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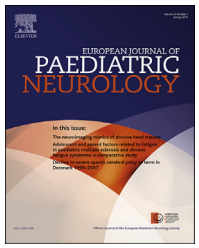

Review article

Bickerstaff Brainstem Encephalitis and overlapping Guillain-Barré syndrome in children: Report of two cases and review of the literature

A. Michev [a], P. Musso [a], T. Foiadelli [a,b,*], C. Trabatti [a], A. Lozza [c], D. Franciotta [d], A.M. Simoncelli [e], S. Savasta [a]

[a] Pediatric Clinic, Foundation IRCCS Policlinico "San Matteo", University of Pavia, Pavia, Italy
[b] Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Italy
[c] Clinical Neurophysiology Service, IRCCS Mondino Foundation, Pavia, Italy
[d] Laboratory of Neuroimmunology, IRCCS Mondino Foundation, Pavia, Italy
[e] Department of Diagnostic Radiology and Interventional Radiology and Neuroradiology, Foundation IRCCS Policlinico "San Matteo", University of Pavia, Pavia, Italy

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ABSTRACT

Bickerstaff Brainstem Encephalitis (BBE) is a rare autoimmune encephalitis, characterized by acute ophthalmoplegia, ataxia and altered state of consciousness. Together with Guillan-Barrè Syndrome (GBS) and Miller–Fisher Syndrome, it forms a spectrum of post-infectious demyelinating diseases. Overlapping forms between BBE and GBS (BBE/GBS) are described in patients with lower limbs weakness and typical signs of BBE, suggesting a combined involvement of Central and Peripheral Nervous System (PNS), but only few reported cases are focused on pediatric population.

We reviewed all cases of pediatric BBE in the literature, to determine if any patient showed features suggestive for BBE/GBS. Data analysis focused on the diagnostic tests performed (e.g. anti-GQ1b antibodies), neuroimaging and nerve conduction studies (NCS). Further attention was given to the therapeutic management and to patients' outcome. We additionally present two previously unreported pediatric cases.

Our review retrieved 19 cases of BBE/GBS, only 2 of which were originally and correctly diagnosed by the authors. The prevalence was higher in male subjects (ratio 3:1) and median age at diagnosis was 8 years. Anti-GQ1b were positive in 46% of the patients, while NCS were altered in 64%. Only 25% of the patients that underwent brain MRI showed abnormal findings.

The incidence of BBE/GBS has been underrated in the past, mostly due to an underestimation of the PNS involvement. We therefore suggest to investigate all patients with a clinical picture suggestive of BBE/GBS through electroencephalogram, NCS, brain and spine MRI in order to promptly achieve the correct diagnosis.

* *Corresponding author*. Fondazione IRCCS Policlinico "San Matteo", Clinica Pediatrica, V.le Camillo Golgi, 19 – 27100, Pavia, PV, Italy. Fax: +39 0382 502876.
E-mail address: thomas.foiadelli@gmail.com (T. Foiadelli).

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Contents

1. Introduction

Bickerstaff Brainstem Encephalitis (BBE) is considered a rare autoimmune encephalitis, first described in 1951 and 1957 by Bickerstaff et al.[1,2] It is clinically characterized by acute ophthalmoplegia, ataxia and disturbed consciousness. Although the exact pathogenesis remains unclear, it is presumably related to an immune reaction, triggered by a previous infection from pathogens like *Campylobacter jejuni*[3], *Mycoplasma pneumoniae*[4] or *Haemophilus influenzae*.[5] The diagnosis relies on clinical features, but it can be supported by neurophysiological studies and magnetic resonance imaging (MRI) of the brain and brainstem.[6] Another supportive element is the presence of serum antiganglioside antibodies (especially anti-GQ1b), which is a feature common to other diseases, such as Guillan-Barré Syndrome (GBS),[7] and Miller Fisher Syndrome (MFS).[8] In fact, some authors have considered BBE, GBS and MFS to be part of an unique spectrum of post-infectious encephalitis and polyneuritis, sharing anti-GQ1b antibodies as a common pathogenetic hallmark.[9] Within this spectrum, overlapping forms of disease between BBE and GBS (BBE/GBS) have been described as expressions of a combined peripheral and a central nervous system (CNS) disease.[6] More recently, a review defined the diagnostic criteria for GBS, BBE and MFS and considered the diagnosis of BBE/GBS in patients with lower limbs weakness associated to the typical signs and symptoms of BBE.[10]

Although several cases of BBE/GBS have been described in adults,[6,11] very few cases are reported in pediatric population. In the hypothesis that the lack of clear diagnostic criteria and specific biomarkers has led to an underestimation of the real prevalence of this form of disease, our purpose is to ascertain whether, among all the cases of pediatric BBE reported in the literature, any could actually show clinical features consistent with overlapping BBE/GBS.

