

Research paper

Electrophysiology of Guillain-Barré syndrome in Bangladesh: A prospective study of 312 patients



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ABSTRACT

Objective: To describe the electrophysiological features in relation to clinical and serological findings of Guillain-Barré syndrome (GBS) in the national neuroscience hospital in Bangladesh. This is one of the few studies that investigated GBS patients using standardized electrophysiology in low-income countries. **Methods:** In a prospective and observational study, we investigated 312 GBS patients by standardized clinical, serological and electrophysiological methods. Unilateral motor and sensory nerve conduction studies (NCS) were performed within two weeks of onset of weakness. Follow up NCS were performed in 189 patients and classified according to eight sets of established GBS criteria. Serology included assessment of anti-GM1 antibodies and anti-campylobacter jejuni lipo-oligosaccharide (LOS) antibodies.

Results: Depending on the criteria used, 44–59% patients had axonal GBS with anti-GM1 antibodies being present in 55–58% and 9–42% patients had demyelinating GBS with anti-GM1 antibodies being present in 7–35%. Conduction block (CB) with demyelinating slowing in the same nerve segment was found in 24% (74/312) patients, and CB without demyelinating slowing in the same nerve segment was found in 18% (56/312) patients, of whom anti-GM1 antibodies were found in 27% and 57% patients respectively. Follow-up NCS showed a change in GBS classification in 11–26% of patients, mainly from demyelinating to axonal GBS.

Conclusions: The predominant subtype of GBS in Bangladesh is axonal but demyelinating GBS also occurs with classification being strongly dependent on the applied criteria.

Significance: The present study demonstrates the importance of reaching international agreement on GBS criteria that should be based on the best evidence.

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1. Introduction

Guillain-Barré syndrome (GBS) manifests with symmetrical muscle weakness with or without sensory symptoms and signs, putatively resulting from immune-mediated nerve damage. Nerve electrophysiological evidence of axon or myelin damage may have important association with the immunological status of the patient, specially the anti-ganglioside antibodies in the patient's serum (Albers et al., 1985; Cornblath, 1990; Hadden et al., 1998;

Ho et al., 1995; Meulstee et al., 1995; Rajabally et al., 2015; Uncini et al., 2017; Van den Bergh et al., 2004). Classification into demyelinating and axonal forms is, however, ambiguous since cut-off values for slowing consistent with demyelination differ between proposed criteria sets, requirements differ between criteria sets, and conduction block was shown to represent demyelination as well as axolemmal dysfunction (Uncini and Kuwabara, 2015; Uncini et al., 2013). Nevertheless, it is recognized that the two most prevalent subtypes are acute inflammatory demyelinating polyneuropathy (AIDP) for Europe and the USA and acute motor axonal neuropathy (AMAN) for Northern China and Japan (Doets et al., 2018). Previous studies have reported that preceding infections with *Campylobacter jejuni* (*C. jejuni*) which induce antibodies to its lipo-oligosaccharides (LOS) and which subsequently

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cross-react to peripheral nerve gangliosides such as GM1 are particularly associated with the axonal forms of GBS.

The present study describes the electrophysiology of GBS in a prospective cohort of 312 patients from Bangladesh. All patients were classified into subtypes according to different sets of criteria to demonstrate the impact of the various classifications and to be able to compare the subtype of GBS in Bangladesh to that of other countries. Moreover we investigated the change in subtype over time by serial electrophysiological studies and the relation with clinical features and IgG antibodies to GM1 and *C. jejuni* lipooligosaccharide (LOS).

2. Methods

2.1. Patients

Between March 2010 and October 2013 we investigated a prospective cohort of 456 patients with suspected GBS admitted to Dhaka Medical College Hospital, Bangladesh. All patients gave written informed consent and the study was approved by the ethics committees of the International Center for Diarrhoeal Disease Research, Bangladesh and Dhaka Medical College, Bangladesh.

After admission patients were examined within 2 days by a neurologist. In 312 patients a diagnosis of GBS could be made according to the National Institute of Neurological Disorders and Stroke criteria for GBS (Asbury, 1978; Asbury and Cornblath, 1990). Demographic and clinical data were recorded using a standardized protocol. Each patient was clinically classified as pure motor GBS or sensorimotor GBS. Disease severity was evaluated by the GBS disability score (Hughes et al., 1978) and the Medical Research Council sum score (MRC sum score) assessed by adding the MRC scores on both sides for elbow flexors, wrist extensors, shoulder abductors, hip flexors, knee extensors, and ankle extensors. The MRC sum score ranged from 60 (normal) to 0 (quadriplegic) (Hughes et al., 2007). In 269 patients CSF was collected on admission. Nerve conduction studies (NCS) were performed within one week of admission in all 312 patients by a neurologist who was trained in the Netherlands. In 189 patients a second NCS was performed within two months after the first NCS.

