Original Article

Comorbidities and Long-Term Outcomes in a Cohort with Myasthenic Crisis: Experiences from a Tertiary Care Center

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Abstract

Introduction: There is scarce literature regarding the clinical course, comorbidities and long-term outcomes after myasthenic crisis (MC). The natural history of myasthenia gravis (MG) in this subset remains uncertain. **Methods:** The study included a cohort admitted with MC (2007–2017) in a tertiary care hospital. The comorbidities, outcomes after discharge, and prognostic factors were analyzed. **Results:** Sixty-two patients (89 episodes of MC) were included. Demographic data was comparable between the early- (<50 years) and late-onset (≥50 years) groups. Comorbidities included stress cardiomyopathy (14.5%), arrhythmias (6.4%), neuropathy (17.7%), pancytopenia (12.9%), encephalopathy (11.2%), neuromyotonia (4.8%), myelopathy (3.2%), and myositis (3.2%). Pulmonary embolism ($P < 0.008$), dysautonomia ($P < 0.002$), sepsis ($P < 0.008$), neuropathy ($P < 0.002$), and phrenic dysfunction ($P < 0.016$) were associated with prolonged ventilation. Majority of the patients (42, 67.7%) had a favorable outcome (disease status) as defined by remission/minimal manifestations at the time of last follow-up (median 36 months, IQR 15–66). Persistent bulbar weakness ($P < 0.001$), neuropsychiatric illness ($P < 0.001$), and comorbidities ($P < 0.017$) were associated with refractory MG. Eighteen patients (29%) had recurrent crisis. Eleven patients succumbed in the cohort. The main predictors of mortality were tumor progression ($P < 0.001$) and cardiac illness ($P < 0.004$). **Discussion:** A comprehensive treatment approach in MC will translate to good short- and long-term outcomes. The main cornerstones of therapy will include (1) Identification of refractory MG with the implementation of phenotype-based therapy; (2) Addressing comorbidities including cardiac autonomic neuropathy, bulbar weakness, phrenic dysfunction; and (3) Meticulous tumor surveillance.

Keywords: Comorbidities, Muscle-specific tyrosine kinase, myasthenia gravis, Myasthenic crisis, Myasthenia Gravis, Refractory Myasthenia Gravis, Thymoma

Introduction

The natural history of myasthenia gravis (MG) is unpredictable. Recent literature supports the role of subgroup classifications, phenotype-based therapy, and long-term immunotherapy in MG.[1] 15–20% of myasthenic patients are affected by the myasthenic crisis (weakness severe enough to require intubation) at least once in their lives.[2,3] Nearly, 10–15% of MG patients have disease refractory to conventional treatment. With advances in intensive care, the mortality rate in myasthenic crisis (MC) has decreased from as high as 42% in the 1960s to 4% at present.[4-7] Majority of the studies have implicated the role of comorbidities in the overall prognosis of patients with MC.[5] A few patients need rehabilitation after hospitalization. The psycho-social and financial burden among "crisis survivors" also require a special mention.[8]

There is scarce data in the literature regarding the long-term follow-up outcomes and disease status in patients following the first episode of MC. So, the natural history of MG (although modified by drugs) in this subset of patients remains uncertain. The data on comorbidities and concomitant diseases associated with the crisis has also been limited to case reports with a lack of systematic studies.

The objectives of the present study included

1. To study the demographic details, comorbidities, outcomes, and prognostic predictors in a cohort of patients admitted with their first episode of MC.
2. To observe the outcomes of the cohort after discharge with respect to disease status (remissions, recurrence of the crisis, and exacerbations), overall survival, and to analyze the associated prognostic factors.
3. To identify the subset of this cohort with refractory MG.

Methods

The study was approved by the Institutional Review Board and Ethics Committee (IRB min 10715/2017). The study included

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retrospective analysis of a cohort of patients (>16 years of age) admitted with MC in the Neuro-Intensive care unit (ICU) of a tertiary care center in south India between 1st January 2007 and 30th October 2017. The diagnosis of MG was based on clinical features, repetitive nerve stimulation studies (RNS), and antibody testing (acetylcholinesterase antibody; AchRAb). Patients with negative AchRAb underwent testing for anti-muscle-specific kinase (MuSK) antibodies. AchR antibody was assessed by radioimmunoassay (RIA) and MuSK antibody by enzyme-linked immunosorbent assay (ELISA).