In addition, we present two previously unreported pediatric cases, diagnosed in our Pediatric Department in Pavia between March 2012 and October 2016, whose clinical, neurophysiological and neuroimaging features were suggestive for BBE/GBS.

2. Cases description

2.1. *Patient 1*

XX, female, second child of unrelated patients, was born full term by vaginal delivery, after a normal pregnancy. At the age of four, she was admitted to our Emergency Service for subacute onset of dysarthria and gait unsteadiness. Four days before admission the patient had presented coughing and vomiting that resolved spontaneously within two days. The patient was drowsy, ataxic, with severe weakness of the lower limbs and areflexia. She was unable to speak and to stand up. Rapidly, she developed urine incontinence. At admission, the Modified Rankin Scale (MRS) was 5. The white blood cell count was 22.900/μL and the serum C-reactive protein 2,49 mg/dl. Cerebrospinal fluid (CSF) analysis revealed an albuminocytologic dissociation with 4 cells/μL (normal range: <1 cells/μL) and proteins 104 mg/dl (normal range: 15–45 mg/dl); serum and CSF analysis were negative for bacterial and viral infections. Antiganglioside antibodies screening, including anti-GQ1b, was negative. A treatment with intravenous immunoglobulins (IVIG, 2 g/kg for 5 days) was started, but two days later, her general conditions worsened and she developed bilateral ptosis, external ophthalmoplegia, facial weakness and swallowing difficulties. Since airways secretions discharge became impaired, the patient was transferred to the Intensive Care Unit. Her conditions spontaneously improved, without the need of airways protection or invasive ventilation

and she was readmitted to our unit two days later. Brain and spine MRI at this point showed a bilateral contrast enhancement of cranial nerves III, VI, XII and of the cauda equina nerve roots (Fig. 1a). Nerve Conduction Studies (NCS), revealed slowed motor conductions with absent F-wave. Auditory evoked brain stem responses were normal. High-dose steroid therapy was then started (i.v. Metilprednisolone, 30 mg/kg/die for five days), with consequent rapid improvement of consciousness and gradual resolution of the ophthalmoplegia. She finally recovered with an autonomous ambulation and a regular oral feeding and. The MRS at discharge was 2. Steroid therapy was switched to oral prednisone and tapered for 4 weeks. After 9 months, NCS revealed normal motor conductions, with a residual slight reduction of the distal sensory conductions. Urine incontinence persisted until one year after the event, then gradually resolved. Follow-up continued for 54 months, without relapses.

2.2. *Patient 2*

XY, male, first child of unrelated parents, was born full-term after an uncomplicated pregnancy by vaginal delivery. At the age of two, he presented with incoordination of movements and gait troubles to the Emergency Service of a primary care Hospital. A flu-like illness was reported one week before hospital admission. Clinical examination revealed dysmetria and intention tremors, areflexia and weakness of lower limbs. The gait was unsteady, with marked ataxic features. Routine blood exams were unremarkable. Brain CT was normal. Eventually a therapy with ceftriaxone, acyclovir and methylprednisolone was started. After 5 days, the patient's conditions worsened and he became lethargic. He developed diplopia, horizontal gaze palsy, and distal weakness progressing to flaccid tetraparesis. Additionally, the patient showed episodes of desaturation and impaired swallowing. Brain MRI showed symmetrical signal alterations of the posterior spinocerebellar tracts in the medulla oblungata, pons and midbrain (Fig. 1b). EEG revealed slowed background activity. Additionally, CSF analysis revealed albuminocytologic dissociation, while anti-Mycoplasma pneumoniae and Echovirus IgM antibodies were detected in serum. A treatment with IVIG (1 g/kg for three days) and azithromycin was finally started. He fully regained consciousness and ophthalmoplegia gradually resolved. Asymmetric flaccid tetra paresis with complete right upper limb paralysis persisted at discharge, 19 days later. One month later, he was admitted to our Pediatric

