Clinical features and outcomes of patients with myasthenia gravis admitted to an intensive care unit: A 20-year retrospective study

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Background. There are limited data on the clinical characteristics and outcomes of patients with myasthenia gravis (MG) admitted to the intensive care unit (ICU) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).
Objectives. The aim was to study the clinical characteristics and outcomes of patients with MG admitted to the CMJAH over two decades.
Methods. A retrospective study was undertaken of patients with MG admitted to the multidisciplinary ICU of CMJAH over a 20-year period, from 1998 to 2017. Demographic data, clinical features, management and outcomes of patients were assessed and reviewed from the case records.
Results. Thirty-four patients with MG were admitted to the ICU during this period: 24 female and 10 male. The mean age ± SD was 37.4 ± 13.0 years, with a range of 16 - 66 years. Four patients were human immunodeficiency virus (HIV)-positive. The mean length of stay (LOS) in ICU was 10.6 ± 20.1 days, ranging from 1 to 115 days. Two patients were diagnosed with MG in the ICU after failure to wean from the ventilator. Overall, 22 patients were intubated and ventilated on admission. Morbidities included self-extubation, aspiration pneumonia and iatrogenic pneumothorax. History of thymectomy was present in 12 patients. The treatments received for MG included pyridostigmine (73.5%), corticosteroids (55.9%), azathioprine (35.3%), plasmapheresis (26.5%) and intravenous immunoglobulin (8.8%). The overall mortality in the ICU was 5.9%.
Conclusion. MG is a serious disorder with considerable morbidity and mortality. It is, however, a potentially manageable disease, provided that appropriate ICU resources are available.
Keywords. Myasthenia gravis, critical care, ICU, Johannesburg, South Africa.

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Contribution of the study
This study provides further insight into the characteristics and outcomes of myasthenia gravis patients in ICU, within a South African context.

Myasthenia gravis (MG) is an autoimmune neuromuscular disorder.[1] Patients exhibit skeletal muscle weakness and fatigue that worsens with repetitive muscle use.[1,2] The condition is caused by antibodies directed against acetylcholine receptors and other proteins in the postsynaptic neuromuscular junction membrane.[1-3] Some patients with MG have a genetic variant, specifically HLA-DRB1 gene polymorphisms, which are associated with an increased risk of late-onset MG.[4] In these patients, the use of eculizumab, an anti-C5 complement inhibitor, has led to a significant reduction in the frequency of exacerbations.[5] Potential biomarkers, including inflammatory cytokines, have been identified that are elevated in patients with MG compared with healthy controls and may possibly be used to diagnose and monitor the disease.[6] However, despite therapy, patients with MG have significantly lower quality of life scores compared with healthy controls.[7]

Within the first two years of diagnosis, approximately 15 - 20% of patients develop a potentially life-threatening myasthenic crisis (MC) necessitating mechanical ventilation and further intensive care unit (ICU) management.[8] MC is mostly provoked by infections, fever, aspiration, inadequate treatment, various medications or surgery.[9] The clinical management is well defined and has led to a significant decline in mortality which, until the early 1960s, was over 40%. Today, this figure has usually been reported to be between 5% and 12%[2,10-12] but higher rates up to 22% have also been reported.[13-17] Data on therapy regimens, outcome and mortality in MC are based mainly on small cohorts [10,11,14,17,18] or on registries.[2,12,16,19]

The exact incidence of MG in South Africa is not known and there are limited data on the clinical characteristics and outcomes of patients admitted to the ICU. The aim of the current study was to document the clinical characteristics and outcomes of patients with MG admitted to an ICU in an academic hospital over two decades in Johannesburg, South Africa.

Patients and methods

This was a retrospective record review undertaken between 1 January

1998 and 31 December 2017, involving 34 patients with MG seen at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) multidisciplinary ICU. The research was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M181036 approval). The data collected included demographics, clinical features, therapy administered and outcomes.

Statistical analysis was carried out with Student's *t*-test, and the Mann Whitney U-test for continuous variables and the chi squared-test, or Fisher's exact test (2-tailed), for categorical variables, as appropriate. The GraphPad Prism 4.0 programme was used to perform the statistical analysis and do graphic representations of the data. A p-value <0.05 was taken to be statistically significant.

