They postulated a “parasympathetic” rate of pupil under a fixed light stimulus declines rapidly. Constriction (parasympathetic, cholinergic) is predominantly a reaction to a light stimulus; more specifically, pupillary abnormalities in iris muscle velocity and acceleration in Infra-red pupillometric studies in myasthenics revealed Autonomic dysfunction is known in myasthenia gravis. comorbidities.

Therapies.

In intensive medical care technology, and immunosuppressive from 70% to present estimates of 5%, due to improvements implicated.

Pathogenic antibodies to the Acetylcholine receptor are primarily responsible. Muscle‑specific kinase and the Agrin‑LRP4 complex, are now implicated. Myasthenic crises related mortality has improved from 70% to present estimates of 5%, due to improvements in intensive medical care technology, and immunosuppressive therapies. The mortality in crisis is mainly related with comorbidities.

Autonomic dysfunction is known in myasthenia gravis. Infra-red pupillometric studies in myasthenics revealed abnormalities in iris muscle velocity and acceleration in reaction to a light stimulus; more specifically, pupillary constriction (parasympathetic, cholinergic) is predominantly affected. Myasthenic pupils “fatigue,”—i.e., oscillation rate of pupil under a fixed light stimulus declines rapidly as compared to controls. Tonic pupils which improved with myasthenia treatment are reported. Since pupillary redilatation velocity remained unaffected, a parasympathetic pupillary deficiency was proposed. Myasthenics have blunted norepinephrine response to forearm ischemia. They also have poor thermoregulation and sleep disturbance, increased fatigue, and impaired functionality. Other phenomena, from isolated gastroparesis to pan-autonomic failure, are reported.

Heart rate variability (HRV) has been studied in myasthenia gravis in noncrises patients [Table 1]. Puneeth et al. demonstrated a statistically significant decrease in the HF component and total variance. They postulated a “parasympathetic” deficiency, resulting from disrupted cholinergic transmission at the preganglionic or postganglionic level. Shukla et al. had reported a sympathetic “hyper-responsiveness,” on rapid rise with.

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in heart rate on tilt, and hand-grip manoeuvres.\textsuperscript{[14]} Nikolić \textit{et al.} reported similar findings on both conventional autonomic testing and HRV analysis in various myasthenic groups, with reduced overall variance and deficiency of HF spectra.\textsuperscript{[15]} They too postulated a sympathetic hyperactivity. Nikolić \textit{et al.} also noted a predilection for supraventricular arrhythmias during Valsalva, again implying a sympathetic hyperactivity on the sinus node. Therefore, studies on HRV have consistently demonstrated a parasympathetic dysfunction, due to loss of high-frequency variability (considered to represent instantaneous vagal modulation) while low frequency (LF) variability remains unaffected. Acetylcholinesterase inhibitors produce improvement in autonomic functions, just as in motor weakness, i.e., in pupillary dysfunction, all changes were seen to reverse with the administration of acetylcholine inhibitors;\textsuperscript{[16]} Shukla \textit{et al.} reported that the abnormal heart rate dynamics also reverted to normal after administration of pyridostigmine;\textsuperscript{[14]} and Vernino \textit{et al.} reported improvement in gastrointestinal symptoms after pyridostigmine.\textsuperscript{[12]} Therefore, impaired cholinergic transmission is the probable basis of autonomic dysfunction.

Autoimmunity was postulated as the basis of this autonomic dysfunction by the discovery of antibodies to autonomic ganglia by Vernino \textit{et al.}\textsuperscript{[17]} and confirmed in therapeutic and experimental models.\textsuperscript{[19]} The ganglionic (alpha 3-type) neuronal acetylcholine receptor (AChR) is responsible for fast synaptic transmission in sympathetic, parasympathetic, and enteric autonomic ganglia.\textsuperscript{[19]} Myasthenic Crisis represents a severe state of myasthenic disease, where autonomic dysfunction has thus far remained uncharacterized. Dysautonomia is likely to parallel the muscle weakness in severity, owing to a similar humoral pathogenesis. Hence, this study was undertaken to study the prevalence and pattern of dysautonomia in myasthenic crisis.

