Section: General Medicine

Original Research Article

THE TITLE OF THE ARTICLE CLINICAL COURSE AND OUTCOME OF MYASTHENIC CRISIS IN A TERTIARY CARE HOSPITAL IN SOUTH INDIA: AN OBSERVATIONAL STUDY

Parvathy K.S.[1], E. Uma Maheshwari[2], Aiswarya G Kumar[3], S. Balasubramanian[4]

[1]Assistant Professor, Department of General Medicine, Government Medical College, Trivandrum, Kerala, India.
[2]Assistant Professor, Institute of Neurology, Madras Medical College, Tamilnadu, India.
[3]Consultant, Department of Neurology, Sunrise Hospital, Kochi, Kerala, India
[4]Director, Institute of Neurology, Madras Medical College, Tamilnadu, India.

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Corresponding Author:
Dr. Parvathy K S,
Email: ksparvathysaneesh@gmail.com.

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Abstract

Background: Despite being the most common disorder of the neuromuscular junction, Myasthenia gravis has an annual incidence of 0.25-2 patients per 100 000 and only 15-20% of these will have a myasthenic crisis. **Aim:** This study aimed to examine the incidence of mortality among patients admitted to the neurology ICU with a myasthenic crisis. **Material and Methods:** Patients admitted to the medical and neurology ICU during the study period with myasthenic crisis were enrolled in this study. The clinical course, along with significant past medical history, explored the onset and duration of myasthenia gravis, triggers, comorbidities, antibody status, electrophysiological diagnosis, thymic status, and previous treatment. Patients diagnosed with myasthenia crisis are given acute crisis management and the outcomes are measured. **Results:** The mean age of onset was 51.5 years in 20 patients with myasthenic crises. 12 were previously diagnosed with myasthenia gravis, and 8 presented with a crisis without prior diagnosis of myasthenia. The mean duration from onset to crisis was 20.3 months. The male-to-female ratio was 1.5:1. Dysphagia is the predominant symptom. The most important triggers are infections and drug defaults. The Myasthenia Gravis Foundation of America (MGFA) score was predictive of outcome. Most patients received IVIG because of its ease of administration and accessibility. **Conclusion:** Early diagnosis and mechanical ventilation with protocol-based ICU care improved survival in myasthenia crisis, with the severity of clinical presentation (MGFA score) directly associated with the outcome. Control and management of trigger factors (drug defaults, sepsis, etc.). Thymectomy had a significant impact on the outcomes.

INTRODUCTION

Myasthenic crisis is associated with a significant mortality rate in patients with myasthenia gravis (5-12%).[1,2] Myasthenic crisis is a complication of myasthenia gravis characterised by worsening of muscle weakness, resulting in respiratory failure that requires intubation or non-invasive mechanical ventilation, or prevents extubation following an elective procedure.[3] Hence, it is important to identify the predictors of this life-threatening complication and to prevent them. Due to the rarity of this condition, our understanding of its complications, treatment outcomes, and prognostic factors remains poor.

This study aimed to improve our understanding of the predictors of severity and outcome of various treatment modalities. This study aimed to examine the incidence of mortality among patients admitted to the neurology ICU with myasthenic crisis, study the determinants of mortality, and study the demographic profile, clinical presentation, investigation results, and treatment outcomes of patients with myasthenia crisis.

MATERIALS AND METHODS

This prospective study was conducted on 20 consecutive patients with myasthenia crisis who presented between June 2021 and June 2023 in the department of neurology at Madras Medical

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College. Patients admitted to the medical and neurology ICU during the study period of 2 years with Myasthenic crisis were identified and enrolled.

Inclusion Criteria

Patients presenting with bulbar and/or generalised myasthenia features, whose diagnosis was confirmed with a repetitive nerve stimulation test or antibody status (acetylcholine receptor or muscle-specific kinase antibody), and patients presenting with clinical features consistent with myasthenic crisis were included.

Exclusion Criteria

Patients diagnosed with ocular myasthenia gravis, clinical features not consistent with myasthenic crisis, myasthenia gravis requiring ventilatory support for indications other than myasthenic crisis (congestive cardiac failure, acute respiratory distress syndrome, etc.), and perioperative myasthenia crisis were excluded.

