



# Determining the Utility of the Guillain-Barré Syndrome Classification Criteria

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**Background and Purpose** Several variants of Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS) exist, but their frequencies vary in different populations and do not always meet the inclusion criteria of the existing diagnostic criteria. However, the GBS classification criteria by Wakerley and colleagues recognize and define the clinical characteristics of each variant. We applied these criteria to a GBS and MFS cohort with the aim of determining their utility.

**Methods** Consecutive GBS and MFS patients presenting to our center between 2010 and 2020 were analyzed. The clinical characteristics, electrophysiological data, and antiganglioside antibody profiles of the patients were utilized in determining the clinical classification.

**Results** This study classified 132 patients with GBS and its related disorders according to the new classification criteria as follows: 64 (48.5%) as classic GBS, 2 (1.5%) as pharyngeal-cervical-brachial (PCB) variant, 7 (5.3%) as paraparetic GBS, 29 (22%) as classic MFS, 3 (2.3%) as acute ophthalmoparesis, 2 (1.5%) as acute ataxic neuropathy, 2 (1.5%) as Bickerstaff brainstem encephalitis (BBE), 17 (12.9%) as GBS/MFS overlap, 4 (3%) as GBS/BBE overlap, 1 (0.8%) as MFS/PCB overlap, and 1 (0.8%) as polyneuritis cranialis. The electrodiagnosis was demyelinating in 55% of classic GBS patients but unclassified in 79% of classic MFS patients. Anti-GM1, anti-GD1a, anti-GalNAc-GD1a, and anti-GD1b IgG ganglioside antibodies were more commonly detected in the axonal GBS subtype, whereas the anti-GQ1b and anti-GT1a IgG ganglioside antibodies were more common in classic MFS and its subtypes.

**Conclusions** Most of the patients in the present cohort met the criteria of either classic GBS or MFS, but variants were seen in one-third of patients. These findings support the need to recognize variants of both syndromes in order to achieve a more-complete case ascertainment in GBS.

**Key Words** Guillain-Barré syndrome, Miller Fisher syndrome, Bickerstaff brainstem encephalitis, Wakerley classification, paraparetic Guillain-Barré syndrome, pharyngeal-cervical-brachial variant.

## INTRODUCTION

Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis worldwide, and is characterized by ascending weakness and generalized areflexia or hyporeflexia, often associated with respiratory muscle weakness and cranial palsies.<sup>1</sup> A well-recognized variant of GBS is Miller Fisher syndrome (MFS), which is characterized by ophthalmoplegia, ataxia, and areflexia, and the two syndromes share a history of antecedent illness and the presence of cerebrospinal fluid (CSF) albumin-cytological dissociation. There have been increasing reports of other localized forms of GBS such as paraparetic and pharyngeal-cervical-brachial (PCB) variants, as well as incomplete forms of MFS such as acute ophthalmoparesis and acute ptosis.<sup>2,3</sup> There have also been reports of central nervous system involvement in the spectrum of MFS referred to as Bickerstaff brainstem encephalitis.<sup>4</sup> This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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(BBE), which shares similar anti-GQ1b antibodies.<sup>4</sup>

The GBS and MFS variants and their forme fruste do not fulfill the current existing diagnostic criteria.<sup>5,6</sup> We recently reported that this limitation resulted in 5% and 24% of GBS and MFS patients, respectively, not being ranked at the highest diagnostic certainty according to the Brighton criteria.<sup>7</sup> The more-recent GBS classification system of Wakerley and colleagues incorporates specific sets of clinical features and the presence of ganglioside antibodies,<sup>8,9</sup> and has been validated in other patient cohorts.<sup>10-12</sup>

The current study investigated the utility of the new GBS classification system in the same GBS and MFS cohort in comparison with the Brighton criteria, and described the clinical, serological, and electrophysiological characteristics of their related variants.

## METHODS

We retrospectively reviewed patients presenting with GBS and MFS to University of Malaya Medical Center (UMMC), Kuala Lumpur from May 2010 to April 2020. At the time of diagnosis, all patients who fulfilled the contemporaneous diagnostic criteria for GBS, MFS, or their related variants.<sup>2,3,5,13</sup> Patients who did not initially fulfill the criteria but upon follow-up did not conform to an alternative diagnosis were also included (corresponding to level 4 of the Brighton criteria).<sup>6</sup> Clinical characteristics including the pattern of limb weakness, bulbar involvement, facial weakness, ocular manifestation, ataxia, and hypersomnolence were evaluated. Patients were then classified based on the new GBS classification and the Brighton criteria (Supplementary Tables 1–3 in the online-only Data Supplement).<sup>8,9</sup> Where applicable, patients were also classified as having the overlap syndrome. Other information collected included age, sex, antecedent infections, durations from onset of symptoms to admission and nadir, Medical Research Council (MRC) sum score<sup>14</sup> at nadir, GBS disability scores (GDSs)<sup>15</sup> at admission and nadir, CSF analysis, mode of treatment, and outcome at 6 months. The MRC sum score is defined as the summation of the MRC scores for six muscle groups, ranging from 0 (total paralysis) to 60 (normal strength),<sup>14</sup> while the GDS is widely used in assessing the functional status of patients with GBS, ranging from 0 (normal) to 6 (death).<sup>15</sup>