### Methods

This study was performed in the neurology Intensive Care Unit (ICU) of the Christian Medical College Hospital, Vellore, a tertiary hospital in Southern India between January 1\textsuperscript{st}, 2014 and March 15, 2015. Scientific and Ethics approval from institutional review board was obtained.

### Study design

A prospective cross-sectional study of patients in myasthenic crises was performed.

### Patients

All adults (>18 years) patients with myasthenic crisis (Myasthenia Gravis requiring mechanical ventilation) were included in the study with informed consent. Myasthenia gravis was defined as clinically fatigable muscle weakness with electrophysiological evidence of neuromuscular transmission defect (compound motor action potential decrement on repetitive nerve stimulation or jitter on single fiber electromyography) and antibodies to AChR or

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**Table 1: Comparison of all studies on heart rate variability in myasthenia gravis and their conclusions**

| Study design          | Peric \textit{et al.} (2011) | Puneeth \textit{et al.} (2013) | Shukla \textit{et al.} (2013) | Nikolić \textit{et al.} (2014) | Present study |
|-----------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------|
| Study design          | Prospective case-control      | Prospective case-control      | Prospective case-control      | Prospective, stratified case-control | Prospective survey |
| Study period          | N/A                           | 2009-2010 (18 months)         | 2003-2005                     | N/A                           | 2014-2015 (14.5 months)         |
| Patients              | MGFA I-III                    | Osmerman Stage I and II only  | All symptomatic myasthenics   | All                           | MGFA V       |
| Sample size           | 21 cases, 21 controls         | 30 cases, 241 controls        | 27 thymoma positive, AChR antibody positive, 25 thymoma negative, AChR antibody positive 23 MuSK positive 23 controls | 16 cases, 29 admissions 9 AChR antibody positive 9 thymoma |

**Measurements**

- Conventional autonomic function tests, HRV analysis
- Reduced HF spectra: Para-sympathetic deficiency on conventional autonomic function tests
- Sympathetic hyper-reactivity and parasympathetic deficiency

**Results**

- Normal time domain and LF, reduced HF spectra: Parasympathetic deficiency on conventional autonomic function tests
- Reduced HF, increased LF: Prominent pupillary, orthostatic and gastrointestinal symptoms

**Inference**

- Para-sympathetic cardiac impairment
- Para-sympathetic hyperreactivity and parasympathetic deficiency

**Annotations**

- LF=Low frequency, HF=High frequency, AChR=Acetylcholine receptor, MuSK=Muscle-specific tyrosine kinase, MGFA=Myasthenia Gravis Foundation of America, N/A=Not available, HRV=Heart rate variability
muscle-specific kinase. Thymus status based on computerized chest tomography, surgical pathology and staging of thymoma and nerve conduction abnormalities were noted in addition to demographic data.

**Instruments and Measurement**

**Composite autonomic symptom scale-31 scoring questionnaire**

As the patients were confined to ICU on ventilator, conventional methods requiring patient cooperation during various respiratory and cardiac manoeuvres were precluded. Hence, the composite autonomic symptom scale 31 (COMPASS-31) autonomic symptom questionnaire was used as an alternative method of assessing autonomic dysfunction.[20] The abbreviated COMPASS 31 score was derived by statistical methods and expert review from the 169 question long COMPASS (Composite Autonomic Symptom Score).[21] It consists of 31 English language questions spanning 6 autonomic domains (gastrointestinal, orthostatic, pupillomotor, secretomotor, vasomotor, and bladder).[20] The score records occurrence symptoms suggesting autonomic dysfunction over the previous 1 year. Points are assigned for each question, and then, each raw domain score is multiplied by a weighting factor to generate the weighted domain score. These are added to obtain the final total score out of 100. This scoring system is a refined, internally consistent, validated method for assessing autonomic symptoms and has been demonstrated to correlate with conventional laboratory methods of assessing autonomic dysfunction. In this study, to identify the spectrum of autonomic dysfunction, the individual weighted domain scores as well as the total sum score was displayed to better describe the pattern of dysfunction in the different autonomic subsystems.

