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Case Series

AN OVERLAP OF GUILLAIN-BARRÉ SYNDROME, MILLER-FISHER SYNDROME, AND BICKERSTAFF BRAINSTEM ENCEPHALITIS PRESENTING AS CLINICAL BRAIN DEATH, A CASE SERIES

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Abstract: *Guillain-Barré Syndrome (GBS), Miller-Fisher Syndrome (MFS), and Bickerstaff Brainstem Encephalitis (BBE) are neuroinflammatory disorders that share common immunopathogenic mechanisms. Although overlapping presentations of these conditions are rare, they pose significant diagnostic challenges, especially when mimicking clinical brain death.* ***Objective:*** *To present a case series of three patients who demonstrated an overlap of GBS, MFS, and BBE, with all patients exhibiting profound neurological impairments, including clinical signs of brain death.* ***Methods:*** *A retrospective review of three cases admitted to the ICU over the last three years was conducted. Detailed clinical profiles, cerebrospinal fluid (CSF) analysis, nerve conduction studies (NCS), and electromyography (EMG) results were reviewed. All patients were treated with intravenous immunoglobulins (IVIG) and therapeutic plasma exchange (TPE).* ***Results:*** *All three patients had a history of preceding infections and were presented with ophthalmoplegia, ataxia, and altered levels of consciousness, progressing to coma. CSF analysis revealed albuminocytological dissociation, and NCS/EMG indicated severe polyneuropathy. Two patients responded positively to IVIG and plasmapheresis, showing significant neurological recovery, while the third patient demonstrated a delayed but spontaneous recovery. All patients eventually achieved full or near-full neurological recovery.* ***Conclusions:*** *This case series highlights the clinical continuum and diagnostic complexity of overlapping GBS, MFS, and BBE, particularly in presentations mimicking brain death. Early recognition and prompt immunomodulatory therapy are crucial in improving patient outcomes, even in cases with severe neurological deficits. Further research is warranted to elucidate pathophysiology and optimize treatment strategies for overlapping neuroinflammatory syndromes.*

Keywords: Bickerstaff Brainstem Encephalitis, Guillain-Barre Syndrome, Miller Fisher Syndrome, Neuroinflammatory Disorders, Plasmapheresis.

Introduction

Bickerstaff's brainstem encephalitis (BBE), Miller Fisher syndrome (MFS),, and Guillain-Barré syndrome (GBS) are related in the pathogenesis of a clinical course.

Guillain-Barre syndrome is a disorder of peripheral nerves characterized by flaccid paralysis and areflexia. GBS is classified into two major subtypes: acute Inflammatory Demyelinating Polyneuropathy (AIDP), which mainly affects the peripheral nerve myelin sheath, and Acute Motor Axonal Neuropathy (AMAN), which attacks the axons of peripheral nerves (1).

Miller-Fisher syndrome is characterized by an acute onset of ataxia, areflexia, and ophthalmoplegia (2). When there is associated with a disturbance in the level of consciousness, the clinical syndrome is called Bickerstaff's brainstem encephalitis (3).

The three disorders share many common features, especially those preceded by infection, albuminocytological dissociation in cerebrospinal fluid (CSF), and, in some cases, the presence of autoantibodies. These common features suggest that BBE, along with MFS and GBS, forms a continuous spectrum of immune-mediated disease in which the peripheral nerves are involved at one end while the central nervous system is affected at the other.

At this moment, we present a series of five cases of patients admitted to our ICU over the last three years. The uniqueness is that all of them showed a clinical continuum of these three clinical entities preceded by a history of infection presented with ataxia and ophthalmoplegia, which progressed to disturbance of consciousness down to the level of deep coma and development of motor weakness with absent reflexes. All showed an albuminocytological dissociation in CSF and had characteristic neurophysiological studies, i.e., Nerve Conduction Studies (NCS) and Electromyography (EMG). Furthermore, all showed substantial improvement in Intravenous immunoglobulins (IVIG), augmented when they underwent therapeutic plasma exchange (TPE). It is rare to find such a clinical presentation where all these syndromes overlap.