A clinical course with significant medical history was obtained. A detailed questionnaire, including onset, duration of myasthenia gravis, triggers, comorbidities, antibody status, thymic status, electrophysiological diagnosis, and previous treatment, was administered.

Patients meeting the diagnosis of myasthenia crisis were given acute crisis management, and the outcome was measured. The outcome was analysed, and the effects of different treatment modalities were compared. Complications that developed in these patients were studied. The recovered patients were followed-up to assess their current status.

The treatment outcomes measured included recovery of the patient from an acute myasthenic crisis and mortality from the disease. Patients were followed up during treatment in the hospital, and the outcomes were measured.

Statistical Analysis

All data collected were coded and entered into a Microsoft Excel sheet which was re-checked and analysed using SPSS statistical software version 25. The Shapiro-Wilk test was used to check the normality of the distribution. Quantitative variables were summarised using mean and standard deviation (SD) or median and interquartile range (IQR), depending on the normality of distribution. Categorical variables are presented as frequencies and percentages. Independent sample t-test and Mann-Whitney test were used to test the statistical significance of differences between means of variables among different independent groups, depending upon the normality of distribution. Pearson Chi-square test and Fisher's Exact test were used for comparing categorical variables between groups. Statistical significance was set at $p < 0.05$.

RESULTS

The demographic profile and salient findings of this study are summarised in Table 1. [Table 1]

Sepsis (10 patients) and drug default (9 patients) were the most important triggers for crises in our patients. Recent changes in immunosuppressants, from azathioprine to mycophenolate mofetil, were the trigger in one patient. Stopping drugs and switching to native medication triggered a crisis in another patient. Hypokalaemia and inadequate dosage of immunosuppressants were the precipitating factors in one patient. No identifiable triggers were identified in the other case. Table 2 shows the data regarding previous medications in 12 patients with known cases of MG. [Table 2]

All the patients were administered pyridostigmine. Nine patients defaulted treatment. Seventeen patients showed a decremental response to Repetitive Nerve Stimulation (RNS). In three patients who presented with a crisis, RNS could not be performed because they required ventilator support from the day of admission and could not be shifted to the electrophysiology laboratory. They were diagnosed on the basis of clinical findings, ice pack tests, and AChR antibody status.

Acetylcholine receptor antibody was positive in 17 (85%) patients and negative in 3 patients. In these three patients, anti-MuSK antibody was also performed, which was negative (double seronegative). Chest CT was performed in all the patients to assess the status of the thymus. Thymoma was present in 8 patients (40%). Twelve patients (70%) had normal thymus glands. Of the 8 patients with thymoma, only 4 underwent thymectomy. None of the patients with normal thymus underwent thymectomy.

One of the patients was a young female with thymoma with pleural metastasis who did not undergo thymectomy, defaulted treatment, and started alternative medication. On admission, her MGFA (Myasthenia Gravis Foundation of America) score was V, and she died. The MGFA clinical classifications of the study population are presented in Table 2.

The MGFA score on admission was V in four patients. Eleven patients had MGFA IVB scores on admission. All the patients required intubation and mechanical ventilator support. Four patients had MGFA IIIB on admission and required non-invasive ventilatory support. One patient was admitted with MGFA IIB who required NIV 5 days after admission due to worsening respiratory insufficiency. The average single-breath count was 11 in our patients. Observations from ICU stay are summarised in Table 3. [Table 3]

The mean duration of the ICU stay was 24 days. The maximum duration of ICU care was 92 days for each patient, and the patient recovered despite the development of multiple complications during the treatment. The number of days in the ICU was the lowest for patients treated with NIV. The mean duration of illness in patients previously diagnosed with myasthenic crisis was one year (12 months). 16 patients received IVIG as the treatment, of which 12 received only IVIG and the other 4 received

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combined treatment.1 patient received IVMP followed by IVIG followed by plasma exchange. The patient recovered after treatment, and 2 patients received IVIG and PLEX. One patient who received combined treatment with IVIG and PLEX died. One patient who received IVIG and IVMP (died). PLEX was not performed due to sepsis.

