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ORIGINAL ARTICLE

Electrodiagnostic subtyping in Guillain–Barré syndrome patients in the International Guillain–Barré Outcome Study

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Abstract

Background and purpose: Various electrodiagnostic criteria have been developed in Guillain–Barré syndrome (GBS). Their performance in a broad representation of GBS patients has not been evaluated. Motor conduction data from the International GBS Outcome Study (IGOS) cohort were used to compare two widely used criterion sets and relate these to diagnostic amyotrophic lateral sclerosis criteria.

Methods: From the first 1500 patients in IGOS, nerve conduction studies from 1137 (75.8%) were available for the current study. These patients were classified according to nerve conduction studies criteria proposed by Hadden and Rajabally.

Results: Of the 1137 studies, 68.3% ($N = 777$) were classified identically according to criteria by Hadden and Rajabally: 111 (9.8%) axonal, 366 (32.2%) demyelinating, 195 (17.2%) equivocal, 35 (3.1%) inexcitable and 70 (6.2%) normal. Thus, 360 studies (31.7%) were classified differently. The areas of differences were as follows: 155 studies (13.6%) classified as demyelinating by Hadden and axonal by Rajabally; 122 studies (10.7%) classified as demyelinating by Hadden and equivocal by Rajabally; and 75 studies (6.6%) classified as equivocal by Hadden and axonal by Rajabally. Due to more strictly defined cutoffs fewer patients fulfilled demyelinating criteria by Rajabally than by Hadden, making more

The IGOS Consortium Members are presented in the Appendix A.

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patients eligible for axonal or equivocal classification by Rajabally. In 234 (68.6%) axonal studies by Rajabally the revised El Escorial (amyotrophic lateral sclerosis) criteria were fulfilled; in axonal cases by Hadden this was 1.8%.

Conclusions and discussion: This study shows that electrodiagnosis in GBS is dependent on the criterion set utilized, both of which are based on expert opinion. Reappraisal of electrodiagnostic subtyping in GBS is warranted.

KEYWORDS
amyotrophic lateral sclerosis, electrodiagnosis, Guillain–Barré syndrome, nerve conduction studies, polyneuropathy

INTRODUCTION

Electrodiagnostic (EDx) studies and, in particular, nerve conduction studies (NCS) are used to support the diagnosis and subtyping of the Guillain–Barré syndrome (GBS), an immune-mediated polyradiculoneuropathy. According to the Brighton Collaboration criteria, NCS findings consistent with GBS are necessary to meet level 1 of diagnostic certainty [1]. GBS is divided into acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor or motor-sensory axonal neuropathy based on electrodiagnostic and pathological hallmarks. In histopathological studies, AIDP demonstrated demyelination and inflammatory infiltrates in spinal roots and peripheral nerves, with or without signs of axonal degeneration [2]. Axonal GBS was characterized by axonal degeneration of motor or motor-sensory fibers without demyelination. Axonal GBS is often associated with ganglioside antibodies and preceding bacterial infections, especially *Campylobacter jejuni*. Preceding viral infections such as cytomegalovirus and Zika virus were more frequently described in AIDP [3].

After the first description of NCS criteria by Asbury et al. in 1978, various other criterion sets were proposed [4–11]. Those proposed by Hadden et al. and Rajabally et al. are amongst the ones frequently used in GBS research [9, 10]. Using these criteria, each NCS variable and then the whole study can be classified into the following categories: axonal, demyelinating, equivocal, inexcitable, normal. Both criterion sets focus on subtyping into axonal and demyelinating subtypes, with a tendency of studies to be more frequently classified as axonal by Rajabally criteria and as demyelinating by Hadden criteria [10]. Moreover, a substantial percentage of studies do not meet either the axonal or demyelinating criteria. According to the previous work by Hadden et al. [9] and Rajabally et al. [10], NCS were classified equivocal in 22.8% and 7.7% and normal in 2.4% and 1.1% respectively. Despite differences in criteria, the contributions of each specific criterion within these sets on subtyping have never been investigated.

In the current study, a detailed description of the differences between the NCS criteria proposed by Hadden and by Rajabally is provided as well as the impact of these differences on final subtyping in patients included in the International GBS Outcome Study (IGOS). The distribution of the motor conduction data in median, ulnar, peroneal and tibial nerves is described [12]. Lastly, it is considered how the GBS criteria are related to the revised El Escorial electrodiagnostic criteria (rEEC) in amyotrophic lateral sclerosis (ALS), serving as a surrogate marker of 'true' axonal neuropathy [13].

METHODS

Study population and protocol, inclusion and exclusion criteria

The current study is based on the first 1500 patients included in IGOS, a prospective observational cohort study [12]. A description of the collection of NCS data in IGOS has been published previously [14]. Inclusion criteria were fulfilment of the diagnostic criteria for GBS (of the National Institute of Neurological Disorders and Stroke) or one of the clinical variants, the presence of NCS with at least two motor nerves examined, and patients presenting within 2 weeks after onset of GBS-related symptoms. Exclusion criteria were study protocol violation, other diagnosis and insufficient clinical and electrophysiological data. Local investigators were free to conduct EDx studies according to their standards, but it was recommended to perform studies twice: the first within 7 days of registration in IGOS, and the second at 4 weeks after. Only the first EDx studies were used for this analysis. For motor conduction the IGOS protocol recommended measuring unilaterally the median, ulnar, peroneal (fibular) and tibial nerves including F-waves (recording sites respectively abductor pollicis brevis muscle, abductor digiti minimi muscle, extensor digitorum brevis muscle and abductor hallucis muscle). Limb temperature control was allowed to be performed by local standards. The study report was uploaded to the online IGOS database and checked.

