Al-Kindy College Medical Journal (KCMJ)

Research Article

Factors associated with Exacerbation of Myasthenia Gravis in a Group of Iraqi Patients

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Article history:
Received 24 March 2023
Accepted 6 May 2023
Available online 30 August 2023

https://doi.org/10.47723/kcmj.v19i2.988

Keywords: Myasthenia Gravis, Myasthenic Crisis and Infection, Predisposing factors, Exacerbations.

ABSTRACT

Background: Myasthenia gravis is an autoimmune disease of the neuromuscular junction that results in fluctuating muscle weakness as well as significant fatigue. Disease exacerbation is a critical condition, and the predisposing factors for it need to be identified to improve preventive measures.

Objectives: Our study aims to determine the predisposing factors for myasthenia gravis exacerbations in a group of Iraqi patients.

Subjects and Methods: A total number of 30 myasthenia gravis patients were admitted to the hospital with an exacerbation of their symptoms, determined as the development of functional disability, dysphagia, or respiratory failure within one month prior to admission. Each patient was assessed by history taking, clinical examination, and investigations to determine the possible exacerbating factor.

Results: There were (56.7%) of patients with infection. Non-compliance to treatment was found in (26.7%) of patients, and medication induced exacerbation was found in (16.7%) of the patients.

Conclusion: Infection is the most common predisposing factor for disease exacerbation and is associated with an unfavorable outcome.

Introduction

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction that results in fluctuating muscle weakness as well as noticeable fatigue that could affect ocular, limb, and bulbar muscle weakness. It has a prevalence of approximately 1 in 5000 (1). There are two main age groups that are mainly affected by MG, the first one is around the age of 30 and the other age group is around 50 years. In the younger cohort, females are more affected than males on the other hand, the older cohort showed that the incidence is more equal between the genders (2,3). The severity of the weakness ranges from mild cases of pure ocular MG in which the patient complained of ptosis and diplopia to severe generalized MG that could even affect the bulbar muscles causing dysarthria and dysphagia.

The majority of MG patients are seropositive for two types of antibodies, these are anti-acetylcholine receptor (AChR) or the muscle-specific tyrosine kinase (MuSK), however, seronegative cases occur in approximately 50% of purely ocular cases and 20% of generalized cases. Being an autoimmune disorder, this disease is thought to be mediated beta and T-cell-dependent immunologic attack targeting the postsynaptic membrane causing damage to the

postsynaptic muscle membrane resulting in simplification of the highly folded surface, and a reduced number and density of AChRs-endings that ends up with abnormal transmission across the neuromuscular junction. This is clinically manifested as fatigable muscle weakness.

Severe respiratory muscle weakness with consequent respiratory failure is reported to be seen in about 15% of patients, and this is known as a myasthenic crisis which is considered a real neurologic emergency that necessitates immediate action and admission to the intensive care unit(1).

Myasthenic exacerbation is classically defined as the development, within a month period, of a minimum of one of the following symptoms: acute respiratory failure, swallowing difficulties, and major functional disability precluding physical activity (4). Moreover, a Myasthenic crisis is the occurrence of MG-related respiratory and/or bulbar muscle weakness that is severe enough to necessitate intubation or noninvasive positive pressure ventilation.

Patients with myasthenic crises need immediate and prompt management in the intensive care unit. This constitutes the concomitant determination of the triggering factors that caused these exacerbations and the safe initiation of potent immunosuppressive therapy. (5). In most cases MG crises, a precipitating event is identified. However, in about 30-40% of cases, no cause could be found. Interestingly, the MG crisis could be the initial manifestation of MG. Various precipitants of MG crises are encountered in clinical practice, this includes recent surgeries, infection, drugs, stress, pregnancy, and the postpartum period. (6).

Intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) are the two modalities of choice to treat patients with MG crises. Plasma exchange may be preferred by some health professionals due to its rapid onset of action. Nevertheless, the choice between these treatments is influenced by practical issues like the patient's comorbidity, institutional preference, the availability of the service, and venous access (7).

Aim of the study

Study aims to determine the predisposing factors for myasthenia gravis and exacerbations in a group of Iraqi patients.

Subjects and Methods

A cross-sectional study was made on 30 patients with myasthenia gravis at Baghdad teaching hospital and Al Imamain teaching hospital in the period from July 2022 to January 2023.

Inclusion criteria

Any adult patient with generalized MG who presented with exacerbation of his symptoms was included. The diagnosis of MG was based on clinical features supported by electrophysiological studies or Serological tests.

