Original Article

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Autonomic Dysfunction in Patients with Guillain-Barré Syndrome in Sub-Acute Phase

Others Section

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ABSTRACT

Introduction: Autonomic involvement is seen in two-thirds of Guillain-Barré Syndrome (GBS) patients.

Aim: To evaluate the pattern and extent of autonomic dysfunction in GBS patients in sub-acute phase and its association with severity in GBS patients.

Materials and Methods: A cross-sectional study was conducted in 29 GBS patients in Department of Neurological Rehabilitation at a tertiary care institute. All consecutive patients diagnosed with GBS fulfilling the inclusion criteria were subjected to laboratory cardiac autonomic tests. To assess the fatigue Fatigue Severity Scale (FSS) was used, disability status was assessed by Hughes Disability Scale (HDS), and muscle weakness was assessed by Medical Research Council (MRC) sum scores. Statistical analysis was done by Stata 11. The significance of p-value was considered at 0.05.

Results: Twenty-nine patients were included with 17 (59%) men and mean age of 31 years. On Heart Rate Variability (HRV) test 26 (90%) patients had reduced power, 15 (52%) patients had sympathovagal balance and 14 (48%) had sympathovagal imbalance with sympathetic dominance. On conventional cardiac testing 16 (55%) patients had cardiac involvement. On tilt table 5 (17%) patients had Postural Orthostatic Tachycardia Syndrome (POTS) and 3 (10%) patients had orthostatic hypotension. Significant association was found on HRV and conventional cardiac autonomic tests with duration between disease onset and testing (p=0.04) and (p=0.01) respectively. Significant association of reduced power was found with presence of antecedent events (p=0.01) and duration between disease onset and testing (p=0.01). Sympatho vagal imbalance showed significant association with presence of respiratory distress and need for ventilator (p=0.04).

Conclusion: Laboratory cardiac autonomic tests are non-invasive and easily applicable to quantitatively evaluate autonomic dysfunction even in severely disabled GBS patients. Autonomic dysfunction is common in patients with pulmonary involvement. However, it has no relation with the severity of motor disability. This study suggests that autonomic dysfunction in GBS should be studied even during the sub-acute phase.

Keywords: Cardiac autonomic tests, Fatigue severity scale, Hughes disability scale, Medical research council sum scores

INTRODUCTION

Dysautonomia occurs as one of the most serious manifestations of Guillain-Barré Syndrome (GBS) [1]. Autonomic involvement is not a prerequisite for diagnosis of GBS but is seen in two-thirds of GBS patients. There is sympathetic hyperactivity in the acute phase which can present as hypertension, hyperhidrosis and tachycardia. Parasympathetic failure occurs during recovery [2]. However, there are still no clear guidelines regarding whether all GBS patients should be routinely screened for Autonomic Nervous System (ANS) neuropathy [3]. Cardiac autonomic dysfunction is frequently asymptomatic and therefore can be missed on diagnosis. There is also non-utilisation of tests for its diagnosis. Availability of simple and reliable tests can be used to predict the dangerous manifestations of autonomic function in GBS patients [4]. There is necessity of monitoring autonomic disturbances in all patients with GBS [5,6]. The mortality rate from autonomic dysfunction now exceeds that of pulmonary involvement. There are no follow-up laboratory studies of autonomic dysfunction in GBS [3]. Therefore, it is difficult to conclude when the autonomic dysfunction improves. Heart Rate Variability (HRV) test is non-invasive and requires no active motor tasks. Therefore, it is possible to administer the test even in severely disabled individuals. The absence of HRV and presence of sympathovagal imbalance predisposes one to the risk of developing arrhythmias [7,8].

There is limited literature on autonomic dysfunction in GBS from India. Autonomic dysfunction in GBS is usually missed at the time of clinical presentation and therefore it is not treated adequately. This can lead to significant mortality in these individuals. We did not come across any literature from India where there is utility of majority of the laboratory autonomic tests as is mentioned in our study. GBS progression occurs within 1-2 weeks and reaches its peak in 2-4 weeks. This is usually referred as the acute phase of GBS. This is followed by the sub-acute phase [9]. Most of the autonomic dysfunction has been studied only when patient has presented in the acute phase. The most commonly done test is HRV. We planned a study to evaluate the pattern and extent of pulmonary and autonomic dysfunction in GBS patients in sub-acute phase and find its clinical correlates. A part of the study which evaluated the pulmonary function in GBS patients in sub-acute phase has already been published [10]. However, the number of patients included in the latter study was 28 as compared to 29 in our current study because one patient was unable to perform spirometry due to severe bilateral facial nerve palsy.