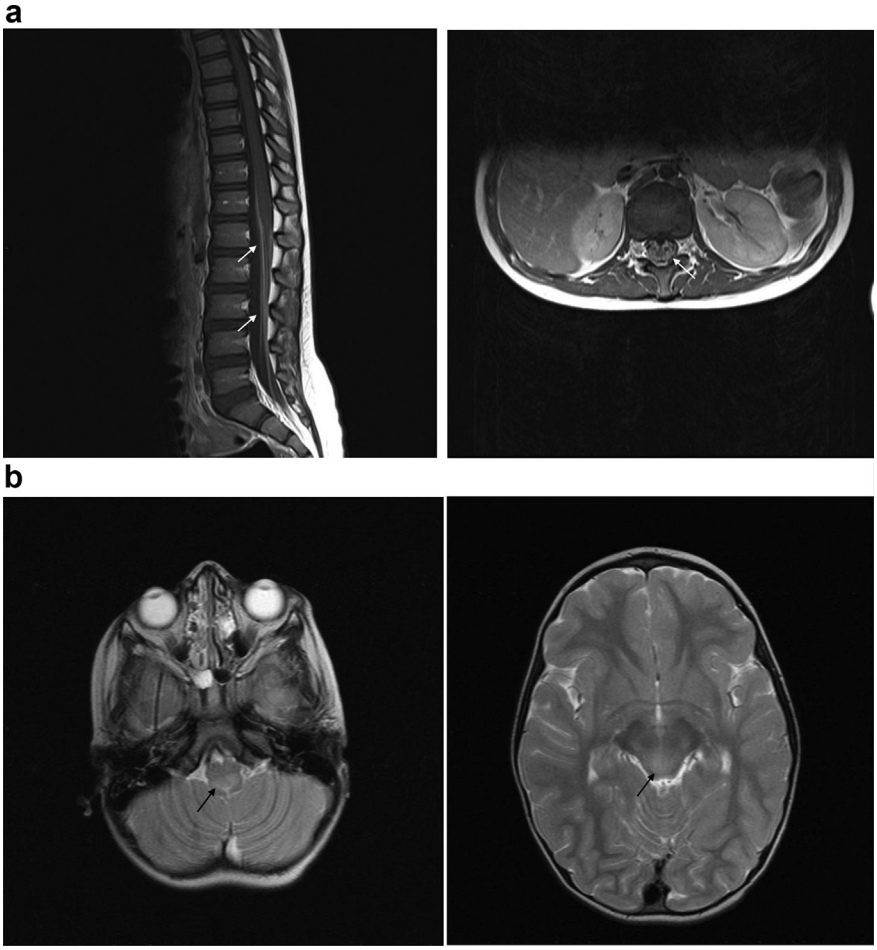

Fig. 1 – a: T1 weighted, post-contrast, spine MRI images in sagittal (left) and transverse (right) sections show enhancement of several cauda equina roots in Patient 1. b: T2 weighted, brain and brainstem MRI images in transverse sections show signal hyperintensity in dorsal brainstem (left) and periaqueductal midbrain (right) in Patient 2.

Neurology Unit for further investigations. The MRS at admission was 4. Anti-GQ1b on blood and CSF were negative. A spine MRI showed enhancement of the cauda equina nerve roots and NCS documented a denervation pattern upon stimulus of the right deltoid and right first interosseous muscles, with unexcitability of the right ulnar nerve. Two additional doses of IVIG were administered and an intensive rehabilitation program was started. Tetraparesis gradually disappeared after the second dose of IVIG. The patient was followed in the outpatient clinic. At 18 months, MRS is 3: gait troubles are fully recovered, but the use of the right upper limb is still limited for persistence of flaccid distal paralysis.

3. Methods

We performed a literature search in the PubMed database using the search query showed in Appendix A. Articles were included in our study if the following eligibility criteria were matched: (1) they provided original data (case reports, case series), (2) the patients reported in the manuscript were younger than 18 years, (3) the manuscript was written in English or Spanish.

The abstracts of the records resulting from the search were screened to exclude those with a non-relevant topic. According to the previously described criteria, other manuscripts were excluded after a full-text assessment. We further checked the reference list of two reviews we retrieved with our search strategy and found additional eligible manuscripts. Each manuscript we identified as eligible, both from our search and from the citation lists of the reviews, underwent a second full-text assessment to exclude the cases not matching the criteria for BBE, listed in Table 1. Among all the cases of BBE retrieved, only those showing features of overlapping BBE/GBS were included in the review. Criteria were based on those published by Wakerley et al. for BBE and BBE with overlapping GBS[10]: typical BBE triad (ophtalmoplegia, ataxia, altered consciousness) and lower-limb weakness. The two additional cases of BBE/GBS, identified from our center and previously described in this article, were included in the review. All the cases retrieved are listed in Table 2.

