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Changes in motor nerve excitability in acute phase Guillain-Barré syndrome

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Abstract

Background: The most common subtypes of Guillain-Barré syndrome (GBS) are acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). In the first days after the onset of weakness, standard nerve conduction studies (NCS) may not distinguish GBS subtypes. Reduced nerve excitability may be an early symptom of nerve dysfunction, which can be determined with the compound muscle action potential (CMAP) scan. The aim of this study was to explore whether early changes in motor nerve excitability in GBS patients are related to various subtypes.

Methods: Prospective case–control study in 19 GBS patients from The Netherlands and 22 from Bangladesh. CMAP scans were performed within 2 days of hospital admission and NCS 7–14 days after onset of weakness. CMAP scans were also performed in age- and country-matched controls.

Results: CMAP scan patterns of patients who were classified as AMAN were distinctly different compared to the CMAP scan patterns of the patients who were classified as AIDP. The most pronounced differences were found in the stimulus intensity parameters.

Conclusions: CMAP scans made at hospital admission demonstrate several characteristics that can be used as an early indicator of GBS subtype.

KEYWORDS

acute motor axonal neuropathy, AIDP, CMAP scan, compound muscle action potential, excitability, Guillain-Barré syndrome

1 | INTRODUCTION

The Guillain-Barré syndrome (GBS) is a subacute disorder of the motor and sensory nerves and nerve roots with a heterogeneous pathophysiology and clinical course.[1] GBS can be divided into distinct subtypes depending on the extent of the peripheral nerve demyelination or axonal degeneration. In clinical practice, patients are classified

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CMAP, compound muscle action potential; CTS, carpal tunnel syndrome; DMCH, Dhaka Medical College and Hospital; GBS, Guillain-Barré syndrome; IQR, interquartile range; MRC, Medical Research Council; Nav, voltage-gated sodium; NCS, nerve conduction studies; S0, stimulus intensity activating the first motor unit; S100, stimulus intensity activating all motor units; S50, stimulus intensity that elicits 50% of the maximum CMAP; SI, stimulus intensity; Step%, step percentage.

by standard nerve conduction studies (NCS) into acute inflammatory demyelinating polyneuropathy (AIDP), and acute motor axonal neuropathy (AMAN).[2,3]

NCS parameters have been related to the risk of developing respiratory insufficiency and final outcome, which is highly variable in GBS.[4,5] Standard NCS provide information on nerve conduction velocity and axonal loss. However, NCS abnormalities need to deviate significantly from the normal range before the AIDP/AMAN distinction can be made.[6] In the first week after symptom onset, NCS might show only minor abnormalities.[7] Furthermore, in this period, reversible conduction failure can occur, mimicking signs of demyelination, in patients who are later classified as AMAN.[8] Reduced nerve excitability may be the first electrophysiological manifestation of GBS[9] and can be assessed by the compound muscle action potential (CMAP) scan.[10] This is a non-invasive, fast, and reproducible electrophysiological method.[11]

In the current study, we investigated early changes in motor nerve excitability by CMAP scan in GBS patients and studied if this can be used as an early subtype discriminator.

2 | METHODS

2.1 | Patients and controls

A prospective case–control study was conducted in GBS patients and age- and country-matched healthy subjects enrolled via Erasmus Medical Center, Rotterdam, The Netherlands, and Dhaka Medical College and Hospital (DMCH), Dhaka, Bangladesh. Inclusion criteria and protocols for collection of clinical and electrophysiological data were the same for both centers. All patients fulfilled the diagnostic criteria for GBS, Miller Fisher syndrome,[12] or other GBS variants and were admitted to the hospital within 2 wk of onset of weakness. The patients had no concomitant clinical conditions. Standardized clinical scores including the GBS disability score,[13] and Medical Research Council (MRC) sum scores[14] were determined for all patients at admission. CMAP scans were performed within 2 days after hospital admission by the same researcher. Standard NCS were performed 7–14 days after the onset of weakness.