MATERIALS AND METHODS

This was a single centre, cross-sectional, hospital-based study in individuals with GBS patients who were admitted in the Department of Neurological Rehabilitation of a tertiary care Institute. The data was collected from 29 patients during April 2015 to November 2015. Institute Ethics Committee approved the study (IEC number: Item No.7.01, Neurosciences).

All consecutive patients diagnosed with GBS {satisfying National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria}, in the age-group 18-65 years, with duration of illness less than or six weeks, who had received treatment based on current guidelines participated in the study [11]. The patients with history of ischemic or other heart disease, arrhythmias, chronic obstructive airway disease, uncontrolled diabetes mellitus, hypothyroidism, alcoholism and patients on mechanical ventilation or tracheostomy were excluded from the study. We also excluded patients on any medication that could affect autonomic function, pregnant women and those not willing to provide informed consent.

Socio-demographic and clinical details of patients was recorded like age, gender, variant of GBS, duration of illness, presence of antecedent factors, history of respiratory distress, need of ventilator support, sensory disturbances like pain and paresthesia were recorded. History of symptoms and signs of autonomic dysfunction such as new onset hypertension, hyperhidrosis, tachycardia, orthostatic hypotension, and bladder and bowel involvement were recorded. A detailed clinical and neurological examination was done in all the patients. In addition, MRC sum scores scale, HDS and FSS, were administered within 24 hours of admission. The autonomic function tests were carried out at Autonomic Laboratory under Department of Neurophysiology of the Institute. All patients received regular rehabilitation program.

Cardiac Autonomic Function Tests

All the tests were carried out under standardised conditions. The following autonomic function tests were performed with a gap of five minutes.

a) HRV

Analog digital converter (Power lab, 16 channels data acquisition system, AD Instruments, Australia) with a sampling rate of 1024 Hz was utilised to convey lead II of the Electrocardiogram (ECG) and breathing signals. The data acquired was stored in a personal computer and analysed offline with the help of HRV Analysis Software V1.1 (Power lab AD instruments, Australia). HRV was recorded and analysed offline as per the guidelines of Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996 (Task force report 1996) [12]. Basal recordings for 15 minutes were taken and a 5 minute artefact/ectopic free segment was then analysed to get time domain and frequency domain parameters of HRV.

Results were categorised as:

- Magnitude of Total Power which reflects overall HRV (Normal/ Reduction)
- Sympathovagal balance/imbalance
- Parasympathetic dominance
- Sympathetic dominance

b) Conventional Cardiac Autonomic Function Test:

1. Deep Breathing Difference (DBD) test {Heart Rate (HR) based test}.
2. Valsalva manoeuvre test (HR based test).
3. Isometric handgrip test {Blood Pressure (BP) based test}.
4. Orthostatic test

- Maximal: minimal ratio (HR based test)
- Fall in systolic blood pressure (BP Based Test)

Grading of autonomic dysfunction based on five standard cardiovascular autonomic function tests was done as:

- Normal: All five tests normal or one abnormal
- Early involvement: One of three HR or BP based tests abnormal and two border line
- Definitive involvement: Two or more HR based tests abnormal
- Severe involvement: Two or more HR based tests abnormal plus one or both BP based tests abnormal or both borderline.

c) Tilt Table Test

Results considered were:

1. **Orthostatic hypotension:** It is described as a fall in systolic blood pressure of 20 mmHg and a rise in diastolic blood pressure of 10 mmHg after three minutes of standing in comparison with blood pressure recorded in supine or sitting position.
2. **The Postural Tachycardia Syndrome (POTS):** Defined as a heart rate increment of 30 beats/minute or greater above the basal heart rate without fall in blood pressure [13].
3. Negative test.

Other study tools included:

- **MRC Scale**

MRC scale ranging from 0-5 is performed for these muscle pairs: abductors (shoulder), flexors (elbow), extensors (wrist), flexors (hip), extensors (knee), and dorsiflexors (ankle). The MRC sum score is a summation of the MRC scale for these muscle groups and can range from 0 (total paralysis) to 60 (normal strength). The scale has good validity and interobserver reliability in patients with GBS [14].