To address the symptomatology during the entire period of crises, the score was administered at exit from the ICU; this would, therefore, include all symptoms encountered during the crises.

**Heart rate variability analysis**

HRV was analyzed by 5-min electrocardiogram (ECG) recording in accordance with the guidelines supplied by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.

A validated physiological data recorder with customized recording, playback and analysis software, developed by the bioengineering department, was used. The sampling frequency was 500 Hz. The beat-to-beat interval was calculated for each beat using the peak R waves. The automatic detection of R waves was inspected and checked manually. From this, an interval tachogram was generated. This was used to generate a spectral pattern of the heart-rate variability using a Fast Fourier Transform-based nonparametric algorithm of averaging windowed periodograms. On this graph, the integral of the power spectral density (i.e., area under the curve, [Figure 1]) within various spectral bands was used to calculate the power of the LF and HF (high frequency) spectral bands. Results were displayed as nus of HF and LF spectra. The bands of spectra used were as follows: LF: 0.04–0.15; HF: 0.15–0.40; LF and HF (LF nu and HF nu) using the following formula: LF nu = (LF/[LF + HF]) ×100; HF nu = (HF/[LF + HF]) ×100. From these values, the ratio of LF nu to HF nu was measured.

All recordings were done with the patient stationary in a reclining or supine position, and all patients were in a similar position at the time of recording. Care was taken for appropriate grounding to avoid electrical artifacts. The recordings were done as per a once weekly schedule; as some patients had multiple serial recordings, the sample with highest LF nu: HF nu ratio (i.e., peak dysfunction) was chosen. By protocol, patients were off pyridostigmine on therapeutic “drug holiday” during the period of ventilator dependency.

**Statistical analysis**

The mean COMPASS 31 scores for individual domains and total were calculated. Statistical association with other disease characteristics was screened for using the t-test or Chi-square test, as appropriate. For analysis of HRV, the mean LF nu: HF nu ratio obtained was compared with the mean LF nu: HF nu from previously published noncrises myasthenic populations using the one sample mean comparison Wilcoxon rank-sum method for nonparametric data. Data were processed using Microsoft Excel (2013) and SPSS (v21, IBM Corp.) software.

**Results**

There were 16 patients admitted during the study, and all were included in the study. COMPASS 31 score was performed on all patients; however, HRV analysis was performed only on 14, due to the following limitations: One patient sought voluntary discharge immediately after admission, before the completing HRV recoding. The other patient had significant cardiovascular comorbidities requiring exclusion-aortic aneurysm, non-ST segment elevation myocardial infarction, and postcardiac arrest resuscitation status. His ECG rhythms were irregular-frequent atrial and ventricular premature complexes, sinus pauses,
benign myasthenic crisis. Hence, QRS complex fiducial point determination was unreliable, and the patient was excluded from HRV analysis.

The mean age of the study population was 41 years with majority of males (12 patients, 75%); males were older while females were younger (mean age 44.6 vs. 30.8 years, \( P = 0.05 \)); crises occurred most commonly in the 1st year of illness (median 7 months, I. Q. R. 3–12). Thymoma and acetylcholine antibody status was present in majority (9 patients, 56%) each. The median crises duration was 44 days (I. Q. R. 26–73). Proven infections were present in 7 patients (43.8%). Phrenic nerve dysfunction was present in 13 (81.3%), of which invasive thymoma (WHO B2/B3) was present in 8 (50%). Some patients had comorbid neurological illnesses: generalized tonic-clonic seizures (3 patients; MRI Brain in one showed T2 hyperintensities in thalamic, insular, subcortical white matter, and cerebellum suggesting a thymoma-associated autoimmune encephalitis); longitudinally extensive transverse myelitis (1 patient, AChR antibody positive, non-thymoma) and neuromyotonia (1 patient, AChR antibody positive, thymoma).