A control was recruited for each patient. Controls were screened to ensure that they had no neurological symptoms or diseases. In Bangladesh, the controls were mainly derived from the same family as the patient; for the Netherlands, the controls originated from an existing database that included healthy controls of various ages. Routine NCS was performed in all control subjects to exclude median neuropathy at the wrist. CMAP scans were performed in the control group using the same protocol as used in patients.

The study was approved by the local Medical Ethics Committee of the Erasmus MC, The Netherlands, and by the Institutional Review Board and the ethical committees at the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh, Bangladesh. All subjects and/or legal representatives gave informed consent.

2.2 | Standard NCS

NCS and CMAP scans were performed on the non-dominant side. Standardized motor NCS were performed of the ulnar, median, peroneal, and tibial nerves. Standardized sensory NCS were performed on the ulnar, median, and sural nerves.[15] If sensory potentials were present, patients were tested for a carpal tunnel syndrome (CTS), by comparing the sensory conduction velocity of the median nerve across the carpal tunnel to the sensory conduction velocity in the palm. For motor nerves, the distal and proximal baseline-peak CMAP amplitudes, distal motor latency, motor nerve conduction velocity, and F-wave latencies were determined. For sensory nerves, the baseline-peak sensory nerve action potential amplitude and sensory nerve conduction velocity were measured. Reference values were derived from Buschbacher et al[15] The NCS were classified according to the Hadden electrophysiological criteria for GBS.[2]

All Dutch patients were warmed with hot water blankets.[16] This was not possible in Bangladesh, due to limited resources. However, the temperature inside the hospital was as high as the outside temperature.

2.3 | CMAP scans

CMAP scans were recorded using the CMAP scan application on a Viking Select EMG system (CareFusion, San Diego, CA). The CMAPs were obtained from the thenar muscles of the non-dominant hand after stimulation of the median nerve at the wrist in all patients and controls. All CMAP scans were performed by the same investigator (J.D.).In CMAP scanning, the nerve is stimulated with gradually increasing stimulus intensities (SIs), ranging from subthreshold to supramaximal values. With increasing SI the recorded CMAP will increase until supramaximal values are reached. Plotting the CMAP amplitudes against the corresponding SIs results in a dose–response curve which defines the CMAP scan. It provides, through its dependence on SI, information on nerve excitability.[11] The presence of multiple large steps points to underlying processes of axonal loss and reinnervation.[17] We defined steps as clear gaps in the CMAP scan that were bounded by plateaus at the upper and lower end of the gap, each of which consisted of at least three consecutive responses of about the same size (disregarding noise).[11] The key parameters of the CMAP scan are provided in Figure 1A. The entire procedure takes approximately 5–10 min.

2.4 | Statistics

All data were tested for normality using Kolmogorov–Smirnov test. Since the data were not normally distributed, non-parametric tests were used for further analysis. Continuous variables were presented as medians and interquartile ranges (IQRs) and were compared using the Mann–Whitney-*U* test. Differences in proportions were determined using the Fishers exact test. All calculations were performed

