Original Article

Phrenic Nerve Conduction Study in the Early Stage of Guillain–Barre Syndrome as a Predictor of Respiratory Failure

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Abstract

Background: Guillain-Barré syndrome (GBS) has unpredictable clinical course with severe complication of respiratory failure. **Objective:** To identify clinical profiles and electrophysiological study particularly non-invasive Phrenic nerve conduction study in patients of early GBS to predict respiratory failure. **Methods:** 64 adult (age≥18yrs) patients of early GBS (onset ≤ 14 days) during the study period from January 2014 to October 2015 were evaluated by clinical profiles of age, gender, antecedent infection, time to peak disability, single breath counts, cranial nerve involvement, autonomic dysfunction and non-invasive Phrenic nerve conduction study. Patients with predisposition factors of polyneuropathy like diabetes mellitus, hypothyroidism, vitamin deficiency, renal failure were excluded. **Results:** Among 64 patients abnormal phrenic nerve conduction study was seen in 65.62% cases (42/64) and 45.23% (19/42) of them developed respiratory failure. Phrenic nerve sum latency, amplitude, duration and area were abnormal in those who developed respiratory failure and they had sum of phrenic nerve latency >28 msec, sum of CMAP amplitude <300 μV, sum of CMAP duration >50 msec and sum of area < 4 mVmS. None with normal phrenic nerve study developed respiratory failure. It was found that age, gender, preceding infection, autonomic involvement and types of GB syndrome had no influence on development of respiratory failure (p>0.05). Rapid disease progression to peak disability, more severe disease, shorter single breath counts and cranial nerve involvement were seen more often in patients with respiratory failure. **Conclusion:** Abnormal Phrenic nerve conduction study in the early Guillain-Barré syndrome might be of great value independently in predicting impending respiratory failure.

Keywords: Guillain–Barre syndrome respiratory failure, early predictor of respiratory failure, phrenic nerve study

Introduction

Guillain–Barre syndrome (GBS) is an acute inflammatory polyradiculoneuropathy with incidence of 0.6–1.5/100,000 population, diagnosed on the basis of defined clinical and laboratory criteria.[1,2] Multifocal segmental demyelination is the pathology of the disease.[3] In GBS, 14%–44% of patients require respiratory support during the course of their illness;[4-5] with a reported mortality of 5%–10% and mostly due to autonomic failure and respiratory failure.[1] As compared to the West, reports from India show a higher mortality and a more fulminant form of the disease.[6-7] Respiratory failure in GBS is mostly due to diaphragmatic weakness; however, it may be due to the involvement of accessory muscles of respiration, intercostal and abdominal muscle weakness, retained airway secretions, atelectasis, and supine posture.[8] Early recognition of respiratory failure in GBS patients is very important as they may benefit from intensive monitoring, early and optimal treatment of neuromuscular respiratory failure. Arterial blood gas analysis, spirometry, particularly forced vital capacity (FVC), and clinical assessments are relatively insensitive methods of detecting respiratory failure, particularly in early progressive stages of GBS.

Only a few studies have evaluated the role of electrophysiology of the phrenic nerve in early stage of GBS patients to detect respiratory failure,[9] and clinical assessment was not correlated with subsequent respiratory failure; however, phrenic nerve conduction studies were proportional to measurements of respiratory functions.[10]

Hence, the aim of the present work is to evaluate the cases of GBS in the early stage by analyzing the history, clinical, and

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electrophysiological profile, particularly the value of phrenic nerve conduction in predicting respiratory failure.

Materials and Methods

We included during the study period from January 2014 to October 2015, total 64 adult patients (age ≥18 years) of GBS who were admitted within 14 days of onset of symptom to our Neurology Department of Bangur Institute of Neurosciences and Institute of Postgraduate Medical Education and Research, Kolkata. This study was approved by the Institutional Ethics Committee of Institute of Postgraduate Medical Education and Research, Kolkata. Patients admitted to our department were enrolled for the study if they fulfilled the clinical and laboratory criteria for GBS[2] and those having predisposition for developing polyneuropathy such as diabetes mellitus, hypothyroidism, vitamin deficiency, or renal failure were excluded from the study.

