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Electrodiagnosis of Guillain-Barre syndrome in the International GBS Outcome Study: Differences in methods and reference values

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HIGHLIGHTS

- Electrodiagnosis (EDx) methodology is heterogeneous across the regions and often differed from the methodology of the applied reference values.
- EDx reference values vary globally among IGOS centers.
- Future studies in Guillain-Barré syndrome patients should use a standardized EDx protocol.

ABSTRACT

Objective: To describe the heterogeneity of electrodiagnostic (EDx) studies in Guillain-Barré syndrome (GBS) patients collected as part of the International GBS Outcome Study (IGOS).
Methods: Prospectively collected clinical and EDx data were available in 957 IGOS patients from 115 centers. Only the first EDx study was included in the current analysis.
Results: Median timing of the EDx study was 7 days (interquartile range 4–11) from symptom onset. Methodology varied between centers, countries and regions. Reference values from the responding 103 centers were derived locally in 49%, from publications in 37% and from a combination of these in the remaining 15%. Amplitude measurement in the EDx studies (baseline-to-peak or peak-to-peak) differed from the way this was done in the reference values, in 22% of motor and 39% of sensory conduction. There was marked variability in both motor and sensory reference values, although only a few outliers accounted for this.
Conclusions: Our study showed extensive variation in the clinical practice of EDx in GBS patients among IGOS centers across the regions.
Significance: Besides EDx variation in GBS patients participating in IGOS, this diversity is likely to be present in other neuromuscular disorders and centers. This underlines the need for standardization of EDx in future multinational GBS studies.

1. Introduction

Guillain-Barré Syndrome (GBS) is a heterogeneous, immune-mediated polyradiculoneuropathy. In clinical practice, electrodiagnosis (EDx), including nerve conduction studies (NCS) and electromyography (EMG), is part of the standard work-up and can reveal features supporting the diagnosis. According to the clinical case definition of the Brighton Collaboration GBS Working Group, EDx findings consistent with polyneuropathy are obligatory to fulfill the criteria for level 1 diagnostic certainty (Sejvar et al., 2011).

EDx was used in the early studies of GBS to demonstrate features supportive of demyelination to better understand the pathophysiology of the disorder (Lambert and Mulder, 1964). The first set of clinical criteria, with a description of the EDx features that were considered strongly supportive of the diagnosis, was developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) committee (Asbury et al., 1978) in order to better recognize the spectrum of GBS. This was a response to the rise of reported GBS after vaccinations for swine flu. After the initial focus on demyelinating forms of GBS (Albers and Kelly, 1989), there were reports of axonal forms of GBS (Feasby et al., 1986; McKhann et al., 1991, McKhann et al., 1993) for which additional criteria were developed in 1995 (Ho et al.). Since then, various other sets of criteria have been proposed, which tend to be more extensive and largely focus on the distinction between demyelinating and axonal subtypes of GBS (Hadden et al., 1998; Rajabally et al., 2015; Uncini et al., 2017).

The frequency of demyelinating and axonal subtypes of GBS varies between geographical regions. Acute inflammatory demyelinating polyneuropathy (AIDP) is the predominant subtype in Europe and North America, and the acute motor (sensory) axonal neuropathy (AMAN, AMSAN) subtypes are more frequent in most parts of Asia (Doets et al., 2018; Islam et al., 2010; Matsui et al., 2018). The GBS subtype can also be determined by nerve pathology studies, which are rarely done, so EDx is considered the standard in

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routine diagnostic work-up. Subtyping in GBS is important to further unravel the relationship between GBS and preceding infections, anti-ganglioside antibodies, prognosis and treatment response. Nevertheless, there are no minimum standards for EDx testing in GBS, for example in terms of extensiveness of the study, when applying these EDx criteria. Obtaining insight into the variability of EDx practice and the possible influence on EDx subtyping is important to improve and implement the diagnostic criteria for GBS.

The International GBS Outcome Study (IGOS) is a multicenter, prospective, observational cohort study, investigating factors that determine and predict the clinical course, subtype and outcome of GBS (Jacobs et al., 2017). IGOS gathered 'real world' EDx data in a large multinational cohort of GBS patients. The aim of this study was to describe the heterogeneity of EDx in current clinical practice, especially the variation in methodology, reference values and extensiveness of testing. The results of EDx testing will be described in a later paper.

2. Methods

2.1. Patient cohort

In this study, we used data from the first 1500 patients included in IGOS ('IGOS-1500' cohort). The IGOS protocol has been published previously (Jacobs et al., 2017) and included patients who fulfilled the diagnostic criteria for GBS of the National Institute of Neurological Disorders and Stroke (NINDS) or one of the variants (Asbury and Cornblath, 1990; Sejvar et al., 2011; Wakerley et al., 2014), had at least one EDx study, presented within 2 weeks of onset of symptoms attributable to GBS, and had given written informed consent. The IGOS protocol (Jacobs et al., 2017) stated that local investigators were free to conduct EDx studies according to their local routine standards, but recommended performing two EDx studies for each patient, the first within 7 days of admission or registration in IGOS, and the second at four weeks after admission or registration in IGOS. When more than one study was done, only the first was used in this study.

Patients were excluded if the diagnosis turned out not to be GBS, clinical or EDx data were absent, or the study protocol was violated. The study was approved by the Medical Ethical Review Committee of the Erasmus University Medical Center Rotterdam and by the local Institutional Review Boards of all participating centers. All patients participating provided informed consent.