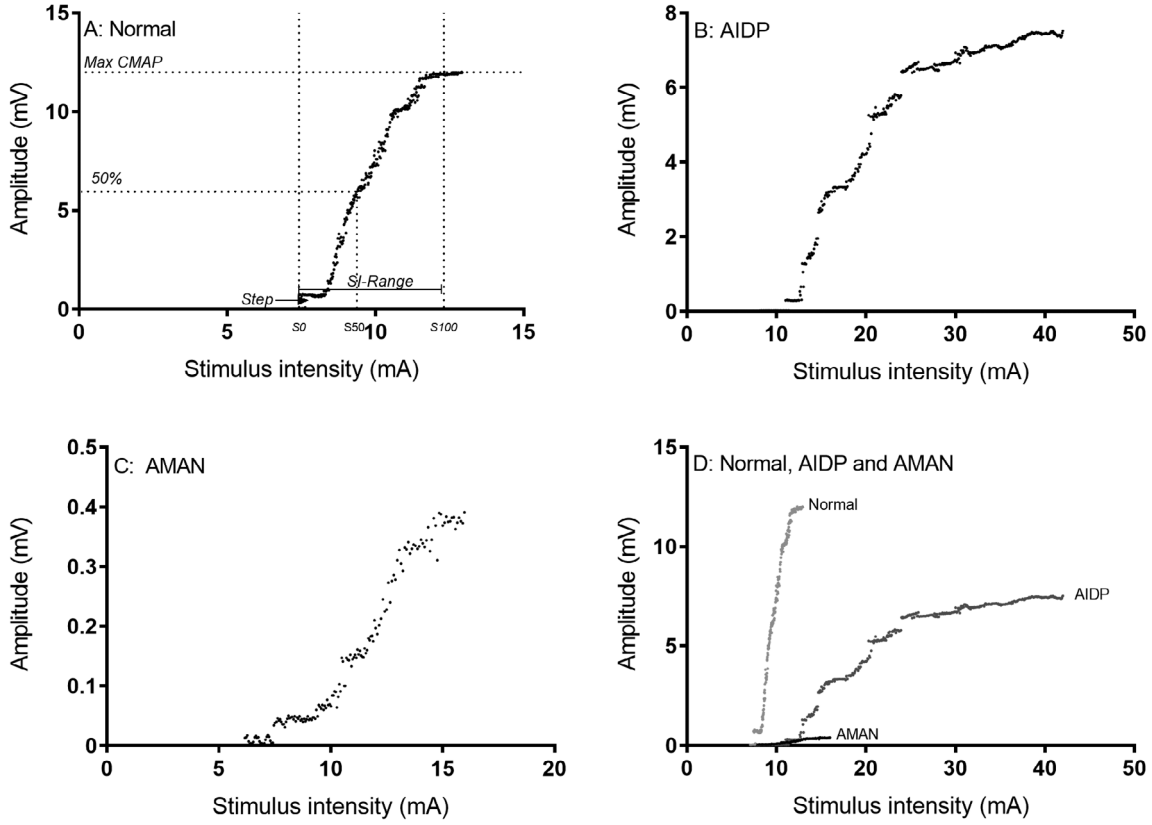

FIGURE 1 CMAP scans of control (A), AIDP patient (B), AMAN patient (C), and control, AIDP, and AMAN patient plotted in 1 panel (D). A, Key variables of the CMAP scan that reflect excitability are: the SI activating the first motor unit (S0), the SI that elicits 50% of the maximum CMAP (S50), the SI activating all motor units (S100), the SI-range (S100-S0), and the relative SI-range ((S100-S0)/ S0). Other key characteristics of the CMAP scan are the maximum CMAP amplitude and the presence of steps, quantified as step percentage (step%).[11] The presence of multiple large steps points to underlying processes of axonal loss and reinnervation[17]

TABLE 1 Demography, neurological deficits, and CMAP scan of GBS patients

Parameter	Dutch GBS patients (n = 19)	Bangladeshi GBS patients (n = 22)	*P*-value
Demography			
Age (y)	50 (38–64)	25 (17–35)	<.001
Sex (male/female)	17/2	15/7	.10
Neurological deficits			
Cranial nerve involvement	11 (58%)	10 (45%)	.55
Sensory deficits	17 (89%)	3 (14%)	<.001
MRC sum score at entry	50 (47–60)	25 (18–43)	<.001
GBS disability score at entry	3 (2–4)	4 (4–4)	<.001
GBS subtypes			<.001
Demyelinating	14 (74%)	1 (5%)	
Axonal	0 (0%)	19 (86%)	
Equivocal	5 (26%)	2 (9%)	

Note: Data are presented as medians (IQR) or number (percentages).

using SPSS 17.0 (SPSS Inc, Chicago, IL). Two-tailed tests were used throughout, a *P*-value <.05 was considered to be statistically significant.