The clinical parameters assessed were age, gender, preceding infection, duration of hospitalization, duration of illness, time to peak disability, Medical Research Council (MRC) sum score, GBS disability score, pattern of involvement/type of GBS, cranial nerve involvement, respiratory involvement, and autonomic involvement.

Severity at admission was assessed by Hughes functional grading (GBS disability score) and the MRC sum score.[11] MRC sum score valuing the strength from 0 to 5 in six muscles (deltoid, biceps, extensors of wrist, iliopsoas, quadriceps, tibialis anterior) in both upper and lower limbs so that the score ranged from 60 (normal) to 0 (quadriplegic). We used GBS disability scale by Hughes and Bihari[4] for assessing functional motor deficits. This was as follows:

0: Healthy; 1: minor symptoms and signs and is able to run; 2: able to walk 5 m without assistance but unable to run; 3: able to walk 5 m with assistance only; 4: chair-bound/bed bound; 5: requires ventilation, and 6: patient is dead.

Electrophysiological examinations were performed within 24 h of admission in all patients using Nihon Coden EMG machine (model Max-280VA) according to standard techniques. Phrenic nerve conduction study was done according to the procedure described by Davis.[12] The patient is supine with head slightly elevated and rotated to the side opposite to the nerve under stimulation. The stimulus delivered rectangular pulse of 0.2–1 ms duration at a frequency of 1 Hz, percutaneously in the neck at the posterior border of the sternocleidomastoid at the level of the upper margin of the thyroid cartilage. Surface recording electrodes placed in the eighth intercostals space with upper electrode G1 (active electrode) in the anterior axillary line and G2 (reference electrode) 3.5 cm distal to G1. The ground strapped over the anterior chest wall or over shoulder. The pulse rate and blood pressure monitored during the procedure of stimulation. The latency of the diaphragmatic compound muscle action potential (CMAP) was measured from the stimulus artifact to the onset of the potential. The peak-to-peak amplitude of CMAP was measured, and the duration and negative area of the diaphragmatic CMAP also measured. Anyone value beyond the normal value of phrenic nerve conduction study (CMAP latency [upper limit] = 8.0 ms, amplitude [lower limit] = 0.33 mV, area (lower limit) = 4.4 mVms, and duration [upper limit] = 25 ms) taken as abnormal phrenic nerve conduction study. Figure 1 shows representative recordings of the diaphragmatic muscle action potential.

Quantitative data were entered into Microsoft excel and then exported to SPSS software, Version 19.0 (Statistical Package for Social Sciences, Chicago, IL, USA) for analysis. Data were analyzed using *t*-test; Mann–Whitney test between the group with and without respiratory assistance and *P* value was considered significant if <0.05. The decision to prescribe respiratory assistance was made by the attending physician in each case without knowledge of the findings on phrenic nerve conduction study.

Results

In our study, a total of 64 adult patients (age above 18 years) were included during the period of January 2014 to October 2015.

Overall age at presentation was 38.37 ± 18.28 years age distribution among those developed respiratory failures was 41.42 ± 19.13 years and among those without respiratory failure was 37.09 ± 17.97 years. Forty patients (62.5%) were male and 24 patients (37.5%) were female. Overall time taken from symptoms onset to admission was 5.81 ± 3.03 days and overall time taken to reach the peak severity of the disease was 5.63 ± 2.69 days; in those who developed respiratory failure, it was 4.10 ± 3.63 days and those without respiratory failure it was 6.26 ± 1.9 days. Forty patients (62.5%) had antecedent infection, and most of them were respiratory tract infection. Most of the patients on admission had Hughes functional Grade 3 and 4 (46/64, 71.87%) followed by Grade 2 and 5 (12.55% and 10.93%, respectively). Those patients who developed respiratory failure it was Grade 3 or more. Forty-eight percent patients (31/64) retained the ability

