Title: Is there an autoimmune encephalitis-like brain metabolism pattern in patients with Bickerstaff brainstem encephalitis?

Authors:
Ramírez-Bermudez Jesús¹,*
Galnares-Olalde Javier Andrés²,*
García-Sarreón Alexis³
Rodríguez-Jimenez Karla³
Mireles Sara³
Martínez-Angeles Victoria¹
Nora Estela Kerik-Rotenberg⁴
Iván Eudaldo Meneses-Diaz⁴
Emilly Alejandra Cortes-Mancera⁴
Fabio Andrés Sinisterra-Solis⁴
Vargas-Cañas Edwin Steven²
López-Hernández Juan Carlos²

1.-Department of Neuropsychiatry, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery.
2.-Department of Neuromuscular Diseases, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery.
3.-Department of Neurology, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery.

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4.-Department of Nuclear Medicine, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery.

*This authors contributed equally to this manuscript as first authors.

**Corresponding author: López-Hernández Juan Carlos**

Email: juanca9684@hotmail.com

Adress: 3877 Insurgentes Sur, La Fama, Tlalpan, México City, 14269, México.

Phone number: Tel/Fax:+52 (55) 5606 3822.

Author´s ORCID:

Ramírez-Bermúdez Jesús: [https://orcid.org/0000-0003-2879-5258](https://orcid.org/0000-0003-2879-5258)

Galnares-Olalde Javier Andrés: [http://orcid.org/0000-0003-3004-6221](http://orcid.org/0000-0003-3004-6221)

García-Serreón Alexis: unavailable

Rodríguez-Jimenez Karla: unavailable

Mireles Sara: unavailable

Martínez-Angeles Victoria: [https://orcid.org/0000-0001-7793-6956](https://orcid.org/0000-0001-7793-6956)

Nora Estela Kerik-Rotenberg: unavailable

Iván Eudaldo Meneses-Díaz: unavailable

Emilly Alejandra Cortes-Mancera: unavailable

Fabio Andrés Sinisterra-Solis: unavailable

Vargas-Cañas Edwin Steven: [https://orcid.org/0000-0001-7156-8275](https://orcid.org/0000-0001-7156-8275)

López-Hernández Juan Carlos: [https://orcid.org/0000-0003-3419-5160](https://orcid.org/0000-0003-3419-5160)
Authors' contributions:
RBJ: writing, review, editing
GOJA: writing, review, editing
GSA: writing, review
RJK: writing, review
MS: writing, review
MAV: writing, review
NEKR: writing, review
IEMD: writing, review
EACM: writing, review
FASS: writing, review
VCES: writing, review
LHJC: writing, review, editing.

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Abstract:

**Background:** Brain 18 FDG PET is very useful in the diagnosis of autoimmune encephalitides against post-synaptic receptors. However, little is known about the metabolic changes in other autoimmune encephalitides, such as Bickerstaff stem encephalitis (BBE).

**Objective:** to report the case of a patient with BBE with an 18 FDG PET study and to review the literature.

**Results:** A 20-year-old man with no relevant history presented to the emergency department due to a clinical picture of 7 days of evolution, characterized by non-painful distal paresthesias in the 4 extremities, diplopia, instability on gait and dysphagia. On the day of his hospital stay, he presented alterations in his awake state. The clinical diagnosis of Bikerstaff's stem encephalitis was made. In his paraclinical tests, the cerebrospinal fluid was normal. He received treatment with human immunoglobulin (2 grams/kg) for 5 days. An 18 FDG PET study reported hypermetabolism in the putamen and bilateral caudate nucleus and bilateral occipital hypometabolism.

**Conclusion:** brain 18-FDG PET may be a subrogate marker for understanding CNS compromise in BBE.
Introduction:

Brainstem Bickerstaff encephalitis (BBE) remains a clinical diagnosis consisting of ophthalmoplegia, ataxia and altered consciousness. It is a rare clinical entity, representing 1.7% of Guillain-Barre syndrome cases \(^1,2\). It is associated with anti-GQ1b antibodies, which are present in 66% of patients \(^3\). Worldwide consensus state that BBE is a "brainstem continuum" of Miller Fisher syndrome (MF). Both entities share the early onset, preceding infection, sensory disturbances (e.g., numbness) in distal extremities, oropharyngeal palsy, abducens palsy and a good outcome and recovery \(^3,4\).