Among the seven patients who succumbed to the illness,1 patient was treated with IVIG and PLEX,1 patient with IVIG and IVMP, two patients with PLEX alone, and three patients with IVIG alone. Among the 13 patients who recovered, 1 patient was treated with IVIG and PLEX, 1 patient was treated with IVIG, IVMP, and PLEX, 2 patients with PLEX alone, and 9 patients with IVIG alone. Ventilator support was required in 14 patients (70%). Among these,10 patients developed VAP (70%). Six patients were treated with intravenous NIV. None of the patients experienced secondary complications. The mean MGFA score of the patients requiring NIV was IIIB. [Table 4]

Ventilator-associated pneumonia was the most common secondary complication observed in our study. The other complications that occurred in our patients were bacteraemia in four patients (20%), cardiac arrhythmia in one patient, and hypocalcaemia in another patient treated with PLEX. The most common cause of bacteraemia and sepsis was central intravenous catheter-related infection (two patients), followed by pneumonia (1patient) and urinary catheter-related infection (one patient). All secondary infections developed in patients requiring ventilator support, and their duration of hospital stay was longer. Both patients who developed central venous catheter CVC-related infections underwent plasma exchange.

All patients who died developed ventilator-associated pneumonia. Among the patients who recovered from the illness, 7 developed VAP. Only 1 patient in our study had a history of myasthenic crisis, and he succumbed to the illness during admission. One of the patients in our study who presented with a crisis was started on IVIG after 5 days due to a delay in diagnosis, and he succumbed to the illness. Current medications included pyridostigmine in all patients, MMF in nine patients (69.3%), steroids in six patients (46.2%), azathioprine in three patients, and neostigmine in one patient. The steroid dose was tapered to < 10 mg/day in 4 patients. Azathioprine was discontinued in some patients and MMF was initiated. [Table 5]

Factors associated with outcome

The mean age of mortality was 54.86±16.97. The mean age of recovery was 49.15±11.65. The mortality rate was higher in the older age groups. Among the 10 patients with early onset myasthenia (≤50 years), 8 (80%) recovered, whereas only 5 of 10 patients (50%) recovered in the late-onset group. Of the 13 male patients, five died (38.5%), and of the seven female patients, two died (28.6%). The mean age of onset was 54.86±17.28 for the patients who died and 47.92±12.16 for those who recovered. The age of onset was lower in recovered patients.

Among the 12 patients who were previously diagnosed with myasthenia gravis, four (33.3%) died and seven (66.7%) recovered. Among the eight patients who presented with a crisis, three (37.5%) died and five (62.5%) survived. Ten patients in our study had prior comorbidities, of which 4 (40%) died. DM was the most common comorbidity. Among those without prior comorbidities, 70% survived. Of the 17 AChRAb-positive patients, 6 (35.3%) died and 11 survived. Of the three patients who were negative for both AChRAb and MUSK, two patients died (66.7%) and one survived.

Twelve patients had a normal thymus, of which five patients died (41.7%). Eight patients had thymoma, of which two patients died (25%). Eight patients had thymoma, of which two patients died. None of the patients underwent thymectomy. One patient had thymoma with pleural metastasis. Four patients who underwent thymectomy recovered. Two patients with thymoma, who did not undergo thymectomy, also recovered. Of these two patients, one was a male of 38 years of age who required 92 days of hospital stay with 86 days of ICU care and was treated with IVIG, PLEX, and IVMP. The patient's MGFA score was IVB on admission, and had severe respiratory insufficiency.

The other patient who recovered was a female, 55 years old, who required 20 days of ICU care and presented with an MGFA score of IV B. Two patients who had not undergone thymectomy died. All patients who presented with an MGFA score of V succumbed to the illness. The median RR was 35, and the SBC was less than 6 in patients who died. Sixteen patients received IVIG, of which 5 died (31.3%), and out of 7 patients who received PLEX, 3 died (42.7%). Ventilator support was required in 14 patients, 50% of whom recovered. Patients who required only NIV did not have any mortality.

Of the 12 diagnosed myasthenic cases, 7 patients had thymoma (58.3%). Among the eight patients whose diagnosis was made during the current admission with crisis, only one patient had a thymoma, and the other seven patients had a normal thymus. Of the eight patients with thymoma, one patient was newly diagnosed during the current admission, and the remaining seven cases were previously diagnosed. Of the 12 patients with a normal thymus, 7 were newly diagnosed and 5 were previously diagnosed.

