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ORIGINAL ARTICLE

Frequency, clinical, and paraclinical characteristics of patients with Bickerstaff brainstem encephalitis in a tertiary-referral neurological center

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Abstract

Background: *Bickerstaff brainstem encephalitis (BBE) presents with consciousness impairment, ataxia, ophthalmoplegia, and areflexia.* **Objective:** *We aim to describe the clinical, paraclinical, and imaging features of patients with BBE from a tertiary-referral neurological center.* **Methods:** *A case series was conducted from an ambispective cohort of patients with Guillain-Barré syndrome (GBS) from 2016 to 2021. Subjects ≥ 18 years and who met Odaka et al. BBE criteria were eligible. Data collected included: age, gender, prior infection, Guillain-Barré disability score (GDS score), time from symptom onset to diagnosis, altered mental state, time from symptom onset to altered mental state, cranial nerve involvement, deep tendon reflexes, ataxia, invasive mechanical ventilation (IMV) requirement, treatment, inpatient delirium, length of stay (days), and protein levels in CSF analysis. Nerve conduction studies (NCS) were performed, as well as neuroimaging (brain magnetic resonance imaging [MRI] and ^{F}18-fluorodeoxyglucose PET-CT). Antiganglioside antibodies panel including anti-GQ1b was solicited.* **Results:** *Four patients (1.7%) met the inclusion criteria. Two patients manifested stupor and two showed somnolence throughout the course of the disease. Three patients required IMV due to bulbar dysfunction. None of the NCS met the criteria for any GBS electrophysiological variant. One patient was positive for IgM GM2 antibodies. One patient underwent 18F-FDG PET-CT, showing generalized cortical hypometabolism.* **Conclusion:** *The frequency of BBE in our population is very low (1.7%). IgM GM2 is another anti-ganglioside antibody related to BBE. Imaging studies such as MRI frequently do not present abnormalities and [^{F}18-FDG-PET scan might be a useful study to describe a metabolism pattern to aid the diagnosis of BBE.*

Keywords: *Guillain Barré. Bickerstaff. Miller fisher. Brainstem encephalitis. GQ1b. Antiganglioside antibodies.*

Frecuencia, características clínicas y paraclínicas de pacientes con encefalitis de Bickerstaff en un centro neurológico de referencia de tercer nivel

Resumen

Antecedentes: *La encefalitis de Bickerstaff (EB) se presenta con alteración del nivel de consciencia, ataxia, oftalmoplejia y arreflexia.* **Objetivos:** *Nuestro objetivo es describir las características clínicas, paraclínicas e imagenológicas de pacientes con EB en un centro neurológico de referencia de tercer nivel.* **Métodos:** *Se realizó una serie de casos de una cohorte*

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ambispectiva de pacientes con Guillain Barré (GB) desde 2016 hasta 2021. Se incluyeron pacientes mayores de 18 años que cumplieron los criterios de Odaka et al. para EB. La información obtenida incluyó: edad, género, infección previa, escala de discapacidad de GB y niveles de proteinas en el LCR, entre otros. Se realizaron estudios de conducción nerviosa, estudios de neuroimagen (RM de encéfalo y 18F-FDG-PET-CT) y panel de anticuerpos antigangliósidos. **Resultados:** *Cuatro pacientes (1.7%) cumplieron los criterios de inclusión. Dos pacientes presentaron estupor y dos somnolencia a lo largo de la enfermedad. Tres pacientes requirieron ventilación mecánica. Ninguno de los estudios de conducción nerviosa cumplió los criterios para alguna variante electrofisiológica de GB. Un paciente tuvo anticuerpos anti GM2 IgM positivos. A un paciente se le realizó 18F-FDG-PET-CT, mostrando hipometabolismo cortical generalizado.* **Conclusiones:** *La frecuencia de EB en nuestra población es muy baja. El anticuerpo GM2 IgM es otro antiganglósido relacionado a EB. La resonancia magnética no presentó anormalidades y el 18F-FDG-PET-CT podría ser un estudio útil para describir un patrón de metabolismo que ayude en el diagnóstico de EB.*