Detailed Cases

Case 1:

A 22-year-old Saudi male with a history of bronchial asthma was admitted on June 22, 2011, with flu, fever, cough, and breathing difficulties. In the emergency department, he was drowsy with carbon dioxide narcosis, necessitating intubation and mechanical ventilation. Post-ventilation, he became conscious but showed no respiratory effort and

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developed bilateral facial weakness, losing movement in his arms and later his legs. Despite having a typical brain imaging result, his lumbar puncture revealed high protein levels, leading to a clinical diagnosis of Bickerstaff brainstem encephalitis (BBE) with Miller Fisher syndrome (MFS) and Guillain-Barré syndrome (GBS) overlap, and he was treated with IVIG without improvement. Subsequent EEGs indicated high-grade encephalopathy and nerve conduction studies showed axonal polyneuropathy. After seven ineffective sessions of plasmapheresis and presenting all clinical signs of brain death except for residual brain activity on EEG, a conservative therapy approach was adopted following discussions with his family and medical team. Remarkably, nearly a year later, on September 20, 2012, he regained consciousness, started supporting his breathing via a tracheal tube, and showed limb movements. He was discharged on November 26, 2012. This case underscores the complexities in diagnosing and managing severe neurological conditions with overlapping syndromes and the unpredictability of patient recovery. (Table 1-3)

Case 2:

A 17-year-old male with no significant medical history presented initially with severe abdominal pain, vomiting, and elevated white blood cells, prompting surgery for suspected acute appendicitis, which was ultimately unremarkable. Subsequently, he developed acute kidney injury (AKI) and was transferred to our hospital for potential continuous renal replacement therapy. The following day, he exhibited decreased consciousness and required intubation and ventilation upon arrival in the ICU, where he rapidly deteriorated into a deep coma with clinical signs indicative of brain death. CT and MRI scans of the brain were unremarkable, while cerebrospinal fluid (CSF) analysis revealed albuminocytologic dissociation. Electroencephalography (EEG) demonstrated severe encephalopathy characterized by excessive slow activity and low amplitude, while nerve conduction studies (NCS) indicated severe motor-predominant polyradiculopathy. Given the clinical history of pseudoappendicitis, hypotonia, areflexia, and CSF findings, a diagnosis of Guillain-Barre Syndrome (GBS) overlapping with Bickerstaff's Brainstem Encephalitis (BBE) and Miller Fisher Syndrome (MFS) was established, and intravenous immunoglobulin (IVIG) therapy was initiated. Within three days, the patient demonstrated improvement by spontaneously opening his eyes and exhibiting feeble respiratory efforts. Subsequent double filtration plasmapheresis sessions further enhanced his condition, leading to limb movement and practical respiratory efforts. After successful weaning from mechanical ventilation, the patient was discharged, illustrating the potential for significant recovery even in severe neurological presentations associated with GBS, MFS, and BBE overlap. (Table 1-3)

Case 3:

A 37-year-old Saudi male was admitted to the ICU via the ER after being transferred from another hospital. He had experienced a short course of an upper respiratory tract infection (URTI) that escalated to dyspnea and drowsiness, necessitating intubation due to type 2 respiratory failure. The patient reported a history of imbalance while walking and double vision. Despite being intubated and mechanically ventilated, his neurological condition rapidly worsened, leading to unconsciousness. Clinical examination revealed hypotonia and areflexia, and the patient exhibited signs indicative of brain death, with no brain stem reflexes observed. Brain imaging revealed no abnormalities, but cerebrospinal fluid (CSF) analysis showed elevated glucose, lactate dehydrogenase (LDH), and protein levels, with a normal cell count. An initial electroencephalogram (EEG) indicated moderate encephalopathy, which progressed to severe encephalopathy in subsequent EEGs. Nerve conduction studies were consistent with a severe form of axonal and demyelinating polyneuropathy. Given the clinical presentation, diagnostic findings, and progressive neurological decline culminating in clinical brain death, a diagnosis of Bickerstaff brainstem encephalitis (BBE) overlapping with Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS) was made. The patient was treated with intravenous immunoglobulin (IVIG), showing rapid improvement over 3 to 5 days, followed by six rounds of plasmapheresis. Post-treatment, the patient regained consciousness, started moving his limbs, and exhibited supported respiratory movements. He continued to recover clinically over the next week and was discharged home. (Table 1-3)

Table 1. Clinical Profile Tables

	Patient 1	Patient 2	Patient 3
Sex	Male	Male	Male
Age	22	17	37
Preceding URTI	+	+	-
Preceding diarrhea	-	-	+