2.2. Data collection

2.2.1. Clinical data

Demographics (age, country, gender, height) and clinical data (clinical GBS variant, GBS disability score) were obtained from the IGOS database. Classifying clinical variants was done by the treating physician to one of the following variants: (1) sensorimotor, (2) pure motor, (3) Miller Fisher syndrome (MFS), (4) MFS-GBS overlap syndrome, (5) ataxic, (6) pure sensory and (7) pharyngeal-cervical-brachial (PCB). The GBS disability score (Hughes et al., 1978) was determined at every visit in IGOS (week 1, 2, 4, 8, 13, 26, 52), but in the current study, the GBS disability score at the visit closest to the NCS was used.

2.2.2. Electrodiagnostic data

The IGOS protocol recommended that EDx should be performed and reported according to a standard format but this was optional. The IGOS protocol recommended: (i) sensory NCS on distal stimulation from the median (recording: digit 2), ulnar (recording: digit 5), radial (optional) and sural nerves, (ii) motor NCS and F waves from the median (recording: *abductor pollicis brevis muscle*), ulnar (recording: *abductor digiti minimi muscle*) and peroneal (recording: *extensor digitorum brevis muscle*) nerves on the non-dominant side, and one nerve on the dominant side (any of these or the tibial nerve (recording: *abductor hallucis muscle)*, (iii) tibial nerve H-reflex (recording: *soleus muscle*). Compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes were recommended to be measured baseline-to-peak. Optionally, needle EMG was performed from *first dorsal interosseous* and *tibialis anterior muscles* as well as from a proximal arm and a proximal leg muscle. Limb temperature management was allowed to be performed according to local standards. The EDx report was uploaded as an attachment to the online database. Most often, this was the original clinical report including graphs but, in a minority, the results were tabulated on the recommended form (Jacobs et al., 2017, Table S2). In this way, it was possible to establish what EDx tests were done (the local EDx protocol) if GBS was suspected.

A questionnaire was sent to the principal investigators of the participating centers after start of IGOS, asking about methodological aspects, source of reference values and possible ambiguities of the results. Methodological aspects that we assessed included how SNAP and CMAP amplitudes were measured (baseline-to-peak or peak-to-peak), stimulus and recording sites for every nerve, direction of sensory nerve conduction (antidromic or orthodromic), usage of height in relation to F-wave latency, limb temperature recordings, and heating policy. We did not analyze CMAP duration, because of insufficient data. Reference values were analyzed in order to detect possible methodological differences between participating centers and the reference values that they apply on their EDx studies.

EDx reference values were divided into published and unpublished and were classified according to their origins. Unpublished reference values were classified as 'local' if developed within the center where they were used, 'Local, adopted' if based on or identical to reference values collected in another, often neighboring center and 'Adopted from Mayo Clinic' if based on Mayo Clinic EMG Laboratory reference values. Published reference values were classified as 'Buschbacher/Chen' if based on Buschbacher's textbook (Buschbacher and Prahlow, 2006) or on those proposed by the Normative Data Task Force of The American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) (Chen et al., 2016), 'Kimura' if based on Kimura's textbook (Kimura, 2013), 'Preston and Shapiro' if originating from their textbook (Preston and Shapiro, 2012), 'Published, other' if they were derived from other published papers, and 'Combination' if multiple reference value sets were combined to one set, often at least partially published. If no reference values were available this was classified as either 'No reference values used' if no specific set of reference values was used and interpretation was based on physician's experience or 'missing' if data about the type of reference values was lacking.

2.3. Statistical analysis

IBM SPSS Statistics 25 was used for analysis. A two-sided P value < 0.05 was considered significant. Chi squared test was used to compare proportions, and one way ANOVA to compare numerical (ordinal) data between the regions.

3. Results

3.1. Demographics

Of the IGOS-1500 cohort, 85 patients were excluded because of a different diagnosis (53 Chronic Inflammatory Demyelinating Polyneuropathy, 32 other), 35 patients because of protocol violations and 7 patients because of missing clinical data. An EDx study was conducted in 1210 (88%) of the remaining 1373 patients. In

this study, a total of 957 patients (70%) in whom EDx data were available were included.

The characteristics of the study population are shown in Table 1. GBS patients were included in 115 centers from 18 counties including Argentina (n = 35), Australia (n = 8), Bangladesh (n = 141), Belgium (n = 20), Canada (n = 23), Denmark (n = 103), France (n = 31), Germany (n = 44), Greece (n = 7), Italy (n = 89), Japan (n = 41), Malaysia (n = 25), The Netherlands (n = 66), South Africa (n = 15), Spain (n = 88), Taiwan (n = 5), United Kingdom (n = 120) and the United States of America (n = 96). The vast majority (93%) of our study population came from Asia, Europe or North America with 8, 68 and 31 participating centers, respectively. The remaining 8 participating hospitals were from Africa (N = 1), Australia (N = 2), and South-America (N = 5). For the cohort as a whole, the median time to EDx was 7 days (IQR 4–11) from onset of GBS related motor and/or sensory symptoms. In a minority, EDx was done later in the course with the maximum done on day 129. This was a case with suspected relapse of GBS who did not undergo an EDx study earlier. The timing of EDx studies in relationship to geography is shown in Fig. 1.

Table 1
Demographics and clinics of study population and timing of electrophysiology.