Nerve-conduction studies (NCSs) were performed as described previously.<sup>16</sup> In brief, at least two limbs were assessed, including four motor nerves, three sensory nerves, and F-waves. Motor studies were performed in the median, ulnar, fibular, and tibial nerves. Sensory studies of the median and ulnar nerves were performed orthodromically, whereas sural nerve studies were done antidromically. Reference values

were derived from normal ranges that were established previously at our laboratory. Two sets of NCSs were performed whenever possible, with the initial NCS done at admission and repeat NCS performed between 3 and 8 weeks after disease onset. NCS data were evaluated to classify patients as acute inflammatory demyelinating polyneuropathy (AIDP), axonal GBS, inexcitable, and equivocal according to the criteria of Uncini et al.<sup>17</sup> Patients with inexcitable, equivocal, and normal classifications were grouped as unclassified for comparison analyses. In addition, we applied our AIDP predictive models<sup>18</sup> to the current cohort, where a score  $\geq 2$  indicated 55% and 64% probabilities of AIDP in early and late NCSs, respectively. The second model was used for patients who had two sets of NCSs, and either the first or second model was used for patients who had only one set of NCSs, depending on the time of the NCS. Patients with a score  $\geq 2$  were considered to have a higher likelihood of AIDP. Serological analyses of serum IgG against ganglioside anti-GM1, anti-GM1b, anti-GD1a, anti-GalNAc-GD1a, anti-GD1b, anti-GT1a, and anti-GQ1b antibodies were also performed as described previously.<sup>19</sup>

The study was approved by the UMMC Medical Research Ethics Committee, and all patients provided written informed consent.

## Statistical analysis

Categorical data are presented as frequencies and percentages, while continuous data are given as mean  $\pm$  standard deviation and range values. Differences in proportion were compared using the chi-square test, and differences in continuous variables were compared using Student's *t*-test. Correlation analysis was performed with the Pearson correlation coefficient. A *p* value of  $<0.05$  was considered statistically significant.

## RESULTS

### Classification of Wakerley and colleagues

There were 132 patients who presented with GBS or one of its related disorders during the study period. All patients could be classified into a specific subtype based on the classification system of Wakerley and colleagues (Table 1). However, based on the Brighton criteria, 16 (12%) patients only reached the lowest level of diagnostic certainty. Among the total cohort, 64 (48.5%) patients had classic GBS, 29 (22%) had classic MFS, 9 (6.8%) had localized GBS subtypes, 7 (5.3%) had MFS subtypes, and 22 (16.7%) had an overlap syndrome. For the localized GBS subtypes, seven (5.3%) patients were classified as the paraparetic variant and two (1.5%) as PCB. There were no patients with acute pharyngeal weakness or bi-

**Table 1.** Wakerley classification of GBS patients and comparison with the Brighton criteria

Wakerley classification	Value	Brighton criteria			
		Level 1	Level 2	Level 3	Level 4
Classic GBS	64 (48.5)	38	19	3	4
GBS subtypes					
PCB variant	2 (1.5)	1	1	0	0
Acute pharyngeal weakness	0				
P-GBS	7 (5.3)	4	1	1	1
BFP	0				
GBS–MFS interface					
Polyneuritis cranialis	1 (0.8)	0	0	0	1
Classic MFS	29 (22)	5	16	3	5
MFS subtypes					
Acute ophthalmoparesis	3 (2.3)	0	1	0	2
Acute ataxic neuropathy	2 (1.5)	1	0	0	1
Acute ptosis	0				
Acute mydriasis	0				
BBE	2 (1.5)	0	0	0	2
Acute ataxic hypersomnolence	0				
Overlap syndrome	22 (16.7)	13	9	0	0
Overlap subtypes					
GBS/MFS overlap	17 (12.9)				
GBS/BBE overlap	4 (3.0)				
MFS/PCB overlap	1 (0.8)				
Total	132 (100)	62 (47)	47 (36)	7 (5)	16 (12)

Data are *n* or *n* (%) values.

BBE: Bickerstaff brainstem encephalitis, BFP: bifacial weakness with paresthesia, GBS: Guillain-Barré syndrome, MFS: Miller Fisher syndrome, PCB: pharyngeal-cervical-brachial, P-GBS: paraparetic GBS.

facial weakness with paresthesia. For the MFS subtypes, three (2.3%) patients could be classified as acute ophthalmoparesis, two (1.5%) as acute ataxic neuropathy, and two (1.5%) as BBE. There were no patients with acute ptosis, acute mydriasis, or acute ataxic hypersomnolence. The patients with an overlap syndrome comprised 17 (12.9%) with GBS/MFS overlap, 4 (3%) with GBS/BBE overlap, and 1 (0.8%) with MFS/PCB overlap. One patient (0.8%) had acute pharyngeal weakness, but she also had bilateral ptosis, complete ophthalmoplegia, and generalized areflexia without ataxia. Based on the existing classification, this patient was classified as polyneuritis cranialis.