2.2. Nerve conduction studies

NCS consisted of a standardized protocol on one side, using a Viking Select EMG system (CareFusion, San Diego, CA, USA). Motor nerve conduction and F waves after 10 distal stimuli were recorded for the median nerve (stimulation: wrist, elbow, and axilla; recording: abductor pollicis brevis muscle), ulnar nerve (stimulation: wrist, below elbow, above elbow, and axilla; recording: abductor digiti minimi muscle), fibular nerve (stimulation: ankle, below fibular head, and popliteal fossa; recording: extensor digitorum brevis muscle), and tibial nerve (stimulation: ankle and popliteal fossa; recording: abductor hallucis muscle). Sensory nerve conduction (antidromic) was investigated in the median nerve (stimulation: wrist and elbow; recording: second digit), ulnar nerve (stimulation: wrist and below elbow; recording: fifth digit), and sural nerve (stimulation: at lower lateral calf; recording behind lateral malleolus). We measured amplitude, duration and area of the negative part of the compound muscle action potential (CMAP), distal motor latency (DML), motor conduction velocity (MCV) per segment, minimal F-wave latency, amplitude of the negative part of the sensory nerve action potential (SNAP) and sensory conduction velocity (SCV) per segment. Reference values are given in Fig. 1 (Buschbacher and Prahlow, 2006).

NCS at onset and follow-up were classified according to the GBS criteria proposed by Albers et al. (1985); Cornblath et al. (1990);

Meulstee et al. (1995); Ho et al. (1995); Hadden et al. (1998); van den Bergh et al. (2004); Rajabally et al. (2015); Uncini et al. (2017). Uncini's criteria, which require two successive NCS, could be applied in 189 patients. NCS abnormalities at the entrapment sites of the ulnar nerve at the elbow and the fibular nerve at the fibular head were not analyzed. Cut-off values for dCMAP amplitude, demyelinating slowing of DML, MCV, and F-latency, conduction block (CB) and increased temporal dispersion (TD) were defined according to the requirements for each of the criteria (Fig. 1). Pseudo CB due to Wallerian degeneration was considered if, in a nerve segment without demyelinating slowing, the 1st NCS showed that the proximal CMAP was lower than the distal CMAP and that this difference fulfilled criteria for CB ($p\text{CMAP}/d\text{CMAP} < 0.7$) whereas the 2nd NCS, performed within 60 days, showed that both CMAPs were of equal size because the distal CMAP had decreased between the 1st and the 2nd NCS. When applying the criteria of Hadden and Uncini, requirements formulated as "at least one of the following in at least two nerves" was interpreted such that the relevant feature had to be present in at least two nerves. We also related the presence of anti-GM1 antibodies to evidence-based criteria for segmental slowing and conduction block since the origin of some of the cut-off values in the above described GBS criteria is unclear; to avoid confusion with other criteria, this analysis is described in paragraph 3.3 (Serology and NCS) and Figs. 2 and 3 only (Van Asseldonk et al., 2005, 2006).

2.3. Serology

Serum anti-GM1 IgG antibodies and antibody reactivity to *C. jejuni* lipo-oligosaccharide (LOS) were assessed by enzyme-linked immunosorbent assay. Patients were considered positive for anti-GM1 IgG antibodies if the optical density was > 0.2 (Z. Islam et al., 2010). Serum antibodies against LOS were quantified using an ELISA as described previously (Kuijff et al., 2005) with some modifications (Z. Islam et al., 2012). Serum was considered anti-LOS positive if the corrected OD was greater than the mean plus three times standard deviation (SD) value of control samples.

2.4. Statistical analysis

Categorical variables are given by percentages and continuous variables by their median and interquartile range (IQR). Differences in categorical variables were examined by Fisher's exact test and differences in continuous variables by Mann-Whitney's *U* test. Correlations between MRC sum-scores were evaluated by Spearman's rank correlation coefficient. SPSS Statistics 20.0 (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Two-sided *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Clinical features

Table 1 lists the clinical features of the patients. Ninety-nine percent of patients reached hospital after development of maximal weakness. On clinical examination 66% of patients had pure motor GBS and 34% had sensorimotor GBS. Median MRC sumscore at nadir was not significantly different between these groups. Mechanical ventilation was required for 14% of patients with pure motor GBS and 25% of patients with sensorimotor GBS. Specific treatment consisted of IVIg in 9% and plasmapheresis in 2% of patients.

