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Does Serial Nerve Conduction Studies with Rajabally Criteria Improve Classification in Guillain-Barré Syndrome?

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Abstract

Background: Guillain-Barré syndrome (GBS) is an acute immune-mediated disorder of peripheral nervous system, mostly triggered by infections or other antecedent events. This study aimed to assess the electrophysiological profile of patients with GBS using serial nerve conduction studies (NCS) and compare two different diagnostic criteria.

Methods: Thirty patients with GBS were enrolled over 18 months. Neurological and disability assessment along with necessary blood and cerebrospinal fluid evaluation was done. NCS was done at admission, day 15, 30 and 90. Patients were classified using Hadden's and Rajabally's criteria and were evaluated for changes in electrophysiological patterns on serial NCS.

Results: At admission, 76.67% had Hughes disability score ≥4. According to Hadden's criteria across time (at admission, on day 15, day 30 and day 90), 58.62%, 52%, 63.64% and 38.1% were classified as primary demyelinating type, while 20.69%, 36%, 22.73% and 28.57% were classified as primary axonal variant, respectively. On the other hand, with Rajabally's criteria, 48.28%, 48%, 40.9% and 33.33% were classified as primary demyelinating, while 48.28%, 44%, 45.45% and 42.86%, respectively were classified as primary axonal variant across the similar timeline.

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Conclusion: Rajabally's criteria is more sensitive for diagnosing primary axonal and more specific for primary demyelinating subtype in early GBS, thereby impacting early treatment decisions and prognosis. Serial NCS further helps classify electrophysiological pattern more accurately, especially with ambiguous initial NCS as well in reversible conduction failure.

Keywords: Guillain-Barré Syndrome; Serial Nerve Conduction Study; Peripheral Neuropathy; Reversible Conduction Failure

Introduction

Guillain-Barré syndrome (GBS) is an acute immune mediated disorder of peripheral nervous system, most commonly triggered by infections or other antecedent events [1]. It affects 0.9 to 2/100,000 persons in a year, with a worldwide distribution [2]. The subtypes of GBS have different incidence rates in different parts of the world. In the Indian context, the incidence of AIDP and AMAN is variable although AMAN is more common in younger patients [3]. There are various electrodiagnostic criteria for classification of GBS. The Hadden's criteria was described in 1998, and it was most commonly utilized for last 2 decades [4,5]. In 2015, Rajabally and colleagues proposed a criteria with more conservative cut offs for demyelinating parameters [6]. While there are a number of electrophysiological criteria used till date for GBS, Hadden's criteria being most commonly used, there is variable sensitivity and specificity for different GBS subtypes [5-8]. The different cutoffs leads to varying degrees of misclassification into axonal and demyelination while many patients remain unclassifiable. As recent literature has showed that serial nerve conduction studies (NCS) at different intervals from onset of GBS helps better classification, reversible conduction failure (RCF) was not previously addressed by most criteria [8]. Further, the lack of a gold standard for a definitive classification and comparison in GBS is an inherent fallacy of all such attempts at subtyping GBS. Thus, the evolution in the understanding of GBS pathophysiology extending to further subtyping underscores the importance of utilizing a conglomerate of clinical, electrophysiological and autoantibody markers for final diagnosis.

Amongst the recent criteria, Rajabally's criteria seems to be more robust and has been reported to be more unequivocal in classification in initial study in GBS [6]. We hypothesized the current study to clarify the utility of the Hadden's and Rajabally's criteria in electrophysiological diagnosis of GBS at baseline and compare the evolution of changes on serial NCS.

Methods

This prospective observational cohort study was conducted at a tertiary care centre in patients of GBS recruited over an 18-month period. The ethical clearance certificate was obtained from the Institutional ethics committee (AIIMS/IEC/2019-20/972). Informed written consent was taken from all the study subjects. All patients fulfilling the following criteria were enrolled in the study.

Inclusion Criteria

1. Fulfil the diagnostic criteria for Guillain-Barré syndrome of the National institute of Neurological Disorders and Stroke (NINDS) revised by Asbury and Cornblath (1990) [7].

2. Fulfil the electro diagnostic criteria for diagnosis of various subtypes of Guillain-Barré syndrome by Hadden et al. [5].

