. Teaching NeuroImages: extensive vasogenic edema in Bickerstaff brainstem encephalitis. *Neurology.* 2016;86(4):e38-e39. doi: [10.1212/WNL.0000000000002309](https://doi.org/10.1212/WNL.0000000000002309)
14. Kwon HM, Hong YH, Sung JJ, Paeng JC, Lee DS, Lee KW. A case of Bickerstaff's brainstem encephalitis; the evidence of cerebellum involvement by SPM analysis using PET. *Clin Neurol Neurosurg.* 2006;108(4):418-20. doi: [10.1016/j.clineuro.2005.01.012](https://doi.org/10.1016/j.clineuro.2005.01.012)
15. Kerik-Rotenberg N, Diaz-Meneses I, Hernandez-Ramirez R, Muñoz-Casillas R, Reynoso-Mejía CA, Flores-Rivera J, et al. A metabolic brain pattern associated with anti-N-methyl-D-aspartate receptor encephalitis. *Psychosomatics.* 2020;61(1):39-48. doi: [10.1016/j.psym.2019.08.007](https://doi.org/10.1016/j.psym.2019.08.007)