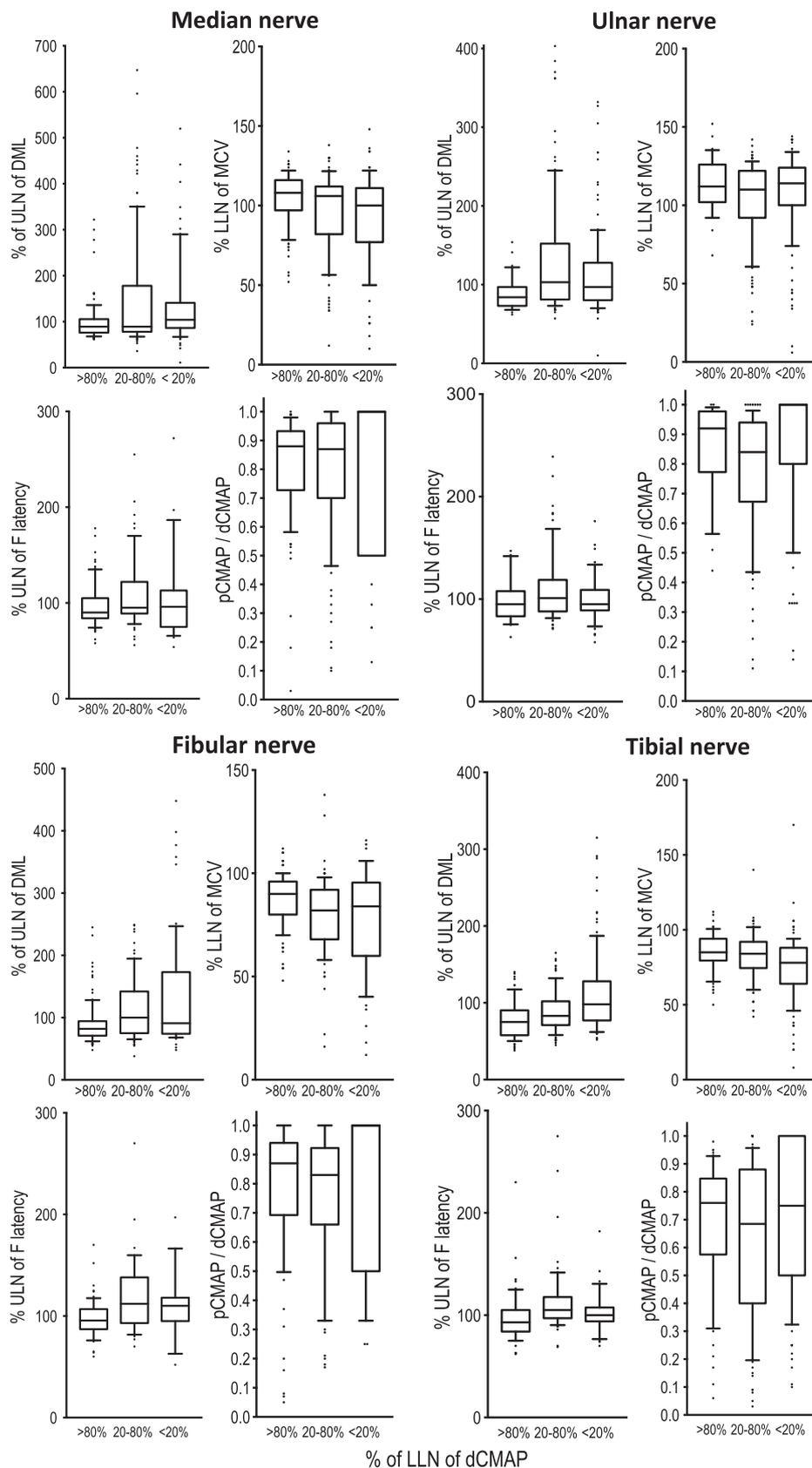


Fig. 1. Motor NCS parameters in 312 Bangladeshi patients with GBS.Box plots showing median, ulnar, fibular and tibial motor NCS parameters expressed as median, inter-quartile range and range. DML = distal motor latency; ULN = upper limit of normal; LLN = lower limit of normal. LLN for distal CMAP amplitude: median nerve, 4.5 mV; ulnar nerve, 7.9 mV; fibular nerve, 2 mV; tibial nerve, 5 mV. ULN for distal motor latency: median nerve, 4.5 ms; ulnar nerve, 3.7 ms; fibular nerve; 6.5 ms; tibial nerve, 6.0 ms. LLN for motor conduction velocity: median nerve, 50 m/s; ulnar nerve, 50 m/s; fibular nerve, 40 m/s; tibial nerve, 40 m/s. ULN for F latency: median nerve (25.7 ms – 34.2 ms), ulnar nerves (26 ms – 33.8 ms), fibular nerve (48.6 – 63.6 ms) and tibial nerve (47.6 ms – 68.5 ms) [Depending on the height and age of the patient] (Buschbacher et al., 2006).