- **HDS**

HDS is used for assessment of outcomes in GBS patients [15]. It includes Grade 0 to 6 (Grade 0=healthy; grade 1=minor symptoms and capable of running; grade 2=able to walk without assistance but unable to run; grade 3=able to walk with assistance; grade 4=bedridden or chair bound; grade 5=requiring assisted ventilation; grade 6=dead).

- **FSS**

It is a self-reported questionnaire. The score on the various questionnaire statements ranges from 1 (indicating no signs of fatigue) to 7 (indicating most disabling fatigue). An average score is calculated and interpreted as a score of 4 and higher indicates fatigue and a score of 5 and higher indicates severe fatigue [16,17].

STATISTICAL ANALYSIS

We analysed autonomic function using following four outcome variables:

1. HRV (sympathovagal balance/imbalance)
2. HRV (Total power)
3. Conventional cardiac function tests (normal/abnormal)
4. Tilt table test (negative/positive/POTS)

The following independent variables were considered for each of the above four outcome variables: age, gender, duration of illness at time of test, presence of antecedent events, ventilator support requirement, bilateral facial weakness, presence of dysphagia, body mass index, presence of autonomic symptoms, presence of co-morbid conditions, electrophysiological diagnosis and other scales like MRC scale, HDS and FSS.

The association between the outcome variables (which were categorical) and the independent variables were assessed using the following statistical tests - for categorical independent variables Fisher's Exact probability test; for continuous independent variables Wilcoxon signed-rank test.

For the outcome variable tilt table test which had three categories we assessed the association with continuous independent variables using Kruskal Walis H test.

Statistical analysis of data was performed by Stata 11. (StataCorp. 2009. College Station, TX). The significance of p-value was adjudged against an alpha of 0.05.

RESULTS

Twenty-nine patients satisfied inclusion criteria in the study period. The mean age was 31±11.71 years (range-18-51 years) and there were 17(59%) men. At the time of admission in the department, the median duration of symptoms was 17 days (range-10-42 days). The median duration at the time of doing the autonomic function tests was 28 days (range-14-45 days). There were 11 (38%) demyelinating and 18 (62%) axonal variants of GBS. Antecedent events were reported in 18 (62%) individuals. There was respiratory distress in four (14%) patients and all four required ventilatory support. Six (20%) patients had facial palsy. Bulbar symptoms were reported in the form of drooling in 4 (14%), dysphagia in 9 (31%), dysphonia in 9 (31%) and requirement of nasogastric tube in 7 (24%) patients. Sensory symptoms were prevalent in the form of neuropathic pain in 15 (52%) and paresthesias in 25 (86%) patients. Bladder symptoms

were present in 5 (17%) cases. Among co-morbidities, 3 (10%) patients had newly diagnosed hypertension. Twenty-seven (93%) patients scored more than 2 on HDS. All the study participants reported fatigue with median of 5 on FSS.

The results of HRV tests were correlated with disease severity and other scales. Fifteen (52%) patients had sympathovagal balance and 14 (48%) had sympathovagal imbalance with sympathetic dominance. On HRV test examination 26 (90%) patients had reduced power.

[Table/Fig-1,2] summarise the clinical correlates of HRV in study patients.

	Sympathovagal Balance, n=15	Sympathovagal Imbalance, n=14	p-value
Age (median) years	25	29	0.930*
Gender (male)	8	9	0.710
Duration of illness (in days) at time of test	21	35.5	0.044*
Presence of antecedent events	9	9	1.000
Ventilator support requirement	0	4	0.042
Bilateral facial weakness	3	0	0.224
Presence of dysphagia	3	6	0.245
Body mass index category [18].			
Underweight	5	8	0.538
Normal	26	5	
Overweight	2	0	
Obesity	2	1	
Presence of autonomic symptoms	1	4	0.169
Co-morbid conditions			
Newly diagnosed hypertension	1	2	0.598
None	14	12	
Electrophysiological diagnosis			
AIDP	6	5	1.000
AMAN	7	6	
AMSAN	2	3	
Association with other scales at admission			
Medical Research Council (MRC) sum score (<36)	1	2	0.598
Hughe's Disability Scale (HDS) score (>3)	14	13	1.000
Fatigue Severity Scale (FSS) >4	14	13	1.000

[Table/Fig-1]: Clinical correlates of heart rate variability in patients with Guillain-Barré Syndrome [18].
*Two Sample Wilcoxon rank sum (Mann-Whitney) test; others, Fisher's-Exact
AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor sensory axonal neuropathy

