Heart rate and blood pressure variability in patients with myasthenia gravis

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Abstract

This cross-sectional case control study included subjects aged between 18 and 65 years with diagnosis of myasthenia gravis (MG) in Osserman's Stage I and Stage IIa and those in remission with positive and negative acetylcholine receptor antibody (AChRAb). They were evaluated for heart rate variability (HRV) and other conventional autonomic functions. Patients with co-morbidities that can affect autonomic nervous system were excluded. Repetitive nerve stimulation test (RNST), nerve conduction test, AChRAb assay, and computerized tomography (CT) of chest were done in all the patients. All patients of MG who fulfilled the inclusion criteria had a minimum drug-free period of 6 h which was followed by HRV and other conventional tests. Thirty subjects fulfilling study criteria and an equal number of age and gender-matched healthy subjects were enrolled as controls. Autonomic function tests revealed significant changes in HRV (both time and frequency domain) parameters suggestive of parasympathetic deficiency as well as shifting of sympathovagal balance towards raised sympathetic tone. With regards to conventional autonomic function tests, there was statistically significant decrease in values of heart rate-based tests as well as blood pressure-based test (isometric handgrip test) in study group compared with controls, again indicative of significant parasympathetic deficiency and minimal sympathetic deficiency. We conclude that in MG, cholinergic transmission is affected more diffusely than previously thought.

Key Words

Blood pressure changes, cholinergic function, heart rate variability, myasthenia gravis, receptors

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Introduction

Myasthenia gravis (MG) is an acquired neuromuscular junction disorder characterized by muscular weakness and fatigability, resulting from the binding of circulating auto antibodie Thymoma was found in two of the six patients positive for the antibody.

Autonomic symptoms help distinguish Lambert Eaton Myasthenic Syndrome (LEMS) from MG.[8,9] A case of autonomic failure is reported in a patient with muscle AChR antibodies (AChRAbs), thymoma, and MG with improvement of symptoms with anticholinesterase therapy.[4] AChRAbs were found to be as high as 50% in patients with autonomic symptoms.[10] This co-existence illustrates that the presence of autonomic symptoms alone does not reliably distinguish MG from LEMS.

The literature is ambiguous regarding the precise pattern and pathophysiology of involvement of autonomic nervous function in MG. Hence, this study is an attempt to look at clinical spectrum of autonomic dysfunction, if any, by heart rate variability (HRV) and by conventional method.

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Materials and Methods

It was a prospective case control study conducted at Department of Neurology and Neurophysiology, NIMHANS, Bangalore, India. Study period was for one and half 1½-year period from 1st August 2009 to 31st December 2010.

Inclusion and exclusion criteria

All subjects aged between 18 and 65 years evaluated at NIMHANS with diagnosis of MG in Osserman's Stage I and Stage IIa and patients in remission were included in the study. Patients with co-morbidities that can affect autonomic nervous system, like diabetes mellitus, bronchial asthma, respiratory dysfunction, cardiac failure peripheral nerve disease, and drugs, were excluded.

Study methodology

Thirty subjects fulfilling study criteria were evaluated from 1st August 2009 to 31st December 2010. An equal number of age and gender-matched healthy subjects were enrolled as controls. A thorough clinical assessment including the presence of any autonomic symptoms was done and details about the drugs and their dosage was also recorded in a predesigned proforma. The duration of symptoms during first consultation, topography of muscle weakness, and course and severity of disease using Osserman's staging were recorded.

Routine nerve conduction studies and repetitive nerve stimulation test (RNST) were carried out using standard protocol in all the patients. The AChRAb was tested using enzyme-linked immunosorbent assay technique. Computerized tomography (CT) of chest was done to look for thymic abnormality.

Autonomic function tests

All patients underwent autonomic function tests. The tests were carried out at the autonomic laboratory of Department of Neurophysiology, NIMHANS, under all standardized conditions. A minimum drug-free period of 6 h was given for subjects who were on Neostigmine/Pyridostigmine before undergoing autonomic function test. The test performer was blinded to cases and controls.