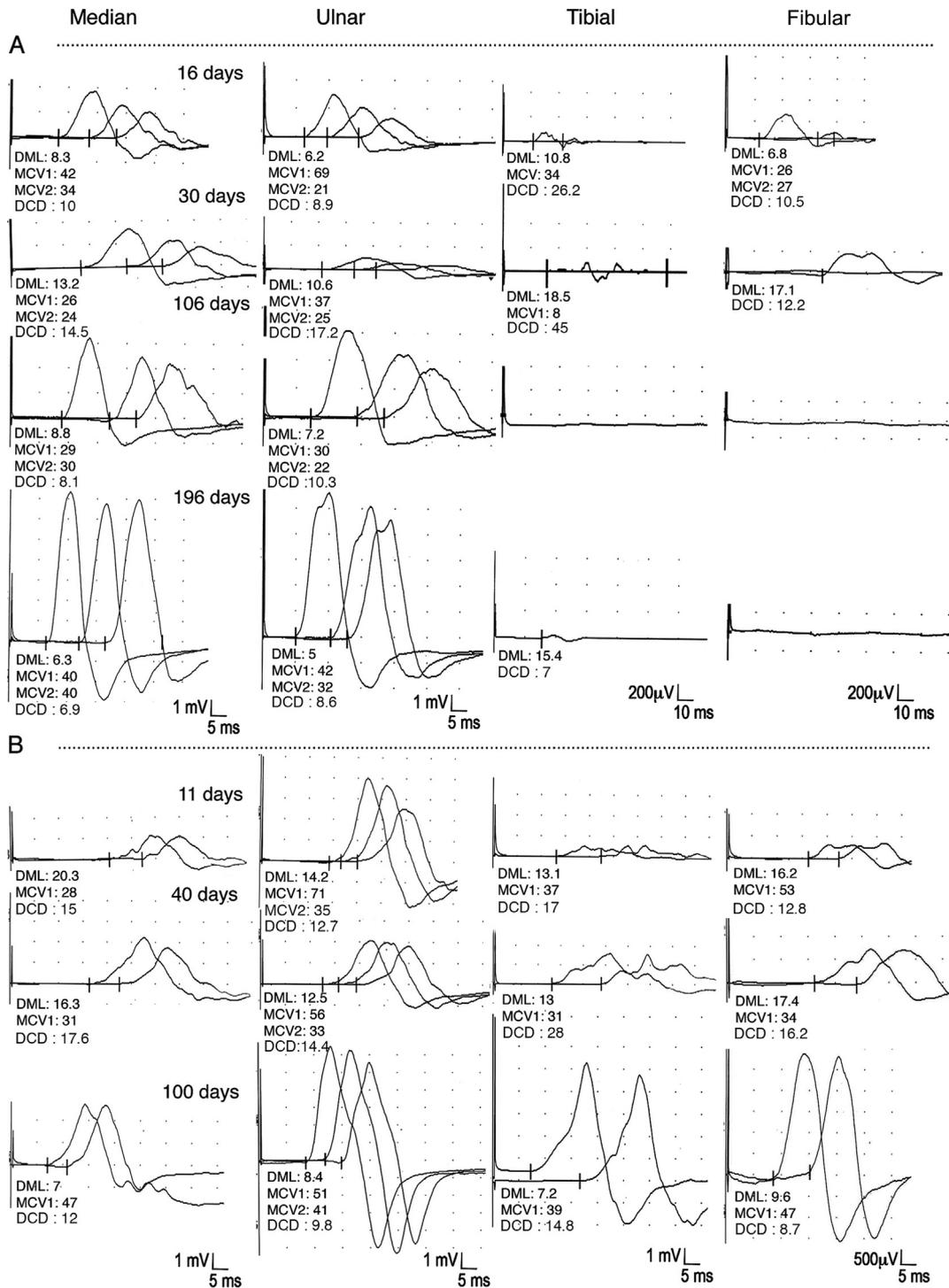


Fig. 2. Serial nerve conduction studies in two GBS patients (A, B) with anti-GM1 antibodies and evidence of demyelination. Patient A had both anti-GM1 and anti-LOS antibodies, indicating a recent *C. jejuni* infection. On admission patient A had demyelinating slowing of median and ulnar nerve DML (or DCD), median nerve upper arm MCV and ulnar nerve elbow MCV; distal CMAPs in the fibular and tibial nerves were below 1mV. At 30 days he had CB in the forearm segments of the median and ulnar nerves and demyelinating slowing of median and ulnar nerve DML, DCD and MCV in forearm, upper arm and elbow segments. At 196 days there still was demyelinating slowing of DML and upper arm MCVs with considerable increase of median and ulnar nerve CMAPs but loss of fibular and tibial nerve CMAPs. Patient B had anti-GM1 antibodies. On admission he had demyelinating slowing of median and ulnar nerve DML and DCD and demyelinating slowing of median nerve forearm MCV and ulnar nerve elbow MCV; distal CMAPs were below 1mV in the tibial and fibular nerves. At day 40 there was demyelinating slowing in the same arm nerve segments; tibial nerve CMAPs had slightly increased so that DML, DCD and MCV now fulfilled criteria for demyelinating slowing. At 100 days CMAP amplitudes had considerably increased but there still was demyelinating slowing of DML or DCD in all nerves and of ulnar nerve elbow MCV. In both patients sensory nerve action potentials (SNAPs) could not be elicited in any nerve on admission and follow-up (not shown).