Clinical data

Demographic and clinical data were obtained from the IGOS database. Patients were classified into one of the following clinical variants: sensorimotor, pure motor, Miller Fisher syndrome (MFS), MFS-GBS overlap syndrome, ataxic, pure sensory and pharyngeal–cervical–brachial variants [14].

Electrophysiological data and subtyping

All patients were classified according to the NCS criteria published by Hadden et al. and Rajabally et al. [9, 10], in this paper referred to as the 'Hadden criteria' and 'Rajabally criteria'. Local reference values were used. Each NCS parameter was expressed as a percentage of the upper/lower limit of normal (ULN, LLN). If reference values were lacking, the previously published (mean) reference values collected from the other participating centers in IGOS were used, in accordance with the local methodology used [15]. Motor nerve parameters used in these criteria and hence in this study were distal compound muscle action potential (dCMAP) amplitude, distal motor latency (DML), F-wave latency, motor conduction velocity (MCV) and proximal-to-distal CMAP amplitude ratio (p/dCMAP ratio). NCS variables from the entrapment sites of the ulnar (groove) and peroneal nerve (fibular head) were excluded, but DML from the median nerve (carpal tunnel) was not. The p/dCMAP ratio from the tibial nerve was excluded according to Rajabally subtyping.

See Table S1 for an overview of the Hadden and Rajabally criteria [9, 10]. A summary is as follows. (1) A study is classified demyelinating, according to both Hadden and Rajabally criteria, if at least two parameters fulfilled the demyelinating criteria within two different nerves. One exception is allowed by Hadden criteria (but not by Rajabally): if two demyelinating parameters are present within one nerve, only if all other nerves are inexcitable, this is also classified as demyelinating. In this study, this is named the Hadden 'exception rule'. (2) A study is classified axonal, both for Hadden and Rajabally criteria, if axonal criteria are fulfilled in (at least) two nerves, without demyelinating features. Rajabally criteria considered the F-wave absence and abnormal p/dCMAP ratio as either axonal or demyelinating features, depending on the other NCS findings. However, according to Hadden criteria, an abnormal p/dCMAP ratio is always considered a demyelinating feature and absent F-waves are unclassifiable, as Hadden criteria only provided criteria for prolongation of F-wave latency. (3) The criteria for equivocal and inexcitable studies are the same for both criterion sets. (4) The criteria for a normal study differ slightly in p/dCMAP ratio (p/dCMAP ratio >0.5 considered normal by Hadden, but >0.7 normal by Rajabally criteria).

Because cutoffs for subtyping differed between criteria, the rEEC criteria were applied to our cohort serving as gold standard for axonal neuropathy [13]. The recently published Gold Coast criteria were based on the rEEC, containing a description of NCS parameters consistent with a pure axonal neuropathy [16]. The authors considered certain motor conduction values not consistent with pure axonal loss, which are called 'red flags', suggesting other diseases such as demyelinating neuropathy. These red flags were DML >130% ULN, F-wave latency >130% ULN and MCV <70% LLN [13]. Also, the presence of conduction block was considered non-compatible with ALS, but without defined cutoff. As Hadden and Rajabally criteria defined their own limits for conduction block, p/dCMAP ratio <0.5 and <0.7 respectively, these cutoffs were used.

Study approval and informed consent

The study was approved by the Medical Ethical Research Committee of the Erasmus University Medical Center Rotterdam, The Netherlands (MEC-2011-477), and by the local institutional review boards of all participating centers. Written informed consent was obtained from all patients or their legal representatives.

Statistical analysis

IBM SPSS Statistics 28 and RStudio (R Version 4.2.3) were used for the analysis. The one-tailed Spearman's correlation coefficient ρ was used in order to calculate the correlation between dCMAP amplitude and the different variables representing conduction velocities (DML, F-wave latency, MCV), because variables were not normally distributed.

RESULTS

Of the first 1500 patients enrolled in IGOS, 203 (13.5%) patients were excluded (52 had chronic inflammatory demyelinating polyradiculoneuropathy; 32 had other diagnoses; 35 because of protocol violation; 84 because of missing clinical and/or electrophysiological data). Of the remaining 1297 patients, 160 patients did not undergo an EDx study. A total of 1137 (87.7%) patients were enrolled in this study. The characteristics of the study population are shown in Table 1. Patients were included from 19 countries, including Argentina ($N=38$), Australia ($N=9$), Bangladesh ($N=145$), Belgium ($N=25$), Canada ($N=24$), China ($N=14$), Denmark ($N=113$), France ($N=33$), Germany ($N=44$), Greece ($N=8$), Italy ($N=113$), Japan ($N=60$), Malaysia ($N=25$), South Africa ($N=26$), Spain ($N=95$), Taiwan ($N=5$), The Netherlands ($N=109$), UK ($N=133$) and United States ($N=118$). All clinical variants were represented, including the predominant sensorimotor variant (60.9%) and pure motor GBS (23.3%). An EDx study was conducted at a median of 7 days (interquartile range 4–11) after onset of GBS-related symptoms.

