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ORIGINAL ARTICLE

Predictors of outcome of myasthenic crisis

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Abstract There is paucity of study on predictors of myasthenic crisis (MC), prolonged ventilation and their outcome, a reason why this study was undertaken. Sixty-four patients with myasthenia gravis (MG) were included whose median age was 45 (6–84) years. Their clinical treatment, presence of thymoma, anti-acetylcholine receptor antibody (AchRAb), thymectomy, comorbidities, offending drugs and occurrence of MC were noted. Patients needing prolonged ventilation (>15 days) were noted. Hospital mortality, MG quality of life (QOL) at discharge and thereafter annual hospital visit, admission, expenditure and work day loss were enquired. Fourteen (21.9 %) patients had MC within 1–120 (median 8.5) months of disease onset within a median follow-up of 48 (3–264) months. The precipitating factors were infection in six, surgery in five, tapering of drugs in two and reaction to iodinated contrast in one patient. Male gender, bulbar weakness, AchRAb, thymoma, surgery and comorbid illnesses were related to MC. Eight of them (57.1 %) needed prolonged ventilation. Half the patients with MC had recurrent crisis (2–4 attacks). Death was not related to MC although MC patients had worse QOL, higher annual treatment expenditure with frequent hospital visit and hospitalization. In conclusion, association of comorbid illness with MC and prolonged ventilation highlights the need of close follow-up and appropriate management.

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Introduction

Myasthenia gravis (MG) is an autoimmune disease of neuromuscular junction in which antibody against acetylcholine receptor (AchRAb) results in destruction of postsynaptic AchRAb through complement-mediated injury. MG is thought to be a disease with grave prognosis, earlier with 40 % morality, but in the recent era, with improving intensive care facility and immune modulating drugs, mortality has dropped to 5 % [1]. The development of myasthenic crisis is a neurological emergency and patient should be ideally treated where he could be intubated and ventilated, and the physician is well conversed with management of myasthenic crisis. About 15–20 % of MG patients may develop myasthenic crisis [2, 3]. Myasthenic crisis (MC) is more common within 2 years of illness and is precipitated by infection, fever, aspiration, pneumonia, inadequate treatment, use of offending drugs, physical and mental stress and following thymectomy or other surgery [4]. Infection is the most common cause in the reported series [5–8]. These patients are also prone to infection due to concomitant use of corticosteroid and other immunosuppressant. Recurrent crisis may also result in high expenditure, work day loss and poor quality of life. In the developing countries MC may be more because of high prevalence of infection, poor hygiene and use of offending drugs by local physician due to unawareness. There is no longitudinal study from northern India evaluating predictors of MC and prolonged ventilation and their subsequent outcome. In this longitudinal study, we

report the frequency and predictors of myasthenic crisis as well as the determinant of prolonged ventilation and outcome.

Materials and methods

Inclusion criteria

The patients with MG attending to neurological service of a tertiary care teaching hospital, India, were included. This study includes patients with prospective follow-up of the patients recruited in last 3 years as well as retrospective information of those patients coming for follow-up who were registered to our institute since 1991. These patients were managed personally by two of the authors (JK and UKM) throughout their illness. Their previous data were retrieved from the computerized hospital information service and discharge summary as well as they were personally interviewed about their earlier period since the diagnosis of MG was made.

Exclusion criteria

Patients with congenital myasthenia, chronic renal failure, liver failure, malignancy, toxins, snake bite and patients with incomplete information were excluded.

Evaluation

A detailed medical history and examination were undertaken. Their demographic data (age, gender, residence, education, dietary habit), history of smoking, alcohol and tobacco consumption, hypertension, diabetes, pregnancy, congestive heart disease and stroke were noted. The medications for comorbidities were also noted and any offending drugs were identified. The onset of myasthenic symptoms such as ocular, limb, bulbar or respiratory was noted and classified as per Osserman classification [9]. The duration of illness, progression of disease and initiation of treatment for myasthenia including the treatment regimen were noted.

During the follow-up, the occurrence of MC and their precipitating causes (fever, infection, surgery, drugs, initiation or withdrawal of steroid, stress, etc.) were noted. The duration of intubation and mechanical ventilation as well as duration of hospital stay were noted. The recurrence of crisis was also noted along with the above mentioned information.