Demography and clinical characteristics	
Total number of patients	957
Sex male/female (ratio)	61/39 (1.56)
Age median years (IQR, range)	51 (34–65; 0–88)
Number patients with age below 18 years (%)	59 (6.1%)
Median body height in cm (IQR)	169 (162–177)
Number of patients (%) – by continent	
Europe	568 (59.4%)
Asia	212 (22.2%)
North America	119 (12.4%)
South America	35 (3.7%)
Africa	15 (1.6%)
Australia	8 (0.8%)
Clinical subtype (%)	
Sensorimotor	564 (60.6%)
Pure motor GBS	219 (23.5%)
Miller Fisher Syndrome	54 (5.8%)
Miller Fisher Syndrome - GBS overlap	50 (5.4%)
Ataxic	17 (1.8%)
Pure sensory GBS	11 (1.2%)
Pharyngeal Cervical Brachial variant	11 (1.2%)
Median GBS disability score at EDx study (IQR)	4 (2–4)
Numbers (%) of patients with GBS disability score	
0	3 (0.3%)
1	36 (3.8%)
2	213 (22.3%)
3	176 (18.4%)
4	437 (45.8%)
5	89 (9.3%)
Missing	3 (0.3%)
EDx - timing and follow up	
Median timing, days (IQR, range)	
Africa	10 (8–14; 3–17)
Asia	7 (4–10.8; 0–66)
Australia	7 (4.5–8.8; 0–13)
Europe	8 (5–12; 0–129)
North America	7 (4–10; 0–41)
South America	6 (3–12; 0–28)
Total cohort	7 (4–11; 0–129)
Patients with follow-up EDx (%)	396 (41.4%)
1 follow up	355 (37.1%)
2 follow up	27 (2.8%)
3 follow up	11 (1.1%)
4 follow up	3 (0.3%)

Abbreviations: EDx = electrodiagnostics; GBS = Guillain-Barré syndrome; IQR = interquartile range.

3.2. EDx study protocol

3.2.1. Motor NCS

An overview of the EDx tests performed (EDx protocol) in different regions is shown in Table 2. There was no relationship between extensiveness of motor and sensory NCS and the severity of GBS. The mean number of motor nerves per study was slightly, but significantly ($p < 0.001$) different between Asia (4.0), Europe (5.0) and North America (4.6). As patients from Bangladesh represented 66.5% of the Asian cohort, the analysis of mean number of motor nerves was repeated after leaving out these patients to determine their possible influence on this part of the study: the same significant differences between regions were found ($p < 0.001$). Median and ulnar nerve conduction studies were most often limited to the forearm segments. For the median nerve, proximal segments were studied in 17.7 % (17.7% axilla to elbow; 3.6% Erb's point to axilla). For the ulnar nerve, testing above the elbow was done in 14.1% (14.1% axilla to proximal elbow; 3.1% Erb's point to axilla). F waves were studied in 78.0 % of median nerves and 77.9% of ulnar nerves. In 14.9% of median nerves and in 14.2% of ulnar nerves, proximal segments were not evaluated, neither by F wave study nor by investigating proximal segments, despite present distal CMAP amplitude of at least 1.0 mV.

Uncommon motor NCS were performed in less than 5% of nerves, including axillary, facial, femoral, musculocutaneous and phrenic nerves. Uncommon recording sites included the *abductor digiti minimi muscle* for tibial nerve and *adductor pollicis,* first *interosseous dorsalis* or *flexor carpi ulnaris muscle* for the ulnar nerve.

3.2.2. Sensory NCS

The extent of sensory NCS was quite variable, ranging from none (12 patients) to 10 sensory nerves (median 4 patients; IQR 3–5). In 5% of patients, sensory NCS studies were restricted to upper limbs or lower limbs only. In the upper limb, the median and ulnar nerves were more frequently examined than the radial nerve, whereas in the lower limb, the sural nerve was more often measured than the superficial peroneal nerve. This pattern was consistent across the regions. Stimulus and recording positions for upper limb sensory NCS differed among centers. For example, distal sensory median nerve testing was done (antidromic and/or orthodromic) at the second digit – palm/wrist segment in 65% of sensory median tests, at third digit – palm/wrist segment in 18%, at palm – wrist segment in 7%, at first digit – wrist segment in 5% and at fourth digit – wrist segment in 2%. Stimulus and/or recording position was missing in the remaining 3%. Proximal sensory NCS was performed in 14% of median nerves (14.2% wrist to elbow; 0.7% elbow to axilla) and in 17% of ulnar nerves (16.8% wrist to distal elbow; 6.2% distal to proximal elbow; 0.4% proximal elbow to axilla). The following sensory nerves were rarely performed: dorsal cutaneous branch of the ulnar nerve, lateral antebrachial cutaneous nerve, lateral dorsal cutaneous nerve of the foot, lateral and/or medial plantar nerve, and saphenous nerve.

3.2.3. Electromyography

EMG was performed in 53% of patients in 58 different muscles, with the first *interosseous dorsalis* muscle (406 times) and *tibialis anterior* muscle (582 times) being the most studied muscles of the upper and lower limbs. Performing EMG differed significantly ($p < 0.001$) between Asia (15.6%) versus Europe (65.3%) and North America (70.6%), where the patients with EMG from the Asian cohort all came from Bangladesh. In the subset of patients where EMG was performed, the median number of muscles tested was 4 (IQR 2–5, range 1–22). The median number of muscles tested differed significantly ($p < 0.001$) between Asia (9.5), Europe (3.3) and North America (5.2). EMG of the upper limb slightly exceeded the lower limb with the face/neck and paraspinal region being a minority.