Involvement of the Central Nervous System (CNS) remains controversial. In the review of Graus et al in 2016, he described this clinical feature as a "decreased level of consciousness", \(^5\). In one of the biggest cohorts to date, Ito found magnetic resonance imaging (MRI) brainstem lesions in 10% cases and 1/3 had pyramidal signs and altered reflexes. Bickerstaff's described something important about neuropsychiatric disturbances in these patients: all of them became drowsy, being this the principal feature of this entity \(^6\).

Miller-Fisher and BBE are considered GBS variants as they share albuminocytological dissociation and antigangliosides. However, in BBE not only the peripheral nerves are compromised, but also some brainstem networks including the corticospinal pathway and the ascending reticular activating system. \(^7\)

There are some reports on the usefulness of 18-FDG positron emission tomography (PET) on changes in brain metabolism in patients diagnosed with autoimmune
encephalitis (AE), such as autoimmune encephalitis due to antibodies against N-methyl aspartate receptor (anti-NMDAr) (8).

There are few studies on changes in brain metabolism in Bickerstaff's encephalitis. The objective of this work is to describe a case of BBE and its changes in the metabolism of 18 FDG PET, and to review the narrative of the literature.
Case report:

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

On arrival, his vital signs and general examination were unremarkable. He was awake and alert, with a flaccid and severe dysarthria. On cranial nerve examination, bilateral complete ophtalmoplegia was noted, as well as bilateral facial and soft palate weakness, without gag reflex. His strength was normal in four limbs, but he had generalized hyporreflexia. A Babinski sign was found bilaterally, and he had bilateral dysmetria and ataxia.

Paraclinical tests showed no abnormalities in blood cell count and kidney and liver function testing. CSF examination demonstrated normal glucose (58 mg/dl), proteins (31 mg/dl) and six mononuclear cells. At first, a Miller-Fisher syndrome was diagnosed. Nevertheless, in his first hours of hospitalization he developed a profound stupor, requiring mechanical ventilation. Infectious etiologies, such as aspiration pneumonia were discarded. Thus, clinical criteria of Bickerstaff’s
Brainstem Encephalitis (BBE) were met, and a 2 g/day dose of intravenous immunoglobulin (IVIg) for 5 days were initiated.

Serological test for HIV, hepatitis-B and C virus and syphilis were negative. CSF cultures and stains were also negative. Anti-GQ1b in serum was negative. An MRI showed no abnormalities, and 18F-FDG PET reported in cerebral parenchyma, bilateral occipital hypometabolism in the dorsolateral cortex, bilateral temporal hypometabolism of right predominance and hypermetabolism in the bilateral and symmetrical striated nucleus, as well as hypermetabolism in the right thalamus. <Image 1>.

Of note in his evolution, the patient developed cardiovascular dysautonomia with variability of his heartbeat without hemodynamic compromise. On his third day of hospitalization, withdrawal of invasive mechanical ventilation was possible due to an improvement of the wakefulness state. However, psychomotor agitation, visual hallucinations requiring intravenous sedation with dexmedetomidine. The patient presented improvement in his wakefulness and confusion states on day 10 of hospital stay and further discharged.
Discussion

Brainstem Bickerstaff encephalitis (BBE) is due to an aberrant immune response after respiratory or gastrointestinal infection, producing antibodies against the ganglioside GQ1b, which is present in 66% of cases. (7) Classically, GBS affects the peripheral nervous system, but in the case of BBE there is involvement of the central nervous system as well (8,9). A main clinical feature in BBE, apart from ophthalmoplegia and ataxia, is altered wakefulness, which is due to impaired functionality of the ascending reticular activating system in the brainstem (8,9). In a retrospective study of 5 patients with BBE, electroencephalograms performed were analyzed, finding dysfunction and abnormalities during sleep, suggesting involvement of the ascending reticular activating system (10). A study of a postmortem BBE patient reported inflammatory changes in the brainstem (9).

The clinical picture of BBE patients starts with diplopia, ataxia, distal paresthesias, alteration of lower cranial nerves (VII, IX and X), alteration of wakefulness (drowsiness, stupor or coma). Subsequently, some patients develop hyperactive delirium, usually accompanied by cardiovascular dysautonomia (variability in heart
rate and/or blood pressure) (4,7). Even though there is CNS involvement, paraclinical studies focused on the blood-brain barrier and structural alterations (CSF cytochemical and MRI of the brain) are mostly normal (4). This normality in ancillary tests occurs in other models of autoimmune encephalitis (AE). One of the main AE described in recent years is against the NMDA receptor, where 52% of patients have non-inflammatory CSF and up to 34.5% of patients have normal MRI (11). Studies report changes in brain metabolism in 18 FDG PET in patients diagnosed with autoimmune encephalitis by clinical criteria, including surface (NMDAr, VGKCc, GAD6, LGI1, etc.) and other antibodies, but did not include patients with BBE. These changes were mainly hypometabolism in several cortical and subcortical brain areas, especially in the temporal and occipital lobes (12).