### Demographic and clinical characteristics

The mean age at diagnosis was 47.2±17.9 years (range 15–78 years) for classic GBS, 48.2±17.1 years (range 19–71 years) for classic MFS, and 46.3±19.2 years (range 13–84 years) for the group of patients with subtypes or an overlap syndrome. There were more males in the classic GBS (65.6%) and classic MFS (51.7%) groups. In total, 71.2% (*n*=94) of patients had antecedent infections, of which 17 (18.1%) had diarrhea and 77 (81.9%) had an upper respiratory tract infection. The over-

all time to admission for all patients was 6.6±5.4 days (range 1–33 days), with 60.6% (*n*=80) of patients having GDS >3. The time to nadir for all patients was 8.7±5.7 days (range 2–42 days), and 65.2% (*n*=86) had GDS >3. Most cases of significant disability were observed in patients with classic GBS, BBE, and overlap syndrome. The single patient with polyneuritis cranialis reached nadir by 4 days with GDS <3.

### Antiganglioside antibodies

IgG against ganglioside antibodies were tested in 102 (77.3%) patients (Table 2), and detected in 26.7% (*n*=12) of patients with classic GBS. The majority had anti-GD1a (13.3%), anti-GalNAc-GD1a (13.3%), anti-GM1 (11.1%), anti-GD1b (11.1%), and anti-GM1b (8.9%) antibodies (Supplementary Table 4 in the online-only Data Supplement). Antiganglioside antibodies were not detected in the localized GBS subtypes (PCB and paraparetic variants) or the single case of polyneuritis cranialis. Antiganglioside antibodies were detected in 50% (*n*=12) of MFS patients: anti-GQ1b (50%) and anti-GT1a (37.5%). Anti-GQ1b antibodies were also detected in both patients with BBE and in one of two patients with acute ophthalmoparesis. The 18 patients with overlap syn-

**Table 2.** Clinical features of GBS patients according to subtypes

Wakerley classification	Value	Sex, M:F	Age, years	Antecedent infection		Time, days		GDS >3		At least one antiganglioside antibody (+)
				Diarrhea	URTI	To admission	To nadir	At admission	At nadir	
Classic GBS										
Total	64 (48.5)	42:22	47.2±17.9 (15–78)	12	32	7.9±6.7 (2–33)	10.5±6.8 (3–42)	53 (82.8)	58 (90.6)	12/45 (26.7)
Axonal GBS	17 (26.6)	14:3	35.2±16.9 (16–70)	6	10	6.7±5.0 (2–21)	8.7±6.3 (3–23)	14 (21.9)	16 (25.0)	10/15 (66.7)
AIDP	35 (54.7)	21:14	51.6±16.2 (15–76)	3	17	8.7±7.6 (2–33)	11.2±7.0 (3–42)	30 (46.9)	32 (50.0)	0/20 (0)
GBS subtypes										
PCB variant	2 (1.5)	2:0	22.5±12.0 (14–31)	1	1	6.0±1.4 (5–7)	6.0±1.4 (5–7)	0	0	0/1 (0)
P-GBS	7 (5.3)	3:4	29.9±12.7 (13–53)	0	5	8.0±5.2 (3–14)	10.6±5.3 (3–16)	3 (42.9)	3 (42.9)	0/7 (0)
GBS–MFS interface										
Polyneuritis cranialis	1 (0.8)	0:1	61	0	1	2	4	0	0	0/1 (0)
Classic MFS	29 (22)	15:14	48.2±17.1 (19–71)	1	21	4.3±1.7 (2–9)	5.3±2.1 (2–12)	5 (17.2)	5 (17.2)	12/24 (50)
MFS subtypes										
Acute ophthalmoparesis	3 (2.3)	3:0	41.3±7.1 (35–49)	0	1	8.3±6.7 (1–14)	9.7±4.5 (5–14)	0	0	1/2 (50)
Acute ataxic neuropathy	2 (1.5)	1:1	26.5±5.0 (23–30)	0	2	5.5±2.1 (4–7)	6.0±1.4 (5–7)	0	0	0/2 (0)
BBE	2 (1.5)	1:1	50.5±16.3 (39–62)	0	2	3.5±2.1 (2–5)	5.0±1.4 (4–6)	2 (100)	2 (100)	2/2 (100)
Overlap syndrome	22 (16.7)	14:8	55.8±17.2 (21–84)	3	12	5.6±3.4 (2–14)	8.2±4.8 (2–21)	17 (77.3)	18 (81.8)	7/18 (38.9)
Overlap subtypes										
GBS/MFS overlap	17	10:7	53.2±17.0 (21–72)	3	9	5.4±3.4 (2–14)	7.7±5.0 (2–21)	13 (76.5)	14 (82.4)	6
GBS/BBE overlap	4	3:1	71.3±8.8 (65–84)	0	2	6.5±4.1 (2–10)	10.3±4.4 (6–15)	4 (100)	4 (100)	0
MFS/PCB overlap	1	1:0	38	0	1	7	10	0	0	1
Total	132 (100)	81:51	47.2±18.0 (13–84)	17	77	6.6±5.4 (1–33)	8.7±5.7 (2–42)	80 (60.6)	86 (65.2)	34/102 (33.3)

Data are *n*, *n* (%), or mean±standard deviation (range) values.