Distribution of motor conduction variables

In 190 patients from 23 centers, reference values ware lacking and here the IGOS derived reference values were applied, in accordance with local methodology used. The distribution of DML, MCV, F-wave latency and dCMAP amplitudes from the ulnar nerve are presented in Figure 1 (see Figures S1–S3 for median, peroneal and tibial nerves). In all four nerves, conduction slowing (prolongation of DML and F-wave latency and decrease of MCV) was significantly correlated to dCMAP amplitudes. For example, the ulnar nerve DML and F-wave latency were negatively ($\rho=-0.36$; $\rho=-0.29$) and MCV was positively correlated ($\rho=0.26$),

TABLE 1 Demographic data of the study population.

Demography and clinical characteristics	
Total number of patients	1137
Age, median, years (IQR, full range)	51 (35–65; 0–90)
Age below 18 years (%)	68 (6.0%)
Male/female (ratio)	61/39 (1.56)
Continent (%)	
Europe	673 (59.2%)
Asia	249 (21.9%)
North America	142 (12.5%)
South America	38 (3.3%)
Africa	26 (2.3%)
Australia	9 (0.8%)
Clinical variant (%)	
Sensorimotor	672 (60.9%)
Pure motor	257 (23.3%)
Miller Fisher syndrome	63 (5.7%)
Miller Fisher overlap syndrome	60 (5.4%)
Ataxic	19 (1.7%)
Pharyngo–cervical–brachial	14 (1.3%)
Pure sensory	13 (1.2%)
Other[a]	6 (0.5%)
Preceding infection	
No/not tested (%)	440/439 (38.7%; 38.6%)
Present, total	258 (22.7%)
Campylobacter jejuni	158 (13.9%)
Multiple infections	38 (3.3%)
Mycoplasma pneumoniae	33 (2.9%)
Cytomegalovirus	14 (1.2%)
Hepatitis E virus	12 (1.1%)
Epstein–Barr virus	3 (0.3%)
GBS disability score at time of EDx study	
GBS-DS median (IQR)	4 (2–4)
0	2 (0.3%)
1	46 (4.0%)
2	249 (21.9%)
3	215 (18.9%)
4	513 (45.1%)
5	108 (9.5%)
Missing	1 (0.1%)
Electrodiagnostic details	
Median number nerves studied (IQR, full range)	4 (4–6; 2–8)
Median timing EDx study in days (IQR, full range)	7 (4–11; 0–129)

Abbreviations: EDx, electrodiagnostic; GBS, Guillain–Barré syndrome; GBS-DS, Guillain–Barré syndrome disability scale; IQR, interquartile range.
[a]Other overlap syndromes, e.g. with Bickerstaff brainstem encephalitis.

all statistically significant ($p < 0.01$). Of all nerves and variables, the tibial DML and dCMAP amplitude had the highest Spearman's correlation coefficient ($\rho = -0.54$).

The ulnar dCMAP amplitude had a left-skewed distribution with unobtainable (<10% LLN) responses in 10.8% (Figure 1). Unobtainable responses were less common in the median nerve

