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Dynamics of Nerve Conduction Studies in Patients With Guillain–Barré Syndrome

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ABSTRACT

Introduction/Aims: The value of electrodiagnostic subtyping of Guillain–Barré syndrome (GBS) is still debated. This study aimed to determine the diagnostic yield, timing, and changes of the electrodiagnostic subtyping in patients with GBS in serial nerve conduction studies (NCS).

Methods: Data were extracted from the International GBS Outcome Study (IGOS) database. Serial NCS were available for 469 patients. For the serial NCS analysis, the intervals between the first and second study were defined as ≥7 and ≤42 days after onset of weakness. All NCS were classified according to the electrodiagnostic criteria sets of Hadden et al. and Rajabally et al.

Results: In NCS conducted within 3 days of onset of weakness, an axonal or demyelinating subtype could be demonstrated in 58.4% (Hadden) and 52.1% (Rajabally). NCS performed at a later timepoint demonstrated a similar yield of axonal and demyelinating subtypes. In patients with motor-sensory and motor GBS, the electrodiagnostic subtype changed on serial NCS in 37.8% (Hadden) and 44.7% (Rajabally). As the subtypes changed in multiple and opposite directions, the total proportion of axonal and demyelinating subtypes remained stable across time points. In patients with motor GBS, both axonal and demyelinating subtypes were found.

Discussion: This study demonstrates the highly dynamic disease course of GBS. The role of NCS remains to support the clinical diagnosis of GBS and should be performed as quickly as possible after onset of weakness. If these early NCS are non-diagnostic, repeating the study should be considered. Electrodiagnostic subtyping offers no additional value.

1 | Introduction

According to the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guidelines on the diagnosis and treatment of Guillain–Barré syndrome (GBS), nerve conduction studies (NCS) are recommended to increase the diagnostic certainty in patients clinically suspected of GBS [1]. A second NCS is advised in case the first study is normal, as abnormalities may take weeks to develop, but the value of a second study is still debated. Previous studies on serial NCS in GBS have shown

Abbreviations: dCMAP, distal compound muscle action potential; DML, distal motor latency; EAN/PNS, European Academy of Neurology/Peripheral Nerve Society; GBS, Guillain–Barré syndrome; GBS-DS, Guillain–Barré syndrome disability scale; IGOS, International GBS Outcome Study; IQR, interquartile range; IVIG, intravenous immunoglobulin; MCV, motor conduction velocity; MFS, Miller Fisher syndrome; NCS, nerve conduction studies; PCB, pharyngeal-cervical-brachial; pCMAP, proximal compound muscle action potential.

For affiliations refer to page 9.

conflicting results on the impact of repeated testing on electrodiagnostic subtyping, likely reflecting differences in electrodiagnostic criteria, timing of initial and follow-up NCS, and the small sample sizes of these studies [2–5].

GBS is an acute and monophasic disease and the early phase is considered to be highly dynamic. Initially, there is a rapid clinical progression, in which patients may develop a limb paralysis and respiratory insufficiency within days after onset. Patients also frequently reach nadir and start to improve already in the 2 weeks after their first symptoms. Both serum anti-ganglioside antibody levels and autopsy findings in GBS vary with timing, and the distribution of nerve involvement in GBS is heterogeneous, as all levels and sites of the peripheral nerve may be affected [6–8]. Considering these variable and rapid changes in the early disease course of GBS, the timing of NCS likely influences the electrodiagnostic results.

Several studies have investigated the electrodiagnostic results in relation to the timing of the NCS, in order to clarify the disease dynamics and to identify early electrodiagnostic markers of GBS. In 1989, Albers and Kelly described an evolving picture with demyelinating features becoming more apparent with time, especially after 2 weeks [8]. Additional studies were conducted focusing on the NCS results in the earlier stage of disease [9–13]. Although mild abnormalities were often encountered, NCS performed within 7 days after disease onset failed to fulfill the electrodiagnostic criteria for GBS in 35%–91%, depending on the criteria sets used [12]. Most previous studies were based on relatively small and selected cohorts of patients, which could have biased the results.

This study aimed to investigate the effect of timing on the diagnostic yield of NCS and on electrodiagnostic subtyping in patients with GBS, and relate these findings to clinical variants.