Palabras clave: *Guillain Barré. Bickerstaff. Miller Fisher. Encefalitis de tallo. GQ1b. Aanticuerpos antigangliosidos.*

Introduction

Guillain-Barré syndrome (GBS) incidence has been described in different reports, varying from 0.8 to 1.9 cases per 100,000 person/year[1,2]. GBS is an autoimmune polyradiculoneuropathy caused by antibodies directed toward axonal gangliosides and myelin proteins following an upper airway or gastrointestinal infection. Several antigangliosides have been described in different GBS variants, such as anti-GQ1b in Miller-Fisher syndrome (MFS) and Bickerstaff brainstem encephalitis (BBE). BBE presents with consciousness impairment, ataxia, ophthalmoplegia, and areflexia[3]. GQ1b antibodies are present in 66% of patients with BBE[4]. More recent classifications consider MFS and BBE as part of the same disease spectrum, noting that they share a similar pathophysiological mechanism, known as the anti-GQ1b syndrome[5].

The first descriptions of BBE were made in 1955 by Bickerstaff in patients with external ophthalmoplegia, ataxia, and altered consciousness with favorable outcome[6]. BBE is very uncommon, with a reported incidence of 0.78/100,000 person/year[2]. Odaka et al. proposed diagnostic criteria for BBE, based solely on its clinical features: (a) progressive, relatively symmetric ataxia by 4 weeks, (b) disturbance of consciousness or hyperreflexia, and (c) preserved muscle strength. Moreover, patients with BBE may present overlap features with MFS or GBS[7].

The most available publications about BBE and its clinical and paraclinical characteristics are known from studies made in Asian population, with few information published regarding Latin American subjects. In this paper, we aim to describe the clinical, paraclinical, and imaging features of a case series of patients with BBE from a tertiary-referral neurological center.

Methods

A case series was conducted from an ambispective cohort of patients with GBS from 2016 to 2021 in a tertiary-referral neurological center. Subjects ≥ 18 years and who met Odaka et al. BBE criteria were eligible[7,8].

The data collected included: age, gender, prior infection, Guillain-Barré disability score (GDS score), time from symptom onset to diagnosis, altered mental state, time from symptom onset to altered mental state, cranial nerve involvement, deep tendon reflexes, ataxia, invasive mechanical ventilation (IMV) requirement, treatment (intravenous immunoglobulin [IVIG], plasma exchange [PE]), inpatient delirium, length of stay (days), and protein levels in CSF analysis.

Nerve conduction studies (NCS) were performed in all patients by an experienced neurophysiologist according to our registered protocol; distal latency, nerve conduction velocity (NCV), and compound muscle action potential (CMAP) were registered for both motor (median, ulnar, tibial, and fibular) and sensory nerves (median and sural). Electrophysiological variants were established according to Hadden et al. criteria[9].

Neuroimaging included brain magnetic resonance imaging (MRI) with contrast (T1, T2 Flair, ADC, and DWI) and positron emission tomography with 18F-fluorodeoxyglucose (18F-FDG PET-CT), and they were reviewed by an experienced neuroradiologist and a nuclear medicine specialist, respectively. Antiganglioside antibodies panel including anti-GQ1b were solicited. The presence of anti-GQ1b antibodies was positive with titers > 500 Bühlmann title units by enzyme-linked immunoabsorbent assay.