All patients satisfied the diagnostic criteria for MG, which required the presence of fatigable muscle weakness with either pathogenic antibodies (AchRAb/MuSK Ab) or a decremental response on RNS (with the exclusion of other diseases).[9] MC was defined asmyasthenic weakness severe enough to require intubation due to airway compromise, secondary to respiratory or bulbar dysfunction. The patients after stabilization and recovery from the crisis were discharged and followed up in the Neuromuscular Clinic. The patients had the facility to access the physicians to communicate any interim illnesses/worsening. The Myasthenia Gravis Foundation of America (MGFA) class, disease status (remission, worsening, and exacerbations), and medication history are routinely documented in the medical records as a standard of care. Only patients with a postcrisis follow-up of at least 1 year were included in the study.

The data collected from our prospectively maintained electronic data base included: (1) Demographic characteristics (age, gender, age at onset, subtype of MG, comorbidities, thymus and thymectomy status, antibody status, precipitating factors, duration of crisis, treatment); (2) MGFA class at discharge after crisis and each follow-up; (3) Timing of remissions, crisis and exacerbations during the follow-up. The diagnosis of thymoma was confirmed by histopathology in all the cases.

The outcome parameters (adapted from MGFA)[10] included complete stable remission (CSR, no symptoms/signs for at least 1 year and no therapy); pharmacological remission (PR, same as CSR except that the patient continued to take some form of medication, excluding cholinesterase inhibitors); minimal manifestations (MM, no symptoms or functional limitations but some weakness detectable by examination). The changes in disease status recorded as worsening, exacerbation, improved, unchanged, and crisis. A minimum of 12-month follow-up was required to calculate CSR and PR.

The number and proportion of patients with different outcome measures during the follow-up were studied. Patients with outcome parameters (remission and minimal manifestations) at the time of follow-up were considered to have a "favorable outcome". Prognostic factors which were analyzed included age at onset, a subtype of MG, antibody status, the status of the thymus, prior thymectomy and presence of comorbidities. MG was defined as refractory if there was a lack of clinical control on immunotherapy, inability to lower immunotherapy without relapse, severe side-effects from immunotherapy or presence of comorbidities-limiting treatment.[11]

Treatment Protocol: All patients with MC were managed in the ICU. Cholinesterase inhibitors were avoided during ventilation to reduce bronchial secretions and increase sensitivity ("drug holiday"). The rescue agents used were plasma exchange or intravenous immunoglobulin (IVIG), depending on the patient comorbidity and hemodynamic stability. Plasma exchange was the first option unless contraindicated. Corticosteroids and immunosuppressants were chosen based on medical comorbidities. Corticosteroids were started after completion of plasma exchange/IVIG. Considering the side-effects of long-term steroids, a steroid-sparing immunosuppressant was added prior to discharge from hospital. Rituximab and cyclophosphamide were considered early if there were features suggestive of refractory MG prior to the crisis. Change of immunosuppressant was made if there was a suboptimal therapeutic response or recurrent crisis despite the use of an optimal dose of the first agent for at least 6-12 months. The doses of agents used were azathioprine (2-3 mg/day), mycophenolate mofetil (1000 mg twice daily), rituximab (375 mg/m^2 once weekly for 4 weeks as induction) and cyclophosphamide (500 mg/m^2 once monthly). In patients with anti-MuSK Ab MG, plasma exchange was preferred over IVIG and rituximab was considered as a first therapeutic option. All patients had a nerve conduction study (with phrenic conductions) and repetitive nerve stimulation studies at the time of admission. The electrophysiological studies were repeated if there was a difficulty in weaning off the ventilator or worsening of neuromuscular weakness.

Statistical analysis

Statistical analysis was performed using SPSS version 16 (Chicago, Illinois). Continuous variables were represented as the mean (standard deviation) and median (interquartile range). Categorical variables were represented as numbers (percentage). Categorical variables were tested for association using Chi-square and/or Fischer's exact test. Multiple binary logistic regression analysis was done to test for statistical significance. *P* value was significant at two-tailed 0.05 level. Survival analysis was done using Kaplan-Meir curves. The log-rank test was used to compare the survival curves.

Results

Sixty-two patients with autoimmune MG (with 89 episodes of crisis) were included in the study. The precipitating factors for the crisis in the cohort were infection in 31 patients (50%), drug withdrawal/induced in 16 patients (25.8%), and post intervention (thymectomy/chemotherapy/radiotherapy) in 9 patients (14.5%). The comparison of demographical variables between the "early onset (<50 years)" and "late onset (≥50 years)" groups is as shown in Table 1. The data was comparable with respect to most of the baseline variables.

"Late onset MG" was more likely to have an invasive thymoma. The comorbidities were high in "late onset MG". The median time to the crisis, after the onset of symptoms, was

shorter in the invasive thymoma group (3.5 months, IQR 2–12 months) compared to noninvasive thymoma (7 months, IQR 2.37–13.25 months) and nonthymomatous group (6 months, IQR 5–14 months). The difference was not statistically significant (*P*-value = 0.71).