Heart rate variability (HRV)

Resting supine lead II electrocardiogram (ECG) and breathing signals were acquired and conveyed through analog digital converter (Power lab, 16 channels data acquisition system, AD Instruments, Australia) with a sampling rate of 1024 Hz. The data was stored in computer and analyzed offline using a software program that allowed visual checking of the raw ECG and breathing signals (Chart program, AD Instruments, Australia). A 5-min artifact free segment from the basal recording was identified and were analyzed using a mathematical technique, fast Fourier Transformation (FFT), to obtain both time and frequency domain parameters of HRV.

Conventional autonomic tests

Deep breathing test

Subjects were asked to breathe slowly and almost fully to their vital capacity taking 5 s for inspiration and 5 s for expiration. Deep breathing difference was calculated from the mean of the differences between maximum heart rate during inspiration and minimum heart rate during expiration of six such cycles.

Valsalva maneuver

Subjects were asked to blow out through the mouth maintaining a pressure of 40 mm Hg for 15 s into a tube, which is connected to a manometer with the narrow other end of tube. The Valsalva ratio was calculated as the ratio of shortest RR interval during phase 2 (immediately after the blow out) to the longest RR interval during phase 4 of the Valsalva maneuver (within 20 s after the blow out). Three trials were conducted and the highest value was taken as Valsalva ratio.

Orthostatic test

Subjects were asked to stand upright from resting supine position and the change in heart rate and blood pressure was recorded immediately at 1st, 2nd, and 5th minute after standing. The maximum:minimum ratio was calculated as the ratio of longest RR interval around 30th beat and the minimum RR interval around 15th beat after standing up.

Isometric handgrip (IHG) test

Subjects were asked to grip a cuff connected to a manometer with their right hand and maintain the handgrip at 1/3rd of their maximal capacity and the heart rate and blood pressure change at 2 min of hand grip was compared with the baseline values.

Grading of autonomic dysfunction, based on conventional autonomic function tests, was done in both patients and controls. The results were correlated among patients and controls as well as with type and stage of MG. The results of the autonomic symptoms, signs, and autonomic function tests were correlated with type and stage of MG.

Statistical methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± Standard deviation (Min-Max) and results on categorical measurements are presented in percentages. Significance is assessed at 5% level of significance. Student *t* test (two tailed) was used to find the significance of study parameters on continuous scale between two groups. Chi-square/Fisher Exa*t* test was used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software, namely, SPSS 15.0 was used for the analysis of the data.

Results

Clinical characteristics

There were 30 patients with 18 females and 12 males. Thirty healthy age and gender-matched controls were taken up for the study. The mean age of patients was 36.2 (±13.6) years and that of controls was 35.9 (±13.3) years. Twenty-eight patients (93.3%) presented with ocular symptoms. Twelve patients (40 %) presented with facial weakness. Ten patients (33.3 %) presented with bulbar symptoms. Twenty-four out of 30 patients reported following symptoms: 14 patients (46.7%) had history of orthostatic dizziness, seven patients (23.3%) had history of abdominal cramps, and constipation was reported by three patients (10 %), but no clinical autonomic signs were present for any of the cases.

Two patients were in Osserman grade I (purely ocular). Twenty-four patients were in Osserman grade IIa. Four patients were in pharmacological remission (not on anti-cholinesterase). Twenty patients had positive AChRAb (66.7 %) while AChRAb was negative in 10 patients (33.3%). CT finding of thymic enlargement was seen in 16 patients (53.3 %). Thymic teratoma and thymic lipoma was seen in one patient each.