3. Presentation within 4 weeks of symptom onset.

4. Inclusion of all males and females >18 years of age, independent of disease severity.

5. Patients with Miller Fisher syndrome and all other variants of Guillain-Barré syndrome, including overlap syndromes.

6. Patients willing to participate in the study and provide written informed consent.

Exclusion Criteria

1. Pregnancy.

2. Known severe allergic reaction to properly matched blood products.

3. Known selective IgA deficiency.

4. Other causes of acute flaccid quadriparesis.

5. Patients not willing to participate in the study.

GBS was diagnosed clinically as areflexic quadriparesis without early bowel and bladder involvement. Both NINDS [7] and Brighton's criteria [9] were used for clinical diagnosis and ascertaining level of certainty. Basic demographic details, clinical profile, neurological examination and evaluation with disability scales was done. Blood workup and cerebrospinal fluid evaluation to rule out GBS mimics was done. Patients were classified into different grades according to Hughes classification and MRC disability scale at entry time, day 15, day 30 and day 90. NCS was done at admission and follow up on day 15, day 30 and day 90. NCS were performed using standard techniques on the 4-channel electromyography system of Nicolet by Natus Inc. on all 4 upper and lower extremities; motor NCS was estimated in median, ulnar, tibial and peroneal nerves, and orthodromic sensory NCS in median, ulnar, and sural nerves. Electrophysiological parameters motor nerves included distal latency (DL), proximal and distal compound muscle action potential (CMAP) amplitude and duration, NC Velocity (NCV), conduction blocks and F-Waves latencies, persistence and chronodispersion; sensory parameters included sensory nerve action potential (SNAP) and sensory NCV were obtained from sensory nerves. Two investigators (AP and SP) analyzed the electrophysiological parameters and electrophysiological classification was done using Hadden's and Rajabally's criteria [5,6]. Changes in electrophysiological patterns on serial NCS were evaluated using both these criteria. Presence of RCF was evaluated in both motor and sensory nerves, on serial electrophysiological studies [8]. RCF was defined as distal CMAP amplitude > 150% of that observed in the first NCS, without increased distal CMAP duration (≤ 120%), or increase of 0.2 or more in the proximal to distal CMAP amplitude ratio compared to initial NCS, without temporal dispersion or improvement of F-wave absence without delayed latencies, in at least two nerves.The data was analyzed using SPSS version 21 software (SPSS Inc., Illinois, and Chicago). Descriptive statistical analysis was mainly used. Whenever needed continuous variables were described with means ± SD.

Results

The study was conducted over 18 months and included 30 patients of GBS. Mean age of patients in the study was 42.97±17.22 years. Majority patients (86.66%) were <60 years with male:female ratio of 5:1. Antecedent events were present in 56.67% patients. Most common antecedent event was upper respiratory tract infections (URTI). The mean interval between onset of antecedent event and symptoms of GBS were 10.875 (±6.07) days [12.25 (±6.54) in patients with URTI; 8.6 (±6.88) in patients with gastroenteritis]. Majority (88.46%) patients achieved nadir within 14 days with mean interval between onset of symptoms and nadir of 9.31(±6.23) days. GBS subtypes noted in this study were AIDP, AMAN, AMSAN, MFS overlap syndrome, paraparetic variant and Bickerstaff brainstem encephalitis. A slight preponderance of AMAN variant [14 (46.67%)] over AIDP [12 (40%)] was noted.

Results of electrophysiological patterns at different intervals have been described in Table 1. Twenty-four (82.76%) patients had clinically normal sensory examination of which, 17 (70.83%) patients had abnormal sensory NCS. At the time of admission, 58.62% of patients were categorized as primary demyelinating (AIDP) pattern according to Hadden's criteria, as compared 20.69% as primary axonal pattern while as per Rajabally's criteria, patients were equally (48.28%) categorized as primary demyelinating (AIDP) and primary axonal pattern. A similar pattern was observed on serial NCS on day 15, 30 and 90, with a greater number of patients categorized as primary demyelinating as per Hadden's criteria, and greater number of patients categorized as primary axonal as per Rajabally's criteria. These findings suggested, Hadden's criteria favored more primary demyelinating category while Rajabally's criteria favored more primary axonal category.