AIDP: acute inflammatory demyelinating polyneuropathy, BBE: Bickerstaff brainstem encephalitis, F: female, GBS: Guillain-Barré syndrome, GDS: GBS disability score, M: male, MFS: Miller Fisher syndrome, PCB: pharyngeal-cervical-brachial, P-GBS: paraparetic GBS, URTI: upper respiratory tract infection.

drome included 4 (22.2%) and 7 (38.9%) with anti-GQ1b and anti-GT1a antibodies, respectively. For the GBS/MFS overlap syndrome, anti-GT1a and anti-GQ1b antibodies were present in six (37.5%) and four (25%) patients, respectively. No IgG antiganglioside antibodies were detected in the GBS/BBE overlap syndrome, but anti-GT1a was detected in the patient with MFS/PCB overlap.

### Electrodiagnostic classification

NCSs were performed in all patients (Table 3), but data were not available for two patients. The final electrodiagnosis was determined based on 2 sets of NCSs in 98 (74.2%) patients and 1 set of NCSs in 32 (24.3%) patients. The mean time from symptom onset to NCSs for patients with one set of NCSs was 15.1±16.3 days (range 2–79 days). Among patients with classic GBS, 35 (54.7%) had AIDP, 17 (26.6%) had axonal GBS, and 1 (1.6%), 9 (14.1%), and 2 (3.1%) were clas-

**Table 3.** Neurophysiological features

Wakerley classification	Criteria of Uncini et al. <sup>17</sup>					Our predictive model
	AIDP	Axonal	Inexcitable	Equivocal	Normal	AIDP probability $\geq 55\%$
Classic GBS	35 (54.7)	17 (26.6)	1 (1.6)	9 (14.1)	2 (3.1)	38/64 (59.4)
GBS subtypes						
PCB variant	1 (50)	0	0	1 (50)	0	1/2 (50)
P-GBS	4 (57.1)	1 (14.3)	0	1 (14.3)	1 (14.3)	4/7 (57.1)
GBS-MFS interface						
Polyneuritis cranialis	0	0	0	1 (100)	0	0/1 (0)
Classic MFS	2 (6.9)	4 (13.8)	0	16 (55.2)	7 (24.1)	1/27 (3.7)
MFS subtypes						
Acute ophthalmoparesis	0	0	0	1 (33.3)	2 (66.7)	0/3 (0)
Acute ataxic neuropathy	1 (50)	0	0	1 (50)	0	1/2 (50)
BBE	0	0	0	2 (100)	0	0/2 (0)
Overlap syndrome	9 (42.9)	2 (9.5)	1 (4.8)	8 (38.1)	1 (4.8)	10/21 (47.6)
Overlap subtypes						
GBS/MFS overlap	7	1	0	7	1	
GBS/BBE overlap	2	1	1	0	0	
MFS/PCB overlap	0	0	0	1	0	
Total	52 (39.7)	24 (18.3)	2 (1.5)	40 (30.5)	13 (9.9)	55/129 (42.6)

Data are *n* or *n* (%) values.

AIDP: acute inflammatory demyelinating polyneuropathy, BBE: Bickerstaff brainstem encephalitis, GBS: Guillain-Barré syndrome, MFS: Miller Fisher syndrome, PCB: pharyngeal-cervical-brachial, P-GBS: paraparetic GBS, URTI: upper respiratory tract infection.

sified as inexcitable, equivocal, and normal, respectively. There were 16 of 29 (55.2%) MFS patients with abnormal sensory conduction, but they did not fulfill the electrodiagnostic criteria for AIDP or axonal GBS, and were therefore classified as equivocal. Among the remaining classic MFS patients, seven (24.1%) had normal NCS findings whereas four (13.8%) and two (6.9%) patients had axonal GBS and AIDP, respectively. Two patients with PCB had either AIDP or equivocal NCS findings. The PCB patient with an AIDP electrodiagnosis underwent two sets of NCSs, whereas the patient with equivocal electrodiagnosis underwent only one set of NCS on day 3 of the illness. Similarly, the two patients with acute ataxic neuropathy comprised one with AIDP and one who was equivocal. Both patients with BBE and the single patient with polyneuritis cranialis had an equivocal electrodiagnosis. Among the paraparetic GBS patients, four (57.1%) were AIDP, one (14.3%) was axonal, one (14.3%) was equivocal, and one (14.3%) had normal NCS findings. The patients with acute ophthalmoparesis comprised one (33.3%) with equivocal findings and two (66.7%) with normal NCS findings. Among the overlap subtypes, nine (42.9%) patients had AIDP, eight (38.1%) were equivocal, two (9.5%) had axonal GBS, one (4.8%) was inexcitable, and one (4.8%) had normal NCS findings. Based on our predictive model, the proportion of patients with AIDP scores  $\geq 2$  and thus with a probability of at least  $>55\%$  of having AIDP was 59% in classic GBS (38 of 64) and 57% in paraparetic GBS (4 of 7). The