Among the eight patients with thymoma, there were four males (two early onset and two late onset) and four females (three early onset and one late onset). Among the early onset cases (≤ 50 years) (5 cases), there were two males (40%) and three females (60%). In the late-onset group, 66.7% (n=2) were men and 33.3% were women. In the early onset group, the majority of the patients had thymoma. In the late-onset group, two-thirds of the patients had thymoma.

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The mean duration of ICU stay was 27 days for patients with thymoma and 22 days for normal thymomatous patients. The median number of days on the ventilator was 20 and 16 days for thymomatous and non-thymomatous cases, respectively. The duration of ICU care for patients who underwent thymectomy was 9 days and 42 days for those who did not undergo thymectomy. The number of days on the ventilator was 7 days for patients who underwent thymectomy and 32 days for those who did not undergo thymectomy.

Of the eight patients with thymoma, four had undergone thymectomy, and only one required ventilator support and recovered. No mortality was observed among the patients who underwent thymectomy. Among the four patients, three had early onset MG (two females and one male) and one (male) had late-onset MG. All 4 patients who did not undergo thymectomy required ventilator support. Two of these patients survived (one female with late onset and one male with early onset), and two died (one female with early onset and 11 males with late onset).

Table 1: Demographic profile and salient findings

Description	Value
Demographic profile	
Age in years [mean, range]	52.50, 44 to 58.75
Sex [Male, Female]	13, 7
Age of onset of myasthenia [mean, range]	51.50, 43.25 to 57.75
Age of onset <50 years [Total; Male: Female]	10; 6:4
Age of onset >50 years [Total; Male: Female]	10; 7:3
Previously diagnosed cases	12
Newly diagnosed during MC	8
Number of patients with generalised MG	20
Clinical symptoms	
Bulbar symptoms	
Dysphagia	18 (90%)
Dysarthria	16 (80%)
Dyspnoea	14 (70%
Nasal regurgitation	13 (65%)
Other symptoms	
Ptosis	15 (75%)
Limb weakness	14 (70%
Diplopia	13 (65%)
Neck flexor weakness	12 (60%)
Comorbidities	**Number (%)**
Diabetes mellitus	7 (35)
Hypothyroidism	3 (15)
Bronchial asthma	2 (10)
Hypertension	1 (5)
CAD	1 (5)
CVA	1 (5)
Nil	10 (50)

MG: Myasthenia Gravis; MC: Myasthenic Crisis; Cad: Coronary Artery Disease; CVE: Cerebro Vascular Accident

Table 2: Previous medications and MGFA (Myasthenia Gravis Foundation of America) Clinical Classification

		N (%)
Previous medications	Pyridostigmine	12 (100)
	Steroid	6 (50)
	Azathioprine	6 (50)
	Mycophenolate mofetil	2 (16.7)
MGFA score	V	4 (20)
	IV B	11 (55)
	III B	4 (20)
	II B	1 (5)

Table 3: Observations from ICU stay

Duration of ICU stay-days	
Mean ± SD	24.45±21.49
Median (IQR)	15.50 (11-30)
Number of days on ventilator-days (N=14)	
Mean ± SD	23.79±21.19
Median (IQR)	17 (10.75-29.50)
Number of days from onset to admission-days	
Mean ± SD	13.20±8.21
Median (IQR)	15 (5.50-18.75)
In-hospital treatment	Number (%)
Plasma exchange (PLEX)	16 (80)

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IV methylprednisolone (IVMP)	7 (35)
IV methylprednisolone (IVMP)	2 (10)
Type of mechanical ventilation support	Number (%)
Invasive Ventilator	14(70)
NIV	6(30)

SD: Standard deviation; IQR: Interquartile Range; NIV: Non-Invasive Ventilation

Table 4: Complications

Complications - N (%)	
Ventilator-associated pneumonia	10(50)
Bacteremia	4(20)
Arrhythmia	1(5)
Hypocalcaemia	1(5)
Nil	6(30)

Table 5: Duration of ICU stay and number of days on ventilator in thymoma and normal patients