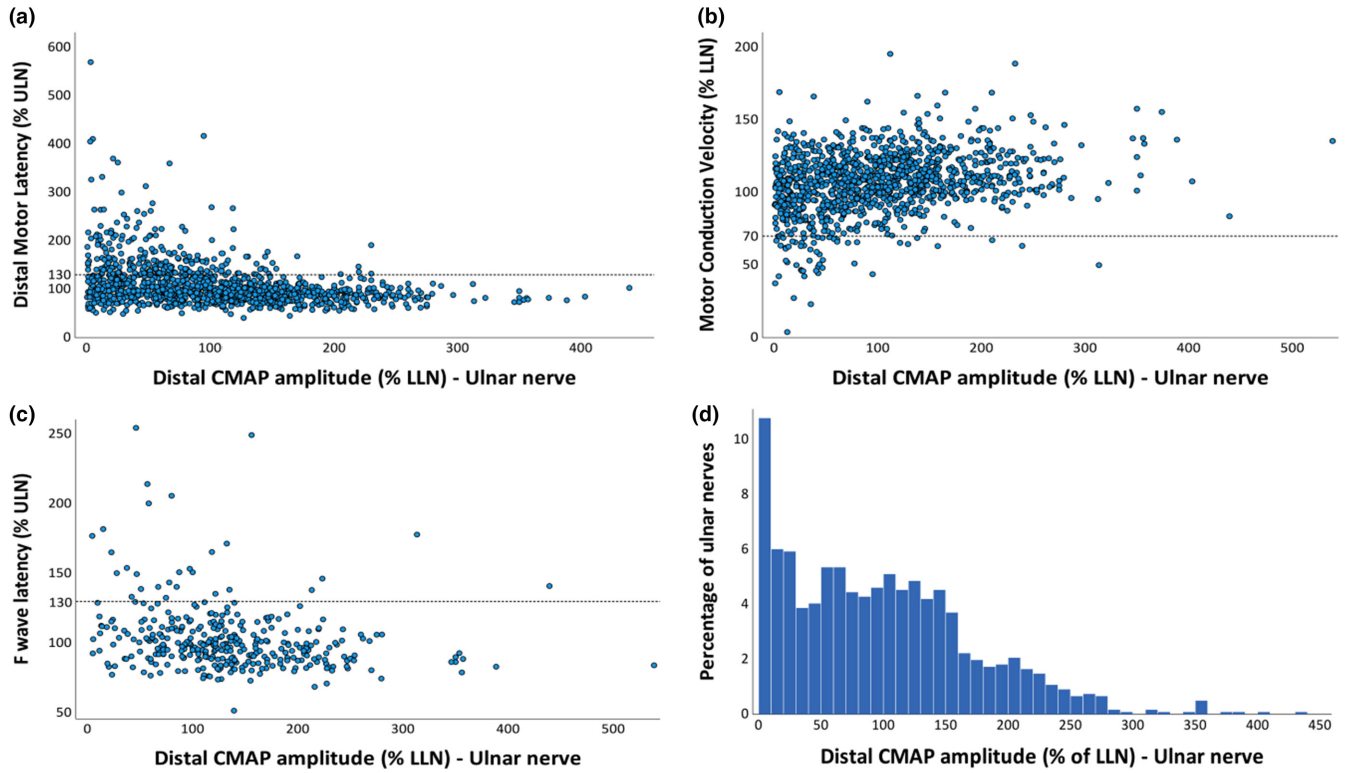

FIGURE 1 Distribution of ulnar nerve NCS variables in IGOS. Ulnar nerve NCS variables: (a) distal motor latency versus dCMAP amplitude; (b) motor conduction velocity versus dCMAP amplitude; (c) F-wave minimal latency versus dCMAP amplitude; (d) distribution of dCMAP amplitude of the ulnar nerves. ULN, upper limit of normal; LLN, lower limit of normal. A line was drawn at the cutoffs for DML (130% ULN), MCV (70% LLN) and F-wave latency (130% ULN) derived from the revised El Escorial (exclusion) criteria.

(8.8%) and more common in peroneal (13.4%) and tibial nerves (16.0%). Distal amplitudes were below 80% of LLN in 45.6% of ulnar, 45.8% of median, 45.3% of peroneal and 52.4% of tibial nerves. Ulnar nerves had normal (≥100% LLN) dCMAP amplitude in 45.4% (median dCMAP amplitude 89.9% LLN). Distal CMAP amplitudes were normal in 46.4% of median nerves (median 90.0%), in 48.5% of peroneal nerves (median 95.0%) and in 40.1% of tibial nerves (median 72.1%).

Classification according to Hadden criteria

According to the Hadden criteria, 56.6% of the studies were demyelinating, 9.8% axonal, 24.3% equivocal, 3.1% inexcitable and 6.3% normal (Table 5). A prolonged DML in two or more nerves was the most often fulfilled criterion for demyelination (41.7% of total cohort), followed by decreased MCV (24.2%), abnormal p/dCMAP ratio (13.4%) and F-wave prolongation (8.8%) (Table 2). Combining two different variables (DML, F-wave, MCV, p/dCMAP ratio) enabled another 13.4% of studies to be subtyped as AIDP (if both separate variables were demyelinating only once). In some cases, multiple rules for AIDP were fulfilled, so these criteria as shown in Table 2 are not mutually exclusive. For example, if in a study three separate variables were demyelinating (e.g., 1 × MCV, 1 × DML, 1 × F-wave), classifying as AIDP is possible by combining MCV and DML, but also by DML and F-wave. An additional 0.5% of the cohort was classified as AIDP by the Hadden 'exception rule'.

A description of the proportion of patients and nerves fulfilling specific variables of the Hadden criteria is provided (Table S2). According to Hadden criteria, the top three individual variables most often fulfilling the demyelinating criteria were (1) prolonged median nerve DML (in 40.2% of median nerves), (2) prolonged peroneal DML (33.5%) and (3) prolonged ulnar DML (29.6%). On a patient level, the demyelinating criteria most often met (at least once) were prolonged DML (55.6% of all patients), reduced MCV (42.8%), lowered p/dCMAP ratio (31.8%) and prolonged F-wave latency (22.0%).

Axonal GBS according to Hadden criteria was present in 111 cases (9.8% of cohort). The individual variable and nerve most often fulfilling the axonal criteria was the dCMAP amplitude of the tibial nerve (52.4%).

Inexcitable studies according to Hadden were present in 35 cases (3.1% of cohort). As allowed by the criteria, 10 cases had the presence of dCMAP amplitude below 10% LLN once (six median, one ulnar and three peroneal nerves). Normal studies were present in 72 cases (6.3% of cohort). The remaining 276 cases (24.3%) were classified as equivocal.