proportions were considerably lower in the other subtypes.

### Comparison of severity, laboratory features, treatments, and outcomes

Comparison analysis was performed between classic GBS, localized GBS subtypes, classic MFS, MFS subtypes, and the overlap syndromes (Table 4). The MRC sum score at nadir was significantly lower in classic GBS ( $37.1 \pm 14.5$ ) than in localized GBS subtypes ( $54.8 \pm 4.0$ ,  $p < 0.001$ ), classic MFS ( $59.7 \pm 1.0$ ,  $p < 0.001$ ), and the MFS subtypes ( $59.4 \pm 1.5$ ,  $p < 0.001$ ), but not when compared with the overlap subtypes ( $30.4 \pm 20.7$ ,  $p = 0.173$ ). Similarly, the GDS at nadir was significantly higher in classic GBS ( $4.1 \pm 0.7$ ) than in the localized GBS subtypes ( $2.8 \pm 1.2$ ,  $p = 0.012$ ) and classic MFS ( $2.5 \pm 0.9$ ,  $p < 0.001$ ).

Mechanical ventilation was required significantly more often in patients with classic GBS (21.9%) than in classic MFS patients (0%,  $p = 0.006$ ), but significantly less often than in the overlap subtypes (63.6%,  $p < 0.001$ ). Lumbar puncture was performed in 115 of 130 (88.5%) patients with a mean time from symptom onset of  $8.7 \pm 5.8$  days (range 1–34 days). Classic GBS patients had a higher CSF protein level ( $1.63 \pm 1.94$  vs.  $0.49 \pm 0.29$  g/L,  $p < 0.001$ ) and cell count ( $4.6 \pm 9.2$  vs.  $0.7 \pm 2.0$  cells/ $\mu$ L,  $p = 0.004$ ) compared with classic MFS patients, but not with the other groups. CSF albumin–cytological dissociation was significantly more frequent in classic GBS than classic MFS (73.2% vs. 41.7%,  $p = 0.007$ ). In the total cohort ( $n =$