Table 1. Clinical and imaging features in patients with BBE

Gender	Patient 1	Patient 2	Patient 3	Patient 4
	Male	Female	Male	Female
Age	60	58	20	22
Prior infection Respiratory tract infection Gastrointestinal infection	 + –	 + –	 – –	 – +
Time from symptoms onset to diagnosis (days)	2	2	16	2
GBD Score	2	3	1	4
Altered mental state	Stupor	Stupor	Somnolence	Somnolence
Time from symptom onset to altered mental state (days)	4	1	7	4
Ataxia	+	+	+	–
Areflexia	+	+	+	–
Ophthalmoplegia	+	+	+	+
Cranial nerve involvement	Bilateral VII, Bulbar	Bulbar	No	Bilateral VII, Bulbar
IMV requirement	+	+	–	+
Other neurological signs	No	No	Babinski	Hemicorporal hypoesthesia, asymmetric weakness.
CSF Proteins	31 mg/dL	54 mg/dL	136 mg/dL	35mg/dL
Treatment	IVIG	PE	Conservative	IVIG
Antigangliosides antibodies	GQ1b (+)	IgG-GQ1b (+) IgG-GT1a(+)	GQ1b (–) IgM-GM2 (+) IgM-GM1 (+)	GQ1b (–) IgG-GT1a(+)
Length of stay (days)	37	23	14	Missing data
Brain MRI abnormalities	–	–	–	–

GBD: Guillain-Barré disability score; IMV: invasive mechanical ventilation.

Results

Two hundred and thirty GBS patients were evaluated between 2016 and 2021. Four patients (1.7%) met the inclusion criteria. Three patients were men, with a median age of 40 (20-60) years. The GDS score on admission ranged from 1 to 4 points; two patients manifested stupor and two showed somnolence throughout the course of the disease. All patients developed ophthalmoplegia. Three patients required IMV due to bulbar dysfunction, and three patients developed delirium during their in-hospitalization. Baseline demographics are presented in table 1.

None of the NCS met the criteria for any GBS electrophysiological variant (Table 2). Patient 2 presented an abnormal sensory nerve action potential in the median nerve (Non-recording) and diminished CMAP for the peroneal nerve. Patient 3 showed increased distal latency for the peroneal nerve in demyelinating values.

Regarding paraclinical studies, two patients showed CSF albumin-cytological dissociation; three patients were positive to GQ1b antibodies, one patient was positive for IgM GM2 antibodies, and one patient resulted positive to IgG GT1a.

MRI was available in three patients, neither of whom presented any brainstem abnormalities (Fig. 1). One patient underwent 18F-FDG PET-CT, showing generalized cortical hypometabolism; hypermetabolism was visualized in the striatum (St) bilaterally (Fig. 2).

Table 2. Nerve conduction studies in patients with BBE

	Patient 1	Patient 2	Patient 3	Patient 4
Median Motor				
Distal latency (ms)	3.9	4.1	3.8	3.6
NCV (m/s)	45	54	57	58
dCMAP (mV)	9.6	5.7	9.4	8.1
Cubital Motor				
Distal latency	3.3	3.3	2.9	3.1
NCV (m/s)	56	58	58	61
dCMAP (mV)	9.2	5.9	7.9	10.3
Tibial				
Distal latency	5.5	4.3	4.5	4.1
NCV (m/s)	40	43	48	52
dCMAP (mV)	7.2	6.6	10.6	19.5
Peroneal				
Distal latency	5.2	4.9	5.9	5.2
NCV (m/s)	41	52	47	58
dCMAP (mV)	5.9	1.7	42	3.8
Median sensitive				
dSNAP µV	19	NR	42.9	61.5
Sural				
dSNAP µV	14.2	2.8	16.6	44.7

NCV: nerve conduction velocity; ms: milliseconds, m/s: meters/second; mV: millivolts; µV: microvolts; dCMAP: distal compound muscle action potential; dSNAP: distal sensory nerve action potential.