4. Results

In total, our search strategy retrieved 36 hits (Fig. 2). A review of the abstracts allowed to eliminate 3 publications, whose topic was not relevant with the purpose of the review. We applied the eligibility criteria to the 33 remaining publications, after a full-text assessment. Nineteen eligible manuscripts[4,12–29] underwent a second full-text assessment that, according to the diagnostic criteria for BBE and BBE/GBS (Table 1), allowed the identification of 12 cases of BBE[4,12–22] and 7 cases of BBE/GBS.[23–39] As shown in Table 2, we included one case whose description did not include signs of ataxia. We figured that, seen the younger age of the patient (7 months), such features may have been difficult to retrieve. The same process of full-text assessment was applied to the manuscripts retrieved from the list of citations of the reviews[12,13] and it revealed 27 cases of BBE and 17 cases of BBE/GBS. We matched all the cases of BBE/GBS, resulting both from our search and from the review's citations, and excluding duplicates: 19 cases of pediatric BBE/GBS were finally identified. The two additional patients treated in our Clinic were not included in the review, but clinical, instrumental and laboratory data are listed in Table 2.

In 2 cases, the diagnosis of BBE/GBS was specifically evoked by the authors.[23,25] Seven cases were diagnosed with BBE (one with an atypical form of BBE), 5 with MFS (one being an overlap MFS/BBE) and 1 with an atypical form of GBS. In 2 other cases the diagnosis was of unspecified brainstem encephalitis. Patient's sex was documented in 17 cases, 13 (68%) being male, with a male:female ratio of 3:1. The median age at diagnosis was 8 years (0,7–17 years). A previous infection was documented in 10/19 patients (53%). Anti-GQ1b titles were reported in 13 cases and resulted positive in 46% of them. Nerve conduction studies resulted altered in 9/14 cases (64%), the majority of patients showing absent F-waves (n = 5) and altered H-reflex (n = 3). The EEG resulted altered in 9/14 cases (64%), most patients showing a slowed activity in delta/theta range. Brain MRI evidenced pathological features in 3/12 cases (25%): one patient showed T2-weighted periacqueductal hyperintensity; another patient presented T1 and T2-weighted brainstem signal hyperintensity; in the third

Table 1 – Clinical criteria for the diagnosis of Bickerstaff Brainstem Encephalitis (BBE), and forms overlapping with Guillain-Barré Syndrome (BBE/GBS)[a].

For BBE, the presence of all the following features:	Altered consciousness Ophtalmoplegia Ataxia
For BBE/GBS, the presence of all the following features	Altered consciousness Ophtalmoplegia Ataxia Lower limbs weakness
For both conditions	Exclusion of other diseases: vascular disease involving the brainstem; Wernicke's encephalopathy; botulism, myasthenia gravis; brainstem tumor; pituitary apoplexy; acute disseminated encephalomyelitis; multiple sclerosis; neuro-Behçet disease; vasculitis; lymphoma.

[a] Based on the criteria published by Wakerley et al. (2014).

patient a T2-weighted hyperintensity was documented along the posterior pons, extending to the rhomboid fossa of the fourth ventricle. Data concerning the therapeutic strategy were exhaustive for 18 patients: five patients (28%) received only supportive cares, 12 patients (67%) received IVIG, either alone or associated to other therapies; one patient underwent only immunoadsorption. The median duration of therapy was 5 days (2–35 days). Eight patients (42%) required intubation and ventilation. The median follow up was 6 months (1–24 months).

Data concerning the follow up were not available for all patients. There is evidence of a monophasic course for all patients, with a full recovery in the majority of cases. Three patients (15.8%) showed minimal residual abnormalities: two patients presented a persistent areflexia and in one patient deep tendon reflexes remained reduced.

5. Discussion

This study included a comprehensive review that allowed us to identify 19 cases with features suggestive of BBE/GBS. In just two of these patients the diagnosis of BBE/GBS was specifically evoked by the authors. In most other cases, the diagnosis was BBE or MFS, even if some cases were considered atypical.