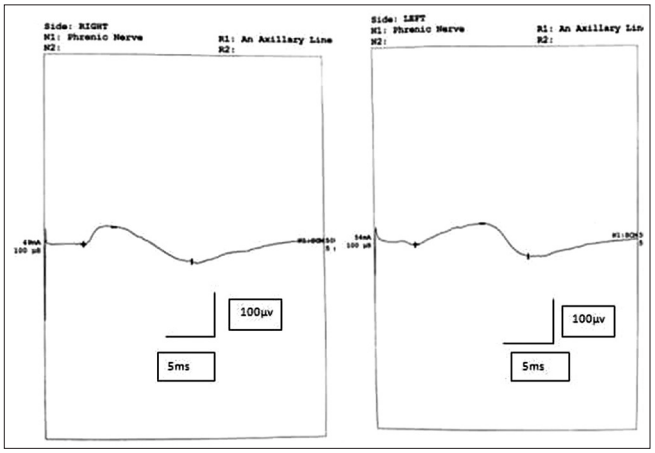

Figure 1: Representative recordings of the diaphragmatic muscle action potential

to walk (Grade 1, 2, and 3) on admission and remaining 52% (33/64) had severe affection (Grade 4 and 5). According to MRC sum score, 39 patients (61%) had score >30, i.e., mild involvement, 23 patients (36%) had moderate (score 11–30), and two patients (3%) had a severe score. Those patients who developed respiratory failure had mostly moderate-to-severe MRC sum score as compared to patients who did not develop respiratory failure.

In our study, 34 patients (53.12%) had cranial nerve involvement and 24 patients (37.5%) had some autonomic involvement. Among those having cranial nerve involvement, 47.05% developed respiratory failure. Cranial nerve involvement for the detection of development of respiratory failure had sensitivity 73.68%, specificity 55.56%, positive predictive value 41.18%, negative predictive value 83.33%, positive likelihood ratio 1.66, and negative likelihood ratio 0.47. Among those having autonomic involvement, 29.16% developed respiratory failure and among those without autonomic involvement, 30% developed respiratory failure. Autonomic involvement did not influence the development of respiratory failure ($P = 0.921$.)

In this study, mean single breath count was 26.7 ± 10.35 (minimum - 10, maximum - 46) and those who developed respiratory failure it was 19 ± 9.21, whereas it was 29.95 ± 9.07 in those who did not develop respiratory failure, i.e., significantly lower in those who developed respiratory failure (the $P = 0.000022$; the result is significant at $P < 0.05$).

According to clinical and electrophysiological study, we found that out of 64 cases, forty were acute inflammatory demyelinating polyneuropathy (AIDP) (62.55%), 14 acute motor axonal neuropathy (AMAN) (21.87%), 8 acute motor and sensory axonal neuropathy (AMSAN) (12.5%), and remaining 2 cases Miller Fisher syndrome (MFS) (3.12%).

Those patients who developed respiratory failure - 57.90% were AIDP, 26.31% were AMSAN, 15.79% were AMAN and those without respiratory failure - 64.44% were AIDP, 24.44% were AMAN, 6.67% were AMSAN, and remaining 4.44% were MFS. There was no significant difference between these two groups ($P > 0.05$).

In our study, two patients had in excitable phrenic nerve study. Remaining 62 patients in the study showed mean phrenic nerve latency on left side 10.37 ± 5.31 ms, on right side 10.56 ± 5.63 ms, and sum latency was 20.93 ± 10.60 ms. Mean phrenic nerve amplitude on left side 364.4 ± 226.6 μV, on right side 357.7 ± 241.6 μV, and sum amplitude was 722.04 ± 455.67 μV. Mean phrenic nerve duration on left side 21.17 ± 6.36 msec, on right side 20.6 ± 5.07 msec, and sum duration was 41.44 ± 10.43 msec. Mean phrenic nerve area on left side 3.1 ± 1.57 mVmS, on right side 3.10 ± 1.56 mVmS, and sum area was 6.27 ± 3.08 mVmS. Table 1 shows a comparison of sum latency, amplitude, duration, and area of phrenic nerve CMAP of case (patients with respiratory failure) and control (patients without respiratory failure).

We found abnormal phrenic nerve conduction study in 65.62% cases (42/64) and normal in remaining 34.38% (22/64) cases. In this study, out of 64 patients, 19 patients (29.68%) developed respiratory failure, seven patients on admission, and remaining 12 developed subsequently during a hospital stay.