Quality of life (QOL) in the patients with MG was assessed by MG-QOL15 at follow-up [10]. The quality of life in children was not used in statistical analysis as many parameters were not applicable to children.

Investigations

Blood counts, ESR, hemoglobin, urinalysis, fasting and postprandial blood sugar, serum creatinine, bilirubin, transaminase, albumin, calcium, phosphorus, potassium and sodium were tested. Blood, urine and endotracheal aspirate culture were done in the patients with suspected infection. All the patients underwent thyroid profile, Ach-RAb and repetitive nerve stimulation test. CT thorax was done using third generation CT scanner or spiral CT scanner. The presence of thymoma or thymic hyperplasia was noted. Electrocardiogram was done in all and echocardiography in selected patients. The patients with thymoma or seropositive MG within 15–55 years of age were advised thymectomy. The operative details including extubation time and biopsy report were noted in the patients undergoing thymectomy.

Definition of myasthenic crisis and prolonged ventilation

Myasthenic crisis was defined as respiratory failure needing mechanical ventilation due to respiratory or bulbar muscle weakness [5]. Following thymectomy, if extubation was not possible after 24 h MC was also considered [11]. Prolonged ventilation was considered when patient required mechanical ventilation for more than 15 days [5].

Treatment

The patients were managed by standard management protocol for MC. Acetylcholine esterase inhibitors were withdrawn at least for 48 h and the patients were mechanically ventilated. Once the spontaneous breathing was adequate to sustain normal oxygen saturation for 30 min, they were prescribed acetyl choline esterase inhibitor and the period of mechanical ventilation was gradually reduced. For weaning, we have used CPAP or T-piece. In the patients requiring prolonged ventilation, tracheostomy was done. Patients on corticosteroid and azathioprine were continued with these medications and naive cases were prescribed prednisolone at a dose of 0.5 mg/kg who did not have apparent infection, uncontrolled diabetes, hypertension or pregnancy. The dose of AchE inhibitors was adjusted according to the clinical need. The occurrence of ventilator-associated complications was noted.

Outcome and follow-up

Death during hospital and QOL at discharge were noted. Patients were advised to come for follow-up at 3–6-month interval or earlier if needed and their clinical conditions

and development of recurrent crisis were noted. In all the patients with MG the number of visits to the hospital, admission due to crisis or aggravation of symptoms, work day loss, and average expenditure of treatment per year were noted. In children and students work day loss was considered if they were unable to go to school and/or play.

Statistical analysis

The patients with MC were compared with those without crisis in terms of their demographic, clinical thymectomy, thymoma, treatment protocol and outcome using Fisher's exact test for categorical and independent *t* or Mann–Whitney *U* test for continuous variables. The patients with MC and with prolonged ventilation (>15 days) were compared with those needing short duration of ventilation ($\leq$15 days) in terms of their demographic, clinical, treatment protocol, precipitating factors and ventilator-associated complications using Fisher's exact test for categorical and independent *t* test/Mann–Whitney *U* test (if the data is normally distributed) for continuous variables. The variable having a two-tailed value $\leq$0.1 was included in multivariate logistic regression analysis for predicting MC and prolonged ventilation. The variable was considered significant if two-tailed *P* value was $\leq$0.05. The statistical analysis was done using SPSS 12 version software.

Results

Sixty-four patients with MG were included whose median age was 45 (6–84) years and 25 (39 %) were females. Twenty-three patients were above the age of 50 years and five were children (<15 years). All the patients were followed up for at least 12 months except one who was followed up for 3 months. The median duration of the follow-up was 48 (3–264) months; 12 patients were followed up for 12 months, 9 for 24 months, 7 for 36 months, 10 for 48 months, 5 for 60 months and 20 were followed up for more than 60 months. At the first visit to us, the severity of MG was Osserman grade I in 6 patients, grade IIa in 27, grade IIb in 23, and grade III in 5 and IV in 3 patients. All the patients had significant decremental response at 3 Hz repetitive nerve stimulation test except five patients with ocular myasthenia whose prostigmine test was positive. AchRAb was positive in 52 (81.3 %) patients. Anti-Musk antibody was done in nine patients who were negative for AchRAb and only one patient was positive. CT/MRI of thorax was done in 54 patients and revealed thymic hyperplasia in 5 and thymoma in 13. Twenty-four patients underwent thymectomy and their biopsy revealed thymoma in 12 and benign thymic hyperplasia in 5 patients.