Data collection:

The data was collected from patients who were admitted to the hospital with an exacerbation of their symptoms. Exacerbation is determined as the development of functional disability, dysphagia, or respiratory failure within one month prior to admission. They were categorized as having exacerbation with or without myasthenic crisis determined by the need for non-invasive ventilation or intubation. Each patient was assessed by history taking, clinical examination, and investigations to determine the possible exacerbating factor.

The exacerbation triggers include one or more of 8 categories: infection (includes infection of the upper respiratory tract, chest, urinary tract, or sepsis), medications (include recent intake of drugs that should be avoided or used with caution in MG), noncompliance to treatment (lack of adherence to treatment), procedure-related (exacerbation occurring after a surgical procedure), pregnancy, social stress, newly diagnosed (patients diagnosed at their exacerbation, did not receive prior treatment for MG), alongside an unknown factor.

The previous treatment for MG was documented. Also, we mentioned the treatment given for each exacerbation, the duration of hospitalization, and the outcome.

There was no patient who presented with exacerbation related to surgical procedures or pregnancy, so these categories were not involved in statistical analysis.(Include this in the exclusion criteria.

Ethical Issue

Prior to the study, we had written consent from each patient. We have explained the aim of our study. Additionally, each patient was informed that he is able to withdraw from the study at any time without any consequences. Patient data is strictly confidential for the medical staff taking care of the patient. The whole data used in this work is privileged to research basis and it was considered highly confidential.

Statistical analysis

We use Statistical Package for social sciences (SPSS) version 26 for both data entry as well as statistical analysis. An Independent sample t-test was used to define the significance of the difference and the chi2 test was used. The odd ratio at 95% CI to estimate risk was used. In our study, a P value of ≤ 0.05 has been considered statistically significant.

Results

A total of 30 patients participated in the study, their mean age was 41.63±14.47 years (53.3% less than 40 years), and the mean duration of disease was 66.43±62.7 months (43.3% during 1-5 years).

Most of them were females, 73.7%. Out of the total patients; 36.70% patients had thymectomy, 13.30% were hypertensive, 20.00% diabetics, 6.70% with IHD, and 6.70% with thyroid Disease. Table 1.

Noncompliance was found among 26.70% of patients. There were 17 patients affected with a variety of infections (Chest infection was found among 9 (52.9%) patients, UTI was found among 2 (11.8%), and URTI was found among 6 (35.3%) patients). There were 5 patients on drugs that worsen myasthenia (One patient (20%) was on Fluoroquinolones, 2 (40%) were on Beta blockers, 1 (20%) on Amikacin, and 1 (20%) on Azithromycin). Table 2.

Table 1: Demographic and clinical data of patients

Variables		No.	%
Age/years Mean±SD		41.63	14.47
Age group/years	< 40	16	53.3%
	≥ 40	14	46.7%
Gender	Male	7	23.30%
	Female	23	76.70%
Duration/months Mean±SD		66.43	62.7
Duration/years	< 1	6	20.0%
	1-5	13	43.3%
	6-10	6	20.0%
	>10	5	16.7%
Thymectomy		11	36.70%
Hypertension		4	13.30%
Diabetes Mellitus		6	20.00%
IHD		2	6.70%
Thyroid Disease		2	6.70%
Total		30	100.00%

Table 2: Factors of exacerbation among patients

Variables		No.	%
Noncompliance		8	26.70%
Infections	Yes	17	56.7%
	No	13	43.3%
Types of Infections	Chest infection	9	52.9%
	UTI	2	11.8%
	URTI	6	35.3%
Total		17	100%
On Drugs	Yes	5	16.7%
	No	25	83.3%
Drugs	Fluoroquinolones	1	20%
	Beta blockers	2	40%
	Amikacin	1	20%
	Azithromycin	1	20%
Total		5	100%

In regard to, pre-exacerbation treatment, there were 25 (83.30%) patients managed with Pyridostigmine (52% of them on 240 mg), 12 (40%) patients managed with Prednisolone (33.3% of them on 5 mg, and 10 (33.3%) patients managed with Azathioprine (60% of them on 100 mg), and 3 (10%) patients managed with Mycophenolate mofetil (66.7% of them on 1000 mg).

The mean duration of hospitalization was 16.23±17.01 days (40.0% hospitalized for 1-7 days).

According to the management at exacerbation/crisis; 53.30% of patients were managed with IVIg, 40.00% of patients were managed with plasma exchange (PLEX), and 6.70% of patients were managed with IVIg+ PLEX. Table 3.