## Composite Autonomic Symptom Scale 31 Score

The mean COMPASS 31 score was 19.5 on 100 [Table 2]. Domain-wise, gastrointestinal symptoms (early satiety, postprandial bloating, abdominal cramps, vomiting, constipation, and diarrhea) were the most prevalent, followed by orthostatism (faintness, dizziness, or difficulty thinking during position change), and pupillomotor symptoms (sensitivity to bright light and difficulty in focusing the eyes). Vasomotor changes (peripheral acrocyanosis) and sudomotor (dryness of eyes, mouth, or abnormal sweating) were uncommon. One case of urinary retention was due to comorbid transverse myelitis [Table 2].

Female sex was associated with significantly higher COMPASS 31 scores \( (P = 0.02) \). There was no significant association with age \( (P = 0.82) \), prior duration of disease \( (P = 0.58) \), length of crises \( (P = 0.94) \), acetylcholine antibody status \( (P = 0.61) \), thymoma presence \( (P = 0.20) \), or nerve conduction abnormality \( (P = 0.57) \).

### Heart rate variability analysis

In the HRV analysis, the power spectrum revealed an abnormal reduction in the HF spectral domain [Figure 1] in thirteen out of fourteen patients analyzed, and the mean LF nu: HF nu ratio was 8.35 (standard deviation 5.4, 95% confidence interval 2.2–12.5). The HF spectra represent “fast” accelerations and decelerations of the heart rate (i.e., oscillations with latency between 2.5 and 6.6 s -inverse of 0.4 and 0.15, respectively, the upper and lower limits of this frequency band), while LF spectra represent oscillations requiring between 6.6 and 25 s (0.15–0.40 s); the former is predominantly vagus mediated whereas the latter is mediated by sympathetics and other factors. As the HF spectra were markedly reduced (i.e., blocked or slowed) whereas the LF was not abolished, these findings are consistent with parasympathetic cardiac dysfunction, with a tilt in the sympathovagal balance in favor of sympathetic overactivity.[22]

Ten out of 14 patients showed a significant HRV ratio >4.8 which reflects parasympathetic dysfunction with sympathetic overactivity. Five patients had ratio >1. However, there were no statistical significant associations were noted. The analyzed parameters included female sex (odds ratio [OR] 1.11 [0.13–9.41], \( P = 0.92 \)), AChR antibody positivity (OR 2.77 [0.44–17.62], \( P = 0.29 \)), invasive thymoma (OR 1.39 [0.40–4.71], \( P = 0.57 \)), and young age of onset (OR 1.11 [0.67–1.82], \( P = 0.64 \)).

The HRV index was also compared with published data from noncrises myasthenic population groups. Five different myasthenia subpopulations with their mean HRV indices were available in the comparison. This population (i.e., crises patients) had higher ratios than four others [Table 3]. The observations suggest that myasthenic patients in crisis reflect the population subset with most severe autonomic dysfunction and altered HRV.

### Discussion

Myasthenia Gravis is an antibody-mediated autoimmune disease where pathogenic antibodies to α-3 ganglionic acetylcholine receptor subunits cause autonomic dysfunction. The strength of this study lies in that to the author’s knowledge; it is the only present study to assess the autonomic dysfunction during myasthenic Crises, a population wherein these symptoms have never been characterized. Owing to ventilator dependency and confinement to ICU with severe motor weakness, conventional autonomic function tests including orthostatic tilt tests, isometric handgrip, and valsalva could not be done. The validated COMPASS 31 autonomic symptom scoring and HRV analysis were performed; the latter was compared with previously published HRV subsets of noncrises myasthenic populations.

The age and gender profile was consistent with the previous reports of myasthenic crises cohorts.[14,23] Acetylcholine antibody prevalence was lower though (56%, vs. 90%
in other studies), while Thymoma prevalence was higher (9 patients, 56%, vs. up to 18% reported elsewhere), possibly indicating a tertiary referral bias.