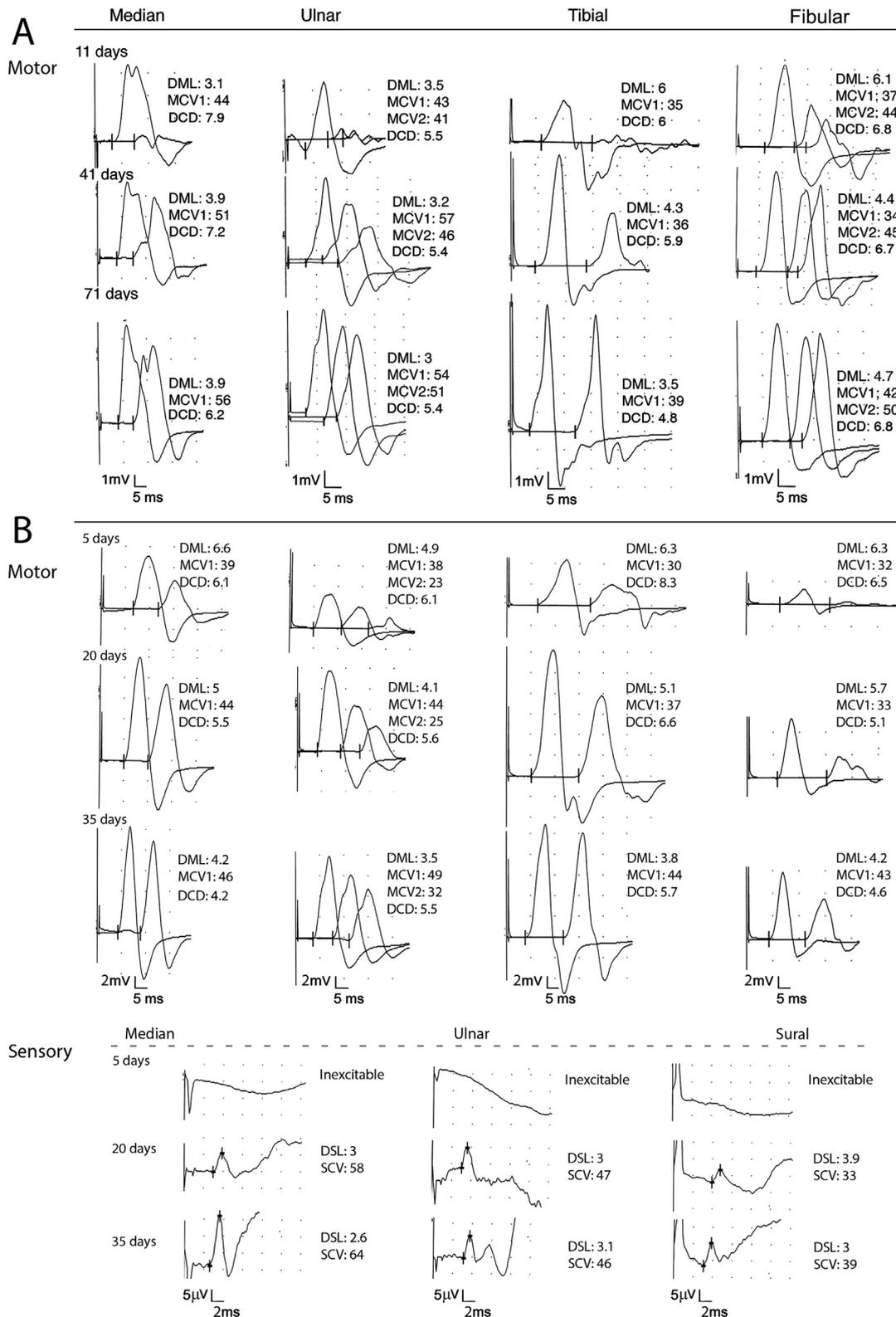


Fig. 3. Serial nerve conduction studies in two GBS patients (A, B) with anti-GM1 antibodies and transient conduction block. Patient A had both anti-GM1 antibodies and anti-LOS antibodies indicating a recent *C. jejuni* infection. On admission patient A had CB in the forearm segments of the median and ulnar nerves and lower leg segment of the fibular nerve and increased TD in the forearm segment of the median and tibial nerves. On day 41, CB and increased TD had disappeared in all nerves, although there was demyelination slowing in the fibular nerve. On day 71 CMAP amplitudes had increased and there was no CB, increased TD or demyelination slowing. Patient B had high anti-GM1 antibody titers but no anti-LOS antibodies. On admission he had CB in the forearm or lower leg segments of the median, ulnar and fibular nerves, demyelination DML in the median and ulnar nerves and demyelination MCV in the forearm and elbow segments of the ulnar nerve and lower leg segments of the fibular and tibial nerves; SNAPs were absent. On day 20 CB had disappeared, except for the ulnar nerve elbow segment; demyelination MCV was still found in the ulnar and fibular nerves. On day 35 there was still demyelination MCV in the ulnar nerve elbow segment; CMAPs had increased and SNAPs were normal. DML = distal motor latency in ms. DCD = distal CMAP duration in ms. MCV1 = motor conduction velocity, in ms, in the forearm or lower leg segment. MCV2 = motor conduction velocity in upper arm for the median nerve and elbow for the ulnar. CB = conduction block. TD = temporal dispersion. Criteria for demyelination slowing (including increased TD) and CB are those by Van Asseldonk (Van Asseldonk et al., 2005, 2006).

Table 1
Clinical and laboratory features on admission in 312 patients with Guillain-Barré syndrome.

Feature	Value (range) or percentage
Gender, age (median, IQR)	204 men / 108 women, 25 years (16–40)
Preceding diarrhea	motor: 59%, sensorimotor: 38%
Preceding respiratory infection	16%
Cranial nerve deficit	65%
Weakness arms/legs	98%
Sensory deficit	26%
Autonomic dysfunction	21%
GBS disability score 2 / 3 / 4 / 5	5% / 13% / 70% / 12%
MRC sumscore at entry (median, IQR)	motor: 24 (4–36), sensorimotor: 24 (4–36)
MRC sumscore at nadir (median, IQR)	motor: 22 (4–34), sensorimotor: 25 (12–36)
Time onset - admission/onset-nadir (median, IQR)	8 days (5–13) / 4 days (3–6)
Time onset - NCS/onset CSF (median, IQR)	10 days (7–15) / 10 days (8–14)
CSF albumino-cytologic dissociation	87% of 269 patients
CSF protein concentration (median, IQR)	128 mg/dL (70–221)
Anti GM1 antibody	44%
Anti LOS antibody	62%
Both Anti GM1 and LOS antibody	38%