Among those patients having abnormal phrenic nerve conduction study, 45.23% developed respiratory failure and 54.77% did not develop respiratory failure. At the time of examination, out of the 42 cases with abnormal phrenic nerve conduction study, in 35 cases, there was no clinical evidence of ventilatory insufficiency. Of these 42 patients with abnormal phrenic nerve conduction study, 12 (28.57%) required respiratory assistance at some stage during the period of observation in the hospital.

In our study, the sensitivity, specificity, positive predictive value, negative predictive value, and positive likelihood ratio of phrenic nerve conduction study for the detection of respiratory failure [Table 2] were 100% (82.35% to 100.00%), 48.89% (33.70% to 64.23%), 45.24% (29.85% to 61.33%), 100% (84.56% to 100.00%), and 1.96 (1.47–2.60), respectively.

Those patients who developed respiratory failure having phrenic nerve sum latency 36.19 ± 7.78 ms, sum amplitude 245.29 ± 37.79 μV, sum duration 45.35 ± 9.86 ms, and sum area 3.859 ± 1.32 mVmS, whereas those who did not develop

Table 1: Comparison of sum latency, amplitude, duration, and area of phrenic nerve compound muscle action potentials of patients with respiratory failure and patients without respiratory failure

Value	Mean±SD		*P*
	Patients without respiratory failure	Patients with respiratory failure	
Sum CMAP latency (ms)	20.93±10.6	36.19±7.78	0.00001
Sum CMAP amplitude (μV)	902.15±407.86	245.29±37.79	0.00001
Sum CMAP duration (ms)	39.96±10.36	45.35±9.86	0.0344
Sum CMAP area (μVms)	7.19±3.07	3.86±1.32	0.00003

CMAP=Compound muscle action potential, SD=Standard deviation

Table 2: Sensitivity, specificity, and predictive values for the diagnosis of respiratory failure with phrenic nerve study

Phrenic nerve study	Statistic value (%)
Sensitivity	100.00
Specificity	48.89
Positive likelihood ratio	1.96
Negative likelihood ratio	0
Positive predictive value	45.24
Negative predictive value	100.00

respiratory failure it was 15.16 ± 3.14 ms, 902.15 ± 407.86 μV, 39.96 ± 10.36 ms, and 7.19 ± 3.07 mVmS, respectively. All the differences are significant (at $P < 0.05$).

Discussion

Respiratory distress is the most important cause of death in GBS in the acute phase.[13] In GBS, multiple factors have been proposed to predict the future need for respiratory support such as FVC <60%, bulbar dysfunction, rapid progression of the illness, and difficulty in raising the head.[14] Diaphragmatic weakness causes progressive hypoxia leading to progressive type 2 respiratory failure.[15,16] Ropper and Kehne's established criteria for elective intubation in GBS patients having bulbar weakness, vital capacity <15 ml/kg, and pO2 on room air <70 mm Hg.[8] Lawn *et al*. proposed the 20-30-40 rule, whereby intubation was considered if the vital capacity, maximum inspiratory pressure, and maximum expiratory pressure fell below 20, 30, and 40 ml/kg, respectively.[17]

Detection of respiratory failure by means of fluoroscopy is not very informative when both halves of the diaphragm are paralyzed and vital capacity measurement is not sensitive enough, particularly early in the course of the illness.[18] van Doorn *et al*.[19] propose regularly monitoring of the respiratory function initially by spirometry every 2–4 h and then every 6–12 h. Although spirometry is considered to be the gold standard test for detecting impaired ventilation, it has some disadvantages, the requirement of portable spirometers in the acute phase due to the instability of the patient, the need for a minimum preparation, and knowledge of the technique by medical personnel and the higher cost.

Clinical assessment and vital capacity measurements, though useful, are not sensitive enough to detect ventilation failure in the early stages as found in Ito *et al*.'s study[10] where clinical assessment was not correlated with phrenic nerve conduction or subsequent respiratory failure, but phrenic nerve conduction studies were proportional to measurements of respiratory functions such as vital capacity and provided the earliest indicator of involvement of respiratory muscles.[20,21]

Davis[12] described a simple surface recording method of phrenic nerve conduction study in humans and confirmed that it represented the true diaphragmatic muscle action potential. Theoretically, phrenic nerve conduction studies could be used as a marker of respiratory muscle weakness.

In this study, we tried to identify features that would predict respiratory failure.