Table 1: Electrophysiological patterns at different intervals

Parameters	Number of Patients N=30 (%)			
Electrophysiological Classification (According to Hadden's criteria)	**Day 0**	**Day 15**	**Day 30**	**Day 90**
Primary Demyelinating	17 (58.62%)	13 (52%)	14 (63.64%)	8 (38.1%)
Primary Axonal	6 (20.69%)	9 (36%)	5 (22.73%)	6 (28.57%)
Inexcitable	4 (13.79%)	2 (8%)	2 (9.09%)	2 (9.52%)
Equivocal	2 (6.9%)	1 (4%)	1 (4.55%)	5 (23.81%)
Normal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	29 (100%)	25 (100%)	22 (100%)	21 (100%)
Electrophysiological Classification (According to Rajabally's criteria)	**Day 0**	**Day 15**	**Day 30**	**Day 90**
Primary Demyelinating	14 (48.28%)	12 (48%)	9 (40.91%)	7 (33.33%)
Primary Axonal	14 (48.28%)	11 (44%)	10 (45.45%)	9 (42.86%)
Equivocal	1 (3.44%)	2 (8%)	3 (13.64%)	4 (19.05%)
Normal	0 (0%)	0 (0%)	0 (0%)	1 (4.76%)
Total	29 (100%)	25 (100%)	22 (100%)	21 (100%)

Table 2: Serial changes in Electrophysiological classification

Change in Electrophysiology Class		Number of Patients N=30 (%)					
		Day 0 to 15	**Day 0 to 30**	**Day 0 to 90**	**Day 15 to 30**	**Day 15 to 90**	**Day 30 to 90**
Hadden's Criteria							
From	**To**						
Demyelinating	Axonal	2(22.22%)	1 (10%)	3 (30%)	0 (0%)	1 (12.5%)	3 (33.33%)
Axonal	Demyelinating	1 (11.11%)	3 (30%)	2 (20%)	3 (100%)	1 (12.5%)	0 (0%)
Demyelinating	Inexcitable	1 (11.11%)	1 (10%)	1 (10%)	0 (0%)	1 (12.5%)	1 (11.11%)
Equivocal	Demyelinating	1 (11.11%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Equivocal	Axonal	1 (11.11%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Demyelinating	Equivocal	1 (11.11%)	1 (10%)	3 (30%)	0 (0%)	3 (37.5%)	3 (33.33%)
Axonal	Equivocal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)	1 (11.11%)
Inexcitable	Axonal	1 (11.11%)	2 (20%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)

Inexcitable	Demyelinating	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (12.5%)	1 (11.11%)
Total		**9 (100%)**	**10(100%)**	**10(100%)**	**3 (100%)**	**8 (100%)**	**9 (100%)**
Rajabally's Criteria		**Number of Patients N=30 (%)**					
From	**To**						
Demyelinating	Axonal	3 (50%)	4 (50%)	5 (41.67%)	1 (33.33%)	3 (33.33%)	2 (33.33%)
Axonal	Demyelinating	2 (33.33%)	2 (25%)	2 (16.67%)	1 (33.33%)	2 (22.22%)	1 (16.67%)
Axonal	Equivocal	1 (16.67%)	2 (25%)	3 (25%)	0 (0%)	1 (11.11%)	1 (16.67%)
Demyelinating	Equivocal	0 (0%)	0 (0%)	1 (8.33%)	1 (33.33%)	2 (22.22%)	1 (16.67%)
Equivocal	Normal	0 (0%)	0 (0%)	1 (8.33%)	0 (0%)	1 (11.11%)	1 (16.67%)
Total		**6 (100%)**	**8 (100%)**	**12 (100%)**	**3 (100%)**	**9 (100%)**	**6 (100%)**

The serial changes in electrophysiological classification at different intervals by using these two criteria are shown in Table 2. The comparative analysis suggested that Rajabally's criteria was able to provide a clearer and more definitive classification with a smaller number of patients showing changes in electrophysiological classification over time.

Using Hadden's criteria in serial NCS, we could identify total 3 patients with RCF. Out of these 3 patients we could pick up RCF reversal in 2 patients on day 15 and for remaining one patient on day 90. However, utilizing Rajabally's criteria in serial NCS, we could identify 4 patients with RCF. Out of these 4 patients, we could identify RCF reversal in 2 patients on day 15, for one patient on day 30 and remaining one patient on day 90. For first 2 patients we could identify RCF on day 15 using both these criteria. For 3rd patient we could identify RCF on day 90 by Hadden's criteria, while using Rajabally's criteria in the same patient we could identify RCF on day 30. In the 4th patient we could not pick up RCF using Hadden's criteria, while using Rajabally's criteria we could pick up RCF on day 90.) Thus, compared to Hadden's criteria, Rajabally's criteria helped to identify RCF earlier.