IQR = inter quartile range. Preceding diarrhea or respiratory infection refers to symptoms in the four weeks preceding onset of weakness. GBS disability score: 2 = able to walk 10 m unassisted but unable to run, 3 = able to walk 10 m with help, 4 = bedridden or chair-bound, 5 = requiring assisted ventilation. CSF = cerebrospinal fluid. CSF albumino-cytologic dissociation = increased CSF protein (>45 mg/dL) with cell count < 50/μL. Motor and sensorimotor refer to clinical examination.

3.2. Nerve conduction studies

Fig. 1 shows motor NCS features at onset. NCS were abnormal according to our reference values in 99% of patients. Distal CMAPs could not be elicited in 12% of median, 19% of ulnar, 21% of fibular, and 12% of tibial nerves. Distal CMAPs could be elicited but were below 20% of the lower limit of normal (LLN) in 27% of median, 38% of ulnar, 20% of fibular, and 31% of tibial nerves. SNAPs could not be elicited in 25% of median, 25% of ulnar, and 16% of sural nerves. SNAP amplitude and SCV were normal in 69% of median, 70% of ulnar, and 84% of sural nerves. The combination of normal SNAP amplitude, normal SCV and decreased CMAP amplitude (below LLN) or absent CMAP was found in 68% of median and 71% of ulnar nerves. An absent median/present sural nerve SNAP pattern occurred in 16% of patients.

Table 2 shows the subtype classification at onset for the 312 patients according to those GBS criteria which do not require a second NCS. For each of these criteria, more patients were categorized as axonal or non-demyelinating than as demyelinating. Classifica-

Table 2
Classification at onset according to seven criteria for Guillain-Barré syndrome (312 patients).

Criteria	Demyelinating	Non-Demyelinating	Normal
Albers	42%	57%	1%
Cornblath	9%	90%	1%
Meulstee	30%	69%	1%
Van den Bergh	32%	67%	1%
	Demyelinating	Axonal	Inexcitable
Ho	30%	44%	25%
Hadden	32%	44%	16%
Rajabally	19%	59%	14%
			Unclassified
			Normal

Patients were classified according to the criteria of Albers et al. (1985); Cornblath (1990); Meulstee and van der Meche (1995); Van den Bergh and Pieret (2004); Ho et al. (1995); Hadden et al. (1998); Rajabally et al. (2015). Classification at onset by the criteria of Uncini et al. (2017) is described in the text as classification by these criteria require a second NCS after onset.

tion depended on the criteria applied with the demyelinating category varying from 9 to 42% and the axonal category from 44 to 67%.

The criteria of Albers, Cornblath, and Van den Bergh distinguished between demyelinating and non-demyelinating GBS whereas the Hadden, Ho, Rajabally and Uncini criteria distinguished between axonal and demyelinating GBS. Out of the 205 patients with clinically pure motor GBS, 52% was classified axonal by Hadden's criteria, 53% by Ho's criteria and 77% by Rajabally's criteria. Out of the 107 patients with sensorimotor GBS, 68% was classified demyelinating by Hadden's criteria, 68% by Ho's criteria and 53% by Rajabally's criteria. Decreased or absent SNAPs were found in 80–98% of cases of demyelinating GBS and in 16–25% of cases of axonal GBS, the percentages depending on the differences in cut-off values for slowing compatible with demyelination, CB and definitions of low CMAP amplitude depending on the criteria applied.

Follow-up NCS was performed in 61% (189/312) of patients after a median interval of 25 days (IQR, 25–50). The second NCS led to a classification change in 26% (49/189) of patients for the Hadden criteria, 22% (42/189) patients for the Ho criteria, 17% (31/189) patients for the Albers criteria, 15% (29/189) patients for the Rajabally criteria, 14% (26/189) patients for the Meulstee criteria, 15% (28/189) patients for the Van den Bergh criteria, and 11% (21/189) patients for the Cornblath criteria (Table 3). For the different criteria this was due to disappearance of CB in 6 to 19 patients, appearance of slowing compatible with demyelination in 8 to 19 patients, disappearance of slowing compatible with demyelination in 2 to 14 patients, disappearance of CMAPs in all nerves in 3 patients, and reappearance of CMAPs in 2 to 6 patients. Classification by Uncini's criteria, which has to be done after the second NCS, was axonal in 60% (114/189) of patients and demyelinating in 25% (47/189) of patients. These criteria had the least number (14/189; 7%) of unclassified GBS patients.

Change of motor CB over time could be assessed in 49 arm and 64 leg nerve segments in 66 patients who had CB (pCMAP/dCMAP < 0.7) at 1st NCS assessment during the acute phase of GBS and had a follow up NCS study within two months. In the 2nd NCS, reversible CB was noted in 29/49 arm and in 22/64 leg nerve segments; pseudo CB was noted in 8/49 arm and 15/64 leg nerve segments. Development of new CB was not noted in any nerve in the 2nd NCS assessment.