In our study among the patients, almost two-third were male and remaining female, about two-third patients had antecedent infection, most patients on admission had GBS disability score 3 and 4 (71.87%), almost half (48%) patients had the ability to walk on admission, most patients (61%) had mild MRC sum score, almost half patients had cranial nerve involvement, and one-third had autonomic involvement. We found AIDP as most common type (62.55%) followed by AMAN and AMSAN (21.87% and 12.5%, respectively).

We attempted to identify these features that might predict respiratory failure. These are simple bedside tests. In our study, age, gender, preceding infection, and type of GBS did not influence the development of respiratory failure ($P > 0.05$). Rapid disease progression to maximum disability influenced the development of respiratory failure. Those who developed respiratory failure reached to the peak severity of the disease earlier than those without respiratory failure ($P = 0.001358$; the result is significant at $P < 0.05$). Sundar *et al*.[22] in a study said that time to peak disability was significantly shorter in the ventilated group (33 h) as compared to nonventilated group (6 days).

Those who developed peak disability earlier having more severe disease as assessed by GBS scoring ($R = 0.4126$). Those patients who developed respiratory failure it was Grade 3 or more and higher grade on admission more likely to develop respiratory failure ($P < 0.00001$). Those patients who developed respiratory failure had mostly moderate-to-severe MRC sum score than those patients who did not develop respiratory failure. The difference between these two groups was significant ($P < 0.05$).

We found that single breath count was significantly low in those patients who developed respiratory failure. Autonomic involvement was not significantly common in those with respiratory support. The presence of cranial nerve involvement was significantly more common in those who developed respiratory failure. Cranial nerve involvement for the detection of development of respiratory failure had sensitivity 74%, specificity 55%, positive predictive value 41%, and negative predictive value 83%. Ventilation support required in five patients (16.67%) who had normal cranial nerve examination on admission lowered its negative predictive value.

We found abnormal phrenic nerve conduction study in 65.62% cases (42/64) and among those with abnormal phrenic nerve conduction study, 19 patients (45.24%) developed respiratory failure; 7/19 patients on admission and remaining 12/19 developed subsequently during hospital stay. They had significantly different phrenic nerve conduction study from those who did not develop respiratory failure.

In a study by Gourie-Devi and Ganapathy[23] abnormalities in phrenic nerve conduction time were observed in 18 out of 28 patients (64.3%) at admission or on subsequent examination and 83.3% of patients with prolonged phrenic nerve conduction time developed ventilatory failure during the course of the illness.

In Zifko *et al*.s' study,[24] with forty GBS patients, they found that only the diaphragmatic CMAP amplitude and the area under the curve were correlated with the need for respiratory support not with diaphragmatic CMAP latency or duration.

In contrast to Zifko's study, we found phrenic nerve sum latency, amplitude, duration, and area, all were abnormal in those who developed respiratory failure and they had sum of phrenic nerve latency longer than 28 ms, sum of phrenic nerve CMAP amplitude <300 μV, sum of CMAP duration >50 ms, and sum of area <4 mVmS.

In a study by Ito *et al*.,[10] all patients with a sum of phrenic nerve latency longer than 30 ms and the sum of the bilateral diaphragmatic CMAP amplitude <0.3 mV required respiratory assistance during the hospital stay.

In our study, although the number of patients who required respiratory assistance was small, the results between those with and without ventilator support were different enough to be statistically meaningful. With normal phrenic nerve study, no one developed respiratory failure (negative predictive value - 100%), with abnormal phrenic nerve study, almost half patients developed respiratory failure and all those who developed respiratory failure had abnormal phrenic nerve study (sensitivity- 100%). Thus, patients with GBS and normal phrenic nerve conduction study are unlikely to develop significant respiratory failure. Hence, phrenic nerve conduction study may be considered independently in predicting respiratory failure.

Conclusion

We conclude that phrenic nerve conduction study was found independently to be a highly sensitive parameter in GBS patients in predicting impending respiratory failure and its routine study might be of great value in early management and reduction of morbidity and mortality.

Limitation

Our study had some limitations such as a small number of patients who developed respiratory failure. Although our results were statistically significant, reproduction with a large number of patients required to confirm the results.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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