In patients with pure sensory GBS ($N = 13$) EDx studies were classified by Hadden criteria as demyelinating ($N = 2$), equivocal ($N = 6$) or normal ($N = 5$). For MFS ($N = 63$) distribution was as

TABLE 2 Hadden criteria: final rules for axonal and demyelinating subtypes.

Demyelinating criteria by Hadden criteria[a]		Percentage of cases (number/total number cases[b])
≥2 × DML prolonged (>110% ULN if dCMAP ≥50% LLN; >120% ULN if dCMAP <50% LLN)		41.7% (452/1084)
≥2 × MCV decreased (MCV <90% LLN if dCMAP ≥50% LLN; <85% if dCMAP <50% LLN)		24.2% (258/1066)
≥2 × p/dCMAP ratio (p/dCMAP ratio <0.5 and dCMAP ≥20% LLN)		13.4% (140/1047)
≥2 × F-wave latency prolonged (latency >120% ULN)		8.8% (83/939)
Combined criteria (two demyelinating variables in two nerves)		
DML and MCV	1 × DML and 1 × MCV	2.2% (24/1080)
MCV and p/dCMAP ratio	1 × MCV + 1 × p/dCMAP ratio	3.1% (32/1041)
MCV and F-wave	1 × MCV + 1 × F-wave	2.5% (25/1005)
DML and p/dCMAP ratio	1 × DML + 1 × p/dCMAP ratio	1.7% (18/1048)
DML and F-wave	1 × DML + 1 × F-wave	1.0% (10/1016)
p/dCMAP ratio and F-wave	1 × p/dCMAP ratio + 1 × F-wave	3.0% (29/979)
Hadden exception rule	Two demyelinating features within one nerve, with dCMAP >10%, others inexcitable	0.5% (6/1110)
Axonal criteria by Hadden		
Distal CMAP <80% LLN in at least two nerves, without demyelinating features (only one demyelinating feature in one nerve allowed if dCMAP <10% LLN)		9.9% (111/1126)

Abbreviations: CMAP, compound muscle action potential; dCMAP, distal compound muscle action potential; DML, distal motor latency; LLN, lower limit of normal; MCV, motor conduction velocity; p/dCMAP, proximal-to-distal compound muscle action potential; ULN, upper limit of normal.

[a]Categories might overlap, for example a patient can fulfill multiple rules: 2 × prolonged DML and also 1 × decreased MCV and 1 × abnormal p/dCMAP ratio.

[b]Each case is only included in the 'total number of cases' if it is possible to fulfill this criterion, for example if only one DML is present in a study, this patient can never fulfill the ≥2 DML rule and therefore is not included in this particular 'total number of cases'.

follows: axonal ($N = 2$), demyelinating ($N = 5$), equivocal ($N = 33$) and normal ($N = 23$).

Classification according to Rajabally criteria

According to the Rajabally criteria, 32.5% of the studies were demyelinating, 30.0% axonal, 28.1% equivocal, 3.1% inexcitable and 6.3% normal (Table 5). A prolonged DML in two or more nerves was the most often fulfilled demyelinating criterion (19.9% of cohort), followed by abnormal p/dCMAP ratio (12.4%), F-wave absence (12.3%), decreased MCV (6.7%) and F-wave prolongation (6.3%) (Table 3). The criteria combining these different variables twice enabled another 4.6% of studies to be subtyped as demyelinating. The different criteria as described in Table 3 are not mutually exclusive: multiple criteria can be met by one patient.

A detailed description on how often individual variables fulfilled the Rajabally criteria in individual nerves is provided in Table S3. The top three individual variables most often fulfilling the demyelinating Rajabally criteria were (1) F-wave absence in peroneal nerve (37.7%), (2) reduced p/dCMAP ratio in peroneal nerve (33.9%) and (3) reduced p/dCMAP ratio in ulnar nerve (25.9%). On a patient level, the demyelinating Rajabally criteria most often met (at least once) were reduced p/dCMAP ratio (52.2%), followed by F-wave absence (43.4%), prolonged DML (35.1%), F-wave latency prolongation (18.2%) and reduced MCV (16.2%).

For axonal GBS multiple criteria were provided, with a reduced dCMAP amplitude in at least two nerves being the most often fulfilled criterion (26.5% of cohort), followed by absent F-waves (11.4%), abnormal p/dCMAP ratio (9.7%) and combined F-wave absence and abnormal p/dCMAP ratio with reduced dCMAP amplitude (1.2%). The individual variable and nerve most often fulfilling axonal Rajabally criteria was the dCMAP amplitude of the tibial nerve (52.4%). Within the axonal subgroup, the axonal feature most often present was the reduced dCMAP amplitude (87.4%).

Rajabally criteria considered F-wave absence and p/dCMAP ratio as supportive features for both demyelinating and axonal subtypes depending on the rest of the study. Of these two criteria, F-wave absence was most often detected in the peroneal nerve (37.7%).

As criteria for inexcitable NCS were the same for Rajabally and Hadden criteria, the same 35 cases fulfilled these criteria. Normal studies were present in 72 cases (6.3% of cohort). The remaining 319 cases (28.1%) were classified as equivocal by Rajabally criteria: an additional 43 equivocal studies compared to Hadden criteria.