5.1. *Evidences of a combined CNS and PNS involvement*

Bickerstaff's brainstem encephalitis, GBS and MFS lie in a spectrum of variable involvement of the PNS and CNS.[30] On one side of the spectrum, GBS and MFS mainly affect the PNS, without signs of encephalopathy: classic GBS causes an ascending flaccid paresis with or without cranial nerves involvement, while MFS features a typical triad of ophtalmoplegia, ataxia and areflexia. On the other side, as it has been extensively demonstrated over the past years, involvement of the CNS is crucial for BBE: along with the autopsy findings described by Bickerstaff,[2] Al-Din[31] and Odaka,[6] there is evidence that sera derived from BBE patients, but not from MFS patients, can generate a blood–brain barrier damage *in vitro*.[32] Some Authors have postulated that even areflexia in BBE could be explained on a central basis, being it a consequence of a mesencephalic and upper pontine reticular formation involvement.[31] However, we believe that if both areflexia and limb weakness are present in the context of a BBE syndrome, this should be defined as an overlapping form of BBE/GBS, where CNS and PNS involvement coexist.

Even if all patients within our review showed clinical features suggestive of a combined CNS and PNS involvement, ancillary investigations, such as EEG/brain-MRI and NCS/spine-MRI (respectively exploring CNS and PNS) evidenced a combined involvement in only 4 cases. This was mostly related to the lack of a systematic use of such investigations for all patients, also considering possible technical limitations for some of them in the pediatric age.

Seen the growing potential in terms of diagnostic skills, we suggest to extensively investigate both CNS and PNS in patients with clinical pictures of overlapping diseases.

5.2. *The role of NCS in the diagnostic workout*

Data concerning NCS show that 64% of patients presented alterations, mostly in the form of absent F-wave or altered H-reflex. It was not possible to verify if the NCS criteria for GBS were fulfilled, but these features are typical signs of focal proximal nerve dysfunction, as often found in radiculopathies.[33,34] Additionally, this finding was consistent with what we observed in the patients treated in our center, since Patient 1 showed a slowed motor conduction with absent F-wave. Patient 2 presented, indeed, a denervation pattern, with unexcitability of the right ulnar nerve.

A study on a larger cohort, including also adults with BBE/GBS, evidenced NCS alterations in 58% of subjects.[6] Interestingly, authors described a predominant axonal dysfunction among BBE/GBS patients, as confirmed by other authors in some later studies.[35,36] This was consistent with the alterations documented in Patient 2.

5.3. *The role of MRI in the diagnostic workout*

As previously discussed in other reviews, brain MRI shows abnormal findings in approximately one third of BBE patients.[6] Data from our review are in line, since 25% of patients presented alterations on brain MRI. In our experience, Patient 2 showed a symmetric enhancement of the posterior spinocerebellar tracts in the brainstem (Fig. 1b).

Interestingly, two of the three patients that underwent a spine MRI and both the patients treated in our center showed abnormal findings, such as hyperintensity and/or contrast enhancement of the cauda equina, the nerve roots and the conus medullaris (see Fig. 1a). Several authors observed similar radiological features in adult and pediatric patients with GBS,[37,38] but diagnosis of GBS is usually made upon clinical and NCS criteria and these alterations are not exhaustive for the diagnosis.

5.4. *The role of anti-GQ1b in the diagnostic workout*

As for anti-GQ1b antibodies, it is still debated their role as markers of disease, since only a percentage of patients presents a positive title (66%–68% in BBE adult patients[5,6]). The literature does not provide sufficient data to determine whether antibodies activity and expression is variable from children to adults. Our review determined a positive title in 46% of patients with BBE/GBS. In other studies on pediatric BBE patients, anti-GQ1b were positive in 43% of cases.[39] As we experienced, timing is crucial for antibodies determination, since their level tends to decrease along the clinical course of disease.[40]

The possibility for anti-GQ1b to have a role in the pathogenesis is plausible, but there is still the need to understand why the presence of anti-GQ1b results in many different clinical presentations. Recently, some authors focused on the role of anti-GQ1b affinity to heteromeric anti-ganglioside complexes in determining the different clinical pictures.[41] We noticed that both our patients presented ophtalmoplegia with a certain delay compared to the other manifestations of BBE/GBS. This was consistent with what we observed in four other patients retrieved with our review. It is to understand

Table 2 – Review of all reported pediatric BBE/GBS cases, demographic and clinical features, management and follow-up.