Plasma exchange or IVIG were the primary rescue treatment in 61 patients. The duration of ventilation was similar in both groups. Four patients underwent thymectomy, while in crisis, in view of newly diagnosed invasive thymoma.

"Comorbidities and concomitant illness" identified during the crisis

The cardiac illness was noted in 12 patients. The spectrum included myocardial stunning (9), cardiac arrhythmias (4), and pericarditis (1). Two patients had both myocardial stunning and cardiac arrhythmias. Bronchopneumonia was diagnosed in 20 patients (32.2%). Other pulmonary comorbidities included underlying bronchiectasis (3) and restrictive lung disease (2). Pulmonary embolism was diagnosed during crisis in 6 patients. Myocardial stunning was diagnosed in patients who had worsening oxygenation, reversible diffuse ST-T wave changes on ECG (not restricted to vascular territories), elevated cardiac troponins, and echocardiogram showing left ventricular (LV) dysfunction. These changes were reversible and patients had symptomatic improvement [Figure 1]. There was a temporal correlation noted with IVIG administration in three cases. Myocardial stunning could also represent a form of cardiac autonomic neuropathy (CAN). A cardiology consultation was obtained in all cases. The type of arrhythmias included artioventricular block (AV) requiring temporary pacing (1), atrial tachycardia (1), nonsustained ventricular tachycardia (1), and ventricular bigeminy (1). It is also important to note that three patients had sudden cardiac death (attributable to arrhythmias) within 3 months of hospital discharge. Cardiac abnormalities were significantly more in late-onset MG ($P = 0.012$). There was no significant association among males ($P = 0.88$), thymoma ($P = 0.61$), and occurrence of cardiac abnormality in our cohort. Cardiac arrhythmias have been depicted in Figure 2a, b and c.

Table 1: Comparison of baseline demographic variables between the "early onset MG (<50 years)"and "late onset MG (≥50 years)" groups

Parameter	Early onset (40 patients)	Late onset (22 patients)	*P*
Male	20 (50%)	15 (68.2%)	0.16
Age at onset (years)	32.22 (10.76)	56.89 (13.28)	<0.001*
Time to crisis (months)	19.16 (32.25)	16.47 (31.44)	0.11
Antibody positive	38 (95%)	22 (100%)	0.18
AChR antibody	32 (80%)	22 (100%)	
MuSK antibody	6 (15%)	-	
Seronegative	2 (5%)		
Thymoma	19 (47.5%)	13 (59.1%)	0.38
Invasive Thymoma	14 (40%)	12 (54.5%)	0.13
Thymectomy Before crisis	10 (25%)	6 (27.2%)	0.84
Precipitating factors Identified			
Infection	21 (52.5%)	10 (45.5%)	0.59
Drug withdrawal/induced	12 (30%)	4 (18.2%)	0.21
Post thymectomy/ chemo-radiotherapy crisis	3 (7.5%)	6 (27.2%)	0.03*
Rescue			
Treatment	35 (87.5%)	10 (45.4%)	<0.001*
Plasma Exchange	9 (22.5%)	12 (54.6%)	0.01*
IVIG			
Comorbidities & concomitant illness	17 (42.5%)	19 (86.4%)	0.001*
Duration of mechanical ventilation (days)	16.87 (10.31)	19.04 (8.88)	0.37

(Data presented as mean (SD))

Peripheral neuropathy was identified in 11 patients. The etiology of the same was determined based on priorsymptoms suggestive of neuropathy, baseline electrophysiological changes, and temporal evolution in those requiring serial nerve conduction studies. The etiologies included critical illness neuropathy (5), paraneoplastic/immune-mediated cause (4), and diabetes mellitus (2). All the patients with neuropathy were males ($P = 0.001$).

Transient encephalopathy was noted in 7 patients. Electroencephalogram (EEG) showed slowing of background activity in all these patients during the encephalopathy. Clinical seizures occurred in 5 patients. The etiology was identified as probable autoimmune encephalopathy (4 patients, 3 patients with thymoma), sepsis-associated encephalopathy (2), and hyponatremia (1) [Figure 2d]. The encephalopathy improved in all patients. There was no significant statistical association with sex ($P = 0.71$), age of onset ($P = 0.89$) or presence of thymoma ($P = 0.21$).

