

A Case Of Miller Fisher Syndrome Overlapped By Bickerstaff's Brainstem Encephalitis, And Guillain-Barre' Syndrome

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1. Abstract

We present a case of a 56-year-old female patient exhibiting overlapping features of Miller Fisher syndrome (MFS), Bickerstaff's brainstem encephalitis (BBE) and Guillain-Barré syndrome (GBS). She experienced dizziness, diplopia and unsteady gait one week following an upper respiratory infection on day 1. On day 2, She demonstrated weakness in all extremities along with deteriorating respiratory function. By day 3, her neurological examination revealed disturbances in consciousness disturbance, ophthalmoplegia, ataxia, symmetrical weakness and areflexia. We established diagnosis of MFS on day 1, GBS on day 2 and overlapping BBE on day 3. Testing for anti-GQ1b, GM1, GD1b, GT1a, and GT1b IgG antibodies returned negative results. The patient underwent two courses of intravenous immunoglobulin (IVIG) therapy alongside treatment with methylprednisolone at a dosage of 1000 mg/day. By day 76 post-treatment initiation, she was able to ambulate independently; however, tendon reflexes remained absent. Our findings support the hypothesis that MFS, GBS, and BBE represent interconnected clinical manifestations within an antibody-mediated spectrum.

2. Keywords:

Miller Fisher syndrome, Guillain-Barré syndrome, Bickerstaff's brainstem encephalitis

3. Introduction

Miller Fisher syndrome (MFS), a variant of Guillain-Barré syndrome (GBS), is characterized by the clinical triad of ophthalmoplegia, ataxia and areflexia. Bickerstaff's brainstem encephalitis (BBE) represents a distinct clinical entity defined by acute ophthalmoplegia, ataxia, altered consciousness, or brisk reflexes. The presence of common anti-GQ1b antibodies in both BBE and MFS suggests a close relationship between these conditions. Overlapping cases of MFS with GBS or BBE have been reported in 15% and 12% of instances respectively [1,2]. Areflexia and cerebrospinal fluid (CSF) albuminocytologic dissociation are observed in both BBE and GBS. Odaka identified that a significant proportion (37 out of 62, 60%) with BBE also presented concurrent axonal GBS [3]. Consequently, some researchers speculate that the etiology of BBE may be similar to that of GBS. Collectively, BBE, MFS and GBS are considered components within a broader clinical spectrum. While overlapping presentations involving MFS with GBS or the overlapping cases between BBE and GBS are relatively common occurrences, reports detailing patients exhibiting overlaps among all three—GBS, BBE, and MFS—are rare. We present a case demonstrating negativity for anti-GQ1b, GM1, GD1b, GT1a, and GT1b IgG anti-ganglioside antibodies.

4. Case Presentation

A 56-year-old female patient arrived at the emergency department presenting dizziness, diplopia and unsteady gait a week following an upper respiratory infection. Neurological examination indicated she was fully conscious; however bilateral abducens function was limited along with vertical gaze impairment. Oropharyngeal palsy was noted while bifacial weakness was absent; no motor weakness was detected in any limb. Deep tendon reflexes were preserved without pathological reflexes observed. An ataxic gait pattern was evident upon assessment leading to her admission under the diagnosis of MFS. On day two post-admission she exhibited severe ptosis preventing spontaneous eye opening; her eyeballs remained fixed centrally with mydriatic pupils lacking light reflexes alongside bifacial weakness manifesting as muscle strength graded at Medical Research Council (MRC) level 3 across all extremities accompanied by absent deep tendon reflexes but positive pathological reflexes noted during examination. Her respiratory status deteriorated necessitating mechanical ventilation support on day three when drowsiness set in alongside progressive limb weakness reducing to an MRC grade level two classification. Sensory testing revealed glove and stocking deficits coupled with diminished vibration sense as well as proprioception around wrists and ankles. The autonomic nervous

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functions including urinary retention, constipation, and hypotension were intact indicating overlap between conditions consistent with both BBE and GBS diagnoses. Electromyography combined with nerve conduction studies confirmed acute motor-sensory axonal neuropathy findings. Magnetic resonance imaging (MRI) conducted on day two which revealed normal cerebral structures. Cerebrospinal fluid (CSF) analysis performed on day 14 showing albuminocytologic dissociation marked by elevated protein levels (1.0 g/L) alongside white blood cell counts measuring only two cells/mm³. The serum and CSF samples were negative for immunoglobulin (Ig) G against GQ1b, IgGs against GM1, GD1b, GT1a, or GT1b (normal range for each antibody <1:40).