Results

There were 34 patients with MG admitted to the ICU between January 1998 and December 2017. The clinical characteristics are shown in Table 1. There were 24 (70.6%) females and 10 (29.4%) males. The mean age ± standard deviation (SD) was 37.4 ± 13.0 years, ranging from 16 to 66 years, illustrating the described classic bimodal age distribution (Fig. 1). There were 21 black patients (16 female and 5 male), 11 white (6 female and 5 male), 1 Indian and 1 of mixed race (both female). The female-to-male ratio among the blacks was greater than 3:1 compared with the whites, among whom the ratio was closer to 1:1. Comorbid illnesses were present in 58.8%, most commonly hypertension and diabetes mellitus. Four patients (11.8%) were human immunodeficiency virus (HIV) positive and were on antiretroviral therapy. Two had hypothyroidism and 1 had Grave's disease. Seven patients had multiple re-admissions; 3 were readmitted once, 2 twice, 1 three times and 1 four times. Twenty-two (64.7%) patients were intubated and ventilated on admission, and the mean length of stay (LOS) ± SD in ICU was 10.6 ± 20.1 days, ranging from 1 to 115 days. Morbidities related to mechanical ventilation included self-extubation (2 patients), aspiration pneumonia (1 patient) and iatrogenic pneumothorax (1 patient). Two patients were diagnosed with MG in the ICU after failure to wean from the ventilator.

The clinical manifestations according to the Myasthenia Gravis Foundation of America Clinical Classification of the study population was mostly Class II, 14 (41.2%) patients (Table 2). Class II indicates that there was mild muscle weakness, with any degree of

Table 1. Clinical characteristics of patients with MG admitted to the ICU (*n*=34)

Demographic data	*n* (%)
Mean age ± SD (years)	37.4 ± 13.0
Female	24 (70.6)
Male	10 (29.4)
Comorbid conditions	
Diabetes mellitus	6 (17.6)
Hypertension	4 (11.8)
HIV-positive	4 (11.8)
Other psychiatric disorders	2 (5.9)
Hypothyroidism	2 (5.9)
Thyrotoxicosis (Grave's disease)	1 (2.9)
SLE	1 (2.9)
Surgical history	
Thymectomy	12 (35.3)
Splenectomy	2 (5.9)
Hysterectomy	2 (5.9)
Caesarean section	1 (2.9)
Tonsillectomy	1 (2.9)
Hip arthroplasty	1 (2.9)
Clinical extent of MG (MG Foundation of America Clinical Classification Class)	
I	1 (2.9)
II	3 (8.8)
IIa	3 (8.8)
IIb	8 (23.5)
III	0 (0)
IIIa	2 (5.9)
IIIb	1 (2.9)
IV	1 (2.9)
IVa	0 (0)
IVb	2 (5.9)
V	4 (11.8)
Unknown	9 (26.5)
Mean LOS ± SD in ICU (days) (range)	10.6 ± 20.1 (1 - 115)
Intubation and ventilated	22 (64.7)
APACHE II (mean ± SD) (range)	9 ± 4 (2 - 18)
Mortality	2 (5.9)

MG = myasthenia gravis; SD = standard deviation; ICU = intensive care unit; HIV = human immunodeficiency virus; LOS = length of stay; SLE = systemic lupus erythematosus.