Other comorbidities noted in the cohort included pancytopenia (8 patients), neuromyotonia (3 patients), and myositis (2 patients). One patient had quadriparesis with difficulty in weaning of ventilator during the ICU stay. MRI showed longitudinally extensive transverse myelitis (LETM). Anti-aquaporin antibody test was negative. Another patient developed myelopathy on follow-up with a magnetic resonance imaging (MRI) showing cervical cord hyperintensity [Figure 2e]. One patient had systemic lupus erythematosus (SLE, ANA 2+ homogenous, anti-ds DNA titre 148 IU/ml, normal <100 IU/ml). Another patient had persistent sicca symptoms with mildly elevated anti-SSA (21 Ru/ml, normal <20 IU/ml). Minor salivary gland biopsy was not done in this patient. Vitiligo was noted in 2 patients and thyroiditis in 20 patients. There was no statistically significant association among sex ($P = 0.52$), age of onset ($P = 0.31$) and presence of thymoma ($P = 0.08$). Six patients had neuropsychiatric manifestations (4, depression; 2, anxiety) with poorly controlled disease ($P < 0.001$).

Abnormal phrenic nerve conductions were identified in 19 patients (30.6%). Six of these patients had invasive thymoma with baseline phrenic dysfunction. Three had a crisis developing in the postoperative period following thymectomy (for thymoma). Causes attributed in the others

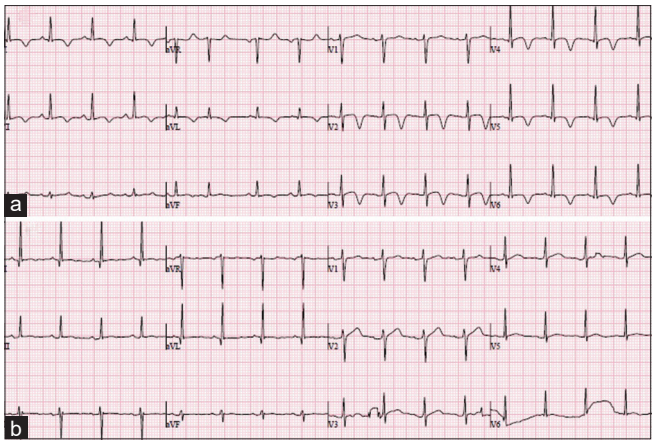

Figure 1: Myocardial stunning noted in a 67-year-old gentleman during a crisis. (a) diffuse T-wave inversions with prolonged QT, (b) reversal of changes in subsequent ECG. Coronary angiogram was normal

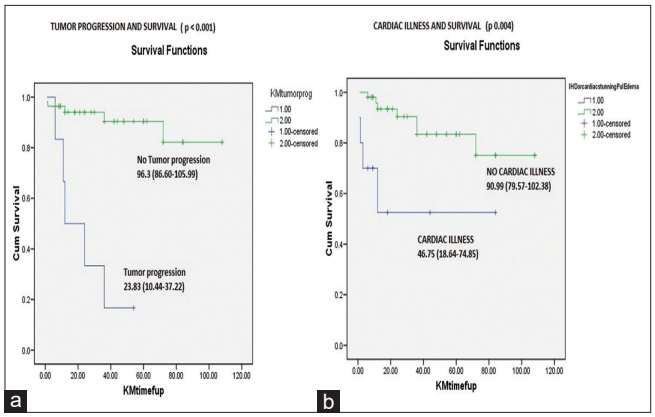

Figure 3: Kaplan-Meir survival analysis curves for mortality. Both (a) tumor progression ($P < 0.001$) and (b) cardiac illness ($P < 0.004$) had a significant association with mortality in the cohort

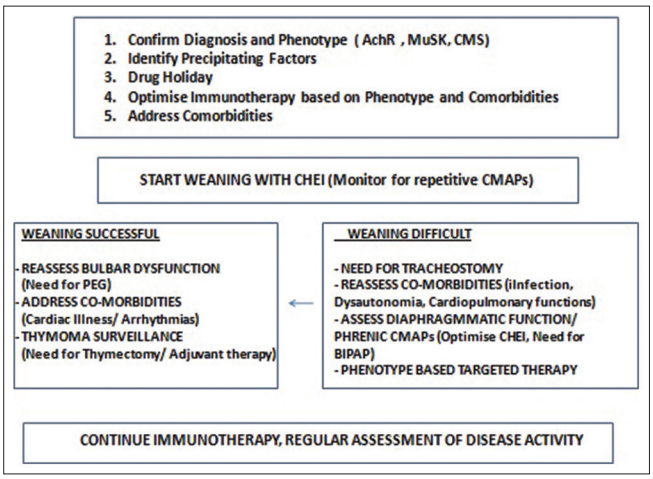

Figure 5: An algorithm for management and follow-up of patients with Myasthenic crisis. (CMS -Congenital Myasthenic Syndrome, CHEI - Cholinesterase Inhibitor, PEG – Percutaneous Endoscopic Gastrostomy)