2 | Methods

2.1 | 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 [14]. Inclusion criteria were fulfillment 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 2 motor nerves examined, and patients presenting within 2 weeks after onset of GBS-related symptoms. Only patients with serial NCS studies were enrolled in this study. For the parts of the analysis using second NCS studies, patients were excluded if the interval between the first and second studies was outside the predefined range of 7–42 days. Other exclusion criteria were study protocol violation, other diagnosis, and insufficient clinical and electrodiagnostic data. Local investigators were free to conduct NCS according to their standards, but it was recommended to perform studies twice: the first within 7 days, and the second 4 weeks after registration in IGOS. For motor conduction, the IGOS protocol recommended measuring unilaterally the median, ulnar, peroneal (fibular), and tibial nerves including F waves (recording over the abductor pollicis brevis, abductor digiti minimi, extensor digitorum brevis, and abductor hallucis muscles, respectively). Limb temperature control was performed per local standards. The study report was uploaded to the online IGOS database. A quality check of the study reports was performed, focusing on outliers and ensuring that the results presented in the report (tables) were consistent with the corresponding figures and marker positions. Inconsistencies were resolved, and if not possible, they were considered missing data. The analysis examining the effect of timing and repeating NCS on electrodiagnostic subtyping was stratified by the clinical subtypes.

2.2 | Electrodiagnostic Data

The first and second NCS studies were both classified according to the criteria published by Hadden et al. and by Rajabally et al. [15, 16] (Table S1). We have used both electrodiagnostic criteria, as both sets are among the ones most frequently used in GBS research. Using both sets also provides an opportunity to assess whether outcomes are independent of the electrodiagnostic criteria. Results (e.g., proportions and percentages) are presented for both the Hadden and the Rajabally criteria, separated by a forward slash (/), to enhance readability. Each NCS parameter was expressed as a percentage of the upper or lower limit of normal. Local reference values were used, if available. If reference values were lacking or not concordant with the NCS methodology used, the previously published reference values collected from the other participating centers in IGOS were used, in accordance with the local methodology used (Table S2 [17]). 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 included. The p/dCMAP ratio from the tibial nerve was excluded according to Rajabally subtyping. Because the electrodiagnostic criteria proposed by Hadden et al. and Rajabally et al. rely on motor nerve conduction, sensory studies were excluded from this study.

2.3 | 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. SPSS version 28 (IBM, Armonk, NY) and RStudio (R Version 4.2.3) were used for the analysis. Chi-squared testing was done in case of categorical data. The Kruskal–Wallis test was applied to assess the differences in GBS disability scale (GBS-DS) and electrodiagnostic subtyping between the groups based on the timing of first NCS. A two-sided p-value < 0.05 was considered to be statistically significant.

3 | Results

From the IGOS-1500 cohort data, data from smaller cohorts of 469, 393, and 331 patients were analyzed (Figure 1).

The first NCS ($N = 469$) confirmed the diagnosis of a polyneuropathy (subtypes axonal, demyelinating, inexcitable) in 62.0%/58.2% (Hadden/Rajabally criteria). Studies were equivocal in 29.6%/33.7% and normal in 8.3%/8.1%. The characteristics of these patients with serial NCS were compared with the patients with only a single NCS (Table 1). The group with serial NCS had a significantly higher age, and the lower proportion of patients under 18 years of age does not fully account for this difference. The serial NCS group also demonstrated an earlier timing of the first NCS after the onset of weakness, as well as a lower GBS disability score. Also, the serial NCS group had a higher proportion of equivocal and normal studies compared to the single NCS group. NCS was more frequently repeated in Europe compared to Asia and North America. Since patients from Asia were underrepresented in the study cohort, the clinical variant of motor GBS was significantly less frequently observed.

The median timing of the first study (7 days) and the interval between the first and second study (24 days) was concordant with the IGOS protocol, although the recommendations were not obligatory. All age categories, clinical variants, and continents were represented, with a dominant presence of middle-aged men with intermediate disease severity (GBS disability median score 3) and the motor-sensory form of GBS.