Variable		Thymus status		P value
		Thymoma (N=8)	Normal (N=12)	
Duration of ICU stay	Mean ± SD	27.88±30.07	22.17±14.41	
	Median (IQR)	14(6.50-43)	19.50(12-29)	0.757
		Thymoma (N=5)	Normal (N=9)	
Number of days on a ventilator	Mean ± SD	33.60±32.62	18.33±10.19	
	Median (IQR)	20(9-65)	16(12-24)	0.548

DISCUSSION

Our study showed a bimodal distribution of age at presentation, as proposed by most authors including Wendell et al. in 2011.[4-7] We had more male patients in both early and late-onset groups in contrast to the previous studies where females outnumbered males in the early onset group and equalled males in the late-onset group.[4] The apparent reversal of male: female ratio is similar to the report by Panda et al. from North India in 2004.[8] The median interval from the onset of myasthenic symptoms to MC in our study was 20.3 months, which following a study conducted by Murthy et al.[9]

In our study, 7 patients were diagnosed with MG during their current admission with crisis (MC). Bulbar symptoms (dyspnoea, dysphagia, and dysarthria) were the predominant clinical presentations in our patients. A strong association was found between severe bulbar symptoms and MC development in the presence of precipitation factors. Infection and drug default constitute the major triggers of MC, similar to other reports.[8-10] The affordability of drugs, accessibility, and lack of awareness may be the key issues leading to drug default in our population. Close vigilance is required when switching from one drug to another and during steroid tapering. Most authors have reported that in up to 30% to 40% of MC cases, no obvious trigger can be identified.[11]

Similar to other studies, the use of accessory muscles for respiration, low single breath count, and oxygen saturation predicted a significantly longer duration of ICU stay and poor prognosis (p=0.011). A higher MGFA score was also predictive of adverse outcomes (p = among the late-onset group), and mortality was found to be high. All patients with MC received early mechanical ventilation, as per the protocol in the ICU settings. Ventilator-associated pneumonia (VAP) is the most common complication, as mentioned in similar studies.[12,13] However, a combination of early and effective mechanical ventilation, adequate antibiotic therapy, and aggressive immunotherapy reduces the duration of MC. Aggressive respiratory intervention comprising the use of suction, intermittent positive pressure ventilation, bronchodilator treatment and chest physiotherapy helps shorten the course of MC.[14]

In the present study, the mortality rate was 35% (7 of 20). Mortality was high in the late-onset group. Although associated with mortality rates as high as 50–80% in the 1960s, MC is now often reported to be fatal in many fewer cases as a result of the development of intensive care techniques. This has largely been achieved by improved intensive care facilities, early mechanical ventilation, management of precipitating factors, use of acetylcholinesterase inhibitors (AChEI), steroids, antibiotics, plasmapheresis (PP) and intravenous immunoglobulin (IVIG). Patients with thymoma develop more frequent episodes of crisis, respond less adequately to immunosuppression, require aggressive therapy with fewer chances of achieving complete remission, and have higher mortality.

In our study population, 40% of patients had thymoma, of which 50% underwent thymectomy and had no mortality. Those who did not undergo thymectomy had a 50% mortality rate. Over time, with improvements in perioperative care, the results of thymectomy have improved, and thymectomy has found its place in the treatment integrity of MG.[15] Those who underwent thymectomy had a better prognosis, especially in young-onset females. The clinical presentation was less severe in those who underwent thymectomy and could be managed with NIV in the majority of cases. Patients who recovered were followed up for 6 months.

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In our study, we did not analyse data related to other parameters that might have affected clinical outcomes, including maximal expiratory pressure and maximal inspiratory pressure, in pulmonary function tests. As it is a rare condition, the cohort size may be too small to derive assertive recommendations. However, compiling data from different regions or populations may be used to validate the current trends mentioned in the literature.

CONCLUSION

Patients presenting with myasthenic crisis have a significant cohort with high mortality. Hence, awareness of the disease is necessary, and physicians should maintain a high index of suspicion. Early diagnosis and mechanical ventilation with protocol-based ICU care improve survival in myasthenia crisis, and the severity of clinical presentation (MGFA score) is directly associated with the outcome. Control and management of trigger factors (drug defaults, sepsis, etc.). Thymectomy had a significant impact on the outcomes.

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