Linear discriminant analysis was used to determine the independent factors that were associated with the GBS-subtypes. Data from controls were used to calculate the lower and upper limits of normal.

TABLE 2 Baseline characteristics and CMAP scan characteristics of subgroups and age matched controls

Parameter	AIDP (n = 15)	AMAN (n = 19)	Controls (n = 41)	*P*-value AIDP-AMAN	*P*-value AIDP-controls	*P*-value AMAN-controls
Baseline characteristics						
Age (y)	50 (38–67)	25 (16–32)	36 (23–56)	.001	.07	.02
Sex (males; n [%])	13 (87%)	13 (68%)		.21		
Onset - CMAP scan (days)	4 (3–9)	8 (5–10)		.06		
Onset – NCS (days)	13 (10–14)	13 (9–15)		.70		
CMAP scan parameters						
Max CMAP (mV)	3.6 (1.1–6.9)	2.3 (0.7–4.3)	10.4 (9.7–12.4)	.26	<.001	<.001
S0 (mA)	10.0 (8.5–12.9)	7.1 (5.9–9.0)	7.4 (5.5–8.4)	.006	<.001	.77
S50 (mA)	16.7 (16.0–26.1)	9.9 (8.2–10.8)	10.5 (7.9–11.4)	<.001	<.001	.82
S100 (mA)	29.0 (26.0–48.9)	13.3 (11.8–16.4)	12.9 (10.8–14.2)	<.001	<.001	.24
Absolute SI range (mA)	20.5 (14.2–27.8)	6.0 (4.9–8.5)	5.4 (4.4–6.8)	<.001	<.001	.11
Relative SI range	2.0 (1.2–2.4)	1.0 (0.6–1.2)	0.8 (0.6–1.0)	.001	<.001	.16
Step %	8.1 (0.6–14.4)	6.5 (0.0–14.9)	1.7 (0.7–3.6)	.63	.01	.03

Note: Data are presented as median (IQR) or as numbers (percentage).
Abbreviations: Absolute SI-range, S100-S0; Relative SI-range, (S100-S0)/S0; Step %, percentage of the CMAP scan that consists of steps.

Values <2.5 percentile and > 97.5 percentile were considered abnormal.

3 | RESULTS

Forty-one consecutive patients with GBS were included (32 males [78%], median age 38 range 9–77 y). Nineteen patients originated from The Netherlands and 22 patients from Bangladesh. Patients from Bangladesh were significantly younger than patients from the Netherlands ($P < .001$).

The Dutch patients differed from the Bangladeshi patients with respect to electrophysiological GBS-subtypes based on the results of the standard NCS at 2 wk, according to the Hadden criteria[2]. GBS in most of the Dutch patients was classified as demyelinating, whereas it was classified as axonal in most patients from Bangladesh (Table 1).

3.1 | CMAP scan in controls

CMAP scans were performed in all control subjects. The CMAP scans from controls from Bangladesh and The Netherlands were first analyzed separately (Supporting Information Table SS1, which is available online). No differences were found in CMAP scan characteristics between these two groups. The data, therefore, were combined and used as a single control group for the rest of the study. The upper and lower limits of normal for the CMAP scan variables were calculated based on the 2.5 percentile and 97.5 percentile and presented Supporting Information Table SS1.