Table 2: Initial Symptoms

	Patient 1	Patient 2	Patient 3
Diplopia	+	+	+
Ataxia	+	+	+
LOC	+	+	+

Table 3: Neurological Signs During Illness

	Patient 1	Patient 2	Patient 3
Coma	+	+	+
Type 2 Respiratory Failure	+	+	+

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External ophthalmoplegia	+	+	+
Internal ophthalmoplegia	+	+	+
Bilateral facial palsy	+	+	+
Bilateral Bulbar palsy	+	+	+
Limb weakness	+	+	+
Muscles stretch reflexes	+	+	+
Sensory disturbance	+	+	+

Table 4. Diagnostic Profile Tables (CSF Findings)

	Patient 1	Patient 2	Patient 3
Glucose	104	132	152
Chloride	127	124	124
LDH	9	23	42
Protien	30.3	92.1	84.7
Cell Count	2	15	

EEG Findings

Patient 1: The EEG findings are consistent with encephalopathy; The recorded activity is slow and disorganized. (Figure 1A)

Patient 2: Abnormal EEG for excessive slow activity and low amplitude, indicating a severe form of encephalopathy. (Figure 2A)

Patient 3: Abnormal EEG with an excessive amount of slow activity. Compatible with severe forms of encephalopathy. (Figure 3A)