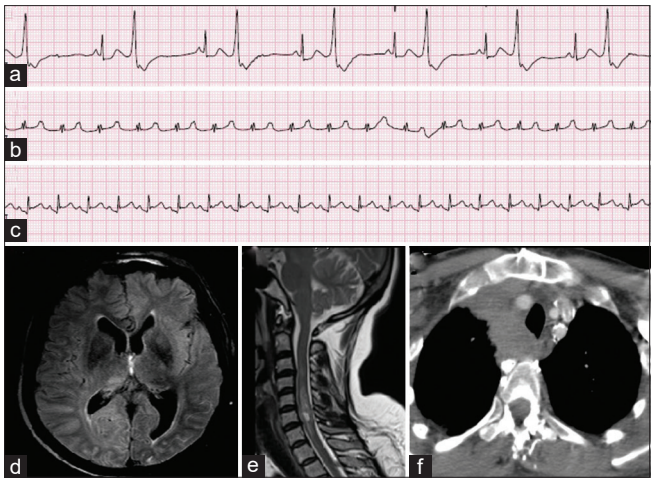

Figure 2: Concomitant Illnesses in Crisis. (a) 49–year-old with ventricular bigeminy, (b) 62–year- old with junctional tachycardia aggravated by pyridostigmine, (c) 57-year-old with diffuse ST elevation and ECHO showing pericarditis, (d) 64-year-old with invasive thymoma and encephalopathy, MRI showing FLAIR sulcal changes in insular cortex and parieto-occipital lobes, (e) 23-year-old with MRI showing cervical cord hyperintensity, (f) 33-year-old with dyspnea and features of thymoma recurrence with superior vena cava syndrome and airway infiltration

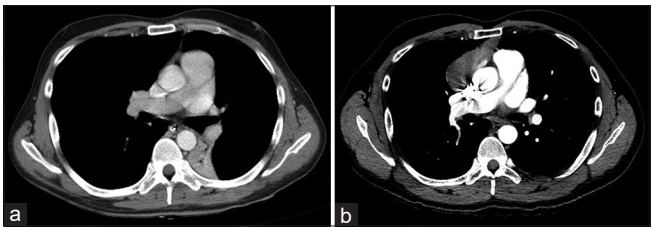

Figure 4: The CT thorax at first admission (a) during the crisis and subsequent CT thorax done after 2 years follow-up (b). The thymoma was not evident on the first scan and was only detected on the second scan

included the severity of MG with functional denervation of the diaphragm (5) and critical illness neuropathy (5). Ultrasound-guided needling of diaphragm showed features of active denervation in 4/5 patients.

Outcomes of crisis and condition at discharge

The median time of mechanical ventilation was 14.5 days (5-43 days). Prolonged ventilation, more than 15 days, was required in 30 patients (48.4%). The factors significantly associated with prolonged ventilation included were male gender , anti-MuSK Ab, pulmonary embolism, autonomic dysfunction, phrenic nerve dysfunction, nosocomial infection, and peripheral neuropathy [Table 2]. On logistic regression, the presence of coexistent neuropathy (P = 0.02) was associated with the need for prolonged ventilation. The median duration of ventilation was longer in the thymoma group (17.6 days, IQR 12.75-27.25 days) compared with non thymomatous group (12 days, IQR 9-17 days) with a trend toward statistical significance (P = 0.08).

Pre-existing comorbidities mainly included hypertension (17 patients), diabetes mellitus (11 patients) and ischemic heart disease (3 patients). None of these were significantly associated with the need for prolonged ventilation (P value = 0.37, 0.20 and 0.32 respectively). The mean duration of ventilation in the patients receiving plasma exchange (16.9 days, SD = 9.90) was shorter than those receiving IVIG (19.52 days, SD = 9.60). The difference was not statistically significant ($P = 0.35$).

Majority of patients (49, 79.1%) had a mild generalized weakness (MGFA ≤2b) at discharge. One patient with invasive thymoma, endobronchial infiltration of tumor, superior vena cava syndrome, and chronic pulmonary embolism died in hospital [Figure 2f]. There were four deaths reported within three months of hospital discharge. All these patients had improved at the time of discharge. Three patients had a sudden cardiac death attributable to cardiac arrhythmia (two of them occurred in sleep). All the three were elderly myasthenics (>60 years) with diabetes mellitus and had documented myocardial stunning during the crisis. One patient with bronchiectasis died due to recurrent infection at a healthcare center near home.