A high prevalence of autonomic dysfunction was noted as per COMPASS31 questionnaire (93%). Gastrointestinal symptoms were the most common, followed by orthostatic dizziness, and symptoms of internal oculomotor dysfunction, i.e., iris and ciliary dysmotility. Sudomotor symptoms of abnormal sweating and vasomotor abnormalities were not prominent. These symptoms may be accounted for by a parasympathetic deficiency. Orthostatic symptoms can arise without postural hypotension, as noted in the postural orthostatic tachycardia syndrome. In confirmation of this, Shukla et al. and Puneeth et al. did not note any significant blood pressure fall during tilt although heart rate rise was prominent.[13,14] One patient from our cohort had persistent orthostatic intolerance even after recovery from crisis and weaning from the ventilator. On doing the tilt test, she had features of postural orthostatic tachycardia [Figure 2].

Cardiac dysfunction in myasthenic crises has also been reported in association with antivoltage-gated potassium channel Kv 1.4 antibodies. One patient (not from study population), a late-onset myasthenia gravis, presented with acute breathlessness. His ECG [Figure 3] showed diffuse ST-T inversions, with left ventricular dysfunction. Coronary angiography showed only minor disease, and ECG changes improved with treatment of crises, possibly due to Kv1.4 antibody myocarditis.[26]

Visual blurring and sensitivity to bright light are rarely asked for in myasthenics but was found prevalent in 67.7% when screened for. Experimental infra-red electronic pupillography studies have demonstrated abnormalities restricted only to parasympathetically mediated pupillary constriction. The gastrointestinal symptoms in myasthenia may be a manifestation bowel hypomotility from parasympathetic dysfunction. Delayed gastric emptying represents parasympathetic dysfunction. Sluggish bowel motility resulting in bacterial overgrowth and deconjugation of bile acids can produce diarrhea and malabsorption. Gastrointestinal dysmotility has been reported in autoimmune myasthenia gravis, where α-3 ganglionic AChR antibodies were shown prevalent. The X-ray abdomen and computed tomography abdomen of one patient who had persistent GI dysmotility has been provided, showing dilated small bowel loops [identifiable by the valvulae conniventes – small bowel mucosal folds – Figure 4].

**Table 3: Mean low frequency in normalized unit: high frequency in normalized unit ratio of crises patients (this study) compared to noncrises myasthenic populations (14 patients)**

| Author (year) | Patients | n | LFnu/HFnu (mean±SD) | P |
|---------------|----------|---|---------------------|---|
| Present study | MGFA-V   | 14 | 8.35±5.4            |   |
| Previous studies | | | | |
| Puneeth (2013) | Osserman I/IIa | 30 | 2.94±0.54 | <0.01 |
| Nikolic (2014) | MGFA-I-IIB no thymoma, ACh antibody positive | 25 | 4.5±5.3 | <0.01 |
| MGFA-I-IIB, MuSK | 23 | 4.5±5.2 | 0.02 |
| MGFA-I-IIB Thymoma, ACh antibody positive | 27 | 9.6±20.3 | 0.43 |
| Peric (2011) | MGFA-I-IIB | 21 | 7.2±17.9 | 0.44 |

Mean LFnu: HFnu ratio is displayed in comparison with other population groups (one sample Wilcoxon signed-rank test for median was performed). Crises patients (this study) had larger LFnu: HFnu ratio (indicating more severe parasympathetic dysfunction) than 4 out of 5 populations (thymoma group from Nikolic et al. was the exception). The differences were statistically significant in three. These findings may suggest an increase in HRV index with increasing myasthenic disease severity. LFnu=Low frequency in normalized unit, HFnu=High frequency in normalized unit, MGFA=Myasthenia Gravis Foundation of America, ACh=Acetylcholine, HRV=Heart rate variability, SD=Standard deviation.
Some objections to parasympathetic deficiency are noted: a loss of parasympathetic tone would produce resting tachycardia, miosis, and signs of resting chronic sympathetic hyperactivity; however, these are conspicuously absent. In prior studies, Shukla et al. had reported no significant difference in resting RR intervals between patients and controls. In pupillary studies, no resting miosis was present, as the iris constriction deficiency only manifested during change in luminescence. These objections may be explained by invoking a dynamic, rather than static, parasympathetic deficiency. This may be considered as a “lag” in parasympathetic response during any state shift, which could explain the “apparent” sympathetic hyperactivity. This lag would produce increased latency for smooth muscle movements such as bowel and iris muscle. The LF spectral shift in heart rate and exaggerated heart rate rise also can be explained by increased latency of the parasympathetic vagal reflex arc. Therefore, parasympathetic “lag” may be the unifying thread behind the myriad symptoms reported in myasthenic crises.