Autonomic function results: [Table 1]

HRV results

There was statistically significant decrease in time domain parameter square root of mean of sum of the squares of

differences between the adjacent RR intervals (RMSSD), and frequency domain parameter HF power in normalized units (HF nu) in study group compared with controls, suggesting parasympathetic deficiency. There was also higher value of - Ratio of LF Power to HF Power (LF/HF) ratio in patients compared with controls suggesting tilting of sympathovagal balance towards sympathetic side. There was a trend noted with standard deviation of RR intervals over the selected time interval (SDNN) and total power in patients compared with controls indicating overall autonomic function deviation.

Conventional autonomic function test

Conventional autonomic tests revealed statistically significant decrease in values of heart rate-based tests (Max:Min, DBD) as well as blood pressure (BP)-based test (IHG) in study group compared to controls. With regard to grading of autonomic dysfunction, one patient had definite autonomic dysfunction. Twelve patients (40%) had early autonomic dysfunction. Seventeen patients had normal grading. There was statistically significant association between age at onset and grading of autonomic dysfunction. Patients with earlier age at onset had significant abnormalities in conventional autonomic function tests. There was no statistical association between duration of illness with grading of autonomic dysfunction. Correlation of AChRAb status (positive Vs negative) with HRV parameters revealed statistical significance in frequency domain parameter [total power (P = 0.038), LF power (P = 0.012)], and a trend was noted with time domain parameter (SDNN and RMSSD). The above findings indicate that autonomic dysfunction is present in MG patients with AChRAb. There was no correlation between thymic abnormality (based on CT scan) and autonomic dysfunction.

Discussion

Impaired neuromuscular junction transmission in acquired MG results from the binding of circulating auto-antibodies specific for nAChR of muscle. Since anti-AChRAbs are heterogeneous in MG patients, and muscle and neuronal receptor subtypes are structurally and functionally homologous, there is a possibility that a portion of these antibodies can recognize the nAChR subtypes expressed by the autonomic ganglia and thymus.

There are two neuronal forms of acetylcholine receptors (nAChRs), α7 and α3 containing nAChR subtypes, present in the autonomic ganglia. Studies have shown range of autonomic symptoms in patients having serum antibodies to α7 and α3 containing nAChRs.[7]

In the present study, the spectrum of autonomic symptoms varied from orthostatic dizziness to gastrointestinal symptoms. This was in accordance with various studies, which reported autonomic disturbances in MG.[11] Two patients reported improvement in constipation with anticholinesterases therapy.

The present study suggests that there is overall autonomic function deviation in subjects with MG when compared with control subjects. This aspect was shown by the decrease in SDNN, total power, and other parameters in both time and frequency domain in HRV tests. There was statistically significant decrease in time domain parameter (RMSSD) and frequency domain parameter (HF nu) in study group compared with controls, suggesting parasympathetic deficiency. There was also higher value of LF/HF ratio in patients compared with controls, suggesting tilting of sympathovagal balance towards increased sympathetic tone. A study also showed a decrease in time and spectral indices depicting parasympathetic deficiency similar to our study.[12] Contrary to our results, there are studies, which have demonstrated sympathetic deficiency in MG patients.[13]

With regard to conventional autonomic function tests, there was statistically significant decrease in values of heart rate-based tests (Max:Min and DBD) as well as BP-based test (IHG) in study group when compared with control group. This indicates significant parasympathetic deficiency as well as mild sympathetic deficiency. Grading of autonomic function revealed definite as well as early autonomic dysfunction in MG subjects. There was statistically significant association between age at onset and grading of autonomic dysfunction. However, although there was a trend noted in correlation of duration of illness with conventional autonomic tests as well as HRV analysis, it was not statistically significant.

Correlation of AChRAb positivity with HRV parameters revealed statistical significance in frequency domain parameter (total power, LF power) and a trend was noted with time domain parameter (SDNN and RMSSD). This finding indicates autonomic function deviations are more common in seropositive MG patients. This is in accordance with previous studies, which have looked at autonomic abnormalities in MG where autonomic abnormalities were seen in patients who have antibodies to AChRs.[7,10] In the present study, there was no correlation of thymic abnormalities with autonomic parameters.