Discussion

This prospective study attempted to look at the clinical and laboratory characteristics of various subtypes of GBS, classify patients by electrophysiological studies using Hadden's and Rajabally's criteria and compare them. Serial NCS were done to look for patterns of recovery and changes in electrophysiological classification over time. The relative diagnostic variability of the two criteria was demonstrated and neurologists and neurophysiologists should be aware of these challenges. Overall, the study demonstrated that compared to Hadden's criteria, Rajabally's criteria was more robust and capable of a more definitive electrophysiological classification in the initial study in more patients without temporal category changes. Axonal GBS was more easily classified early, specially with RCF, compared with Hadden's criteria that favored demyelinating category. While initial clinical features and antiganglioside antibody profiles are usually similar in GBS with and without RCF, typical AIDP may differ. Therefore, the prognostication and management protocols can be tailored by a better classification and serial NCS though a head to head comparison of treatment response was not undertaken by the authors.

There are various electrodiagnostic criteria for classification of GBS. The electrophysiological classification in

the present study was done by using both Hadden's and Rajabally's criteria at admission and follow up on day 15, day 30 and day 90 to see if there were significant variations in the classification across criteria [5,6]. This was based on recent studies that showed that the Hadden criteria may underdiagnose the axonal subtype of GBS leading to recent attempts to modify the electrodiagnostic criteria [4,6,8]. As noted in Table 1, the most prevailing electrophysiological class at admission in our study was primary demyelinating according to Hadden's criteria. However, on using Rajabally's criteria, patients were equally distributed between both the categories. It was also interesting to note that we were able to pick up a greater number of patients with sub-clinical sensory abnormalities with help of sensory NCS. The addition of sensory NCS to criteria needs to be probed in later editions of electrophysiological classifications [4,8].

There have been previous attempts to understand the utility of serial NCS in GBS such as Mani et al who conducted a retrospective study in southern India [10]. They utilised Cornblath's, Hadden's and Rajabally's criteria for electrophysiological classification to look for category change in serial NCS. After the first NCS, 71% patients were categorized as primary demyelinating and 29% patients as primary axonal according to Hadden's criteria, while 45.2% patients were categorized as primary demyelinating and 54.8% patients as primary axonal according to Rajabally's criteria. Rath et al attempting to look for influence of timing of NCS and value of repeated NCS in GBS, reported that first NCS classified 70% as primary demyelinating and 6% as primary axonal according to Hadden's criteria, while 38% were classified as primary demyelinating and 30% as primary axonal according to Rajabally's criteria [11]. In another study, using Hadden's criteria, Uncini et al found 67% to have AIDP, 18% axonal GBS, and 15% to have equivocal electrodiagnosis on the first NCS [12]. The results of our study are comparable to these studies in the diagnostic utilities of these criteria on first NCS. This confirmed that Hadden's criteria over-diagnosed AIDP which were better classified as axonal by Rajabally's criteria.

Utilizing the concept of RCF as possible evidence of axonal pathology and nodopathy, the Rajabally criteria may help in earlier classification of GBS subtype and may help eliminate need for serial NCS to rule out RCF [6]. A greater number of patients were classified as primary axonal as compared to primary demyelinating using Rajabally's criteria including those with inexcitable nerves while it was the reverse with Hadden's criteria. Uncini et al also showed the Rajabally's criteria as being more sensitive for diagnosing primary axonal and less sensitive but more specific for primary demyelinating category [4,13]. On the other hand, Hadden's criteria is more simplified for categorization with the cut offs. For demyelinating GBS being very narrow. Thus, many patients are easily classified as primary demyelinating. On the contrary, in Rajabally's criteria, cut offs for classification as primary demyelinating are more conservative requiring in addition to conduction block (defined as proximal/distal CMAP ratio < 0.7 instead of <0.5), one more demyelinating feature in any other nerve to classify as primary demyelinating. Thus, this criterion does not rely only on CMAP values for classification into primary axonal category and presence of conduction block but without any demyelinating feature in any other nerve is also taken into consideration. This helps in identification of RCF correctly. Hadden's criteria relies only on CMAP values for classification as primary axonal category and can easily misclassify many patients having RCF as primary demyelinating instead of primary axonal type. Therefore, with the help of Rajabally's criteria we could identify RCF more accurately.