Selection of immunotherapeutic agent was based on disease phenotype, severity, and comorbidities. The post crisis immunotherapy received was as follows: intermittent plasma exchange (4), IVIG (6), cyclophosphamide (16), mycophenolate (20), azathioprine (12), and rituximab (9). Presence of invasive thymoma in a large number of patients accounted for the high proportion of cyclophosphamide use in the cohort. Corticosteroids were tapered and stopped after initiation of second-line immunotherapeutic agents in 38 patients. Six patients were required to switch to rituximab during follow-up visits.

Follow up

Median duration of follow-up was 36 months (IQR 15-66 months); 38.6% had a follow-up for 1-2 years, 8.7% for 2-3 years, 12.2% for 3-4 years, 8.7% for 4-5 years and 31.8% had follow-up for ≥5 years. Persistent bulbar weakness (even after 6 months) was observed in 16 patients.

Refractory MG: The clinical course in 17 patients (27.4%) was consistent with criteria defined for refractory MG. The break-up of this group according to refractory criteria was as follows: not clinically controlled on immunotherapy 10 patients (58.8%), inability to lower immunotherapy without clinical relapse 3 patients (17.6%), side effects from immunotherapy 1 patient (5.8%), co-morbidities limiting treatment 3 patients (17.6%). Eight of them had thymoma. The characteristics associated with refractory MG included: persistent bulbar weakness (OR 11.47, 95% CI 3.72-35.31, $P < 0.001$), neuropsychiatric illness (OR 13.23, CI 1.66-105.23, $P < 0.001$), and presence of comorbidities (OR 1.68, CI 1.16-2.44, $P < 0.02$). Six patients with refractory MG succumbed to death in the cohort. Of the remaining 11 patients, 6 patients (54.5%) with refractory MG were in "well controlled" disease status (remission/minimal manifestations) at last follow-up compared with 36 patients (90%) in the non-refractory MG group (P = 0.015)

Recurrent crisis: Eighteen patients (29%) required hospitalization due to the recurrence of the crisis. The number of episodes of crisis during follow-up was one (10 patients, 16.1%), two (7 patients, 11.3%), and three (1 patient, 1.6%). The main predictor of the recurrent crisis was a persistent bulbar weakness (OR 3.14, CI 1.38-7.14, P P = 0.005). Tumor progression was found in 6 patients (18.8% of thymomas). The median time to develop a second episode of the crisis was 15 months (IQR 12-21 months).

Outcome at last follow-up: The disease status/outcome at last follow-up was CSR (2,3%), PR (28,45%), MM (12,19%), Improved (9,14%) and death (11,18%). The causes of mortality (after 6 months of first crisis) were tumor progression in 5 patients and chronic kidney disease in 1 patient. Two patients had second malignancy in addition to the thymoma. The association of potential predictors with mortality in the cohort has been depicted in Table 3. The impact of cardiac illness and tumor progression on overall survival rates has been depicted in the Kaplan-Meir survival curves [Figure 3].

The proportion of patients with the good outcome at last follow-up for each immunotherapeutic agent was as follows: oral agents– azathioprine/mycophenolate mofetil (90.6%);

Table 2: Factors associated with need for prolonged mechanical ventilation (>15 days)

Factor	OR (95% CI)	*P*
Male sex	1.6 (1.01-2.52)	0.04*
Early onset MG	1.86 (0.91-3.80)	0.07
Anti-MuSK Ab	2.15 (1.62-2.85)	0.013*
Anti-AchR Ab	1.44 (0.22-9.33)	0.69
Thymoma	1.55 (0.94-2.56)	0.07
Time to crisis <6 months	1.20 (0.74-1.90)	0.46
Thymectomy before crisis	1.06 (0.45-2.48)	0.88
Invasive Thymoma	1.45 (0.8-2.64)	0.21
Cardiac stunning	2.48 (0.71-8.75)	0.13
Pulmonary embolism	2.33 (1.72-3.15)	0.008*
Autonomic dysfunction	2.37 (1.28-4.35)	0.002*
Nosocomial infection	2.98 (1.22-7.98)	0.008*
Coexistent Neuropathy	10.667 (1.40-78.37)	0.002*
Phrenic nerve dysfunction	1.98 (1.10-3.57)	0.016*

Table 3: Factors associated with mortality in the cohort

Factors	OR (95% CI)	*P*
Male sex	1.61 (1.09-2.36)	0.06
Early onset (<50 years)	1.73 (0.68-3.41)	0.13
Duration of ventilation (> 15 days)	1.68 (1.04-2.72)	0.07
Invasive thymoma	1.70 (0.96-3.02)	0.11
Persistent bulbar weakness	2.18 (1.28-3.70)	0.01*
Tumour progression	15.71 (2.18-112.83)	< 0.001*
Cardiac illness	3.09 (1.04-9.14)	0.004*

rituximab (86.7%); and cyclophosphamide (75%). The immunosuppressants were generally well- tolerated. Blood counts, liver functions and renal functions were monitored regularly while on azathioprine, mycophenolate, and cyclophosphamide. There were two cases with persisting leucopenia in the azathioprine group requiring drug withdrawal and reduction in dose, respectively. One patient developed symptomatic hepatitis attributable to mycophenolate. One patient in the cohort developed tuberculosis on follow-up.