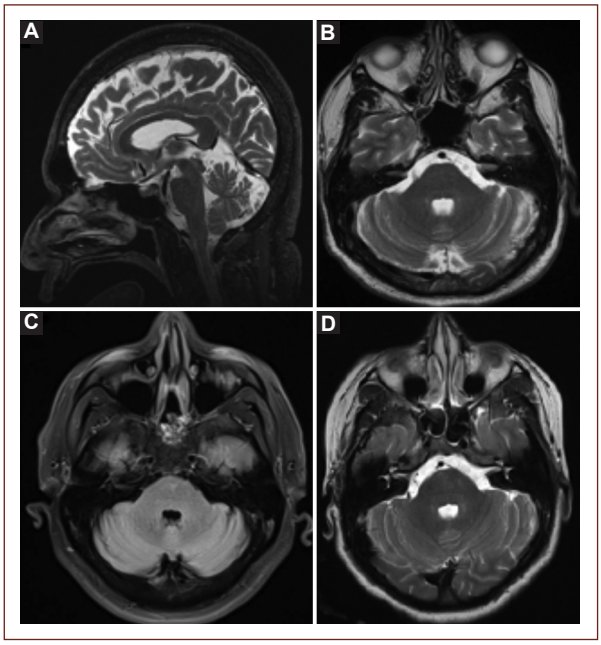

Figure 1. Normal brain MRI in subjects with BBE. **A:** sagittal T2; **B:** axial T2 from patient 1; **C:** axial T2 FLAIR from patient 2; **D:** axial T2 from patient 4.

Discussion

The most observational studies, either case series or cohort studies regarding BBE were performed in Asian countries such as China and Japan, reporting an annual incidence of 0.7/100,000 person/years[2]. In one observational study from a single center in Southeast China, the frequency of BBE was 4.7% among 170 patients with GBS[10]. Before this article, little was known about the frequency of BBE among clinical phenotypes of GBS in Latin American countries. Our group had previously reported a frequency of BBE/MFS overlap in 1.5% of patients[11]; currently with more patients included in our GBS cohort. In our center, 1.7% of cases met criteria for BEE.

MFS and BBE are caused by antiganglioside GQ1b antibodies in 80% and 66% cases, respectively; thus, it has been suggested recently that these two clinical entities are part of the same spectrum: anti GQ1b syndrome. Both phenotypes also may overlap[5,12]. In one study that included 60 patients with MFS, 11% overlapped with BBE[13]. In our population, two patients diagnosed with BBE also met the criteria for MFS. Other antiganglioside antibodies related to BBE include GM1, GD1a, GD1b, and GT1a[12]. In our patients, three showed

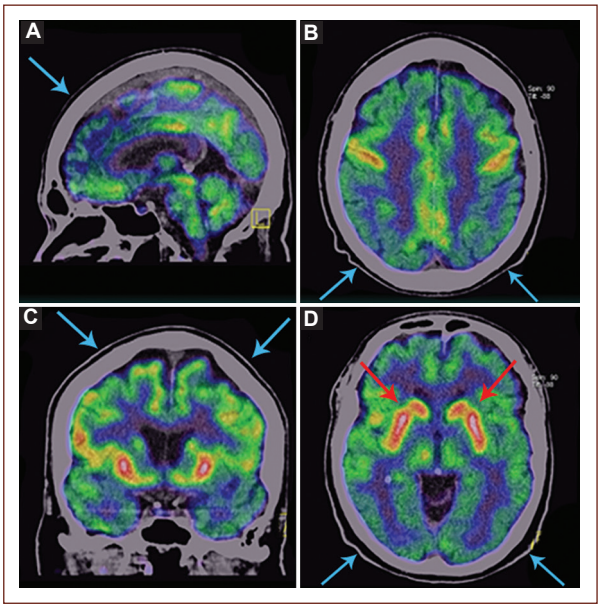

Figure 2. An illustrative brain [^{F}18-FDG-PET scan obtained from patient 1 at 4 weeks after onset of symptoms. **A-D:** sagittal, axial, coronal, and axial views showing regions of hypometabolism including the occipital lobe (OL), parietal lobe (PL), and frontal lobe (FL) bilaterally, cerebellum and brainstem (blue arrows). Hypermetabolism visualized in the striatum (St) bilaterally (red arrows). Metabolic patterns were visualized using TrueD (Siemens, Medical Solutions, Germany).

positive GQ1b antibodies, and another patient, who was negative for GQ1b antibodies, had positive antibodies to IgM GM1 and IgM GM2; the former has not been reported in the previous studies concerning BBE.