The patient diagnosed with MFS, BBE and GBS was treated with intravenous immunoglobulin (IVIG 0.4 g/kg/d) starting on day 2 for a duration of 5 days. Due to persistent limb weakness, she received a second course of IVIG treatment on day 15, and was administered methylprednisolone at a dosage of 1000 mg/d for five consecutive days. Her consciousness and bulbar symptoms began to improve by day 8, while her limb strength increased to MRC grade 3 by day 12. However, mechanical ventilation was successfully weaned off on day 26. By day 31, She exhibited spontaneous eye movement. On day 76, her muscle strength had improved to MRC grade 5, allowing her to walk unassisted; however,

tendon reflexes remained absent.

5. Discussion and Conclusions

To our knowledge, overlapping cases of MFS-BBE-GBS have been previously reported in 7 instances (Table 1)[2,4-9]. Table 1 presents the clinical profiles of the 8 patients studied. There was a female predominance with male-to-female ratio of 3:5. The mean age onset was 52 years. 6 patients exhibited upper respiratory symptoms, while one case presented with fever and myalgia. Unsteady gait and diplopia were the most commonly observed initial presentations, with some patients developing both the same day. All patients experienced external ophthalmoplegia, ataxia, and tetraparesis, additional findings included blepharoptosis, internal ophthalmoplegia, bulbar palsy, brisk tendon reflexes and paresthesias. Several patients required mechanical ventilation during the acute phase due to deteriorating respiratory status, however, no fatalities occurred. According to diagnostic criteria for BBE, all the patients demonstrated impaired consciousness (ranging from drowsiness to coma) or brisk tendon reflexes. The overlapping entities typically manifested within 1 week. However, the overlap duration varied from day 5 to day 42 among reported cases.

Table 1: Reported cases of overlapping Miller Fisher Syndrome, Guillain-Barré syndrome and Bickerstaff's brainstem encephalitis

Case	Gender /Age	Initial presentation	antecedent infection	Clinical course	Antiganglioside antibody	Albumino cy-tological dissociation	NCS	MRI	Outcome	Treatment	
1	M/20	unsteady gait	Cough,	MFS day 1;	Anti-GM1, GD1a, GQ1b and GT1a negative	P64 mg/mL,	AMSAN	normal	walk with support day 132	Dexamethasone and prednisone	
			rhinorrhea,	BBE day 12;		C 2/uL					
			wheezing dyspnea	GBS day 21		day 21					
2	F/72	Diplopia,	upper respiratory infection	MFS day 1;	Anti-GM1 GD1a, GQ1b, and GT1a positive	P 30 mg/dL, C 2/uL	AMSAN	normal	recovered 10 months	IVIG and immunoadsorption	
		unsteady gait		GBS day 3;		day 3					
				BBE day 5							
3	F/76	Diplopia,	Fever and myalgia	MFS day 1;	Anti-GQ1b ;1:1600 ,GM1, GD1b, GT1a and GT1b negative	P94.8mg/dL,C5/mm ³ day 1	AMSAN	normal	walk with support day 247	IVIG and methylprednisolone	
		ophthalmoplegia		GBS day 3;							
				BBE day 5							
4	M/56	Diplopia,	Mild cough	MFS day 1;	Anti-GD1a and GQ1b	P 1.58 g/L,	AMSAN	normal	walk with support 4 month	IVIG and PE	
		unsteady gait,		GBS 1 week;	positive	C1 × 106/L					
		hands tingling		BBE 6 weeks		day 7					