First Author, Year	Age (Years), Sex	Relevant signs & symptoms				Authors diagnosis	Neuroimaging: MRI/CT	NCS	EEG	anti-GQ1b	ACD	Infectious agent	Management		Ventilation	Follow up (months)
		Consciousness	Gait/Coordination	Oculomotion	Limb strength								Treatment	Duration (days)		
Bickerstaff, 1957	11, M	Drowsiness, confusion	Bilateral limbs ataxia	Paralysis of conjugate ocular movements	Flaccid limbs weakness	BBE	NP	NP	NP	NP	N	None	Supportive	NP	N	12
Schain, 1971	3, F	Lethargy	Truncal and gait ataxia	Bilateral abducens palsy	Transient gene-realized paralysis	Brainstem encephalitis	CT: medullary enlargement	NP	Unremarkable	NP	N	None	Supportive	NP	N	NA
Eggenberger, 1993	2, M	Sleepiness	Trunk and limb ataxia	Complete ophthalmoplegia	Flaccid tetraparesis	MFS	CT: unremarkable	EMG: absent H and F waves, low amplitude median and peroneal CMAP; borderline increase in facial nerve latency.	Unremarkable	NP	N	None	IVIG + PP	30	Y	NA
Ragosta, 1993	9, F	Stupor	Ataxia	Ophthalmoplegia	Flaccid paralysis	MFS	CT: unremarkable	Unremarkable	Generalized slowing	NP	N	Rubeola	Supportive	NP	Y	6
Kikuchi, 1997	7, M	Coma	Ataxia	Diplopia	Flaccid weakness	BBE	MRI: Periaqueductal hyperintensity (T2-weighted)	Unremarkable	Diffuse delta activity and theta activity	Positive	N	M. pneumoniae	IA	7	N	4
Bradshaw, 2001	5	Sleepiness	Ataxia	Ophthalmoplegia	Leg weakness	GBS (atypical)	CT: unremarkable	Multifocal demyelination	NP	NP	Y	None	Supportive	NP	N	NA
Yuki, 2000	17, M	Drowsiness, confusion	Ataxic gait	External ophtalmoplegia	Tetraparesis	BBE	MRI: unremarkable	Unremarkable	Diffuse theta and delta activity	Positive	N	C.jejuni	Steroids + IVIG	12	N	1
Reyes, 2001	11, M	Somnolence, confusion	Ataxia	Opthalmoplegia	General limb weakness	Benign encephalitis of brainstem	CT: unremarkable MRI: brainstem signal hyperintensity (T1/T2-weighted)	Signs of demyelinating polyneuropathy, with conduction block	Unremarkable	NP	N	Herpes simplex	Supportive	NP	Y	NA
Matsumoto, 2002	4, M	Somnolence	Ataxic gait	Complete ophthalmoplegia	Reduced muscle strength	MFS	MRI: unremarkable	No F waves were elicited in the left median and post-tibial nerves	Spikes (left fronto-central lobes) and generalized high voltage. Slow wave bursts (occipital lobes).	Positive	N	Influenza B	IVIG	5	N	24
Kimoto, 2006	17, M	Somnolence	Ataxia	Ophthalmoplegia	Severe limb weakness	Not mentioned	Not reported	NP	Not reported	Positive	Y	C. jejuni	Not reported	NP	N	NA
Damasceno, 2008	15, F	Somnolence	Cerebellar ataxia	Diplopia, left oculomotor nerve palsy.	Muscle weakness	BBE/MFS	NP	NCS: Reduced amplitude of muscle action potential in facial nerves, right median and right ulnar nerves; diffusely absent F-responses and H-reflex.	NP	Negative	Y	None	Steroids + IVIG	5	N	5
Kim, 2010	9, F	Drowsiness, stupor	Intermittent ataxia	Complete ophtalmoplegia	Reduced strength in upper and lower limbs	BBE	MRI: unremarkable	Unremarkable	Slow activity with irregular, high amplitude delta waves	Negative	N	M.pneumoniae	IVIG + Steroids	5	Y	3