3.1 | Electrodiagnostic Subtyping and Timing

In 469 patients data on both electrodiagnostic subtyping and the timing of the first study were available (Figure 1). We categorized the timing of the first studies into four groups, relative

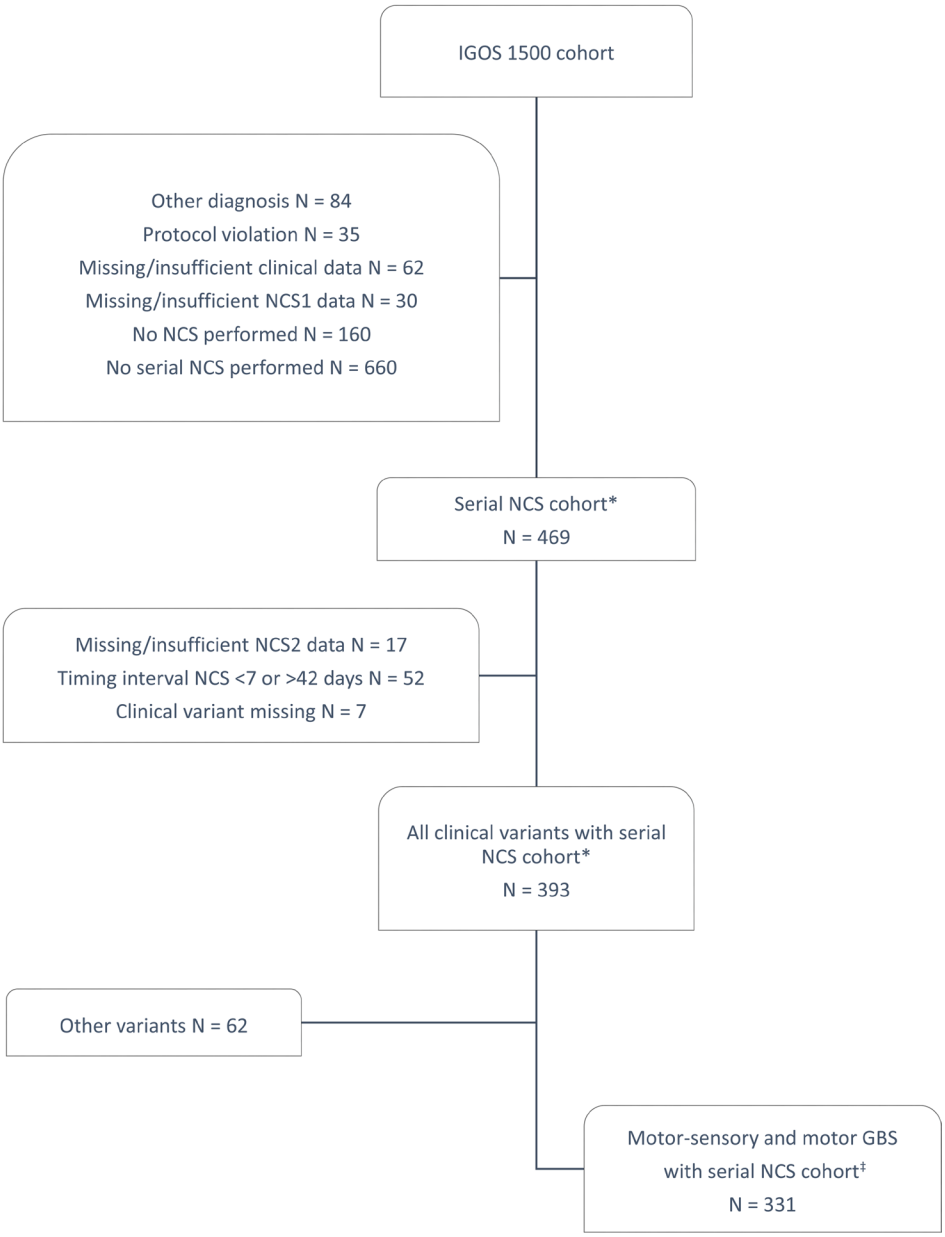

FIGURE 1 | Flowchart and selection of patients.

TABLE 1 | Patient characteristics of the study group with serial NCS, compared to the group with a single NCS.