Generalized MG patients were prescribed prednisolone (0.5–0.75 mg/kg) and azathioprine (2–3 mg/kg). Prednisolone was not prescribed to the ocular MG patients and those with uncontrolled diabetes and hypertension, pregnancy, severe osteoporosis and elderly (>65 years of age). Azathioprine was not prescribed to children and pregnant MG patients. The doses of cholinesterase inhibitors were variable depending on need of the patients (median dose 180 mg, 90–345 mg/day). With these medications, 53 (82.8 %) patients could return to their occupation.

Myasthenic crisis

Fourteen (21.9 %) has myasthenic crisis within 1–120 (median 8.5) months of disease onset; eight patients within 2 years and six after 2 years of onset of MG. The precipitating factors were infection in six, post thymectomy in five, tapering of drugs in two and one patient had crisis after administration of iodinated contrast agent for CT scan.

Predictors of myasthenic crisis

On univariate analysis MC was more frequent in males compared to females (85.7 vs 54 %; $P = 0.03$). Patients with MC had significantly higher AchRAb compared to those without MC (29.37 $\pm$ 8.30 vs 15.3 $\pm$ 0.55 nmol/ml; $P = 0.01$). Presenting severity of MG ($P = 0.02$), presence of bulbar weakness (71.4 vs 8 %; $P < 0.01$), thymoma (50 vs 14.2 %; $P < 0.01$) and thymectomy (50 vs 34 %; $P < 0.01$) were associated with MC compared to those without. The frequency of comorbid illness was significantly higher in patients with MC than those without crisis (64.3 vs 10 %; $P < 0.0001$). The other variables such as age ($P = 0.33$), dose of azathioprine ($P = 0.72$), prednisolone ($P = 0.14$) and dose of choline esterase inhibitors ($P = 0.94$), however, were not related to MC. The details are summarized in Table 1. On multivariate analysis none of the variables were significantly related to myasthenic crisis. Seven (50 %) patients had recurrent crisis; all had bulbar weakness and all but one were males. Two patients had crisis twice, four patients thrice and one had four times.

Prolonged ventilation

Out of 14 patients who developed MC, 8 (57.1 %) needed prolonged ventilation ranging from 16 to 60 (median 36) days. Female patients, comorbid illness, thymectomy surgery, thymoma and ventilator related complications were significantly related to prolonged ventilation. The initial severity of MG, precipitating cause of crisis, hemoglobin, serum albumin and treatment were not related to prolonged ventilation. Hospital stay was insignificantly longer in

Table 1 Relationship of clinical and laboratory findings in the patients with and without myasthenic crisis (MC)

Parameters	MC ($N = 14$, 21.9 %)	No MC ($N = 50$, 78.1 %)	P value
Age in years	47.55 ± 16.0	41.76 ± 19.8	0.33
Male	12 (85.7)	27 (54)	<0.01
Severity of MG			
Grade 1	1 (7.1)	5 (10)	0.02
Grade 2a	5 (35.7)	22 (44)	
Grade 2b	4 (28.5)	19 (38)	
Grade 3	1 (7.1)	4 (8)	
Grade 4	3 (21.4)	0 (0)	
Recurrent infection	7 (50)	10 (20)	<0.01
Bulbar weakness	10 (71.4)	4 (8)	<0.01
AchRAb titer (nmol/ml)	29.37 ± 8.3	15.3 ± 0.55	0.01
Thymoma	6/12 (50)	6/42 (14.2)	<0.01
Thymectomy	7 (50)	17 (34)	0.03
Corticosteroid (mg/day)	12.2 ± 4.5	10.2 ± 3.07	0.14
Azathioprine (mg/day)	83.3 ± 28.8	75 ± 28.8	0.72
CE inhibitor (mg/day)	204.0 ± 93.5	205.9 ± 64.2	0.94
Comorbid illness	9 (64.3)	5 (10)	<0.01

Percentage values are given within brackets

CE choline esterase, *MG* myasthenia gravis

prolonged intubated group (39.8 ± 42.9 days) compared to those patients who were intubated less than 15 days (10.6 ± 6.1 days, $P = 0.07$). All these eight patients with prolonged ventilation were tracheostomized. The details are summarized in Table 2.