Gologorsky, 2013	12, M	Lethargy	Unsteady gait	Diplopia and absence of horizontal gaze	Bilateral leg weakness	BBE (atypical)	MRI (brain): T2 hyperintensity along the posterior pons extending to the rhomboid fossa of the fourth ventricle	Unremarkable	NP	Negative	N	None	IVIG + Steroids	10	Y	NA
Ajena, 2013	6	Drowsiness	Ataxic gait	Ophthalmoplegia	Generalized weakness	MFS	Unremarkable findings	H-reflex of soleus muscles absent	Unremarkable	Positive	N	None	IVIG	35	Y	NA
Rho, 2014	2, M	Coma	Gait disturbance	Restriction in lateral gaze	Decreased muscle strength	BBE/GBS	MRI (brain and spine): unremarkable	NP	Slow wave bursts overlying bilateral occipital lobes	Negative	N	Epstein-Barr Virus	IVIG + Steroids	5	Y	12
Pavone, 2014	12, M	Coma	Ataxia	Right eye deficit of abduction	Symmetric lower limbs weakness	BBE	Unremarkable findings	Absent F-waves	Diffuse slow activity in theta/ delta range	Positive	N	Cytomegalovirus	Steroids + IVIG	2	N	12
	8, M	Diplopia	Ataxia	Diplopia	Muscle weakness in legs	BBE	Unremarkable findings	NP	Diffuse slow activity in theta/ delta range	Negative	Y	None	IVIG	2	N	NA
Arias, 2015	4, M	Altered mental status	Ataxia	Ophtalmoplegia	Muscle weakness in all limbs	BBE	TC (brain): unremarkable MRI (brain): unremarkable MRI (spine): Mild T2 hyperintensity in the cauda equina.	EMG: chronic neurogenic patterns NCS: motor axonal polyneuropathy in upper extremities, absent F waves	Unremarkable	Negative	N	Picornavirus	IVIG	5	N	NA
Chong Yi Fong, 2018	0.7, M	Encephalopathy	Not described[a]	Bilateral ophtalmoplegia	Progressive ascending paralysis	BBE/GBS	MRI (brain): unremarkable MRI (spine): lumbar spine nerve root enhancement extending to the cauda equina.	Absent median, ulnar, posterior tibial and common peroneal CMAPs, and absent median, ulnar, radial and sural SNAPs.	Moderate encephalopathy	Negative	Y	None	IVIG + Steroids + PP	20	Y	NA
Patient 1	4, F	Drowsiness	Ataxia	Ophtalmoplegia	Lower limbs weakness	BBE/GBS	MRI: Enhancement of cranial nerves III, VI XII and cauda equina nerve roots.	Slowed motor conduction, absent F-wave	Diffuse slow activity in theta range	Negative	Y	None	IVIG + Steroids	50	N	54
Patient 2	2, M	Lethargy	Ataxia	Horizontal gaze palsy	Flaccid tetraparesis	BBE/GBS	MRI (brain): signal alterations of posterior spinocerebellar tracts in medulla oblungata, of pons and midbrain. MRI (spine): enhancement of cauda equina roots and conus medullaris.	Denervation pattern upon stimulus of right deltoid and right first interosseous muscle; unexcitability of right ulnar nerve.	Diffuse slow activity.	Negative	Y	M. pneumoniae	IVIG	74	N	18

ACD: Albuminocytologic Dissociation; BBE: Bickerstaff's Brainstem Encephalitis; CT: Computed Tomography; EEG: electroencephalogram; EMG: Electromiography; GBS: Guillain-Barré Syndrome; IA: Immunoadsorption; IVIG: Intravenous Immunoglobulin; MFS: Miller Fisher Syndrome; MRI: Magnetic Resonance Imaging; NA: Not Available; NCS: Nerve Conduction Studies; NP: Not Performed; PP: plasmapheresis.

[a] See text, section 4.