	Serial NCS group $N=469$	Single NCS group $N=660$	p
Demography and clinical characteristics			
Age median years (IQR, full range)	53 (39–66, 0–86)	50 (31–64, 1–90)	<0.01
Age below 18 years (%)	15 (3.2)	52 (7.9)	<0.01
Male/female (ratio)	286/183 (1.6)	404/256 (1.6)	0.94
Continent (%)			<0.01
Europe	332 (70.8)	334 (50.6)	<0.01
Asia	74 (15.8)	175 (26.5)	<0.01
North America	38 (8.1)	103 (15.6)	<0.01
South America	19 (4.1)	19 (2.9)	0.28
Africa	4 (0.9)	22 (3.3)	<0.01
Australia	2 (0.4)	7 (1.1)	0.32
Clinical variant (%)			0.04
Motor-sensory	291 (62.0)	376 (57.0)	0.17
Motor	92 (19.6)	165 (25.0)	0.02
Miller Fisher syndrome	33 (7.0)	29 (4.4)	0.07
Miller Fisher overlap syndrome	27 (5.8)	33 (5.0)	0.63
Ataxic	8 (1.7)	11 (1.7)	0.10
Pharyngo-cervical-brachial	7 (1.5)	7 (1.1)	0.54
Pure sensory	3 (0.6)	10 (1.5)	0.17
Other	0	6 (0.9)	0.04
Missing	8 (1.7)	23 (3.5)	0.07
Timing of NCS from onset of weakness[a] (IQR, full range)			
1st NCS	7 (4–10, 0–35)	8 (5–12, 0–129)	<0.01
2nd NCS	31 (21–38, 4–400)	NA	NA
Interval between 1st–2nd NCS	24 (14–29, 1–393)	NA	NA
NCS subtyping (% Hadden/Rajabally)			<0.01/<0.01
Axonal	7.7/29.4	11.2/30.5	0.05/0.71
Demyelinating	52.9/27.3	59.4/36.2	0.03/<0.01
Equivocal	29.6/33.7	20.3/24.1	<0.01/<0.01
Inexcitable	1.5/1.5	4.1/4.1	0.01/0.01
Normal	8.3/8.1	5.0/5.2	0.03/0.05
GBS disability score at first NCS (%)			<0.01
0	0	2 (0.3)	0.51
1	18 (3.8)	26 (3.9)	0.92
2	124 (26.4)	125 (18.9)	<0.01
3	107 (22.8)	105 (15.9)	<0.01
4	184 (39.2)	328 (49.7)	<0.01
5	36 (7.7)	70 (10.6)	0.09

(Continues)

TABLE 1 | (Continued)

	Serial NCS group $N=469$	Single NCS group $N=660$	p
GBS-DS median (IQR)	3.0 (2.0–4.0)	4.0 (3.0–4.0)	<0.01
Treatment (%)			
No	39 (8.3)	142 (21.5)	<0.01
Yes	430 (91.7)	518 (78.5)	<0.01
IVIG	391 (83.4)	450 (68.2)	<0.01
Plasma exchange	36 (7.7)	64 (9.7)	0.24
Prednisolone	1 (0.2)	1 (0.2)	NA
Dexamethasone	0	1 (0.2)	NA
IVIG and subcutaneous Ig	1 (0.2)	1 (0.2)	NA
Cyclophosphamide	1 (0.2)	1 (0.2)	NA

Abbreviations: Ig, immunoglobulin; IQR, interquartile range; IVIG, intravenous immunoglobulin; NA, not applicable; NCS, nerve conduction studies.
[a]Timing of NCS in days as medians (IQR, full range).

to the onset of GBS-related symptoms: ≤3 days, 4–7 days, 8–14 days, and >14 days (case with latest timing of 35 days), see Figure 2. Patients with early NCS (≤7 days vs. >7 days) were affected more severely (median GBS-DS 4.0 vs. 3.0), but this was not significant ($p=0.06$). Overall, electrodiagnostic subtyping by either Hadden or Rajabally criteria was not significantly influenced by the timing of the NCS. In studies performed within the first 3 days of onset, a substantial proportion of patients could already be classified as axonal or demyelinating, both according to the criteria of Hadden and Rajabally (axonal: 4.2%/31.3%; demyelinating: 54.2%/20.8%). After 2 weeks, the proportion with a demyelinating subtype increased (77.1%/56.3%) and the proportion with an axonal subtype decreased (2.1%/12.5%), but this was not significant ($p=0.06$). So, the proportion of axonal and demyelinating subtypes did not significantly differ between early and late NCS. Inexcitable studies were scarce, and only observed in studies performed after 3 days of onset, i.e., 1.1% of studies between 4–7 days and 2.5% between 8–14 days. Serial studies showed that even in later stages NCS might change into or persist as inexcitable (Figure S1), with 14 of 16 inexcitable second NCS performed between 14–66 days after onset of symptoms. Presence of an equivocal study ranged from 30.6%/36.7% during first 3 days and from 30.8%/34.1% for the first 2 weeks. Despite the progressive nature of GBS in the first weeks, a normal or equivocal initial study was still observed in a subset of patients undergoing late testing (> 14–35 days), accounting for 20.9%/31.3%.