3.3. Serology and NCS

In the 217 GBS patients who had pure motor involvement on NCS, anti-GM1 antibodies were detected in 122 patients and anti-GM1 and anti-LOS antibodies in 111 patients. Depending on the criteria applied, demyelinating GBS was found in 0–34 patients with anti-GM1 antibodies and in 0–30 of patients with anti-GM1

Table 3
Changes in GBS classification for 189 patients after follow-up NCS.

Criteria	Onset (n)	Follow up (n)				
		Demyelinating	Axonal	Inexcitable	Unclassified	Normal
Albers	Demyelinating (79)	59		18		2
	Non-demyelinating (105)	8		95		2
	Normal (4)	1		0		3
Cornblath	Demyelinating (16)	14		2		0
	Non-demyelinating (169)	14		151		4
	Normal (4)	1		0		3
Meulstee	Demyelinating (56)	39		15		2
	Non-demyelinating (129)	6		121		2
	Normal (4)	1		0		3
Van den Bergh	Demyelinating (63)	45		16		2
	Non-demyelinating (122)	7		113		2
	Normal (4)	1		0		3
Ho		Demyelinating	Axonal	Inexcitable	Unclassified	Normal
	Demyelinating (56)	46	2	0	7	1
	Axonal (84)	2	77	0	5	0
	Unclassified (45)	10	10	0	21	4
	Normal (4)	1	0	0	0	3
Hadden	Demyelinating (61)	47	9	0	4	1
	Axonal (83)	0	74	1	8	0
	Unclassified (33)	4	10	2	14	3
	Inexcitable (8)	2	4	2	0	0
	Normal (4)	1	0	0	0	3
Rajabally	Demyelinating (34)	32	0	0	1	1
	Axonal (117)	3	109	2	3	0
	Unclassified (26)	4	4	1	14	3
Uncini	Inexcitable (8)	2	4	2	0	0
	Normal (4)	1	0	0	0	3
	Normal (4)	47	114	11	14	3

n = number of patients. Classification by the criteria of Uncini et al. (2017) is described in the text.

and anti-LOS antibodies; axonal GBS was found in 64–122 patients with anti-GM1 and in 60–111 of patients with anti-GM1 and anti-LOS antibodies. In the 95 patients who had sensory-motor involvement on NCS, anti-GM1 antibodies were detected in 7–16 patients and anti-GM1 and anti-LOS antibodies in 1–7 patients. Depending on the criteria applied, demyelinating GBS was found in 2–11 patients with anti-GM1 antibodies and in 1–4 of patients with anti-GM1 and anti-LOS antibodies; axonal GBS was found in 0–14 patients with anti-GM1 and in 0–7 of patients with anti-GM1 and anti-LOS antibodies. Based on the second NCS study, 0–23 patients with demyelinating GBS had anti-GM1 antibody and 0–16 patients with demyelinating GBS had both anti-GM1 and anti-LOS antibodies.

These serological features were related to demyelinating slowing and CB as defined by the criteria of Van Asseldonk (Van Asseldonk et al., 2005). Demyelinative slowing was found in 172 patients of whom 29% had both anti-GM1 and anti-LOS antibodies (Fig. 2A), 7% had only anti-GM1 antibodies (Fig. 2B) and 24% had only anti-LOS antibodies. CB with demyelinating slowing in the same nerve segment according to these criteria was found in 74 patients of whom 19% had both anti-GM1 and anti-LOS antibodies, 8% had only anti-GM1 antibodies, and 20% had only anti-LOS antibodies. CB without demyelinating slowing was found in 56 patients of whom 53% had both anti-GM1 and anti-LOS antibodies (Fig. 3A), 4% had only anti-GM1 antibodies (Fig. 3B) and 27% had only anti-LOS antibodies.

3.4. Clinical features, serology and NCS

Among the 215 (69%) patients with clinically pure motor GBS, 193 (90%) patients had pure motor and 22 (10%) patients had sensory motor involvement on NCS. Among the 80 (26%) patients with clinically sensory-motor GBS, 65 (81%) patients had sensory-motor and 15 (19%) patients were pure motor involvement on NCS. Among the 22 patients who had clinically pure motor but

sensory-motor involvement on NCS; anti-GM1 antibodies, anti-LOS antibodies or both the antibodies were present in 4 (18%), 8 (36%) and 3 (14%) cases respectively. And in 15 patients who had clinically sensory-motor but pure motor involvement on NCS; anti-GM1 antibodies, anti-LOS antibodies or both the antibodies were present in 6 (40%), 7 (47%) and 5 (33%) cases respectively. In 17 patients, sensory involvement could not be elicited due to inadequate communication. In these patients pure motor and sensory-motor involvement on NCS were found in 12 (71%) and 5 (29%) patients respectively.