Thymus status

Thymectomy was done in 39 patients. Thymoma was present in 32 patients with invasive thymoma in 26 patients. Seven patients had thymic hyperplasia. Sixteen patients had thymectomy before their first crisis, 19 had thymectomy after their first crisis. Majority of patients with prior thymectomy (87.5%) had good outcome at follow-up (OR 1.08, 95% CI 0.86-1.37, $P = 0.52$).

Four patients had thymectomy, during their ICU admission for the crisis, after stabilization with plasma exchange. Twenty patients received adjuvant therapy (radiation/chemotherapy). Progression of tumor with metastasis was seen in 7 patients. Two patients were diagnosed with thymoma, only on a follow-up visit, as the thymic mass was not evident on the initialcomputed tomography (CT) thorax. [Figure 4]

Discussion

Recent studies in MG have focused on the aspects of subgroup classification, phenotype-based therapy, the relevance of thymectomy in non thymomatous MG and the need for long-term immunotherapy[1,11]. There have been increasing reports on comorbidities and concomitant autoimmunity in MG.[4,5,12] The factors associated with prolonged duration of the crisis include atelectasis, ventilator associated pneumonia, male gender, and older age.[13,14] However, there have been only few studies which have analyzed the nature of comorbidities and the long-term follow-up outcomes of MG after crisis.[6,15] Cohen *et al.* in one of the earliest series on MC had reported mortality during a crisis (25%), out of hospital mortality (3%), recurrence of crisis (34%) and remission/improvement (16.4%).[6] With current advances in critical care and treatment, one would expect the outcomes to be significantly better.

This study of the cohort included MG patients who had been admitted with their first episode of MC in our Neuro-ICU. The salient features of the study included a relatively large number of patients (62 patients admitted with 89 episodes of crisis) with a reasonably long duration of follow-up in our Neuromuscular clinic. There was a high proportion of thymoma in the cohort.

Cardiac comorbidities need special mention in view of the high prevalence and morbidity associated with the same in our cohort. The heart muscle has been identified to be a potential site of inflammation in MG with giant cell myocarditis well-described. The spectrum of cardiac involvement includes stress cardiomyopathy, neurogenic cardiac stunning, cardiac conduction defects, and pericarditis. These are more likely to occur in the elderly and those with severe MG. Antibodies against striated muscles (anti-titin, anti-ryanodine, and anti-Kv 1.4 antibodies) have been implicated.[16]

Stress cardiomyopathy occurs in the setting of physical/emotional stress, autonomic dysfunction, and circulating catecholamines with usual occurrence in the early morning. The clinical presentation mimics an acute myocardial infarction with symptoms of chest pain and dyspnoea. A possibility of stress cardiomyopathy or neurogenic cardiac stunning is considered, in the presence of diffuse reversible ECG changes (T inversions, occasional ST elevations). with mild elevation of cardiac troponins and characteristic echocardiographic changes.[17] There is a prompt resolution of symptoms after treatment of the MC.[18-20] The syndrome is often observed in patients with coexistent Grave's disease, ischemic heart disease, and myositis. Most of the patients receive standard management for acute coronary syndrome. Fluid restriction and judicious use of diuretics have an important role in treatment. It is important to note that IVIG and plasma exchange could worsen stress cardiomyopathy due to fluid overload and hemodynamic instability, respectively.[21,22] Cases of coronary vasospasm and AV blocks with pyridostigmine have been described.[17,23] The prevalence of cardiac dysfunction in our cohort was similar to previous observations by Cohen *et al.* (19.7%) and Alsheklee *et al.* (8.2%). Probably, the prevalence of cardiac morbidity is under-reported.[4,6]

The concerns about sudden cardiac death secondary to cardiac autonomic neuropathy (especially in elderly) warrant a close follow-up with optimal medical care (including drugs such as cardioselective beta-blockers, amiodarone) and Holter monitoring. Need for interventions such as auto-implantable cardiac defibrillators (AICD) and cardiac revascularization should be assessed. High mortality rates from cardiac arrhythmias have been mentioned in previous studies.[5,6,24] Other comorbidities in the cohort included were encephalopathy, neuropathy, neuromyotonia, pancytopenia, myositis, and occurrence of LETM. These concomitant illnesses have been described in the setting of MG.[25-27] Biomarkers such as anti-striational antibodies, anti-VGKC antibody, anti-aquaporin, and nicotinic ganglionic receptor antibodies can help validate the prevalence of these disorders in systematic studies. Valuable clues may also be obtained from genome-wide association studies (GWAS) and type of common human leukocyte antigen (HLA)-alleles.[28]