Since early NCS are sometimes considered non-diagnostic, we investigated whether the timing of the first NCS influenced the likelihood of subtype reclassification in the follow-up studies. Accordingly, this would be reflected in a higher frequency of subtype changes following early NCS compared to those performed later in the disease course. However, our findings did not support this as subtype changes were not related to the timing of the initial NCS. In studies performed ≤3 days, subtype changes occurred in 40.0%/42.9%. For studies conducted between 4–7 days, this was 43.1%/45.8%, while in those performed between 8–14 days, this occurred in 33.7%/37.7%.

3.2 | Electrodiagnostic Subtyping in Clinical Variants

For this analysis, 393 of 469 cases were eligible (Figure 1), with known clinical variants, subtyping of first and second NCS, and with a predefined interval between the first and second study of 7–42 days. See Table 2 for an overview of the electrodiagnostic subtyping in all forms and clinical variants of GBS. In patients with motor-sensory GBS, the electrodiagnostic subtype changed more often if classified according to Rajabally compared to Hadden ($p=0.01$), but in other variants, there were no significant differences. In literature, NCS studies in motor GBS are often assumed to reflect axonal pathology. In our cohort, patients with motor GBS exhibited demyelinating subtypes in the initial and follow-up studies, and a consistent demyelinating classification across both studies was observed in 21.8%/5.1% of cases. Patients with the Miller Fisher syndrome (MFS) and MFS-GBS overlap syndrome mostly showed normal or equivocal studies. In addition, axonal and demyelinating studies were present in MFS, MFS-GBS overlap syndrome, and ataxic variants, irrespective of the criteria used.

3.3 | Electrodiagnostic Subtyping at First and Second NCS in Motor-Sensory and Motor GBS

Finally, we focused on electrodiagnostic subtype changes in serial NCS in the subset of 331 patients with only the motor-sensory and motor form of GBS (Figure 1). The interval between the first and second NCS was median 24 days and varied from 7–42 days. The electrodiagnostic subtype classification based on the first and second NCS and their changes are presented in Figure 3. Among patients with motor-sensory and motor GBS, a change in the electrodiagnostic subtype was observed in 37.8%/44.7%. The top 3 changes in the electrodiagnostic subtyping by using the Hadden criteria were (1) demyelinating to equivocal (24.0% of all changes), (2) equivocal to demyelinating (23.2%) and (3) demyelinating to axonal/inexcitable (17.6%). These changes accounted for 64.8% of all changes between first and second NCS. Top 3 changes by using the Rajabally criteria were (1) axonal to equivocal