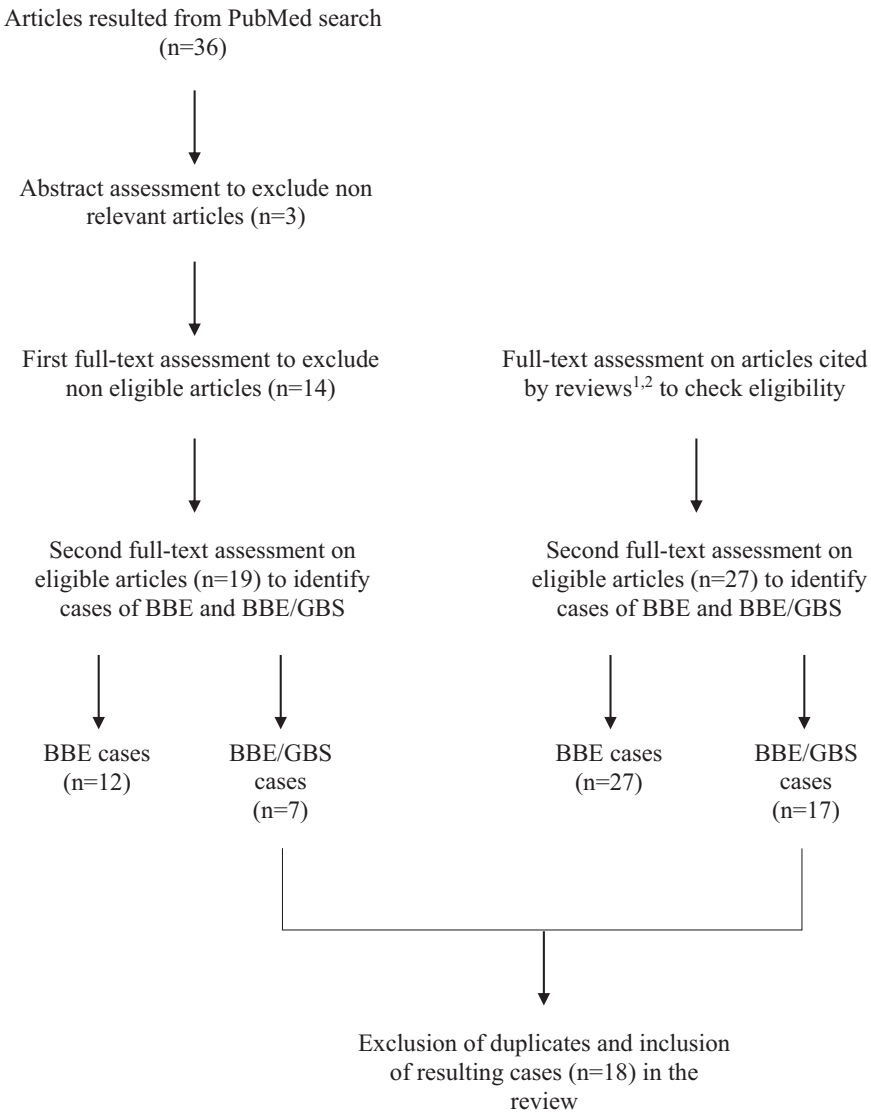

Fig. 2 – Search and review strategy.

whether such fine differences within the clinical presentation of a same disease may be explained by a different profile of affinity of anti-ganglioside antibodies.

5.5. *Patients management and therapeutic approach*

To date, no controlled trials for the treatment and management of BBE/GBS have been made in children. General supportive measures, such as respiratory support (if needed), hemodynamic and fluid balance are usually part of the initial management.[42] Investigations to establish an etiologic diagnosis should always be made,[43] since both bacteria and viruses are reported as triggers of disease.[3–5] Our review documented a concurrent infection in 53% of the patients, M. pneumoniae and C. jejuni being the most frequently involved microorganisms (n = 2, respectively). In terms of treatment, IVIG have shown a beneficial effect in GBS[44] and BBE patients and are widely accepted as a first-line therapy.[26,42,45] Plasmapheresis and/or steroids are often associated in cases that are more complicated: high-dose intravenous methylprednisolone (20–30 mg/kg/day) for 3–5 days, followed by oral steroid taper (prednisone 1 mg/kg/day) for 4–6 weeks is recommended with a class III level of evidence in adult population.[43]

In our review, the majority of patients (67%) were treated with IVIG, alone or associated to corticosteroids. In 2 cases IVIG were associated to plasmapheresis. A considerable amount of patients (39%) needed the support of ventilation. Here, it is unclear if the need for ventilation was secondary to an involvement of the respiratory centers of the brainstem, to a reduced strength of the respiratory muscles, or to both conditions. The understanding of this process may be helpful to determine if BBE/GBS patients are more susceptible to develop a respiratory failure compared to patients with BBE alone. Interestingly, only 24% of patients with BBE/GBS described by Odaka et al. required assisted ventilation.[6]

Finally, 15.8% of the pediatric patients in our review showed minimal residual neurological alterations during their follow up. Patient 2 showed a persistent right upper limb weakness. Data concerning adults showed residual neurological alterations in 23% of the patients.[6]

6. Conclusions

In this review, we described cases of encephalitis sharing the classical features of BBE together with signs of acute peripheral involvement typically seen in GBS. This condition has been probably underdiagnosed in the past years and to ascertain this assumption, we attempted to retrospectively retrieve all the pediatric cases previously described in the literature. For the majority of patients, diagnosis relied on the clinical features, but certain neurophysiological and neuroradiological findings supported the evidence of a combined PNS and CNS involvement.

In this purpose, we suggest that a diagnostic approach comprehensive of NCS, EEG, brain and spine MRI to all pediatric patients with a clinical picture of BBE/GBS, would be more adequate to determine the correct diagnosis.

The coexistence between GBS and BBE may give rise to a different pattern of complications, response to therapy and outcome, than observed in patients with BBE alone. We, hence, remark the importance to study BBE/GBS with large cohorts of pediatric patients, in order to create a consensus on diagnostic criteria (including the role of the ancillary investigations), treatment and management of the disease.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2018.11.008.

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