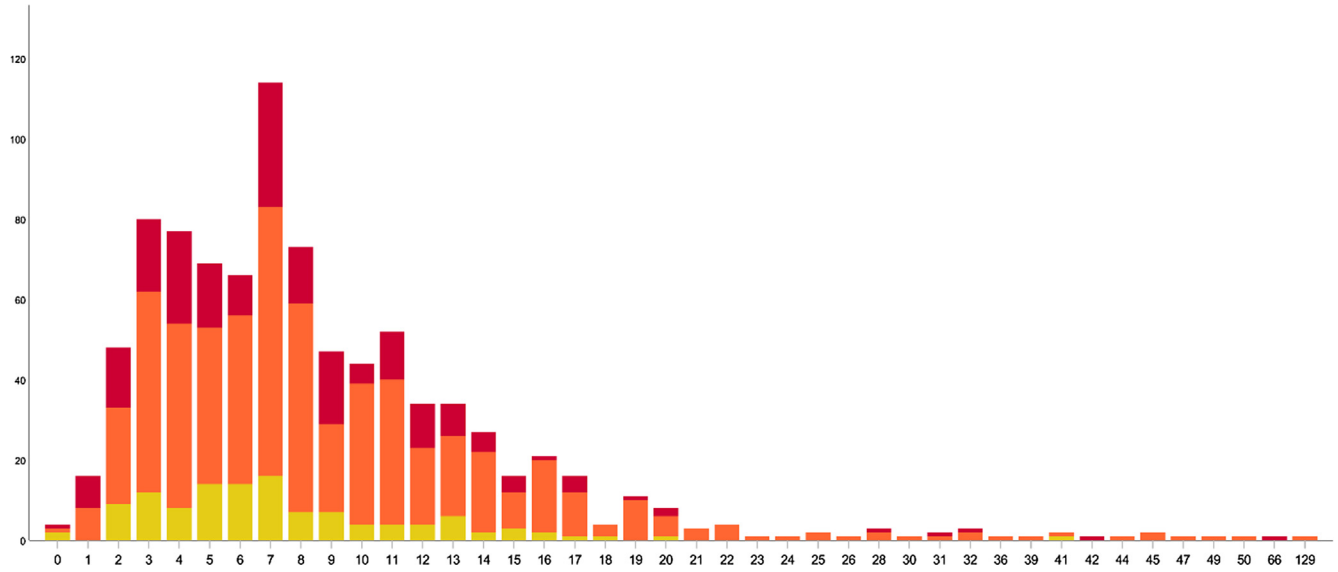

Fig. 1. Timing of first EDx after start of clinical neurological symptoms, stratified by continent. X-axis: timing of electrophysiologal study (days); Y-axis: number of patients. EDx: electrodiagnostics. / Red: Asia / Orange: Europe / Yellow: North America.

3.2.4. Other EDx testing

The tibial H reflex was performed in 31%, and the blink reflex in 6% of patients. Other techniques were performed in a minority of the cohort. Techniques in Table 2 grouped together as 'other' were: H-reflex recorded at *biceps brachii* muscle (N = 1), *flexor carpi radialis* muscle (N = 1), *triceps brachii* muscle (N = 1), *quadriceps femoris* muscle (N = 2), Turns-Amplitude ratio analysis (N = 2) and single-fiber EMG (N = 4).

3.3. Methodological variability

3.3.1. Limb temperature management

Data on temperature management were missing in 28 of 115 centers. In the remaining 87 centers, 70.1% (61 centers) had a policy to warm patients prior to the EDx study if necessary and 29.9% (26 centers) did not warm their patients. Increasing limb temperature was achieved in multiple ways with some centers having more than one option to increase temperature. The majority of centers used warming with hot water baths (32 centers), followed by different types of blankets (15), heating pads (12), infrared (9), and/or hot air blower systems like a hairdryer (3).

3.3.2. Methodology in motor NCS

The NCS methodology differed between centers. In general, motor NCS were similar, with fixed stimulus and recording positions using surface electrodes. There were differences in how CMAP amplitudes were measured. Amplitudes were recorded as baseline-to-peak in 68% of participating centers, peak-to-peak in 25%, both in 2% and missing in 5%. The proportion of centers using peak-to-peak measurements varied between North America (3%), Asia (25%) and Europe (34%).

3.3.3. Methodology in sensory NCS

Sensory NCS methodology was more variable than in motor NCS (Table 3). Surface electrodes were used for recording in all centers, with one center that used a combination of surface and needle electrodes (near-nerve technique). SNAP amplitudes were more frequently measured baseline-to-peak than peak-to-peak in Asian (64.1%) and North American (76.6%) centers, but in European centers the majority of SNAP amplitudes were measured peak-to-peak (60.9%). Sensory nerves were tested antidromically in most centers. Orthodromic testing was rare in radial and lower limb nerves, but more common in evaluating median and ulnar nerves. In European centers, median and ulnar sensory nerves were measured orthodromically in 43.1% and 59.0% respectively. These proportions were lower in the Asian (median nerve 25.0%; ulnar nerve 37.5%) and North American (median nerve 33.3%; ulnar nerve 24.0%) centers. The vast majority of centers used an antidromic technique for sural nerve conduction (92.7%).