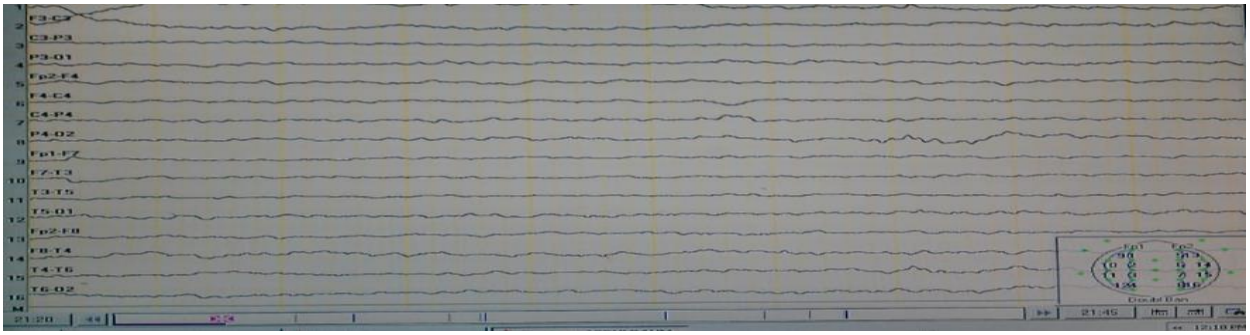

Figure 1A

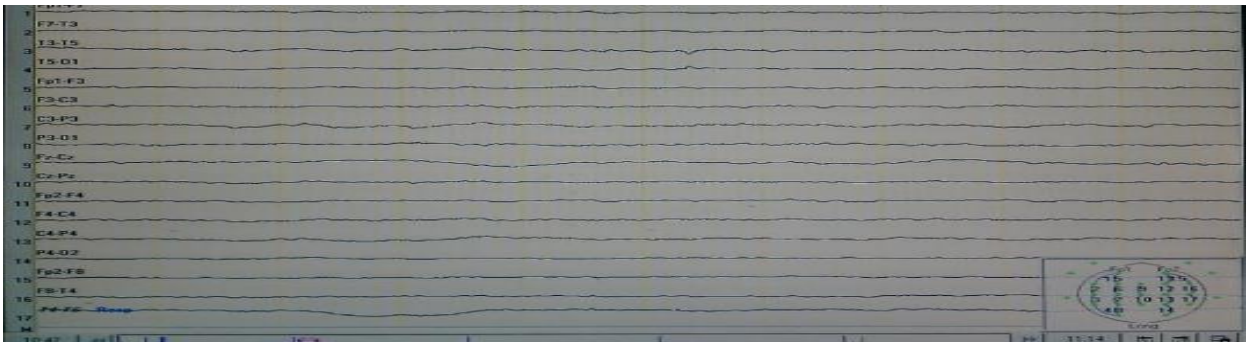

Figure 2A

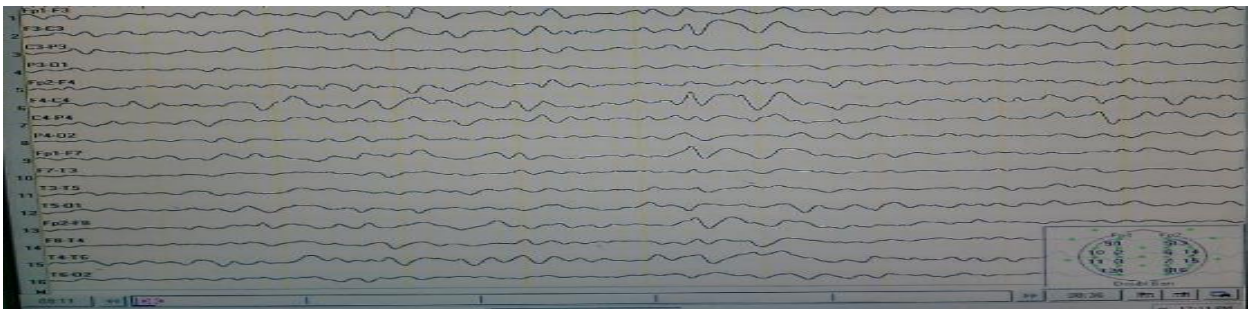

Figure 3A

NCS Findings

Patient 1: Extreme nerve polyneuropathy in all limbs, including facial nerves, probably axonal, with denervation on EMG. (Figure 1C)
Patient 2: Findings compatible with a severe polyradiculopathy motor more than sensory going with variant GBS. (Figure 2C)
Patient 3: Findings compatible with a severe form of axonal and demyelinating form of polyneuropathy? Uremic polyneuropathy? Diabetic polyneuropathy?

The brain images of all patients were unremarkable.

Treatment and Management:

In this case, a series of three patients presenting with Guillain-Barré Syndrome (GBS), Miller Fisher Syndrome (MFS), and Bickerstaff Brainstem Encephalitis (BBE) overlap, initially mimicking clinical brain death, varied responses to treatment were observed. Two patients demonstrated significant recovery following intravenous immunoglobulin (IVIG) and plasmapheresis administration, regaining neurological functions and motor strengths close to their baseline levels. However, The third patient did not respond to these treatments but recovered nearly a year later without further medical intervention. Ultimately, all patients achieved full or nearly complete recovery, highlighting the diverse recovery trajectories and the potential for spontaneous improvement in severe neuroinflammatory conditions.