Electrophysiology of GBS subtype is dynamic. GBS subtypes evolve pathophysiologically and electrophysiologically during the disease course. RCF is a typical example of a dynamic change and suggests nodopathy. RCF may be accompanied by prolongation of distal motor latency and reduction of motor conduction velocity that normalize in parallel with CMAP amplitude but without temporal dispersion. These findings may be confusing as, in the common belief; slow conduction velocity is assumed to be a characteristic of a demyelinating process. Therefore, only serial studies may provide a full understanding of the GBS pathophysiology [4]. In our study with serial NCS, we evaluated the category shift at different intervals with both Hadden's and Rajabally's criteria and serial changes in each case according to these criteria. As is evident from the distribution of patients using both these criteria at different intervals on follow up, the number of patients classified as equivocal by both criteria was noted to increase with time, suggesting progressive improvement in nerve conductions.

According to both the criteria, minimal changes in electrophysiological patterns were seen between day 15 and day 30. The majority of the electrophysiological category changes between day 15 – day 90 and day 30 – day 90 were due to improvement in nerve conductions. Thus, for majority patients accurate electrophysiological classification could be done by day 15. We could also infer from our cases with RCF that Rajabally's criteria can identify a greater number of patients with RCF and relatively early in the course as compared to Hadden's criteria.

There is a lack of studies internationally as well as from India looking at the utility of serial NCS in the management of patients with GBS [4,6,10,14]. Mani et al investigating the utility of serial NCS studies in GBS concluded at an average interval of 2 weeks between studies [10]. No longer was follow up done in that study. A shift in electrophysiological category was noted in 9.6% as per Hadden's criteria and 16.1% as per Rajabally's criteria. In our prospective study with NCS done at 4 occasions spanning over 3 months, 36% as per Hadden's criteria and 24% as per Rajabally's criteria showed shift in category. Uncini et al found that 23.6% of patients changed subtype, using Hadden's criteria and the majority of the shifts were from AIDP and equivocal groups to axonal GBS [4]. In our study also majority shifts were between primary demyelinating to primary axonal category. This was mainly due to the recognition of RCF by serial NCS. A single NCS can't distinguish between demyelinating conduction block and RCF and can misclassify patients with axonal GBS as having AIDP. RCF is an a posteriori diagnosis and can be identified only on serial NCS.

On the other hand, the major reason for shifts from axonal GBS to AIDP was the misclassification of subtypes due to inherent flaws in the criteria. With the Hadden's criteria, there is a tendency for underdiagnose of axonal GBS, primarily due to misclassification as AIDP [4]. We could conclude from our study that for the best possible classification of GBS, serial NCS up to 2-4 weeks is suggested as second NCS after 15 days helped in the most accurate electrophysiologic classification. Uncini and Kuwabara et al have suggested at least two NCS in the first 4–6 weeks of the disease [8,14]. Shahrizaila et al have suggested that performing NCS at two-time intervals, 1st NCS at admission and 2nd NCS at an interval of 3–8 weeks after disease onset can make an accurate electrodiagnosis of GBS [15].

Most studies on electrophysiology in GBS till date involve small numbers of subjects in order to avoid inter-performer variability. The current study also has limited sample size which may not be sufficient to fully reflect the electrophysiological characteristics of all GBS patients. While there are several electrophysiology criteria for GBS are described in literature, the authors utilised and compared the most commonly used criteria for the study.

Potential areas for future research may include replication of our results in more extensive, probably multicenter patient groups. Different criteria can be used for classification and comparison as well such as Uncini's criteria or that may focus on the use of other tests in addition to NCS. Future studies may attempt further revisions of electrophysiological criteria are required for accurate classification of patients with single NCS only. Even though Rajabally's criteria has more stringent cut offs, we require stricter criteria to prevent misclassification. Majority of criteria for electrophysiology classification are based on only motor conduction studies only. Sensory conduction abnormalities should also be included for classification. With the understanding of RCF and nodo-paranodopathies, criteria should recognize them robustly. We should not rely only on DML for classification as demyelinating subtype as can lead to misclassification. Considering abnormalities in DML and CV as well as temporal dispersion, will improve specificity for demyelination and prevent misclassification.

Conclusion

This study has highlighted that the Rajabally's criteria is more sensitive for diagnosing axonal GBS and less sensitive but more specific for demyelinating GBS than Hadden's criteria. If single NCS is done to classify patients with GBS, Rajabally's criteria should be used. However, serial NCS should be done in all GBS to help understand pathophysiology and guide further management. If multiple serial NCS is not possible, a minimum of two NCS should be done in every patient, first at admission and the next between 15-30 days.

Ethical Publication 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.

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Disclaimer

NIL

Disclosure of conflict of Interest

None of the authors has any conflict of interest to disclose.

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