3.4. Reference values

3.4.1. General characteristics of the NCS reference values

Details about the reference values used are described in Table 4. Reference values were provided by 103 centers (89.6%). In the remaining centers, reference values were not used in 2 (1.7%) or were not provided in 10 centers (8.7%). Textbook reference values were used in 22.6%, but a detailed description on the origin of these values was lacking. In 35.9% of the centers the reference values used, were the same for all age groups. In both motor and sensory NCS, reference values were sometimes applied despite differences in NCS methodology between the reference and actual study. For example, in 19.6% of centers, CMAP amplitudes were measured peak-to-peak and compared to reference values that applied baseline-to-peak motor amplitudes.

3.4.2. Motor nerve conduction reference values

An overview of motor nerve reference values for the four most frequently tested nerves is given in Table 5 and for sensory nerves in Table 6, stratified by methodology. Motor reference values were highly variable. For example, lower limits of normal for peroneal CMAP amplitude differed >6 times (baseline-to-peak, range 0.8–5.0 mV) and 15 times (peak-to-peak, range 0.4–6.0 mV) and for tibial nerve >4 times (baseline-to-peak, range 1.7–8.0 mV) and >10 times (peak-to-peak, 1.0–10.5 mV).

3.4.3. Sensory nerve conduction reference values

Sensory NCS reference values were highly variable, for example up to 10-fold for antidromic sural and orthodromic median SNAP amplitude (peak-to-peak). In contrast to motor nerve reference values, reference values for peak-to-peak sensory amplitudes are not necessarily higher than baseline-to-peak amplitudes.

Table 2
Overview of electrophysiological testing in first EDx in IGOS.

	% Total cohort	Europe % (N=568)	Asia % (N=212)	North-America % (N=119)	South-America % (N=35)	Africa % (N=15)	Australia % (N=8)
Motor NCS							
Number of motor nerves tested							
1	0.1	0.2	0	0	0	0	0
2	2	3	0	3	0	0	13
3	13	13	16	12	3	0	13
4	44	34	74	48	29	7	25
5	12	13	6	18	6	47	0
6	14	20	2	6	26	20	12
7	6	8	0	8	17	0	12
8	7	8	2	3	17	27	25
9	0.9	0.7	0	3	3	0	0
10	0.2	0.4	0	0	0	0	0
Site of motor testing[#]							
Upper limb only	0.9	0.7	0	3	3	0	13
Lower limb only	1	2	0	2	3	0	0
Upper and lower limb	98	98	100	96	94	100	88
Median (APB)	94	90	100	93	97	100	100
Ulnar (ADM)	95	92	100	96	91	100	100
Ulnar (FDI)	2	2	0	3	0	0	13
Peroneal (EDB)	95	94	95	93	97	93	75
Peroneal (TA)	8	7	0	25	9	20	0
Tibial (AH)	88	87	88	88	87	100	88
Facial (multiple)	4	6	0	6	0	0	0
Other*	5	4	9	3	3	0	0
Sensory NCS							
Number of sensory nerves tested							
0	1	2	0	0.8	0	0	0
1	2	3	0	2	6	0	0
2	6	8	0.5	8	6	0	25
3	35	28	61	24	24	47	0
4	29	29	25	31	37	13	38
5	13	12	10	28	9	7	12
6	7	9	3	3	20	33	0
7	2	3	0	0.8	0	0	0
8	3	4	0.5	2	0	0	12
9	1	2	0	0	0	0	12
10	0.9	2	0	0	0	0	0
Site of sensory testing[#]							
Upper limb only	3	3	0.5	4	11	0	25
Lower limb only	2	3	0	2	0	0	0
Upper and lower limb	94	92	100	93	89	100	75
Median	89	85	100	84	94	100	100
Ulnar	88	86	100	78	77	100	88
Radial	32	34	17	61	3	0	50
Sural	82	72	100	93	89	100	75
Superficial peroneal	23	21	25	38	0	0	38
Other**	2	2	1	3	0	0	0
EMG							
Myography done	53	65	16	71	40	13	25
Upper limb	48	60	14	65	37	0	25
Face / neck	2	1	0	6	3	0	13
Lower limb	44	54	13	57	34	13	25
Paraspinal	4	4	6	6	0	0	0
Other							
Blink reflex	6	8	0.5	8	0	0	13
H-reflex m. soleus	31	32	42	22	0	7	13
Multi MUAP analysis	5	8	0	0	0	0	0
Myoelectric T-reflex	2	3	0	0	0	0	0
Repetitive stimulation	3	4	0.5	0.8	3	0	0
Other***	1	2	0	0	0	7	0

proportion of patients with at least one side tested. */**/*** see text. All percentages at or above 1% were rounded off (no decimal) and below 1% with one decimal. Abbreviations: ADM = *adductor digiti minimi*; AH = *abductor hallucis*; APB = *abductor pollicis brevis*; EDB = *extensor digitorum brevis*; EDx = electrodiagnostics; EMG = electromyography; FDI = *first interosseous dorsalis*; Hoffmann reflex = H-reflex; IGOS = International Guillain-Barré Outcome Study; MUAP = motor unit action potential; NCS = nerve conduction studies; TA = *tibialis anterior*; T-reflex = deep tendon reflex.