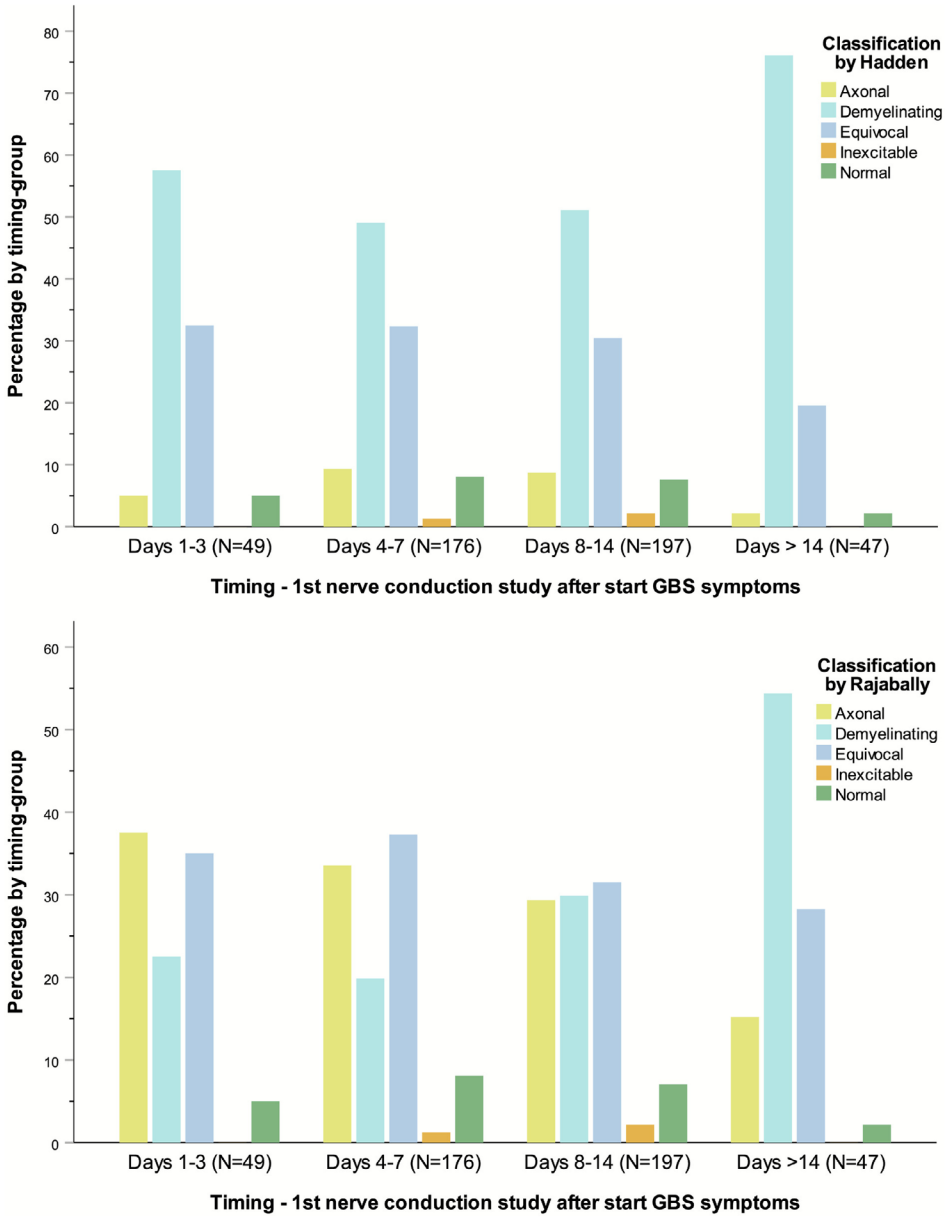

FIGURE 2 | Timing first study versus classification by Hadden (A) and Rajabally (B) criteria.

(19.6%), (2) axonal to demyelinating (15.5%) and (3) equivocal to demyelinating (13.5%). Together these 3 changes accounted for 48.6% of all changes. In 37.0%/36.9% of patients whose initial study did not meet the polyneuropathy criteria, due to normal or equivocal findings, the second study did reveal a polyneuropathy (axonal, demyelinating, or inexcitable), highlighting the additional value of follow-up studies in initially inconclusive cases. Nevertheless, in 19.0%/21.1% of cases both initial and follow-up studies remained normal or equivocal, underlining the existence of a patient subgroup where electrodiagnostic testing remained inconclusive, even after repeated evaluation. Patients with motor-sensory or motor GBS who exhibited repeatedly normal or equivocal studies demonstrate a relatively mild clinical course, as reflected by a median GBS disability score of 2 (at 4 weeks) and improving to 1 (at 6 months), irrespective of the electrodiagnostic criteria used (Table 3).

4 | Discussion

This study showed that in serial NCS, the subtype classification in individual patients often changed, reflecting the highly dynamic disease course in the early stage of GBS. The changes in subtype occurred in multiple and opposite directions, highly varied between patients and were observed in the subtype criteria of both Hadden and Rajabally. Overall, the total proportion of axonal and demyelinating subtypes at group level remained stable across time points.

There is controversy on the optimal timing of NCS for confirmation of the diagnosis and for defining the electrodiagnostic subtype of GBS. Early support of the diagnosis of GBS is warranted for the further management, and therefore performing NCS as early as possible may be advocated [13]. On the other hand, several smaller studies have suggested that

TABLE 2 | Electrodiagnostic subtyping of 1st and 2nd study and frequency of subtype changes, according to Hadden and Rajabally criteria, in different GBS clinical subtypes.