Outcome

Four patients died; two with myasthenic crisis and two without. One patient with MC died in the hospital and three after discharge (two at home and one at local hospital). The causes of death are summarized in Table 3. Patients with crisis had worse QOL at discharge (17.5 vs 8.5; $P = 0.02$), higher annual treatment expenditure (Rupees 40,150 vs 31,328; $P = 0.03$) and more frequent consultation (3.9 vs 1.6; $P = 0.003$) and hospitalization (3.1 vs 1.5; $P = 0.01$) compared to those without MC. The details are summarized in Table 4.

Discussion

In our study, 21.9 % patients developed MC, majority developed MC within 2 years of symptoms which was most frequently precipitated by infection followed by thymectomy surgery and drug tapering. Male gender, comorbid illness, severity of illness, bulbar weakness, AchRAb titre, thymoma and thymectomy were related to MC and they had worse QOL at discharge, frequent hospital visit and hospitalization and higher annual treatment expenditure. More than half needed prolonged ventilation especially in the patients with comorbid illness. Myasthenic crisis, however, was not related to death.

Table 2 Determinants of prolonged ventilation in the patients with myasthenic crisis

Parameter	Ventilation > 15 days ($N = 8$, 57.1 %)	Ventilation < 15 days ($N = 6$, 42.9 %)	P value
Male	6 (75)	6 (100)	<0.01
Age in years	49.62 ± 18.1	44.3 ± 14.4	0.56
Duration of ventilation	36.7 ± 14.2	6.3 ± 1	0.01
Thymoma	3/7 (42.8)	0/6 (0)	<0.01
Thymectomy	4/8 (50)	1/6 (16.6)	<0.01
AchRAb raw value	7 (87.5)	5 (83.3)	0.42
AchRAb (nmol/ml)	31.1 ± 10.6	27 ± 4.9	0.56
Comorbidities	4 (50)	5 (83.3)	<0.01
Bulbar symptom	6 (75)	4 (66.6)	0.27
Crisis after surgery	4 (50)	3 (50)	0.88
Complications during ventilation	6 (75)	0 (0)	0.01
Pneumonia	6 (75)	3 (50)	<0.01
Septicemia	6 (75)	3 (50)	<0.01
Diarrhea	1 (14.2)	0	<0.01
Corticosteroid	6 (75)	2 (33.3)	<0.01
Tracheostomy	8 (100)	0 (0)	<0.01
Death	1 (14.2)	1 (16.6)	0.69
Hemoglobin (g %)	10.6 ± 2.7	13 ± 1.8	0.08
Albumin (g/dl)	3.4 ± 0.6	3.5 ± 0.5	0.65

Percentage values are given within brackets

Table 3 Causes of death in the patients with myasthenia gravis

Patient	Group	Age in years	Causes of death	Died at home/ hospital
1	Crisis	84	Pneumonia, septicemia, thalamic bleed, Koch's lung, knee osteoarthritis	Hospital
2	Crisis	53	CAD, during coronary bypass developed cardiac arrest	Hospital
3	No crisis	11	Aspiration asphyxia during drinking a glass of milk	Died at home
4	No crisis	18	Cause not known	Died at home

CAD coronary artery disease

Table 4 Comparison of clinical, quality of life and economic burden in the patients with and without myasthenic crisis during the follow-up

Parameters	MC ($N = 14$, 21.9 %)	No MC ($N = 50$, 78.1 %)	*P* value
Follow-up in months	61.2 ± 62.9	68.6 ± 66.7	0.39
Quality of life at discharge	17.5 ± 12.9	8.5 ± 12.0	0.02
Death	2 (14.2)	2 (4)	0.02
Expenditure/year in INR	40,150 ± 18,855	31,328 ± 17,663.9	0.03
Number of hospitalization	3.1 ± 2.1	1.5 ± 1.6	0.01
Work loss days/year	261.1 ± 255.6	12.1 ± 251.9	<0.01
No of consultation	3.9 ± 2.6	1.6 ± 2.1	<0.01
Hospitalization days/ year	77.4 ± 79.7	18.5 ± 39.3	<0.01