4. Discussion

The IGOS recommended that EDx should be performed according to a standard template but many centers chose not to follow this and use the local procedures. EDx data were thus collected in many different ways, with different methodology and interpreted with markedly variable reference values. This might influence diagnosis and EDx subtyping in GBS patients and probably also in patients with other neuromuscular diseases, especially polyneuropathies, and in other centers not participating in IGOS,

Table 3
Sensory nerve conduction and methodological variability in IGOS centers.

	Antidromic		Orthodromic	
	BP n (%) [#]	PP n (%)	BP n (%)	PP n (%)
Median and Ulnar	41 (42.7)	20 (20.8)	9 (9.4)	26 (27.1)
Radial	45 (49.5)	36 (39.6)	3 (3.3)	7 (7.7)
Superficial peroneal	43 (48.9)	39 (44.3)	3 (3.4)	3 (3.4)
Sural	46 (47.9)	43 44.8)	4 (4.2)	3 (3.1)

[#] methodological aspects of sensory NCS. This shows the proportion of centers applying the specified methods. Cases were excluded if information about methodology was lacking, methodology was operator-dependent and not center-dependent, or if > 1 method was applied within the same patient. Abbreviations: BP = baseline-to-peak amplitude measurement; IGOS = International Guillain-Barré Syndrome Outcome Study; PP = peak-to-peak amplitude measurement.

Table 4
Characteristics of the reference values sets used in centers participating in IGOS.

Reference value sets	Number (%)
Total centers	115 (100)
Number of centers - with reference values	103 (90)
Number of centers - not using reference values	2 (2)
Number of centers - reference values not provided	10 (9)
Origin of reference value sets	Number of 103 centers (%)
Local	36 (35)
Local, adopted	14 (14)
Buschbacher/Chen	14 (14)
Kimura	2 (2)
Adopted from Mayo Clinic	4 (4)
Preston and Shapiro	10 (10)
Published, other	8 (8)
Combination	15 (15)
Reference value set characteristics	Number of 103 centers (%)
CMAP amplitudes BP / PP / Missing	43 / 8 / 52 (42/ 8 / 51)
SNAP amplitudes BP / PP / Missing	39 / 15 / 49 (38 / 15 / 48)
Direction sensory nerve conduction	
Sensory reference values antidromic	38 (37)
Sensory reference values orthodromic	2 (2)
Sensory reference values both ortho- and antidromic	17 (17)
Direction of sensory NCS missing	46 (45)
F wave reference values dependent on length Yes / No / Missing	37 / 61 / 5 (36 / 59 / 5)
NCS Dependent on age Yes / No / Missing	44 / 37 / 22 (43 / 36 / 21)
NCS Dependent on gender Yes / No / Missing	16 / 65 / 22 (16 / 63 / 21)
Distance for DML specified Yes / No	44 / 59 (43 / 57)
Methodological discrepancies	Number of centers (%) *
CMAP amplitude measured (BP) versus reference values (PP)	1 (2)
CMAP amplitude measured (PP) versus reference values (BP)	10 (20)
SNAP amplitude measured (BP) versus reference values (PP)	5 (9)
SNAP amplitude measured (PP) versus reference values (BP)	16 (30)
Antidromic technique versus orthodromic reference values	1 (2)
Orthodromic technique versus antidromic reference values	8 (14)

[*] Percentage from the group where both methodology of EMG and reference value set is known. Summed rounded percentages may not be equal to 100%. Abbreviations: BP = baseline-to-peak amplitude measurement; CMAP = compound muscle action potential; DML = distal motor latency; IGOS = International Guillain-Barré Syndrome Outcome Study; NCS = nerve conduction studies; PP = peak-to-peak amplitude measurement; SNAP = sensory nerve action potential.

although this was not part of our analysis. In previous multicenter GBS studies (Albers et al., 1985; Cornblath et al., 1988; Hadden et al., 1998), these problems were addressed by using local EDx standards (machine settings, protocols, reference values, and techniques), but without a thorough description of EDx study protocols, methodological aspects and origin of the reference values.

4.1. Study timing and protocol

The timing of EDx studies in IGOS was relatively early in the course of the disease, with 50% performed within the first week after symptom onset and 75% in the first 11 days. This is also the time-frame in which clinicians and patients would want diagnostic and prognostic information in current clinical practice. While studies were performed after 11 days in 25% of patients, the value of delaying studies to increase the likelihood of abnormal studies is likely to be outweighed by the diagnostic value of an early study, particularly when ruling out GBS mimics.

The way motor NCS were performed, was quite similar in the participating centers, by studying the four main motor nerves: median, ulnar, peroneal and tibial. Other motor nerves, for example, axillary and radial nerve, were tested infrequently. Variability in motor NCS is not desirable, because the majority of GBS EDx criteria sets are based predominantly on motor NCS. There was a slight but significant difference in the number of motor nerves investigated between regions. In Europe and North America, more nerves per EDx were tested than in Asia. As the distribution of demyelinating lesions may be patchy, testing fewer nerves may reduce the probability of detecting demyelinating subtypes. There was also variability in whether and how proximal nerve segments were evaluated. Most often, F waves were used for evaluation of proximal segments and, less often, this was tested by stimulation of proximal nerve sites. But, it was not uncommon that in patients the median (14.9%) and ulnar (14.2%) proximal nerve segments were not evaluated, despite the reported high diagnostic yield (Berciano et al., 2017). In some cases, this might be explained by already 'sufficient' abnormal EDx results, which made it unnecessary to extend the EDx study. Avoiding direct proximal nerve stimulation might possibly be explained by the more complex technique with possible co- or submaximal stimulation, the time consuming aspect, and the possibility of a more painful procedure.