4. Discussion

The present study is one of the few that investigated electrophysiological GBS criteria in low-income rather than high-income countries (Alam et al., 1998; Kalita et al., 2008; Van den Bergh and Pieret, 2004). Since only 11% of our patients received treatment with either IVIg or plasmapheresis the NCS results on follow up are therefore less likely influenced by specific immunotherapy. Despite the difference in criteria the majority of our patients in Bangladesh had axonal GBS as was also shown in previous, smaller studies (M. B. Islam et al., 2016; Z. Islam et al., 2010). We conducted our study in a government hospital, attended by lower middle class or poor people who had severe GBS and who could not afford immune therapy. These conditions predispose for the AMAN subtype of GBS, which is known to be associated with gastroenteritis due to *C. jejuni* (Z. Islam et al., 2010). The majority of patients reported from India and Pakistan had demyelinating GBS, were treated with IVIg or plasma exchange and had a good outcome with low mortality (Kalita et al., 2014; Shafiqat et al., 2006).

The described patients in these countries were affluent members of the population who could afford expensive immune modulatory treatments. Economic growth in a country improves nutritional status as well as hygiene practices and eventually

influences immune status and reduces exposure to specific types of infections. This may possibly explain the reported change in the predominant subtype of GBS in China from AMAN to AIDP over the last few decades (Liu et al., 2018).

Our finding that 13 patients with anti-GM1 antibodies had nerve conduction slowing fulfilling evidence-based criteria for demyelination is remarkable and is in agreement with an earlier report from the Netherlands (Drenthen et al., 2011). It is likely that these antibodies were related to a preceding *C. jejuni* infection since they were associated with presence of anti-LOS antibodies. This finding suggests that anti-GM1 antibodies may induce primary demyelination, possibly due to co-reactivity with GM1 epitopes that are not only expressed on the nodal axolemma but also on perinodal Schwann cell loops (Gong et al., 2002; Sheikh et al., 1999).

In some GBS criteria, CB is exclusively regarded as evidence of demyelination, probably as other causes of CB were unknown at the time these criteria were developed (Albers et al., 1985; Cornblath, 1990; Hadden et al., 1998; Meulstee and van der Meche, 1995). However, serial follow-up NCS in patients with axonal GBS, immunohistochemistry studies in rabbit models of AMAN, and intraneural injections of ganglioside antibodies in rats have revealed that antibody- and complement-mediated damage to nodal sodium channel clusters may also induce CB (Capasso et al., 2003; Kokubun et al., 2010; Kuwabara et al., 1998; Susuki et al., 2007, 2012; Uncini et al., 2010). These findings suggest that serial NCS could be used to differentiate CB due to sodium channel damage, which resolves within a few weeks and is not associated with demyelination (reversible CB), from CB due to demyelination, which resolves over months and is associated with demyelination. This distinction may, however, be uncertain as CB is likely to be classified as demyelinating due to presence of increased TD if nodal sodium channel damage and *para*-nodal demyelination co-exist in the same nerve.

The GBS criteria applied in the present study should be interpreted with some caution. First, the evidence for cut-off values for demyelination (including DML, MCV, F wave latencies and temporal dispersion) defined in current GBS criteria has not been published in peer-reviewed journals. These cut-off values agree globally, but not exactly, with others that were defined on the basis of slowing in motor neuron disease (Van Asseldonk et al., 2005) or on comparison of slowing in demyelinating versus axonal forms of biopsy proven hereditary neuropathy (Buchthal and Behse, 1977). The cut-off values in current GBS criteria and in the criteria for demyelination of Van Asseldonk et al. (Van Asseldonk et al., 2005) both assume that, if slowing exceeds values encountered in disorders with loss of motor axons, it must be due to demyelination. This is, however, not necessarily true for GBS since disruption of voltage-gated ion channel clusters in the node and juxtaparanode may also induce slowing (Novakovic et al., 1998; Susuki et al., 2007). Second, animal models showed that maximal conduction velocity can be normal in mild to moderate demyelination so that DML, MCV and F latencies not fulfilling demyelination criteria do not exclude demyelination (Saida et al., 1980). Obviously, this problem cannot be solved by applying very liberal cut-off values for demyelination since mild slowing can be caused by mild demyelination, nodo-paranodopathy, and acute loss of fast conducting motor axons that is not sufficient to give rise to decreased CMAPs. As to the latter, studies using advanced motor unit number estimation methods showed that there may be considerable loss of motor units despite normal distal CMAP amplitude (Sleutjes et al., 2020). Third, although NCS findings on follow-up NCS have recently been proposed as a gold standard to finally define the true GBS subtypes (Chan et al., 2017; Shahrizaila et al., 2013; Uncini et al., 2017), they may well reflect

effects of secondary demyelination or axon loss not related to the original subtype.

5. Conclusion

This prospective study of 312 patients with GBS from Bangladesh showed that the predominant subtype of GBS in Bangladesh is axonal. Demyelinating GBS also occurred but subtype classification strongly depended on the applied criteria. Independently of the criteria used, anti-GM1 antibodies were not only found in axonal but also in a proportion of patients with demyelinating GBS and in a proportion of GBS patients with CB, both with and without demyelination in the same nerve segment had anti-GM1 antibodies. Most importantly, our study demonstrates the relevance of reaching international agreement on GBS criteria that needs to be based on the best available evidence from the literature. In the near future, hypothesis-free and criteria-free analysis of NCS findings in large cohorts of GBS patients by machine learning may reveal clinically useful patterns of clinical, electrophysiological and serological features.

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Conflict of interest

No authors have financial, professional or personal conflicts of interest that may influence this manuscript to disclose.

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