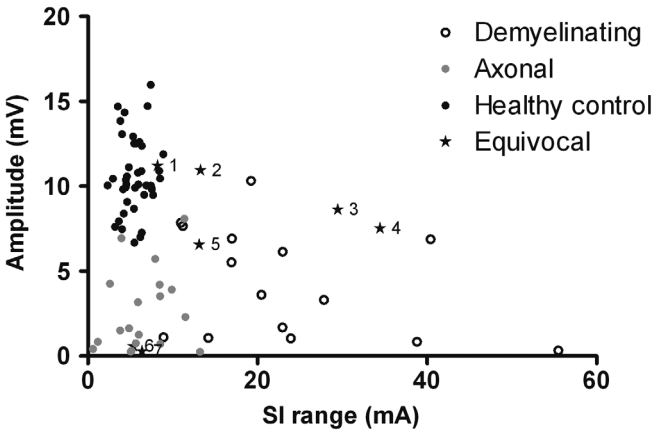

FIGURE 2 Maximum CMAP amplitude versus SI range of patients with NCS classified as demyelinating, axonal, and equivocal, and of controls. Equivocal (stars) patients 1 and 2 are Dutch patients with hyporeflexia and cranial nerve paresis. Patients 3 and 4, Dutch patients with classical Miller Fisher syndrome. Patient 5, Dutch patient with ptosis, limb weakness, and areflexia. Patient 6, patient from Bangladesh with severe limb weakness. Patient 7, patient from Bangladesh with severe limb weakness and cranial nerve paralysis

3.2 | CMAP scan in relation to GBS subtype

Based on the upper and lower limits of normal, 38 (93%) of the 41 patients showed abnormalities in the CMAP scan. Of these 41 patients, 15 (37%) were classified as AIDP, 19 (46%) as AMAN, and

7 (17%) as equivocal. The AMAN patients were significantly younger than the AIDP patients (median 25 y and 50 y, respectively; $P = .001$).

CMAP scans performed at hospital admission showed a difference in SI variables between AIDP and AMAN patients. Typical examples of the CMAP scans of the patients with AIDP and AMAN are provided in Figure 1B-D. The most pronounced differences were found in the S50, S100, and absolute SI-range (Table 2).

Linear discriminant analysis identified the combination of maximum CMAP amplitude and absolute SI range as the parameters that best separate the different subgroups. Plotting the maximum CMAP-amplitude versus the absolute SI-range for the AIDP, AMAN, and controls resulted in distinct patterns for the three groups (Figure 2).

3.3 | CMAP scans in equivocal patients

Seven patients were classified as equivocal based on NCS. Two showed the "axonal pattern" (low amplitudes, normal SI ranges; patients 6 and 7 in Figure 2). These two patients came from Bangladesh and were classified as equivocal because they had conduction blocks in combination with an otherwise axonal NCS. Two other equivocal patients had CMAP scans that showed the "demyelinating pattern" (normal amplitudes, high SI-ranges; patients 3 and 4). These were both Dutch patients with a classical Miller Fisher syndrome (ophthalmoplegia, ataxia, areflexia). In addition to absent H-reflexes, their standard NCS were normal. The 3 remaining equivocal patients (patients 1,2 & 5) had a "normal CMAP scan pattern". Patient 1 and 2 were Dutch patients with hyporeflexia and cranial nerve paresis. Patient 5 was a Dutch patient with ptosis, mild limb weakness, and areflexia.

4 | DISCUSSION

In this study using the CMAP scan within the spectrum of patients with GBS, we show that the majority of patients already have electrophysiologically demonstrable nerve dysfunction at hospital admission. In this very early stage of disease, 93% of the patients show various types of abnormalities in the CMAP scan. In this stage of GBS, which is important for early diagnosis, monitoring, and start of treatment, abnormalities in nerve electrophysiology may support clinical decision making. Furthermore, the results in the current study show that the CMAP scan may also be used as a first and rapid screening technique, that might aid early distinguishing between different subtypes of GBS.

4.1 | CMAP scan differences between AIDP and AMAN

The CMAP scan patterns of patients who were classified as AMAN were distinctly different compared to the CMAP scans patterns of the patients who were classified as AIDP. The division into the "demyelinating" and "axonal" subgroups was primarily based on differences in SI variables. Probably, these differences in the excitability of peripheral nerves reflect the variation in underlying pathophysiology between these subtypes of GBS.

The mechanism of conduction failure and excitability changes in AIDP is not well understood. One possible mechanism in the early phase of demyelinating GBS might be related to the presence of edema. Pathological studies found edema to be among the earliest changes in peripheral nerves in GBS, followed by swelling and irregularity of the myelin sheaths.[18] This edema might result in a shunting of the applied current away from the Ranvier nodes and, hence, result in higher SIs needed to depolarize the axon.