Motor nerves were more often tested than sensory nerves, which also could be explained by the focus of NCS criteria sets on motor NCS. In GBS, sensory NCS is used to detect sensory involvement, especially in a sural sparing pattern. To investigate sural sparing pattern, besides the sural nerve, at least one other sensory (upper limb) nerve has to be investigated, depending on the definition used (Hiew and Rajabally, 2016). Also, a sufficient number of sensory nerves needs to be tested to reliably differentiate between AMAN and AMSAN. The number of sensory and motor NCS may be influenced by the IGOS protocol for EDx (Jacobs et al., 2017), although this protocol was optional and not followed very strictly. There were wide variations in the way the sensory nerves

Table 5
Motor NCS reference values in IGOS.

	Median – APB	Ulnar – ADM	Peroneal – EDB	Tibial - AH
	median (IQR; full range)			
Distal motor latency (ms) by distance				
> 5-6 cm – ULN	4.1 (4.0-4.5; 4.0-4.6)	3.3 (3.0-4.1; 3.0-4.3)		
> 6-7 cm – ULN	4.2 (4.0-4.4; 4.0-4.4)	3.4 (3.3-3.5; 3.1-3.6)	5.6 (*; 5.5-5.7)	5.7**
> 7-8 cm – ULN	4.5 (4.3-4.5; 4.2-4.6)	3.8 (3.7-4.0; 3.7-4.0)	6.0 (5.5-6.0; 4.9-6.5)	6.1 (6.0-6.1; 6.0-6.5)
> 8 – ULN			6.5 (6.1-6.5; 5.0-6.5)	5.8 (5.6-5.9; 5.0-6.1)
unknown distance - ULN	4.2 (4.0-4.4; 3.0-4.8)	3.4 (3.1-3.6; 2.2-4.5)	5.7 (5.1-6.3; 4.0-7.0)	6.0 (5.7-6.2; 4.0-8.0)
Baseline-to-peak amplitude (mV) - LLN	4.0 (4.0-5.0; 3.0-7.9)	5.5 (4.5-6.0; 2.8-7.9)	2.0 (2.0-2.5; 0.8-5.0)	4.0 (3.0-4.1; 1.7-8.0)
Peak-to-peak amplitude (mV) - LLN	5.5 (4.4-7.0; 2.0-15.5)	7.3 (5.2-9.5; 5.0-12.3)	3.0 (2.0-5.0; 0.4-6.0)	5.0 (4.0-10.0; 1.0-10.5)
Distal MCV (m/s) - LLN	49 (48.0-50.0; 40.0-60.0)	49.4 (48.0-50.0; 40.0-61.0)	40.0 (40.0-41.9; 36.2-50.0)	40.0 (40.0-41.0; 34.0-50.0)
Minimal F wave latency (ms) - ULN	31.0 (30.0-32.0; 25.0-35.0)	31.0 (30.3-32.0; 25.0-35.0)	56.0 (55.0-58.0; 48.0-64.2)	56.9 (55.0-58.5; 49.0-67.0)

If the same set of reference values was used in multiple participating centers, this set was included only once. *No IQR available if value was based on less than 4 values; ** no full range if based on only one reference value. Every individual median value in this table is based on a different number of reference values, ranging from 1 to 72. Abbreviations: ADM = *abductor digiti minimi;* AH = *abductor hallucis;* APB = *abductor pollicis brevis;* EDB = *extensor digitorum brevis;* IGOS = International Guillain-Barré Syndrome Outcome Study; IQR = interquartile range; LLN = lower limit of normal; MCV = motor conduction velocity; ms = milliseconds; mV = millivolt; ULN = upper limit of normal.

Table 6
Sensory NCS reference values in IGOS, grouped by methodology.

		Median nerve – Digit II / III	Ulnar nerve – Digit V	Superficial radial nerve – snuffbox	Sural nerve – lateral malleolus
		median (IQR; full range)			
Antidromic	SNAP amplitudes baseline-to-peak	15.0 (10.0–20.0; 4.1–20.9)	10.0 (8.2–12.0; 5.0–18.0)	15.0 (12.5; 18.0; 7.0–20.0)	5.0 (4.0–7.0; 2.5–10.0)
	SNAP amplitudes peak-to-peak	10.0 (10.0–20.0; 10.0–24.0)	10.0 (10.0–19.5; 8.0–20.3)	15.0 (11.0–19.2; 10.0–40.0)	6.6 (5.0–10.0; 2.0–20.0)
	Distal SCV	48.5 (45.0–50.0; 39.9–60.0)	49.0 (45.0–50.0; 39.9–60.0)	50.0 (46.0–50.0; 40.0–65.0)	40.0 (39.0–41.0; 35.9–50.0)
Orthodromic	SNAP amplitude baseline-to-peak	9.0 (7.0–15.0; 5.0–20.0)	5.0 (4.5–10.0; 3.0–19.0)	14.0 (*; 10.0–16.0)	5.8 (*; 3.5–8.0)
	SNAP amplitude peak-to-peak	9.8 (6.0–17.0; 4.0–40.0)	5.0 (5.0–7.4; 2.0–15.0)	28.0 (*; 25.0–31.0)	5.0 (3.7–6.3; 2.7–10.0)
	Distal SCV	48.0 (44.3–50.0; 37.1–53.0)	47.0 (44.3–49.4; 37.9–50.0)	50.0 (40.2–50.0; 38.4–50.0)	40.0 (40.0–44.8; 40.0–47.0)