	Clinical subtype						
	Motor-sensory (*N* = 253)	**Motor (*N* = 78)**	**MFS (*N* = 27)**	**MFS-GBS overlap (*N* = 20)**	**Ataxic (*N* = 7)**	**PCB (*N* = 6)**	**Pure sensory (*N* = 2)**
Hadden 1st study							
Axonal	12	14	1	2	0	0	0
Demyelinating	162	38	1	3	3	3	0
Equivocal	67	21	17	8	3	2	1
Inexcitable	2	3	0	1	0	0	0
Normal	10	2	8	6	1	1	1
Hadden 2nd study							
Axonal	12	15	0	2	1	0	0
Demyelinating	161	25	2	1	2	3	0
Equivocal	60	30	14	10	3	2	1
Inexcitable	10	4	0	1	0	0	0
Normal	10	4	11	6	1	1	1
Rajabally 1st study							
Axonal	68	39	2	3	2	1	0
Demyelinating	93	15	0	0	2	2	0
Equivocal	81	19	17	10	2	2	1
Inexcitable	2	3	0	1	0	0	0
Normal	9	2	8	6	1	1	1
Rajabally 2nd study							
Axonal	48	33	2	3	1	1	0
Demyelinating	105	15	1	1	1	1	0
Equivocal	78	22	14	10	4	3	1
Inexcitable	10	4	0	1	0	0	0
Normal	12	4	10	5	1	1	1
Electrodiagnostic subtype change *N* (%)							
Hadden	82 (32.4%)	43 (55.1%)	7 (25.9%)	6 (30.0%)	4 (57.1%)	2 (33.3%)	0 (0%)
Rajabally	105 (41.5%)	43 (55.1%)	5 (18.5%)	4 (20.0%)	4 (57.1%)	1 (16.7%)	0 (0%)

Abbreviations: GBS-MFS, Guillain–Barré syndrome—Miller Fisher Overlap syndrome; MFS, Miller Fisher syndrome; PCB, pharyngeal-cervical-brachial variant.

early NCS may not show sufficient diagnostic potential [8, 10]. To overcome this dilemma, it has been proposed to postpone or repeat NCS after 2 weeks, or to revise the electrodiagnostic criteria to increase their sensitivity [12]. Despite this, the recently updated EAN/PNS guideline does not include recommendations regarding the timing of NCS. In the current study, we showed that NCS conducted within the very early stages of GBS (≤ 3 days) could already demonstrate a polyneuropathy on NCS in the majority of patients, and the timing of NCS does not increase the diagnostic yield, although the subtype may change. Yet, in individual patients, a repeat study may be considered if NCS are non-diagnostic, as 37% of these patients showed evidence of a polyneuropathy on the second study. This finding is in line with the "good practice point" in the EAN/PNS GBS guideline about repeating NCS in these patients [1]. Some patients show abnormalities in early NCS that normalize on repeated testing, further indicating that postponing NCS does not necessarily improve the diagnostic yield.

The subtype classification was influenced by the set of diagnostic criteria used. In the current study, classification according to the Hadden criteria resulted in a higher frequency of the

FIGURE 3 | First and second nerve conduction studies in motor-sensory and motor GBS ($N = 331$), classified according to the criteria of Hadden et al. (A) and Rajabally et al. (B).

TABLE 3 | First and second nerve conduction studies in motor-sensory and motor GBS ($N = 331$), classified according to the criteria of Hadden et al. (A) and Rajabally et al. (B).

Hadden/Rajabally criteria		NCS2					
		Axonal	**Demyelinating**	**Equivocal**	**Inexcitable**	**Normal**	**Total**
NCS1	Axonal	7/50	9/23	8/29	1/4	1/1	26/107
	Demyelinating	11/12	146/75	30/17	11/4	2/0	200/108
	Equivocal	7/17	29/20	46/50	0/4	6/9	88/100
	Inexcitable	1/1	2/2	0/0	2/2	0/0	5/5
	Normal	1/1	0/0	6/4	0/0	5/6	12/11
	Total	27/81	186/120	90/100	14/14	14/16	331

Note: Exact numbers belonging to Figure 3.

demyelinating subtype, while the Rajabally criteria resulted in more frequent axonal and equivocal subtypes, in agreement with previous studies [4, 18, 19]. The finding that the electrodiagnostic subtypes are volatile when assessed serially further adds to the complexity of classifying GBS in distinct electrophysiological subtypes.

Previous studies have reported a strong association between the motor form of GBS and the axonal electrodiagnostic subtype [20, 21]. In the few reports on patients with motor GBS presenting with initial demyelinating features, these often disappeared on follow-up evaluations [21]. In contrast, the current study demonstrates that motor GBS encompasses both axonal and demyelinating electrodiagnostic subtypes, irrespective of the electrodiagnostic criteria used. Consequently, the current study supports the existence of an acute, motor neuropathy of the demyelinating subtype. On the other hand, pathologically confirmed proximal segmental demyelination was described in a case of motor GBS with an axonal subtype [22]. Apparently, the electrodiagnostic subtype cannot be used as a comprehensive substrate for the underlying disease processes. Further studies are required to better define the clinical manifestation of GBS in relation to the electrodiagnostic findings, including investigations of preceding infections, antibodies, and other biomarkers of disease.