**Table 4.** Comparison of disease severity, laboratory features, treatments, and outcomes

Features	Classic GBS (n=64)		Localized GBS subtypes (n=9)		Classic MFS (n=29)		MFS subtypes (n=7)		Overlap syndrome (n=22)		
	Axonal GBS (n=17)	AIDP (n=35)	Overall	Value	p <sup>†</sup>	Value	p <sup>‡</sup>	Value	p <sup>§</sup>	Value	p <sup>  </sup>
<b>Severity</b>											
MRC sum score at nadir	42.3±11.6 (17-54)	34.1±14.9 (3-56)	37.1±14.5 (0-56)	54.8±4.0 (50-60)	<0.001*	59.7±1.0 (50-60)	<0.001*	59.4±1.5 (56-60)	<0.001*	30.4±20.7 (0-57)	0.173
GDS at nadir	4.0±0.4 (3-5)	4.2±0.8 (2-5)	4.1±0.7 (2-5)	2.8±1.2 (1-4)	0.012*	2.5±0.9 (1-4)	<0.001*	2.9±1.3 (1-5)	0.053	4.3±1.1 (2-5)	0.339
MV	1/17 (5.9)	12/35 (34.3)	14/64 (21.9)	0/9 (0)	0.119	0/29 (0)	0.006*	1/7 (14.3)	0.640	14/22 (63.6)	<0.001*
<b>CSF analysis</b>											
CSF protein, g/L	1.82±3.10 (0.15-12.12)	1.61±1.23 (0.26-4.70)	1.63±1.94 (0.15-12.12)	1.23±0.71 (0.26-2.16)	0.571	0.49±0.29 (0.26-2.16)	<0.001*	0.86±0.78 (0.32-2.21)	0.386	1.57±1.68 (0.22-6.44)	0.895
CSF WCC, cells/μL	5.5±8.2 (0-30)	3.1±4.8 (0-21)	4.6±9.2 (0-56)	1.1±2.5 (0-7)	0.295	0.7±2.0 (0-7)	0.004*	1.6±3.6 (0-8)	0.475	3.5±9.7 (0-34)	0.654
AC dissociation	10/16 (62.5)	26/30 (86.7)	41/56 (73.2)	6/8 (75)	0.915	10/24 (41.7)	0.007*	3/5 (60)	0.528	15/21 (71.4)	0.875
<b>Antiganglioside antibody</b>											
GM1	5/15 (33.3)	0/20 (0)	5/45 (11.1)	0/8 (0)	0.322	10/24 (0)	0.090	0/6 (0)	0.390	0/18 (0)	0.141
GM1b	4/15 (26.7)	0/20 (0)	4/45 (8.9)	0/8 (0)	0.380	0/24 (0)	0.132	1/6 (16.7)	0.547	0/18 (0)	0.191
GD1a	6/15 (40)	0/20 (0)	6/45 (13.3)	0/8 (0)	0.273	1/24 (0)	0.230	0/6 (0)	0.341	1/18 (5.6)	0.375
GalNAc-GD1a	5/15 (33.3)	0/20 (0)	6/45 (13.3)	0/8 (0)	0.273	0/24 (0)	0.061	1/6 (16.7)	0.824	0/18 (0)	0.103
GD1b	5/15 (33.3)	0/20 (0)	5/45 (11.1)	0/8 (0)	0.322	2/24 (8.3)	0.716	0/6 (0)	0.390	2/18 (11.1)	1.000
GT1a	2/15 (13.3)	0/20 (0)	3/45 (6.7)	0/8 (0)	0.452	9/24 (37.5)	0.001*	2/6 (33.3)	0.039*	7/18 (38.9)	0.002*
GO1b	1/15 (6.7)	0/20 (0)	2/45 (4.4)	0/8 (0)	0.543	12/24 (50)	<0.001*	3/6 (50)	<0.001*	4/18 (22.2)	0.030*
<b>Neurophysiology</b>											
AIDP	N/A	N/A	35/64 (54.7)	5/9 (55.6)	0.961	2/29 (6.9)	<0.001*	1/7 (14.3)	0.042*	9/21 (42.9)	0.346
Axonal	N/A	N/A	17/64 (26.6)	1/9 (11.1)	0.314	4/29 (13.8)	0.172	0/7 (0)	0.118	2/21 (9.5)	0.104
Unclassified	N/A	N/A	12/64 (18.8)	3/9 (33.3)	0.311	23/29 (79.3)	<0.001*	6/7 (85.7)	<0.001*	10/21 (47.6)	0.009*
<b>Treatment</b>											
Immunotherapy	16/16 (100)	32/35 (91.4)	58/62 (93.5)	8/9 (88.9)	0.610	11/29 (37.9)	<0.001*	3/7 (42.9)	<0.001*	19/22 (86.4)	0.295
IVIg	8/16 (50)	26/35 (74.3)	42/62 (67.7)	6/9 (66.7)	0.103	10/29 (34.5)	0.001*	3/7 (42.9)	0.001*	17/22 (77.3)	0.001*
PLEX	8/16 (50)	6/35 (17.1)	16/62 (25.8)	2/9 (22.2)	0.001*	1/29 (3.4)	0.001*	0/7 (0)	0.001*	2/22 (9.1)	0.001*
<b>Outcome</b>											
GDS <3 at 6 months	11/15 (73.3)	29/34 (85.3)	46/58 (79.3)	7/7 (100)	0.183	28/28 (100)	0.009*	5/5 (100)	0.258	13/19 (68.4)	0.330

Data are n (%) or mean±standard-deviation (range) values.

\*p<0.05, †Classic GBS vs. localized GBS subtypes, ‡Classic GBS vs. classic MFS, §Classic GBS vs. MFS subtypes, ||Classic GBS vs. overlap syndrome.

AC: albumin-cytological, AIDP: acute inflammatory demyelinating polyneuropathy, CSF: cerebrospinal fluid, GBS: Guillain-Barré syndrome, GDS: GBS disability score, IIVIg: intravenous immunoglobulin, MFS: Miller Fisher syndrome, MRC: Medical Research Council, MV: mechanical ventilation, N/A: not applicable, PLEX: plasma exchange, WCC: white cell count.

113), the CSF protein concentration was significantly correlated with the MRC sum score ( $r=-0.339$ ,  $p<0.001$ ) and GDS ( $r=0.238$ ,  $p=0.011$ ) at nadir. In comparison with classic GBS, patients with classic MFS and the MFS subtypes more frequently had anti-GQ1b (both: 50% vs. 4.4%,  $p<0.001$ ) and anti-GT1a (classic MFS: 37.5% vs. 6.7%,  $p=0.001$ ; MFS subtypes: 33.3% vs. 6.7%,  $p=0.039$ ) antibodies. Anti-GQ1b and anti-GT1a antibodies were also significantly more common in the overlap subtypes than in classic GBS (anti-GQ1b: 22.2% vs 4.4%,  $p=0.030$ ; anti-GT1a: 38.9% vs. 6.7%,  $p=0.002$ ). An electrodiagnosis of AIDP was significantly more common in classic GBS patients (54.7%) than in classic MFS (6.9%,  $p<0.001$ ) and the MFS subtypes (14.3%,  $p=0.042$ ). In contrast, an unclassified electrodiagnosis was significantly less common in classic GBS (18.8%) than in classic MFS (79.3%,  $p<0.001$ ), MFS subtypes (85.7%,  $p<0.001$ ), and the overlap subtypes (47.6%,  $p=0.009$ ).