If only a proportion of the axons are involved, this will lead to a high S100 (the diseased axons are less excitable) in the CMAP scan, with a normal S0 (determined by the healthy axons) and an increased SI range (difference between SIs needed to activate the most healthy axon [S0] and the least excitable axons [S100]). If all axons are involved, this could result in an increase of all SI parameters. Further experimental studies, preferably combined with pathology, are required to elucidate these mechanisms.

For "axonal" GBS patients the presumed mode of action is mediated by antibodies to various types of gangliosides or ganglioside complexes,[19] which leads to a complement-mediated disruption of voltage-gated sodium (Nav) channel clusters at the Ranvier nodes.[20] Dysfunction of the Nav-channels results in blockage of the action potential independently of the applied current. Such an explanation is consistent with both the reduced maximum CMAP amplitude and normal SIs in the CMAP scans of axonal patients.

The current classification of GBS patients as AMAN or AIDP is based on findings in NCS. Multiple sets of electrophysiological criteria have been developed to identify demyelination.[2,3,7,21] Yet, no set is generally accepted and the optimal time to perform NCS is still debated. Furthermore, various studies have demonstrated the existence of reversible conduction failure and conduction blocks in presumably axonal patients, which makes the differentiation between primary demyelinating GBS and primary axonal GBS even more difficult.[2,3,22] Indeed, two of our patients from Bangladesh were classified as equivocal because they had conduction blocks in combination with otherwise axonal NCS. The CMAP scans of these two patients showed the "axonal" pattern. The predominantly axonal NCS gives reason to believe that, in these patients, the "axonal pattern" in the CMAP scan truly results from an "axonal" GBS.

4.2 | Study limitations

For the discrimination between AMAN and AIDP, NCS data collected and analyzed at 2 wk were used as a golden standard for subtyping. However, we did not have an independent method, such as pathological data, to confirm a definitive subtype diagnosis. Furthermore, since we did not compare CMAP scans at admission with NCS at admission, it is unknown if NCS performed at admission would also have been able to discriminate between AMAN and AIDP at that time point.

For the purpose of the present study, we wished for patients with AIDP and AMAN to be represented equally. Because of the

geographical spread of these subtypes, we decided to include patients from Bangladesh and The Netherlands.[23] Bias might have been introduced at this point. Most "axonal" patients originated from Bangladesh, and most "demyelinating" patients came from The Netherlands. Furthermore, the patients differed with regard to various demographic characteristics including age. However, since we found no differences between the CMAP scans of the younger Bangladeshi controls and the older Dutch controls, we cautiously conclude that the differences between our patients are not a result of just a geographical or age difference.

Due to infrastructural factors in Bangladesh, the time interval between symptom onset and hospital admission in the AMAN patients was longer than in the Dutch AIDP patients. Thus, the time between symptom onset and first CMAP scan is longer for the AMAN patients, although this difference was not statistically significant. Future studies should preferentially include AMAN and AIDP patients from the same country and also incorporate serial NCS performed at the same time as the CMAP scan, and after at least 2 wk, since classification of the GBS subtype may change over time. This was not feasible in the current study. However, all of the AIDP patients had sensory deficits, making it unlikely that they were erroneously classified as AMAN. It cannot be excluded that they might have been classified as an AMSAN in a later stage, however AMSAN is rare.

Although in healthy subjects the reproducibility of the CMAP scan is good,[11] this has not been tested in patients with GBS or other neuropathies. Studies on the reproducibility of the CMAP scan in patients with GBS and other neuropathies are needed. The CMAP scan is performed only in the distal part of one nerve and in GBS the pathological process is initially often segmental. Despite this limitation, the CMAP scan is a promising, very easy, and quick method for determining the GBS subtype, at least in a subset of patients.

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CONFLICTS OF INTEREST

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ETHICAL PUBLICATION STATEMENT

The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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