Our study has several limitations. As indicated, our study and others are hampered by the lack of a gold standard, and studies on nerve pathology are scarce [7]. Therefore, the accuracy of NCS in assessing pathological processes such as axonal degeneration, axonal dysfunction, demyelination, and proximal

nerve ischemic injury cannot be determined. This is further complicated by concomitant pathological processes, often presenting with a mixed picture, such as secondary axonal degeneration in demyelinating subtypes and a decline in nerve conduction velocities in axonal degeneration and dysfunction. This may contribute to the subtype changes in various directions between the initial and follow-up studies. Therefore, the dichotomous view of axonal degeneration versus demyelination is no longer tenable, and several other factors need to be considered and further refined, such as specific markers of axonal degeneration and antibodies. Second, the participating centers in IGOS are mostly specialized neuromuscular centers and are probably biased toward the more severely affected cases [23]. This subgroup of patients with serial NCS was slightly different from the other patients in IGOS with only a single NCS. This group of patients with serial NCS was older and less severely affected, as indicated by the lower GBS disability scores and more frequently showed equivocal and normal NCS results. The performance of a second NCS may have been influenced by the lack of a clear electrodiagnostic category from the first study. However, this study has a firm representation of the whole spectrum of GBS patients, including those with lower GBS disability scores. In a less selected GBS cohort, a smaller proportion of severely diseased patients might lower the diagnostic yield of the NCS in the early phase. Third, although IGOS recommended data collection of NCS according to a fixed protocol, this was optional. Nevertheless, in this serial cohort, the recommendations regarding the timing of the first and second studies were strictly followed. Serial studies were more often performed in Europe, compared to Asia and North-America. This might favor the proportion of demyelinating subtype in this serial NCS cohort, as this is the dominant subtype in Europe. Reproducing these findings in a future standardized study with a fixed set of reference values may help to overcome these limitations.

This study revealed that the diagnostic yield of axonal and demyelinating subtypes in early and later NCS was similar. The electrodiagnostic subtyping is influenced by both the timing and the electrodiagnostic criteria applied, and frequently changed in multiple directions upon serial testing. Therefore, we believe that a "final" electrodiagnostic subtype cannot be determined, a conclusion also reached by others [3]. Rather, an electrodiagnostic subtype can be determined at a specific time point in the disease course, but this does not fully represent the ongoing pathology. This may explain why the relationship between clinical variants and electrodiagnostic subtypes remains diverse. Likely, the electrodiagnostic subtype at one point in time, especially early, must be combined with many other factors such as antibodies and preceding infection to get a full picture of GBS. The aim of NCS in clinical care remains to support the clinical diagnosis of GBS, and at present, electrodiagnostic subtyping offers no additional value.

Author Contributions

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Ethics Statement

We 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.

Conflicts of Interest

Dr. Dimachkie has received grants from Alexion/AstraZeneca, Alnylam Pharmaceuticals, Amicus, Argenx, Bristol-Myers Squibb, Catalyst, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, The Myositis Association, and UCB Biopharma/RaPharma. The remaining authors declare no conflicts of interest.

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. **Figure S1:** Electrodiagnostic subtyping of the second study related to interval between first and second study. All clinical variants with serial NCS cohort ($N = 393$). Subtyping of second study if first study was (A) demyelinating according to Hadden (left, $N = 210$) and Rajabally (right, $N = 112$), (B) axonal according to Hadden (left, $N = 29$) and Rajabally (right, $N = 115$) and (C) equivocal according to Hadden (left, $N = 119$) and Rajabally (right, $N = 132$). **Table S1:** dCMAP = distal compound muscle action potential; DML = distal motor latency; LLN = lower limit of normal; MCV = motor conduction velocity; pCMAP = proximal compound muscle action potential; ULN = upper limit of normal. **Table S2:** m. APB = abductor pollicis brevis muscle; m. ADM: abductor digiti minimi muscle; m. EDB = extensor digitorum brevis muscle; m. AH = abductor hallucis muscle; ms = milliseconds; cm = centimeters; mV = millivolt; m/s = meter per second; *non-existing reference values because of non-physiologic distance.