Other studies have shown increased incidence of memory disturbances and various reports of detrusor areflexia, proposing a role for central cholinergic neural network in the pathophysiology.[14,15]

Table 1: Comparison of autonomic tests between cases and controls

HRV variables[$]	Study group (n=30) Mean±S.D.	Control group (n=30) Mean±S.D.	P value
SDNN (ms)	27.31±2.66	35.91±2.64	0.073
RMSSD (ms)	17.32±3.89	30.75±3.75	0.008
LF nu	55.32±2.94	45.26±0.081	0.049
HF nu	26.56±2.20	44.94±1.04	<0.001
LF/HF	2.94±0.54	1.09±0.08	<0.001
DBD (bpm)	16.65±1.46	22.14±1.03	0.034
Valsalva ratio	1.47±0.25	1.43±0.21	0.461
Max: Min	1.24±0.19	1.44±0.27	0.002
IHG (mm of Hg)	11.77±7.48	16.17±8.48	0.038
OTB (mm of Hg)	5.83±3.39	3.73±5.60	0.085

$: Square root transformed for statistical analysis and back transformed for presentation, n=Number of patients and controls, SDNN=Standard Deviation of RR intervals over the selected time interval, RMSSD= Square root of mean of sum of the squares of differences between the adjacent RR intervals, LF nu= LF power in normalized units, HF nu= HF power in normalized units, LF/HF= Ratio of LF Power to HF Power, DBD= deep breathing difference, bpm= Beats per minute, OTB= Orthostatic fall in systolic BP, IHG= Isometric hand grip

In MG, where the main pathology is due to auto-antibodies against AChRs, the decrease in parasympathetic activity can be thought of as due to decrease in ACh signal processing at these synapses. This can be postulated to occur at different levels. At the periphery where the postganglionic nerve supplies the heart, the reduction in the ACh activity can be due to one reason, particularly considering the fact that parasympathetic response is faster and dominant over sympathetic response. Studies have shown that immune attack is also seen against smooth muscles of heart supporting the hypothesis.[16] At a higher level, were the preganglionic and postganglionic neurons interact in the autonomic ganglia, most of the synapses use ACh as the neurotransmitter. Autonomic ganglia are considered as an integrating center rather than just a relay station where information in the form of neuronal signals converge and diverge before passing to the next level.

Previous studies have shown the possibility of autoimmune autonomic dysfunction in some cases of myasthenic syndromes like LEMS.[17] Even though autonomic ganglia are not damaged as a whole, a small amount of the ACh receptors can be thought to be damaged due to the antigen–antibody reaction in MG at the autonomic ganglia level. Since the preganglionic neuron diverge the information to more neurons in the case of sympathetic system in contrast to that of parasympathetic system where the preganglionic fibers contact a few postganglionic neurons, the impact can be postulated to be small in case of sympathetic nervous system than parasympathetic function.

The study results implicate autonomic function abnormalities with a predominant parasympathetic deficit in subjects with MG. Increased parasympathetic activity has been shown to attenuate the release of proinflammatory cytokines and sympathetic activity has been postulated to increase the release and activity of inflammatory cytokines.[18] In MG, the impairment in the parasympathetic activity can be possibly related to the inflammatory processes due to antibody interaction as shown by correlation between decreased HF and seropositivity. There was overall autonomic deviation in seropositive MG patients. Autonomic dysfunction also correlated with age at onset of the disease as well as the duration of the illness.

The limitations of this study are that autonomic dysfunction was not segregated into preganglionic or postganglionic abnormalities and the antibodies against AChR in autonomic ganglia were not done, which could have helped for better characterization of autonomic dysfunction.

Conclusion

The results of present study demonstrate the presence of diffuse cholinergic dysfunction in MG manifesting as significant parasympathetic and mild sympathetic deficiency. There is need for studies with larger cohort and longer study period.

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