In patients with pure sensory GBS ($N = 13$) studies were classified by Rajabally as axonal ($N = 1$), demyelinating ($N = 1$), equivocal ($N = 6$) or normal ($N = 5$). For MFS ($N = 63$) distribution was as follows: axonal ($N = 4$), demyelinating ($N = 3$), equivocal ($N = 32$) and normal ($N = 24$).

TABLE 3 Rajabally criteria: final rules for axonal and demyelinating subtypes.

Demyelinating criteria by Rajabally criteria[a]		Percentage of cases (number/total number cases[b])
≥2 × DML prolonged (>150% ULN)		19.9% (216/1087)
≥2 × MCV decreased (<70% LLN)		6.7% (72/1068)
≥2 × F-wave latency prolonged (either latency >120% ULN in dCMAP ≤50% or >150% ULN in dCMAP <50% LLN)		6.3% (58/923)
≥2 × F-wave absence (dCMAP ≥20% LLN) with additional demyelinating parameter in other nerve		12.3% (113/921)
≥2 × p/dCMAP ratio <0.7[c] with additional demyelinating parameter in other nerve[a]		12.4% (129/1039)
Combined criteria (two demyelinating variables in two nerves)		
DML and MCV	1 × DML and 1 × MCV	1.3% (14/1085)
MCV and F-wave latency	1 × MCV and 1 × F-wave latency	1.4% (14/1007)
DML and F-wave latency	1 × DML and 1 × F-wave latency	1.9% (19/1005)
Axonal criteria by Rajabally		
Distal CMAP <80% LLN in at least two nerves, without demyelinating features (only one demyelinating feature in one nerve allowed if dCMAP <10% LLN)		26.5% (298/1126)
F-wave absence in two nerves with dCMAP ≥20% LLN, without demyelinating features (only one demyelinating feature in one nerve allowed if dCMAP <10% LLN)		11.4% (105/921)
p/dCMAP ratio <0.7[c] in two nerves, without demyelinating features (only one demyelinating feature in one nerve allowed if dCMAP <10% LLN)		9.7% (101/1039)
F-wave absence in one nerve with dCMAP ≥20% LLN or p/dCMAP ratio <0.7[c] in one nerve, with in addition dCMAP <80% LLN in one other nerve; without demyelinating features (only one demyelinating feature in one nerve allowed if dCMAP <10% LLN)		1.2% (13/1078)

Abbreviations: CMAP, compound muscle action potential; dCMAP, distal compound muscle action potential; DML, distal motor latency; LLN, lower limit of normal; MCV, motor conduction velocity; p/dCMAP, proximal-to-distal compound muscle action potential; ULN, upper limit of normal.

[a]Categories might overlap, for example a patient can fulfill multiple rules: 2 × reduced MCV and also 1 × prolonged DML and 1 × prolonged F-wave latency.

[b]Each case is only included in the 'total number of cases' if it is possible to fulfill this criterion, For example if only one DML is present in a study, this patient can never fulfill the ≥2 DML rule and therefore is not included in this particular 'total number of cases'.

[c]Excluding tibial nerve.

TABLE 4 Classification according to Hadden criteria versus Rajabally criteria.

		Hadden classification					
		Axonal	Demyelinating	Equivocal	Inexcitable	Normal	Total
Rajabally classification	Axonal	111	155	75	0	0	341
	Demyelinating	0	366	4	0	0	370
	Equivocal	0	122	195	0	2	319
	Inexcitable	0	0	0	35	0	35
	Normal	0	0	2	0	70	72
	Total	111	643	276	35	72	1137

Comparison of classification according to Hadden criteria versus Rajabally criteria

In 68.3% ($N=777$) of patients, the final NCS classification was the same, and in the remaining 31.7% ($N=360$) subtyping differed (Table 4). In patients with clinical variants pure sensory GBS ($N=13$) classification differed in 15.4% ($N=2$) and in MFS ($N=63$) in 6.3% ($N=4$). 277 of studies (24.4%) were classified demyelinating by Hadden criteria but not by Rajabally criteria ($N=155$ axonal, $N=122$ equivocal). Therefore, fewer patients fulfilled demyelinating criteria by Rajabally criteria ($N=370$) than by Hadden criteria ($N=643$), making more patients eligible for either axonal or equivocal classification by Rajabally. 75 patients (6.6%) were classified axonal by Rajabally, but equivocal by Hadden criteria, because absent F-waves and reduced p/dCMAP ratio serve as supportive for axonal subtyping by Rajabally criteria only. Four equivocal studies by Hadden were classified demyelinating by Rajabally criteria. Of these, two were based on absent F-waves and two on a p/dCMAP ratio of 0.5–0.7 (both variables supportive of demyelination by Rajabally but not by Hadden). The latter was also responsible for another two cases classified

TABLE 5 Revised EI Escorial criteria in axonal and demyelinating GBS patients, as classified by Hadden criteria and Rajabally criteria.