Percentage values are given within brackets

INR Indian national rupees

This study for the first time from India evaluated comprehensively the predictors of MC and prolonged ventilation as well as impact of MC on QOL and subsequent medical problems. Myasthenic crisis has been reported in 15–20 % patients with MG [3] worldwide and 7.5–22 % from India [12, 13]. Our study also had the similar findings. In our study, comorbid illnesses was related to crisis highlighting the need of management of these conditions. Comorbidities in a patient with MG have also been attributed to mortality [5, 14]. The patients who died in our study also had comorbidities; ischemic heart disease, diabetes and hypertension in one and both ischemic heart disease and hypertension in the other.

The frequency of infection and drug-induced MC were similar to other studies [5, 7, 8, 13]. In addition to the reported predictors of myasthenic crisis such as old age, severe disease and bulbar involvement, we have found high AchRAb, and male gender in relation to MC. Association of comorbidities in MC may be due to poor reserve, inability to prescribe higher dose of corticosteroid in diabetics, use of anti-diabetic and antihypertensive drugs in these patients which are potentially offending. Raised AchRAb may be an indicator of more severe illness as it is more frequently positive in generalized myasthenia (80–90 %) compared to ocular (30 %) [15, 16]. We have subjected patients for thymectomy who had thymoma and those generalized MG patients between 15 and 55 years of age with positive AchRAb. Frequency of thymoma as well as thymectomy was related to MC. In the reported literature, thymoma has been attributed to MC [17]. In our earlier study, patients with thymoma had worse outcome at 1 year compared to those without thymoma [18]. On multivariate analysis, none of the variables, however, were related to MC.

In our study, 57.1 % patients with MC needed prolonged ventilation, and patients with ventilator related complications and comorbid illness needed more frequently prolonged ventilation. Predictors of prolonged ventilation have been evaluated in one study only [5] and none evaluated predictors of MC and prolonged ventilation from India [6–8]. Thomas et al. [5] reported old age, baseline severity and ventilator related complications as predictors of prolonged ventilation. Prolonged ventilation was associated with three fold increase in hospital stay (63 vs 22 days) and two fold dependence at discharge (77 vs 36 %). Our patients were intubated and ventilated for longer duration (median 15.5 days, 16–60 days) compared to reported literature in which median duration was less than 2 weeks [6, 7]. This may be due to infrequent use of plasma exchange and IVIg during MC. We have used prednisolone during mechanical ventilation once the patients were free of infection, atelectasis and pneumonia. The frequency of ventilator related complications, and tracheostomy requirement in our study is similar to reported literature [6, 7, 19].

About half the patients with MC had recurrence of crisis in a median follow-up of 60 (12–264) months. Thomas et al. [5] also reported recurrence of crisis in one-third of patients. Patients with recurrent crisis in our study had poor QOL.

The present study for the first time evaluated the impact of MC in the subsequent follow-up. More annual visit to doctor and admission suggest poor response to treatment and more fluctuating course. The prevalence of infection and high ambient temperature may also result in more frequent worsening in MG. In Uttar Pradesh, India, temperature raises up to 45 °C during summer to 3° to 0° C during winter. The QOL was significantly better in patients who did not have crisis. These results suggest need of close follow-up and timely reporting of the patients who experienced crisis.

The limitation of the present study is retrospective nature and relatively small number of patients. The retrospective nature of study, however, was to some extent overcome by personal interview of the patients and retrieval of data from a computerized hospital information system. Myasthenia gravis is a rare disease and ours is a single center study of the MG patients who were treated by two of the authors personally for last 23 years, Small numbers may, however, influence in the statistical power.

Further prospective multi-centric study is needed with interventional trial in patients with MC, so that their morbidity and mortality may be reduced.

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Conflict of interest There is no conflict of interest to declare.

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