	Power normal, n=03	Power reduced, n=26	p-value
Age (median) years	27	25	0.857*
Gender (male)	2	15	1.000
Duration of illness (in days) at time of test	14	29	0.0108*
Presence of antecedent events	3	15	0.0180
Ventilator support requirement	0	4	1.000
Bilateral facial weakness	0	3	1.000
Presence of dysphagia	0	9	0.532
Body Mass Index category			
Underweight	1	12	0.765
Normal	2	9	
Overweight	0	2	
Obesity	0	3	
Presence of autonomic symptoms	0	5	1.000
Co-morbid conditions			
Newly diagnosed hypertension	0	3	1.000
None	3	23	
Electrophysiological diagnosis			
AIDP	3	8	0.114
AMAN	0	13	
AMSAN	0	5	
Association with other scales at admission			
Medical Research Council (MRC) sum score (<36)	0	3	1.000
Hughe's Disability Scale (HDS) score (>3)	3	24	1.000
Fatigue Severity Scale (FSS) >4	3	24	1.000

[Table/Fig-2]: Clinical correlates of heart rate variability (Total power) in patients with Guillain-Barré Syndrome.
*Two Sample Wilcoxon rank sum (Mann-Whitney) test; others, Fisher's-Exact
AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor sensory axonal neuropathy

On conventional cardiac autonomic testing 13 (45%) patients had no cardiac autonomic dysfunction, 11 (41%) patients had definitive, 3 (7%) patients had severe and 3 (7%) patients had early cardiac involvement [18]. [Table/Fig-3] summarises the clinical correlates of conventional cardiac autonomic tests in study patients.

	Result normal, n=13	Result abnormal, n=16	p-value
Age (median) years	25	36.5	0.261*
Gender (male)	8	9	1.000
Duration of illness (in days) at time of test	21	35	0.0107*
Presence of antecedent events	8	10	0.952
Ventilator support requirement	0	4	0.107
Bilateral facial weakness	3	0	0.078
Presence of dysphagia	2	7	0.130
Body mass index category			
Underweight	5	8	0.175
Normal	6	5	
Overweight	2	0	
Obesity	0	3	
Presence of autonomic symptoms	2	3	1.000
Co-morbid conditions			
Newly diagnosed hypertension	0	3	0.232
None	13	13	
Electrophysiological diagnosis			
AIDP	5	6	0.083
AMAN	8	5	
AMSAN	0	5	
Association with other scales at admission			
Medical Research Council (MRC) sum score (<36)	11	15	0.573
Hughe's Disability Scale (HDS) score (>3)	11	16	0.192
Fatigue Severity Scale (FSS) >4	11	16	0.192

[Table/Fig-3]: Clinical correlates of cardiac autonomic function tests in Guillain-Barré Syndrome patients.
*Two Sample Wilcoxon rank sum (Mann-Whitney) test; others, Fisher's-Exact
AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor sensory axonal neuropathy

On tilt table testing five (17%) patients had POTS and 3 (10%) patients had orthostatic hypotension. Rest 21 (72%) patients had normal test results. The analysis showed there was no statistically significant difference between the three results of the tilt tests either for median

age (p=0.90), or, median duration of admission (p=0.425). [Table/Fig-4] summarises the clinical correlates of tilt table test in study patients.

	Negative, n=21	POTS, n=5	Positive, n=3	p-value
Age (median) years	25	25	42	0.900*
Gender (male)	13	3	1	0.830
Duration of illness (in days) at time of test	27	27	40	0.425*
Presence of antecedent events	12	3	3	0.655
Ventilator support requirement	0	0	4	0.079
Bilateral facial weakness	3	0	0	1.000
Presence of dysphagia	6	1	2	0.446
Body mass index category				
Underweight	11	2	0	0.338
Normal	7	2	2	
Overweight	1	1	0	
Obesity	7	0	1	
Presence of autonomic symptoms	4	0	1	0.409
Co-morbid conditions				
Newly diagnosed Hypertension	3	0	0	1.000
None	18	5	3	
Electrophysiological diagnosis				
AIDP	8	1	2	0.468
AMAN	8	4	1	
AMSAN	5	0	0	
Association with other scales at admission				
Medical Research Council (MRC) sum score (<36)	3	0	0	1.000
Hughe's Disability Scale (HDS) score (>3)	19	5	3	1.000
Fatigue Severity Scale (FSS)>4	19	5	3	1.000

[Table/Fig-4]: Clinical correlates of Tilt table test in GBS patients.
*Kruskal Walis test; others, Fisher's-Exact
AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor sensory axonal neuropathy

DISCUSSION

Our study was carried out to describe autonomic function tests in patients with GBS in sub-acute phase. The recording was obtained within six weeks after onset of illness. None of the HRV results had statistically significant correlation with severity (MRC, HDS) and other scales (FSS) in GBS. However, significant association was found with duration of illness at time of test and with presence of respiratory distress and need for ventilator.