The mean duration of ventilation and predictors of need for prolonged ventilation were similar from previous reported studies. Autonomic dysfunction, peripheral neuropathy, and phrenic nerve dysfunction were shown to be associated with delayed extubation. There is a scarce mention of these factors in the literature. Phrenic nerve dysfunction was observed in the setting of sepsis, cardiac dysfunction, severe MG, thymoma

with phrenic infiltration, and critical illness neuropathy (CIN). Phrenic neuropathy could also be an immune-mediated entity or restricted form of CIN with "functional denervation" of the diaphragm.[29,30] Prospective studies will help validate the role of these factors in prolong ICU stay.

In a study by Liu *et al.* on long-term outcomes after MC, high rates of recurrence of crisis (60.6%) were noted.[31] The rates of recurrence (29%) were relatively lower in the present study. Conventional medications (azathioprine, mycophenolate, cyclophosphamide) are effective in the treatment of MG. It is important to identify patients with "refractory MG" as they represent a distinct clinical entity with a different immunopathological mechanism and therapeutic strategies. MuSK -MG causes antibody-mediated disruption of the neuromuscular junction without the binding complement.[32] This subset tends to respond better to plasma exchange and rituximab. Cell-based assays (CBA) may be required for estimating their exact prevalence.[33] Newer medications like rituximab, eculizumab, belimumab are capable of providing better disease control in refractory cases.[32] Novel agents scuh as Granulocyte Monocyte – Colony Stimulating Factor (GM-CSF) enhance regulatory T-cell function and suppress polyclonal T-cell proliferation with therapeutic benefits.[34] The use of colony-stimulating factors can also be combined using immunoablation with a high dose of cyclophosphamide. Five patients in our cohort received GM-CSF injections.

Due importance needs to be given to Persistent bulbar weakness and diaphragmatic weaknesswhich could lead to the recurrent crisis. Interventions such as percutaneous endoscopic gastrostomy (PEG) and use of bilevel positive airway pressure (BIPAP), for respiratory support, could help in symptomatic improvement and prevent further crisis till the time remission is achieved. The psychological and financial stress associated with recurrent hospitalization will be reduced by these interventions. Depression is an under-recognized entity which is associated with refractory MG. Treatment options for the same are limited in the setting of MG.

An early tracheostomy in patients, likely to require prolonged ventilation, would help in easier weaning andreduced duration of ICU stay with the resultant less financial burden. A patient- guided physician-supervised approach to weaning might be warranted in a selected group of patients. Infections in autoimmune neuromuscular disorders could occur due to both, immune dysregulation secondary to disease and as side effects of immunotherapy. Vaccination and antibiotic prophylaxis could prevent recurrent infections (which potentiate crisis). Azithromycin and fluoroquinolones should be avoided considering their unfavorable profile in MG. Myasthenic worsening, with high ambient temperatures in tropical countries, during summer also needs a mention.

Tumor progression was significantly associated with mortality in the cohort. This emphasizes the need for regular tumor surveillance and aggressive adjuvant therapy (RT/chemo) in this group of patients. Based on this discussion, an algorithm for treatment and follow-up of patients with MC has been depicted in Figure 5. This could especially be of value in resource- crunch settings in the developing countries.

The main limitation is the retrospective nature of the study. A prospective study would provide a more accurate prevalence of comorbidities. There could be an inherent selection bias with more severe patients (with comorbidities, thymomas, refractory MG) being admitted, as our hospital is a tertiary referral care center. Comprehensive antibody testing could not be done in all the patients with comorbidities, considering their non availability during earl periods of the study. No reliable comparisons could be made about the different treatment regimens, considering the retrospective nature of the study.

Conclusions

Comorbidities (still under-reported) influence the severity and outcomes in patients with MC. Prospective studies with biomarkers and data from GWAS will give a more reliable estimate of their prevalence. The mainstays of management include optimal immunotherapy for the crisis, an aggressive approach to comorbidities with special reference to CAN, addressing bulbar and diaphragmatic weakness, phenotype-based therapies and meticulous tumor surveillance. Overall, efficient management of an acute exacerbation of MG will translate into favorable long-term outcomes.

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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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Conflicts of interest

There are no conflicts of interest.

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