The diagnosis of BEE is based on its unique clinical features. In general, patients are classified as BBE if there is evidence of central nervous system involvement, either alterations in the level of consciousness or pyramidal signs[8]. As reported in a case series by Odaka et al., prior infection was present in 60-80% of patients, and CSF albumin-cytological dissociation was found in 25-75% of cases[7]. In our series, only two patients had CSF albumin-cytological dissociation and we found antecedent of infection in three cases.

GBS has been classically described as a post-infectious autoimmune entity with exclusive affection to the peripheral nerves; however, BBE also involves CNS structures[14]. The mechanism by which the GQ1b antibodies cause clinical manifestations is because GQ1b is highly expressed in muscle spindles, important proprioceptive transducers within the muscles, and when binded to the anti GQ1b antibodies they produce the characteristic combination of symptoms[2,14]. The same is not the case with BBE, where little is known about the pathophysiological mechanism in which the ascending reticular activating system of the brainstem is involved. It has been hypothesized that there may be GQ1b among the brainstem structures; but this has not been proven[2]. One histopathologic postmortem study reported perivascular inflammation on the brainstem[6], and another study demonstrated changes on the BBB permeability in the area postrema that may allow some molecules, such as antibodies, to penetrate the CNS[15]. Other studies have shown brainstem involvement in BBE with MRI with findings that correspond to changes of intensity in 11% of cases[12]. In our population, none of the patients had abnormalities on the MRI.

In recent years, 18F-FDG PET-CT has been used in the diagnosis of primary brain autoimmune processes; with the most applicability to NMDA autoimmune encephalitis[16]. There is less information on the utility of 18F-FDG PET-CT in other autoimmune diseases of the CNS, and to the best of our knowledge, this diagnostic modality has not been widely explored in BBE. One patient in our study underwent 18F-FDG PET-CT, and it demonstrated cortical hypometabolism including the occipital lobe, parietal lobe, and frontal lobe bilaterally; cerebellum and brainstem. Even though the diagnosis of BBE remains clinical and serological, the 18F-FDG PET-CT may be useful in the diagnosis and follow-up of these patients, but more studies are needed.

In general, there are few changes in NCS of patients with MFS or BBE. The most frequent findings consist of H reflex abnormalities[12]; in our population this was not found. Reports also show that there may be changes among motor and sensitive nerves, but such findings do not fulfill criteria for any variant of GBS as it was the case within our patients. The blink reflex is an electrophysiological study that might be helpful to document the brainstem involvement in BBE[17]; unfortunately, it was not performed in any of our patients. Nevertheless, we suggest performing it in the future cases.

MFS and BBE have shown good functional outcome[6,18] and the most patients will not require treatment with IVIG or PE. Treatment is warranted for patients who present with GBS overlap features, bulbar cranial nerve palsies, and BBE overlap[19]. All our patients were treated; and even though three of them required IMV due to bulbar dysfunction, all patients recovered at 3-month follow-up.

It has previously been reported that patients with BBE develop hyperactive delirium after recovering from alterations in the level of consciousness[20]. In our series, three patients developed hyperactive delirium; out of which, two did not improve with conventional treatment (Quetiapine, haloperidol, and/or pregabalin) and required dexmedetomidine for delirium management.

Conclusion

The frequency of BBE in our population is very low (1.7%). IgM GM2 is another antiganglioside antibody related to BBE. Imaging studies such as MRI frequently do not present abnormalities and [^{F}18-FDG-PET scan might be a useful study to describe a metabolism pattern to aid the diagnosis of BBE.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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