EI Escorial criteria					
	DML >130% (*N*)[a]	MCV <70% (*N*)	F-wave latency >130% (*N*)	Conduction block[b] present (*N*)	Total percentage of cases (*N*)
Axonal GBS					
Hadden (*N* = 111)	0.9% (1)	0.9% (1)	0% (0)	0% (0)	1.8% (2)
Rajabally (*N* = 341)	23.5% (80)	1.8% (6)	1.2% (4)	62.5% (213)	68.6% (234)
Demyelinating GBS					
Hadden (*N* = 643)	74.7% (480)	27.8% (179)	22.2% (143)	46.0% (296)	93.3% (600)
Rajabally (*N* = 370)	86.5% (320)	39.7% (147)	33.2% (123)	65.1% (241)	96.2% (356)

Abbreviations: CMAP, compound muscle action potential; dCMAP, distal compound muscle action potential; DML, distal motor latency; GBS, Guillain–Barré syndrome; LLN, lower limit of normal; MCV, motor conduction velocity; p/dCMAP, proximal-to-distal compound muscle action potential.

[a]Revised EI Escorial 'red flag' criteria present in patients (at least once).

[b]Conduction block defined by their own criteria: Hadden criteria p/dCMAP ratio <0.5 and dCMAP ≥20% LLN; Rajabally criteria p/dCMAP ratio <0.7, excluding tibial nerve.

normal by Hadden but equivocal by Rajabally criteria. Finally, two cases were equivocal by Hadden criteria because of abnormal tibial p/dCMAP ratio with the rest of the study being normal. These were classified normal by Rajabally criteria.

Revised EI Escorial criteria

Guillain–Barré syndrome patients were classified according to the rEEC (Table 5). These red flags were fulfilled in 1.8% of axonal GBS by Hadden criteria and in 68.6% by Rajabally criteria. The rEEC most frequently fulfilled in axonal GBS by Rajabally criteria were the presence of a conduction block (62.5% of cases) and prolonged DML (23.5%). In six axonal GBS cases the MCV criterion (<70% LLN) was fulfilled, but this was only possible in the case of reduced dCMAP amplitude (<10% LLN) as this was allowed by both Hadden and Rajabally criteria.

DISCUSSION

In this study of 1137 patients with GBS, electrodiagnostic neurotyping according to Hadden and Rajabally criteria agreed in 68.3% but there was a significant number in which they did not agree (31.7%). This was explained by the more strictly defined cutoffs for demyelination in the Rajabally criteria. Therefore, fewer patients fulfilled demyelinating criteria by Rajabally (*N* = 370) than by Hadden (*N* = 643), making more patients eligible for either an axonal (*N* = 155) or equivocal (*N* = 75) classification.

It is confirmed that for all four motor nerves (median, ulnar, peroneal, tibial), variables denoting conduction slowing were significantly correlated with (reduction of) dCMAP amplitudes [17–19]. Whilst more sophisticated criteria could be developed, such as detailed equations relating the conduction parameters to amplitudes [20], in practice they are difficult to apply.

Our study showed that, for both Hadden and Rajabally criteria, the criterion of prolonged DML (in at least two nerves) was the most frequently met demyelinating criterion (Hadden criteria 41.7%; Rajabally criteria 19.9% of all studies). The most frequently met axonal criterion was the reduced dCMAP amplitude (in at least two nerves) according to both Hadden criteria (9.9% of studies) and Rajabally criteria (26.5% of all studies).

Criteria for demyelinating GBS are crucial in both AIDP and axonal GBS, as exclusion of demyelinating features is a hallmark in axonal GBS, according to both Hadden and Rajabally criteria. Cutoffs for demyelinating criteria varied between the two criteria sets. As ALS is generally considered an axonal motor neuropathy, rEEC and the successive Gold Coast criteria for ALS proposed NCS criteria suggestive of disease processes other than ALS [13, 16]. Using these ALS red flag criteria which suggest that a neuropathy is not axonal, 68.6% of axonal GBS cases according to Rajabally criteria fulfilled these criteria. For Hadden criteria, this was only 1.8% of axonal cases. This underlines the importance of cutoffs showing how the usage of different criteria leads to different conclusions based on the same data. Also, as the rEEC criteria were developed in ALS and not in GBS, and also based on expert opinion, selecting the optimal criteria is not possible.

Subtyping GBS by NCS criteria is complicated by the lack of a gold standard. Multiple criterion sets were published before, including the more recently developed criteria by Uncini et al. requiring a second EDx study and sensory data [11]. Although NCS subtyping is suggested to reflect the underlying pathological process, that is, axonal degeneration or demyelination of peripheral nerves, pathological studies to confirm this are usually not available. Moreover, this dichotomous view as usually stated as AIDP versus acute motor axonal neuropathy is probably too simplistic: axonal degeneration is