If the same set of reference values was used in multiple participating centers, this set was included only once. For median and ulnar sensory nerves, only reference values were used for the digit to wrist trajectory. *No IQR available if value was based on less than 4 values Every individual median value in this table is based on a different amount of reference values, reaching from 1 to 57. Abbreviations: BP = baseline-to-peak sensory amplitude; IGOS = International Guillain-Barré Syndrome Outcome Study; IQR = interquartile range; NCS = nerve conduction study; SCV = sensory conduction velocity; SNAP = sensory nerve action potential.

were tested, which could be explained by the fact that certain sensory nerves can be tested in multiple ways. For example, median sensory NCS can be performed antidromically by stimulation at the palm or wrist and recording from digits 1 to 4 and orthodromically by stimulation at digits 1 to 4.

In 53% of patients, EMG was done, often in a distal upper or lower limb muscle. EMG is the most sensitive way to detect axonal degeneration. The early timing of EDx studies is likely to be the main reason why almost half of the cohort did not undergo EMG, as signs of denervation and reinnervation were not expected to show up within the first week. Also, the lack of EMG in EDx criteria sets could contribute to this.

4.2. Methodological aspects

Methodological variability was more prominent in sensory than in motor nerve testing. Possible other methodological differences, not part of our analysis, were measurement of distal motor and sensory latency on a predefined or variable distance, CMAP duration and area measurement (negative peak versus negative and

positive peak), interpretation of F wave by various variables (minimal F wave latency; F-M interval, F wave persistence), determination of sensory latency (onset versus peak latency), determination of CMAP and SNAP marker positions (by hand versus by machine) and the use of machine tools (for example: filter settings, averaging of sensory potentials, artefact suppression).

Besides the methodological variability in EDx testing in daily practice, this variation was also present in the reference values used. Methodological aspects of the actual EDx study did not always match with methodology of the applied reference values. As amplitudes are larger by measuring peak-to-peak compared to baseline-to-peak, using baseline-to-peak reference values while amplitudes were measured peak-to-peak will underestimate low amplitudes. As low motor amplitudes are necessary in axonal EDx subtyping, the incorrect application of reference values could have led to an underestimation of axonal GBS. A substantial proportion of centers did not provide methodological data from their reference values.

4.3. Reference values

Differences in reference values complicate the comparison of NCS results in multicenter studies such as IGOS. Since the GBS EDx criteria for subtypes are exclusively based on motor nerve conduction, the marked range of motor reference values could influence the subtyping. The same conduction velocity would be considered a clear feature of demyelination in one center, whilst it was completely normal in another. The variability in sensory reference values used in practice could influence the evaluation of sensory nerve involvement and sural sparing pattern, according to the various definitions (Hiew and Rajabally, 2016). Also, some clinicians did not use a defined set of reference values which complicates subtyping further. Although the mean reference values for motor and sensory NCS were reasonable, a few outliers were responsible for the marked variability. The outlier reference values all came from locally collected (adopted) reference value sets. A detailed description on how local reference values were gathered by centers in the past, was frequently lacking and also beyond the scope of this paper. Factors that were likely to be attributable for these differences were differences in age, number of cases used for reference value collection, gender, health status, height, and machine (filter) settings.

5. Limitations

Although this study contains the largest EDx cohort in GBS patients, the study has several limitations. First, because these EDx data were collected in centers participating in IGOS, we are uncertain as to how widespread the issues about variability raised in this paper are. As participating centers were mostly specialized academic centers, variability in non-specialized centers is likely to be even more extended. Second, due to participation of specialized neuromuscular centers in IGOS, there has been a selection bias towards the more severely diseased GBS patients as was shown by Al-Hakem et al. (2019). However, this study showed that the extensiveness of NCS was not related to severity of GBS, indicating that differences in EDx protocol are better explained by local practice in conducting NCS. Testing in complex intensive care settings might have influenced individual studies. Third, the IGOS recommendation to perform EDx in accordance to a fixed protocol, although optional, will have lessened variability in EDx protocol. Despite this influence, EDx protocol variability is large and probably underestimated. Fourth, several important aspects of EDx including limb temperature, EDx inter-evaluator variation, variability between neurophysiologists within the same center, machine settings and NCS electrode and marker placement policy were not standardized or part of the analysis. Fifth, the potential impact of the presented variability on EDx subtype classification was not part of the current study, but will be subject to a future analysis.

6. Conclusions

This study shows an extensive variation in the current clinical practice of EDx diagnostic work-up in patients with GBS across the regions. Given the current variation in protocol, methodology, and reference values, there is a need for standardization of EDx in future multinational studies. In GBS multicenter trials as in other multi-center neuropathy trials, the following should be done: (1) standardize the EDx study protocol for GBS, including sensory nerve and motor nerve conductions, EMG and machine settings, (2) implement training sessions to ensure uniformity, (3) use a uniform set of reference values based on identical methodology, and (4) standardize the EDx report. If GBS EDx subtyping is done, then one of the published criteria sets should be used.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A

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