Neurotransmission slowing in cholinergic synapses may explain this lag phenomenon. The ganglionic (alpha 3-type) neuronal AChR is responsible for fast synaptic transmission in sympathetic, parasympathetic, and enteric autonomic ganglia. Damage to postsynaptic ganglionic acetyl-choline receptors would lead to lowered excitatory postsynaptic potentials and increased latency in a feedback loop. Thus, parasympathetic “lag” is likely to represent the autonomic system parallel of weakness due to neuromuscular junction blockade.

The HRV results suggest increasing severity in crises as compared to noncrises myasthenics. Crisis patients had higher mean LF nu: HF nu ratios than most noncrises populations [Table 3]; the only exception belonging to the heterogenous thymoma group involving sicker patients-up to myasthenia Gravis Foundation of America IIB. This parallels motor weakness and thus reflects a similar autoimmune humoral pathogenesis.

These findings have therapeutic implications and practical utility. Abrupt challenges to the parasympathetic system as in postural tilt and valsalva can produce dangerous sympathetic hyperactivity and cardiac arrhythmias, as reported by Nikolić et al. and are to be strictly avoided. These precautions are applicable during the period of convalescence since after tracheostomy and prolonged ventilation, gradual, staged ambulation to sitting posture followed by standing is performed. Feeding schedules should be modified to account for slowed intestinal transit times. Sudden bright lights should be avoided to reduce discomfort. Caution in the use of adrenergic and vagolytic drugs is also advised as these would further aggravate the sympathovagal imbalance.

Concerns may arise regarding potential confounding bias in the ICU environment from infections, metabolic parameters, ambient temperature, status of hydration, and many unmentioned factors. The authors contend that in the ICU environment, ambient temperature, hydration, electrolyte status, and feeding schedules are strictly controlled and ought not to cause confounding. Since the prevalence of proven infections in the population was 43.8% (7/16), which is less than the prevalence of dysautonomia (93%), we believe there is a valid basis for attributing dysautonomia to the disease per se. Elimination of unknown biases requires finding a suitable ventilated control group which is not prone to dysautonomia. However, autonomic dysfunction is widely prevalent in common acute neurological emergencies such as transverse myelitis and Guillain-barre syndrome, precluding their usage as controls.

Some limitations of this study included non-demonstration of antibody titers to α3 ganglionic AChR subunit, to correlate with clinical and electrophysiological autonomic dysfunction. Quantitative sudomotor axon reflex testing availability for precise estimation of postganglionic sudomotor function may improve discrimination between cholinergic and noradrenergic involvement and strengthen the study conclusions. Further studies addressing these limitations are desirable. Within these limitations, the present study findings are likely to be valid in view of the presence of a dose-response relationship (i.e., increasing severity of autonomic dysfunction in crises than noncrises groups [Table 3], and the conformity of the pattern of dysautonomia to that which is reported previously in noncrises myasthenic populations, hence suggesting a common pathophysiological basis.

**Conclusions**

Myasthenic crisis is a complex autoimmune syndrome with dysfunction involving multiple organ systems, related to increased latency of parasympathetic responsiveness. A comprehensive management protocol incorporating different domains of autonomic dysfunction needs to be included for providing holistic patient care.

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**Conflicts of interest**

There are no conflicts of interest.
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