Immunotherapy was initiated in 100 of 130 (76.9%) patients. Treatment was more frequent in classic GBS patients (93.5%) than in patients with classic MFS (37.9%,  $p<0.001$ ) and the MFS subtypes (42.9%,  $p<0.001$ ). Classic MFS patients achieved a good outcome (GDS  $<3$ ) at 6 months more frequently than did classic GBS patients (100% vs 79.3%,  $p=0.009$ ) irrespective of treatment. The remaining GBS subtypes ( $n=25$ ) had similar outcomes to classic GBS patients, and 84.7% of the entire cohort had GDS  $<3$  at 6 months.

## DISCUSSION

This study applied the new GBS classification system to a cohort of patients diagnosed with GBS and its related disorders. Each patient could be classified based on their clinical characteristics into a specific subtype, in contrast to 12% of the total cohort not reaching the higher levels of diagnostic certainty when applying the Brighton criteria. Patients with classic GBS and its variants were more likely to have AIDP and were negative for antiganglioside antibodies. In contrast, the majority of patients with MFS and its variants had a lower probability of AIDP but were positive for antiganglioside antibodies. Close to half of the patients in which GBS overlapped with one of the variants had a high probability of having AIDP, and there were also positive serological findings in more than one-third of them.

The largest proportion of patients (49%) in our cohort had classic GBS, although this was lower than previously reported frequencies of up to 71%.<sup>10,12</sup> However, the frequency of classic MFS (22%) was similar to those in other Asian cohorts<sup>4,20,21</sup> but higher than those in Western cohorts.<sup>22,23</sup> Subtypes of GBS and MFS were rare, accounting for up to 12% of patients, which is consistent with previous reports of 4–15% of local-

ized GBS subtypes and 2–5% of MFS subtypes.<sup>10,12</sup> The frequencies of PCB (2%) and paraparetic GBS (5%) in the present study were similar to those in other studies.<sup>2,10–12,24,25</sup> Isolated BBE was found in 2% of our GBS patients, consistent with a previous report of 3% in Japan<sup>10</sup> but lower than a report of 7% in children.<sup>25</sup> Other variants such as the bifacial weakness with paresthesia, acute ptosis, and acute ataxic hyper-somnolence were not seen in our cohort, although the possibility of these variants being underrecognized cannot be excluded.

A particularly interesting finding in the present cohort was of a high frequency of overlap syndromes (17%), most of which were the GBS/MFS overlap subtype (17 of 22, 77%), which on its own accounted for 13% of the entire GBS population. This was higher than previous reported frequencies of 3–5%.<sup>10,12</sup> The frequencies of GBS/BBE overlap (3%) and MFS/PCB overlap (1%) were similar to those found in other studies.<sup>26,27</sup> We also had a single case of polyneuritis cranialis with clinical characteristics of bulbar palsy, ophthalmoplegia, ptosis, and areflexia. Wakerley and Yuki considered this variant a separate entity that represents an interface between GBS and MFS.<sup>9</sup> However, it could be argued that its features are within the MFS spectrum, especially given the presence of ophthalmoplegia and areflexia. Other previous authors have suggested the term “acute bulbar palsy-plus syndrome,” which has close associations with the anti-GT1a antibodies.<sup>28</sup> The latter classification is worth considering as a separate entity to “polyneuritis cranialis,” which is nondescript.

There have been conflicting reports of neurophysiological subtypes of the GBS variants. PCB has been reported as predominantly axonal,<sup>29,30</sup> but one of our two cases was highly likely to have had AIDP and the other was equivocal. We found that most cases of paraparetic GBS had AIDP on electrodiagnosis. Previous reports have varied with the electrodiagnostic criteria used.<sup>10–12</sup> A study of a French cohort found that 6 of 12 (50%) patients had demyelinating subtypes<sup>11</sup> when the Hadden criteria were used, but this changed to axonal in 8 (67%) of the patients when the Rajabally criteria were used. Other studies have also predominantly found the axonal electrodiagnostic subtype irrespective of the criteria used.<sup>12</sup> It is unclear as to why our cohort differed from those in other studies. One possibility is the infective profiles differing between countries; for example, *Campylobacter jejuni* infection as reported in cases of PCB<sup>29–32</sup> and paraparetic GBS<sup>33,34</sup> elsewhere is rarely associated with GBS in Malaysia.<sup>35</sup> In the current study, 56% of the classic MFS patients and its variants presented only sensory abnormalities, and thus were classified as equivocal similar to previous reports.<sup>26,36,37</sup> We also found that the probability of AIDP was lower in the MFS spectrum of disease and the overlap syndromes.