Majority of the studies have reported autonomic dysfunction during the acute phase of the disease and found that autonomic dysfunction tends to improve by three months [19]. The median time between onset of illness and test was 28 days in the current study. Our study reports presence of sympathovagal imbalance in 14 (48%) patients during the sub-acute phase of GBS and emphasises the need to monitor and manage these patients for likely complications even during the sub-acute phase.

There are conflicting reports regarding the relationship between the autonomic involvement and the degree of motor disturbance. Many studies suggest that autonomic dysfunction is present more often in those with severe motor deficits and with respiratory failure, while others found no relationship between the severity of autonomic dysfunction and the degree of motor disturbances [19-24]. The MRC sum score was ≤36 in 26 out of 29 study participants. Our findings support the latter studies with no relation between the presence of autonomic dysfunction and the severity of motor disability. However, we found a positive correlation between autonomic dysfunction and presence of respiratory distress (p-value of 0.04).

Tuck RR et al., in their study on seven GBS patients found that in two patients the heart rates were fixed and greater than 100/min and in three there was postural hypotension. Four patients had abnormal baroreflex sensitivity and in two out of three patients the heart rate response to Valsalva's manoeuvre was impaired [21]. In our study 3 (10%) out of 29 patients had orthostatic hypotension on tilt table testing and 16 (55%) patients had abnormal conventional cardiac autonomic tests.

Samadi M et al., in their study on 28 children with GBS measured HRV, motor function of the upper limbs and disability scores at admission and compared the results with 20 healthy matched subjects [24]. Autonomic dysfunction was present in half of children with mild GBS and it showed no significant association with disease severity. In our study, HDS score was ≥3 in 27 out of 29 patients and showed no significant association with any of the laboratory autonomic tests.

Lyu RK et al., conducted a study on nine patients with Fisher Syndrome (FS) and found autonomic function abnormalities in up to 83% of patients. There was improvement in most autonomic function tests after 4-12 weeks. They also concluded that sympathetic fibres were more likely to be involved [25]. We also observed that in our study 48% patients showed sympathovagal imbalance during sub-acute phase though all had sympathetic dominance.

A study by Yerdelen D et al., concluded that there is involvement of both the parasympathetic and sympathetic systems in GBS and HRV test can detect early autonomic dysfunction in patients with GBS [7].

Our study participants consisted of primarily axonal subtype (n=18) compared with demyelinating subtype (n=11). Our study results are in accordance with study by Samadi M et al., and Asahina M et al., that AMAN is not necessarily generally associated with marked autonomic dysfunction [24,26]. They found that the patients with Acute Inflammatory Demyelinating Polyneuropathy (AIDP), demonstrated hyperactivities of the cardio-sympathetic system, and the patients with Acute Motor Axonal Neuropathy (AMAN) had normal cardio-vascular function.

Garssen MP et al., observed severe fatigue, expressed as a mean FSS score of 5.0 or more was present in 60% of all GBS patients [27]. Ranjani P et al., reported presence of fatigue at admission was associated with ventilator requirement (p=0.021) implying that fatigue was more prevalent in severe form of disease [28]. Though 27 (93%) patients in our study were severely fatigued, we did not find any significant association between FSS scores and autonomic dysfunction in our study. That could be attributed to small sample size.

With the study results, we emphasise that autonomic function tests should be performed in GBS patients to assess any abnormality and its resolution even during the sub-acute stage.

LIMITATION

The study had small sample size and there was no follow-up, so resolution of autonomic dysfunction could not be determined.

CONCLUSION

Laboratory cardiac autonomic tests are non-invasive and easily applicable to quantitatively evaluate autonomic dysfunction even in severely disabled GBS patients. Autonomic dysfunction is common in patients with pulmonary involvement. However, it has no relation with the severity of motor disability. This study suggests that autonomic dysfunction in GBS should be studied even during the sub-acute phase.

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