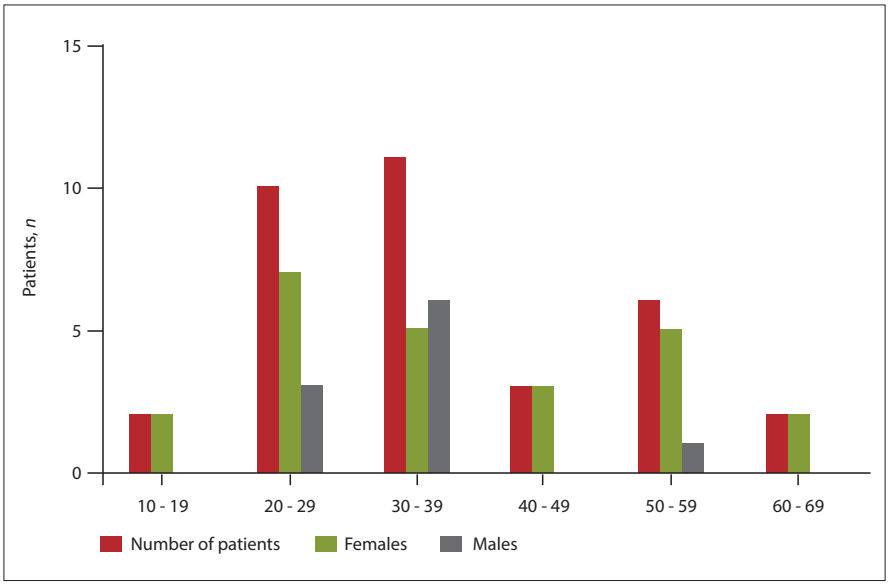

Fig. 1. Age categories of patients with MG.

ocular involvement.[20] In a significant proportion, the clinical grade could not be quantified as the necessary data were not documented. Two (5.9%) patients died; one patient who had had a previous splenectomy presented with community-acquired pneumonia and septic shock (duration of ICU stay was 15 days) and the other had a cardiac arrest following a massive upper gastrointestinal haemorrhage after a LOS of 12 days. The mean APACHE II ± SD score of the group was 9 ± 4 and ranged from 2 to 18.

Discussion

We report the clinical characteristics and outcome following ICU admission of patients with MG over a 20-year period. We found that MG was an uncommon primary diagnosis but, among those who were admitted, the mean age was approximately 37 years, and the yearly incidence of ICU admission ranged between 1.65 and 1.76 cases per annum. Although the current study has a small sample size, it demonstrated that acute exacerbations of MG continue to be associated with significant morbidity and mortality. In our study, despite almost two-thirds of patients having received mechanical ventilation on admission, the overall ICU mortality rate was low relative to other studies from Africa[21] and was more comparable with those of high-income countries.[10,22] In a study from a resource-poor setting in South East Nigeria among patients with a median age of 29 years (range 20 - 42 years), collected over 13 years from 1992 to 2004, mortality was 27.3% and cause of death mainly due to sepsis.[21] These results are in contrast to a mortality of 10.5% in a study from the United Kingdom,[16] 6.4% in one from Australia - New Zealand[23] and 12% in the German multicentre myasthenic crisis study.[9] In 2009, Alshekhlee *et al*.[2] studied all patients admitted to hospital with MG and compared those with MG alone with those who had had a MG crisis from 1 000 hospitals in the USA between 2000 and 2005. In this study, the hospital mortality rates for MG and MC were 2.2% and 4.5%, respectively, but no information on mortality rates among ventilated patients was available. Non-invasive ventilation (NIV) could be used to support respiratory function and could prevent the need for intubation, reducing the risk of complications such as pneumonia and atelectasis. The positive pressure provided has the potential to improve gas exchange and reduce the work of breathing.[9,24] In addition, NIV could be used as a bridge to recovery or as step-down therapy post invasive mechanical ventilation. In the current study, whereas none of the patients underwent NIV, a retrospective analysis of a large cohort of patients with MG and respiratory failure found that it was associated with reduction in days of ventilator support and length of ICU stay, and a lower ICU mortality.[9] However, the impact of NIV on ICU stay, duration of ventilation and mortality in patients with MG is still not well established.

Of note, in the current study, 4 patients were known to be HIV positive, and they all survived. However, not all patients were tested for HIV as testing was performed only if clinically indicated and after obtaining consent.

The incidence of MG worldwide has been reported to be 5.3 per million persons per year.[25] The incidence in South Africa, is however, unknown. In 2010, a systematic review of population-based epidemiological studies in MG indicated a paucity of data from low- and middle-income countries (LMICs).[25] However, a study from Cape Town, South Africa, demonstrated an incidence of 11.2 per million persons per year of anti-acetylcholine receptor antibody positive MG (AChR-MG).[26] The reason for the greater incidence in this study relative to that of other LMICs was not addressed in the paper but may be due to availability of superior diagnostics, geographic genetic variations, different sample sizes and/or other factors. In the current study, the incidence of MG in Johannesburg, South Africa, could not be estimated as the cohort was small.