Discussion

Bickerstaff and Cloake presented three cases of ophthalmoplegia in 1951 under the title " me encephalitis and rhomboencephalitis," pointing towards similarities of this condition to GBS. They were of the opinion that a viral etiology was likely, and the features were due to brainstem involvement.
In 1956, Miller Fisher published his famous paper on a syndrome of ophthalmoplegia, ataxia, and areflexia. He suggested that this syndrome was an unusual variant of GBS because of raised CSF protein and the absence of deep tendon reflexes (2).
A year later, Bickerstaff published another paper reviewing his previous cases and describing four others (3). He again considered them as a form of encephalitis distinct from GBS. Many of his patients had albuminocytological dissociation and marked drowsiness.
The same year, Smith and Walsh described two case reports as "syndrome of external ophthalmoplegia, ataxia and areflexia (Fisher)"(4).
The reporting of such cases continued. Goodwin and Poser reported the Fisher syndrome in 1963 (5), and Patel et al. called it 'Miller Fisher syndrome' in 1966 (6).
Debate about the peripheral or central nature of such syndrome continued to rage in literature, and cases with abnormal CT brains were reported.
A subsequent publication from a group of investigators, including Bickerstaff, strongly favored the idea of encephalitis in a paper that described some 18 patients (7).
In 1983, a case report of a patient with Miller-Fisher syndrome who developed supranuclear gaze palsy was taken as solid evidence of the central origin of the syndrome (8).
Ropper, in 1983, in the same journal where Meienberg reported a case of Miller Fisher with supranuclear palsy, discussed the relation between the central nervous system and GBS. The same year, Ropper and Shahani proposed the mechanism of ataxia in Miller-Fisher syndrome.
In 1987, Al-Din described two cases in which there was an altered state of consciousness and motor nerve dysfunction, in addition to the triad of Miller Fisher. He presented a "spectrum hypothesis" in which Guillain-Barre syndrome and the syndrome of ophthalmoplegia, ataxia, and areflexia are at the opposite ends of a broad spectrum, although clinically and pathologically distinct. He regarded his cases in the middle of that spectrum (9).
The arrival of MRI turned the tide in favor of the concept that BBE and MF are the same entity.
Acute immune-mediated polyneuropathies are classified under the eponym Guillain-Barré syndrome (GBS) after the authors of early descriptions of the disease. Guillain-Barré syndrome is a heterogeneous condition with several variant forms. Most often, GBS presents as an acute monophasic paralyzing illness provoked by a preceding infection.
GBS occurs worldwide. While all age groups are affected, the incidence increases by approximately 20 percent with every 10-year increase beyond the first decade of life. In addition, the incidence is more significant in males than in females.
The cardinal clinical features of Guillain-Barré syndrome (GBS) are progressive, relatively symmetric muscle weakness accompanied by absent or depressed deep tendon reflexes. Patients usually present a few days to a week after the onset of symptoms. The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles.
Studies show that GBS is associated with the following clinical features:
Ascending paralysis, but in about 10%, it may start in facial muscles or upper extremities.
In 10 to 30% of patients, severe respiratory muscle weakness develops, necessitating ventilatory support (10).
Facial weakness occurs in more than 50 percent of cases, and oropharyngeal weakness eventually occurs in 50 percent.
Oculomotor weakness occurs in about 15 percent of patients.
More than 80 percent of patients experience weakness accompanied by paresthesias in the hands and feet, but sensory abnormalities on examination are frequently mild.
Pain, typically located in the back and extremities, can be a presenting feature and is reported during the acute phase by 66 percent of patients with all forms of GBS.
Dysautonomia occurs in 70 percent of patients and manifests as symptoms that include tachycardia (the most common), urinary retention, hypertension alternating with hypotension, orthostatic hypotension, bradycardia, other arrhythmias, ileus, and loss of sweating. Severe autonomic dysfunction is significant to recognize since this is occasionally associated with sudden death (11).
Unusual features of GBS include papilledema, facial myokymia, hearing loss, meningeal signs, vocal cord paralysis, and mental status changes. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has also been reported in association with GBS.

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Historically, Guillain-Barré syndrome (GBS) was considered a single disorder. It is now recognized as a heterogeneous syndrome with several variant forms. Each form of GBS has distinguishing clinical, pathophysiologic, and pathologic features.

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common form in the United States and Europe, representing approximately 85 to 90 percent of cases. The clinical variant Miller Fisher syndrome (MFS), characterized by ophthalmoplegia, ataxia, and areflexia, occurs in 5 percent of cases in the United States and 25 percent in Japan.

Acute motor axonal neuropathy (AMAN) and acute sensorimotor axonal neuropathy (AMSAN) are primary axonal forms of GBS. These forms are frequently observed in China, Japan, and Mexico but comprise an estimated 5 to 10 percent of GBS cases in the United States.

Other, less frequent clinical variants are recognized and listed below. (See 'Other variants' below.)

As noted above, AIDP is the most common form in the United States and Europe, representing approximately 85 to 90 percent of cases. The typical clinical features are progressive, relatively symmetric muscle weakness accompanied by absent or depressed deep tendon reflexes.

Conclusion

Only a handful of examples of GBS, MFS, and BBE overlap can be found in the literature. (12–18). This case series underscores the heterogeneity in the clinical course and treatment response of patients with overlapping GBS, MFS, and BBE presenting with severe neurological impairment. The initial presentation resembling brain death poses significant diagnostic and prognostic challenges. However, albuminocytologic dissociation in CSF, unremarkable brain imaging, severe encephalopathy on EEG, and mixed axonal and demyelinating features on NCS should prompt consideration of these treatable autoimmune neuropathies.

The varied responses to treatment highlight the importance of individualized patient management. While IVIG and plasmapheresis are effective for many, some patients may recover spontaneously over a prolonged period. This finding emphasizes the need for ongoing clinical vigilance and support, even in cases where initial treatments appear unsuccessful.

Overall, the total or near-full recovery of all three patients, regardless of the treatment response, is a testament to the potential for neurological recovery in severe autoimmune neuropathies. It also reinforces the necessity for early recognition and treatment, patience, and long-term support for patients and their families navigating these complex conditions.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.

It is approved by the department concerned.

Consent for publication

Approved

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Conflict of interest

The authors declared an absence of conflict of interest.

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Concept & Design of Study

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