often present in demyelinating subtypes and decline in nerve conduction velocities resembling a demyelinating process might also be present in axonal neuropathies with conduction slowing being CMAP amplitude dependent [17–20]. Also, in early stage GBS axonal degeneration and demyelination might be preceded by endoneurial edema, especially in proximal nerve trunks [2]. Our results confirmed these previous findings of amplitude-related conduction slowing, which was explained by loss of large, faster-conducting nerve fibers [21] and the abnormal slow conduction velocities in regenerating motor fibers [22]. In the acute stage of GBS, conduction slowing might represent demyelination or reversible conduction failure [23] as well as loss of fast-conducting motor nerve fibers by Wallerian-like axonal degeneration. Discriminating the role of each process finally resulting in conduction slowing in an individual patient is complex, although some factors might be helpful: (1) excessive temporal dispersion of the CMAP (except the tibial nerve) is generally considered a demyelinating process [24]; (2) follow-up NCS studies might reveal reversible conduction failure but are not useful in the early stages; and (3) conduction slowing in ALS patients showed mild to moderate signs of conduction slowing, but exceptions with severe conduction slowing were present although the European Federation of Neurological Societies/Peripheral Nerve Society chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) criteria were never fulfilled [21]. Therefore, in GBS, unraveling the underlying pathological process based on EDx studies alone is limited. In the classification of GBS, besides the results of EDx studies other features should also be taken into account such as clinical characteristics, anti-ganglioside antibodies, infectious antecedents and biomarkers for axonal loss (e.g., neurofilament light chain, peripherin) in order to get a better understanding of the full spectrum of subtypes and the heterogeneity of GBS, and future studies in IGOS might contribute to this.

This study shows that classifying subtypes in GBS is dependent on the NCS criteria used. Therefore, performing and classifying NCS studies in GBS needs a fundamental reappraisal. First, in the absence of a gold standard it is unknown which are the right criteria to use. The above showed that many axonal studies of Rajabally criteria met red flag criteria for demyelinating neuropathy suggesting an underestimation of demyelinating subtypes. Contrarily, the pathological process in ALS is considered axonal degeneration, whereas axonal GBS might also represent (reversible) axonal dysfunction, which is represented in Rajabally criteria but not in Hadden criteria. Second, GBS classifications should be rethought more holistically, see above, since the NCS classification can be controversial depending on which criteria are used. Third, the preoccupation in clinical trials to use only EDx data to classify subjects seems misguided as subjects can be classified differently depending on the criteria used.

AUTHOR CONTRIBUTIONS

Samuel Arends: Conceptualization; investigation; writing – original draft; methodology; visualization; formal analysis; writing – review and editing; data curation. **Judith Drenthen:** Conceptualization; writing – review and editing; supervision. **Laura de Koning:** Methodology; data curation; software; validation. **Peter van den Bergh:** Conceptualization; writing – review and editing; supervision. **Robert D. M. Hadden:** Writing – review and editing; supervision; conceptualization. **Satoshi Kuwabara:** Writing – review and editing; supervision; conceptualization. **Ricardo C. Reisin:** Writing – review and editing; supervision; conceptualization. **Nortina Shahrizaila:** Writing – review and editing; supervision; conceptualization. **Senda Ajroud-Driss:** Writing – review and editing. **Giovanni Antonini:** Writing – review and editing. **Shahram Attarian:** Writing – review and editing. **Claudia Balducci:** Writing – review and editing. **Tulio Bertorini:** Writing – review and editing. **Thomas H. Brannagan:** Writing – review and editing. **Guido Cavaletti:** Writing – review and editing. **Chi-Chao Chao:** Writing – review and editing. **Govind Chavada:** Writing – review and editing. **Klaus-Ulrich Dillmann:** Writing – review and editing. **Mazen M. Dimachkie:** Writing – review and editing. **Giuliana Galassi:** Writing – review and editing. **Gerardo Gutiérrez-Gutiérrez:** Writing – review and editing. **Thomas Harbo:** Writing – review and editing. **Badrul Islam:** Writing – review and editing. **Zhahirul Islam:** Writing – review and editing. **Hans Katzberg:** Writing – review and editing. **Susumu Kusunoki:** Writing – review and editing. **Fiore Manganelli:** Writing – review and editing. **James A. L. Miller:** Writing – review and editing. **Julio Pardo:** Writing – review and editing. **Yann Pereon:** Writing – review and editing. **Yusuf A. Rajabally:** Writing – review and editing. **Soren Sindrup:** Writing – review and editing. **Mark Stettner:** Writing – review and editing. **Antonino Uncini:** Writing – review and editing. **Camiel Verhamme:** Writing – review and editing. **Michal Vytopil:** Writing – review and editing. **Waqar Waheed:** Writing – review and editing. **Bart C. Jacobs:** Conceptualization; investigation; funding acquisition; writing – review and editing; methodology; supervision; formal analysis. **David R. Cornblath:** Writing – review and editing; methodology; formal analysis; supervision; conceptualization; investigation.

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CONFLICT OF INTEREST STATEMENT

Dr. Dimachkie serves or recently served as a consultant for Abata/Third Rock, Abcuro, Amicus, ArgenX, Astellas, Cabaletta Bio, Catalyst, CNSA, Covance/Labcorp, CSL-Behring, Dianthus, Horizon, EMD Serono/Merck, Ig Society, Inc, Ipsen, Janssen, Medlink, Nuvig, Octapharma, Priovant, Sanofi Genzyme, Shire Takeda, TACT/Treat NMD, UCB Biopharma, Valenza Bio and Wolters Kluwer Health/UpToDate.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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

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APPENDIX A

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