Table 2. The Myasthenia Gravis Foundation of America (MGFA) clinical classification according to symptoms[20]

Class	Clinical symptoms
I	Any ocular muscle weakness
II	Mild weakness. May have ocular muscle weakness of any severity.
IIa	Predominantly affecting limb, axial muscles or both. May also have lesser involvement of oropharyngeal, respiratory muscles, or both.
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
III	Moderate weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IIIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles, or both.
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IV	Severe weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IVa	Predominantly affecting limb, axial muscles or both. May also have lesser oropharyngeal muscle involvement.
IVb	Predominantly affecting oropharyngeal, respiratory muscles or both. May also have lesser or equal involvement of limb, axial muscles or both. Includes patients requiring feeding tubes.
V	Defined by intubation with or without mechanical ventilation, except when utilised during routine postoperative management.

Table 3. Treatment received for MG patients in ICU

Treatments received	*n* (%)
Pyridostigmine (P)	25 (73.5)
Corticosteroids (CS)	19 (55.9)
Azathioprine (AZA)	12 (35.3)
Plasmapheresis (plasma)	9 (26.5)
Intravenous immunoglobulin (IVIG)	3 (8.8)
Combination therapy	
P + AZA + CS	6 (26.5)
P	4 (17.6)
P + CS	4 (11.8)
P + AZA + plasma	3 (8.8)
P + AZA + CS + plasma	3 (8.8)
CS	3 (8.8)
P + plasma	2 (5.9)
P + CS + IVIG	1 (2.9)
P + IVIG	1 (2.9)
CS + IVIG	1 (2.9)
P + CS + plasma	1 (2.9)
Other medications	
Antiretroviral therapy	4 (11.8)
Thyroxine	2 (5.9)
Neomercazole	1 (5.9)

The current study found that MG was more common in females, which is consistent with both national and international literature.[1,25,27] MG is also increasingly recognised in the older population;[1,23,25] however, the average age in the current study was much younger at 37 years with only 17.6% of the current cohort over the age of 50 years. These findings are inconsistent with studies from abroad. The mean age at ICU admission is generally markedly older, as in Australia and New Zealand, where it is 65 years.[23] Similarly, in most other studies, patients were much older, generally above 50 years.[9,23,28,29]

A delayed diagnosis of MG can have adverse consequences, including progression of the disease to the point of respiratory failure, reduced quality of life owing to muscle weakness manifested by an inability to work, participate in leisure activities or to maintain relationships. The associated more-frequent hospitalisations, more intensive treatment, and longer recovery periods all significantly increase healthcare costs.[30] The current study highlights the need to be aware of and vigilant for MG in the differential diagnosis of acute respiratory failure, particularly when there is apparent weakness with elevated partial pressure of carbon dioxide, or there is failure to wean from the ventilator, as was seen in 2 (5.9%) patients in the current study.

The gradual reduction in mortality and length of stay for patients admitted to the ICU with respiratory failure[9,22,23,25] is probably due to advances in treatment options that have also evolved over time. For example, immunomodulatory therapies such as intravenous immunoglobulin (IVIG), plasma exchange and rituximab have been found to be effective in treating MG, and these treatments were not widely available in earlier years.[31,32] Interestingly, in the current study, comparing the first 10 years with the latter decade, there were no major differences in terms of mortality, length of ICU stay, duration of mechanical ventilation and mortality.

In our study, almost 60% of patients were managed with corticosteroids, 35% with azathioprine, 26% with plasmapheresis and almost 9% IVIG. Whereas only a minority of patients in the current cohort received IVIG or plasma exchange, these modalities have recently been found to be equally effective for management of exacerbations and, of these two, IVIG, though costly, has been found to be better tolerated and more accessible (Table 3).[33]

The current study has certain limitations that should be addressed in future research. The facility in which the study was conducted is a single, tertiary-care institution and is a referral centre. This, along with the fact that the study was retrospective in nature, implies that the findings may not be applicable to other institutions or the broader population.

Conclusion

An audit of the characteristics and outcome of patients with MG admitted to the multidisciplinary ICU at CMJAH was conducted. The morbidity and mortality rates of patients with MG admitted to ICU were low. Despite the acute risk of mortality associated with severe exacerbations of MG, the overall prognosis was favourable. The appropriate management of these patients requires availability of specialised intensive care facilities.

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