The current study detected the antiganglioside antibodies anti-GM1, anti-GM1b, anti-GD1a, anti-GalNAc-GD1a, and anti-GD1b IgG in classic GBS patients with an axonal form of GBS, similar to previous studies.<sup>1,8,10,23,38-40</sup> In axonal GBS, antiganglioside antibodies have been shown to target gangliosides such as GM1 and GD1a, which are strongly expressed at the nodes of Ranvier.<sup>41,42</sup> Binding of the antibodies to the nodal axolemma activates the complement cascades, leading to the disappearance of voltage-gated sodium-channel clusters and focal disruption of axoglial junctions, resulting in a continuum of nerve dysfunction ranging from temporary conduction failure to axonal degeneration.<sup>41,42</sup> Anti-GQ1b and anti-GT1a IgG antibodies were detected in the patients with classic MFS, MFS subtypes (acute ophthalmoparesis and BBE), and overlap subtypes (GBS/MFS overlap and GBS/BBE overlap), which is consistent with previous reports.<sup>10,26,43,44</sup> MFS patients typically display IgG antibodies against ganglioside GQ1b, which are strongly expressed in human oculomotor, trochlear, and abducens nerves and muscle spindles, and can explain the manifestations of ophthalmoplegia and ataxia.<sup>44</sup> Previous studies have also found an association between anti-GT1a antibodies and PCB.<sup>29,31,32</sup> An immunohistochemical study showed that GT1a was strongly expressed in the human glossopharyngeal and vagal nerves, accounting for oropharyngeal and cervicobrachial weakness.<sup>45</sup> We did not detect anti-GT1a antibodies in our PCB patients, but did find this antibody in a patient with MFS/PCB overlap. A study of 100 PCB patients found anti-GT1a antibody in 81% of the patients with MFS/PCB overlap.<sup>31</sup> The association of antiganglioside antibody profiles with paraparetic GBS is less clearly defined, although anti-GD1a, anti-GM1, and anti-GQ1b antibodies have been reported.<sup>33,46</sup> None of our paraparetic GBS patients were positive for antiganglioside antibodies. Anti-GD1b and anti-GQ1b IgG antibodies are typically associated with acute ataxic neuropathy,<sup>47</sup> but they were not present in our two patients. A study has shown that GD1b is expressed on human dorsal root ganglion neurons, which would result in sensory ataxia clinically.<sup>48</sup>

As expected, our classic GBS patients had the lowest MRC sum score and highest GDS at nadir and need for ventilatory support compared with localized GBS, classic MFS, and the MFS subtypes. Another particularly interesting observation was that the need for mechanical ventilation was greater in the overlap subtypes than in classic GBS. This might be explained by the BBE/GBS patients also having altered levels of consciousness and the PCB/MFS patients having bulbar involvement. There is a need for airway protection in both of these clinical presentations.

This study also showed that the severity of GBS (as indicated by the MRC sum score and GDS at nadir) was correlated

with the concentration of CSF protein. This was significant in our classic GBS patients, who had higher levels of CSF protein and mild pleocytosis compared with classic MFS, consistent with previous reports.<sup>49,50</sup> Most (94%) of the classic GBS patients were treated with immunotherapy, either intravenous immunoglobulin or plasma exchange, but 20% of these patients remained disabled with GDS >3 at 6 months. This is consistent with the rate of disability reported in the literature.<sup>1,24</sup> In contrast, MFS patients had good outcomes with GDS <3 at 6 months irrespective of treatment.<sup>21,26</sup>

The current study found that 12% of the included patients had variants of GBS that were either localized forms of GBS or MFS subtypes. This is significant given that this group of patients would be overlooked when applying the two most widely used GBS diagnostic criteria.<sup>5,6</sup> This problem is further highlighted by our recent validation study of the Brighton criteria finding that one-quarter of the MFS patients did not reach the highest diagnostic certainty, which required the presence of the complete triad of ophthalmoplegia, ataxia, and areflexia.<sup>7</sup> The Brighton Collaboration GBS Working Group acknowledged this limitation, but considered the subtypes of GBS and MFS to be rare (<1%).<sup>6</sup> Other criteria also do not consider these variants,<sup>5</sup> further limiting their potential to capture the full GBS spectrum.

One of the limitations of the study was that the localized forms of GBS and MFS subtypes such as acute pharyngeal weakness, acute ptosis, or acute mydriasis may not have presented to clinicians and therefore were not captured.

In conclusion, we found the new GBS classification of Wakkerley and colleagues to be helpful in further classifying the specific subtype of GBS including its forme fruste and variants. Recognizing the full spectrum of clinical presentations in GBS will allow more-complete case ascertainment, leading to a better understanding of the disease as well as facilitating treatment decisions and prognoses.

### Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2021.17.2.273>.

### Author Contributions

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### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.



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