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5	F/43	Diplopia,	upper respiratory infection	BBE day 1;	Anti-GM1 positive and	P: 0.67 g/L,	Demyelinating	normal	walked independently day 27	IVIg
		hands and feet tingling,		GBS day 9;	GQ1b negative.	C:0 × 106/L				
		legs weakness		MFS day 10						
6	M/61	Diplopia,	No reported	MFS day 1;	Anti-GQ1b (1:2560);	Not reported	AMSAN	Normal	recovered muscle strength and mild ataxia day 240;	IVIg
		unsteady gait		GBS day 2;	anti- GM1, -GD1a, -GD1b and					
				BBE day 4	-GM2 absent					
7	F/34	Diplopia,	upper respiratory infection	MFS day 1;	High anti-GQ1b	Not reported	Not reported	Not reported	Recovered 5 month	PE
		unsteady gait		GBS day 2;						
				BBE day 5						
8	F/56	Diplopia,	upper respiratory infection	MFS day 1;	Anti-GQ1b GM1, GD1b, GT1a, and GT1b negative	P 1.0 g/L,	Demyelinating	normal	walk unassisted day 76;	IVIg and methylprednisolone Our case
		unsteady gait		GBS day 2;		C 0 × 106/L				
				BBE day 3		day 8				

AMSAN indicates acute motor sensory axonal neuropathy; IVIg, intravenous immunoglobulin; NCS, nerve conduction study; PE, plasma exchange.

Albuminocytological dissociation was detected in most GBS and MFS cases [10], including 6 MFS-BBE-GBS patients, exception of two cases no reported. Approximately 23-30% of BBE patients exhibit abnormal lesions on MRI [2], conversely, 7 cases showed normal MRI results while one case remains unreported. Consistent with previous reviews, anti-GQ1b antibodies were identified in 5 out of 8 cases, additionally, 2 patients also tested positive for anti- GT1a and anti-GD1a IgG antibodies. Abundant GQ1b gangliosides and their corresponding epitopes are present in cranial

nerves III, IV, and VI, however, accumulate in peripheral nerves as well as muscle spindle afferents and brainstem reticular formation areas. The presence of anti-GQ1b antibodies may partly elucidate the mechanisms behind ophthalmoplegia and ataxia seen in MFS as well as disturbances of consciousness associated with BBE [11,12]. Anti-GD1a and anti-GM1 antibodies are generally linked to AMAN [13], although some MFS or overlapping GBS and BBE patients with ophthalmoparesis or recurrent cranial nerve palsy also show elevated levels [5, 14,15]. Negative serum anti-ganglioside antibody results in 2 cases suggest that MFS-BBE-GBS may possess a broader immunologic basis rather than being solely mediated by autoantibodies against specific ganglioside complexes.

Table 2: The clinical signs of overlapping MFS-BBE-GBS cases

case	ophthalmoplegia	blepharoptosis	mydriasis	bulbar palsy	ataxia	conscious	areflexia	tetraparesis	paresthesias	Worsened respiratory
1	+	-	-	-	+	+	+	+	-	-
2	+	+	+	-	+	+	+	+	-	+
3	+	+	+	+	+	+	+	+	-	+
4	+	-	-	+	+	+	+	+	-	-
5	+	-	+	+	+	-	-	+	+	-
6	+	-	-	+	+	+	+	+	+	+
7	+	-	+	-	+	+	+	+	+	-
8	+	+	-	+	+	+	+	+	+	+

“+”:the clinical signs exist; “-”:the clinical signs absent or no-reported

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Acute motor sensory axonal neuropathy was observed in 5 cases, consistent with previous findings that a significant proportion (37 out of 62, 60%) of BBE patients exhibit concurrent axonal GBS [3]. These patients presented with acute motor and sensory axonal neuropathy without demyelinating features. Nevertheless, most patients with MFS and GBS experience favorable natural recoveries, with 66% of BBE patients achieving complete remission after 6 months [3,16]. Distal motor conduction blocks resolved within 10 weeks, however, intermediate and proximal nerve segment conduction blocks emerged and unusually persisted for 4 to 7 months [17,18]. The electrophysiological features may elucidate why the majority of MFS-BBE-GBS overlapping cases listed in table 1 demonstrated favorable outcomes, despite receiving varied treatments involving multiple sessions of IVIG, plasmapheresis (PE), steroids or immunoadsorption. These overlapping cases support the hypothesis that MFS, GBS, and BBE represent a continuous clinical spectrum characterized by antibody-mediated involvement of both the central nervous system and peripheral nervous system. However, the underlying pathophysiology remains under investigation.

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