There is little information on changes in brain metabolism in patients with BBE. We previously published a series of cases of BBE within this series: a 60-year-old male patient clinically presented as BEE with normal CSF, unaltered MRI and positive anti-GQ1b antibody. 18-FDG PET was performed, reporting hypometabolism in occipital lobes (2). This previously reported patient had similar characteristics to the current patient reported (Table 1). Another study of Nerrant reported the case of a 32-year-old woman diagnosed with BBE, who presented changes in intensity on MRI due to vasogenic edema located in cerebellum and brain stem. In addition, in the 18-FDG PET study, he 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; 18-FDG PET was also performed demonstrating bilateral cerebellar hypometabolism (14).

Due to the little information from previous studies, we cannot conclude that there is a characteristic pattern in 18-FDG PET in BBE, but the most frequent finding is hypometabolism in the occipital lobes. More studies with a larger number of patients are still required. (15). Speaking of similar diseases, a meta-analysis that included 21 articles analyzing 444 patients, Bordonne et al. evaluated the most frequent sensitivity and metabolic patterns in autoimmune encephalitis, reporting that in anti-NMDAR encephalitis, hypometabolism in posterior associative cortices, mainly the occipital lobes, has a sensitivity of 88% (74-95%). Representing an early biomarker to discriminate anti-NMDAr encephalitis from other autoimmune encephalitis (8). This may be an early subrogate 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 showed a pattern of brain metabolism similar to other autoimmune encephalitides, such as anti-NMDAr. This is consistent with other case reports, showing it may be a subrogate marker for understanding CNS compromise in BBE. However, there is little information in the literature and more studies are required.

**Data Availability Statement (DAS)**

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The data that support the findings of this study are available on request from the corresponding author, [JCLH].

**Figure:**

**Figure 1:** PET/CT with 18F FDG metabolic pattern of Bickerstaff brainstem encephalitis  
A) Upper row in sagittal cut shows occipital hypometabolism (blue arrows).  
B) Intermediate row axial cut shows hypermetabolism of putamens and caudate nuclei (red arrows) and occipital hypometabolism (blue arrows).  
C) Syngo Scenium, corroborates occipital hypometabolism (blue arrows).

**Tables:**

**Table 1:** summarizes information from previous reports of Bickerstaff brainstem encephalitis and our current patient with changes in brain 18F-PET-FDG metabolism.

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| Table 1: Baseline characteristics of our patient vs other case reports |
|---------------|----------------|----------------|----------------|----------------|
| 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 | Ophtalmoplegia, VII, bulbar nerves. | Ophtalmoplegia, VII, bulbar nerves. | Ophtalmoplegia, VII, bulbar nerves. | Diplopia (non-specified) |
| IMV requirement | (+)            | (+)             | (-)            | (-)             |

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<table>
<thead>
<tr>
<th>CSF</th>
<th>No ACD</th>
<th>No ACD</th>
<th>No ACD</th>
<th>1.01 gr/L of protein, 123 cells (neutrophills)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with IgIV</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>Antibodies:</td>
<td>Anti-GQ1b (-)</td>
<td>Anti-GQ1b (+)</td>
<td>Anti-GQ1b (-), Anti-GM1 IgM (+)</td>
<td>Anti-GQ1b (-), Anti-GD1a (+)</td>
</tr>
<tr>
<td>MRI image</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Vasogenic edema in brainstem and cerebellum white matter.</td>
</tr>
<tr>
<td>Brain 18F-PET-FDG Metabolism</td>
<td>Hypometabolism in the occipital and temporal lobes; hypermetabolism in striatal nuclei.</td>
<td>Hypometabolism in occipital lobes and cerebellum, hypermetabolism in bilateral striatum</td>
<td>Hypometabolism in the cerebellum.</td>
<td>Bilateral temporo-parieto-occipital hypometabolism.</td>
</tr>
</tbody>
</table>

ACD: albumin-cytologic dissociation; CSF: Cerebrospinal fluid; IgIV: Intravenous Immunoglobulin; IMV: invasive mechanical ventilation; UTRI: upper tract respiratory infection;