Table 3: Management of patients before and after exacerbation/crisis

		No.	%
Hospitalization/days Mean±SD		16.23	17.01
Hospitalization/days	1-7	12	40.0%
	8-14	10	33.3%
	15-30	4	13.3%
	>30	4	13.3%
Management before exacerbation/crisis			
Pyridostigmine		25	83.30%
Doses	180	8	32.0%
	240	13	52.0%
	360	4	16.0%
Prednisolone		12	40.00%
Doses	5 mg	3	25.0%
	10 mg	4	33.3%
	15 mg	2	16.7%
	20 mg	2	16.7%
	30 mg	1	8.3%
Azathioprine		10	33.30%
Doses	50 mg	1	10.0%
	100 mg	6	60.0%
	150 mg	3	30.0%
Mycophenolate mofetil		3	10.00%
Doses	1000 mg	2	66.7%
	2000 mg	1	33.3%
Rituximab		2	6.70%
Management at exacerbation/crisis			
IVIg		16	53.30%
PLEX		12	40.00%
IVIg+PLEX		2	6.70%
Total		30	100.00%

There were 15 (50%) patients who suffered exacerbation without myasthenic crisis and 15 (50%) patients who suffered exacerbation with myasthenic crisis.

As an outcome; there were 28 (93.3%) patients have been improved and 2 (6.7%) patients have died.

The distribution of patients according to different variables and cases was elucidated in Table 4.

Discussion

Myasthenia gravis patients go through phases of disease fluctuation, including periods of deterioration, improvement, and remission (8). Much earlier research highlighted important variables including age and gender that affected the clinical course of MG (9). Despite advancements in treatment, 10–20% of MG patients develop myasthenic crises during the course of their illness (10,11). Statistics report an about 3 to 8% mortality rate despite intense medical care (12).

Regarding disease duration in this study, the majority of patients (63.3%) presented within the first 5 years of disease onset, which goes with previous studies of Khadikar et al. and Grob et al. that found disease exacerbation tends to occur in the first few years of disease onset (8,9).

In this study, (36.7%) of patients had thymectomy, and (63.6%) of them did not require mechanical ventilation. According to a previous study by Soleimani et al., myasthenic patients who had thymectomy experienced fewer and less severe instances of myasthenic crises (13).

Table 4 Distribution of factors of exacerbation among patients according to the cases

BMI: body mass index; ASA: American society of anesthetists: eGFR Glomerular filtration rate

Variables		MG Cases				P value	OR (95% CI)
		Exacerbation without crisis		Exacerbation with crisis			
		No.	%	No.	%		
Noncompliance	Yes	5	62.5%	3	37.5%	0.68	Reference
	No	10	45.5%	12	54.5%		2 (0.38-10.5)
Infections	Yes	9	52.9%	8	47.1%	1	Reference
	No	6	46.2%	7	53.8%		1.3 (0.31-5.58)
Types of Infections	None	6	46.2%	7	53.8%	0.051	Reference
	Chest infection	2	22.2%	7	77.8%		3 (0.44-20.31)
	UTI	2	100.0%	0	0.0%		0.5 (0.25-1.1)
	URTI	5	83.3%	1	16.7%		0.17 (0.015-1.9)
On Drugs	Yes	3	60.0%	2	40.0%	1	Reference
	No	12	48.0%	13	52.0%		1.6 (0.2-11.46)
Drugs	None	12	48.0%	13	52.0%	0.48	Reference
	Fluoroquinolones	0	0.0%	1	100.0%		0.52 (0.35-0.8)
	Beta blockers	2	100.0%	0	0.0%		0.48 (0.31-0.7)
	Amikacin	1	100.0%	0	0.0%		0.48 (0.312-0.7)
	Azithromycin	0	0.0%	1	100.0%		0.52 (0.35-0.76)
Stress	Yes	3	60.0%	2	40.0%	1	Reference
	No	12	48.0%	13	52.0%		1.62 (0.2-11.4)
Newly Diagnosed	Yes	0	0.0%	3	100.0%	0.22	Reference
	No	15	55.6%	12	44.4%		2.25 (1.47-3.4)
Unknown	Yes	3	50.0%	3	50.0%	1	Reference
	No	12	50.0%	12	50.0%		1 (0.16-5.98)

Newly diagnosed MG appeared to be associated with exacerbation with myasthenic crisis, with no significant difference, (OR=2.25, 95% CI= 1.47-3.4, P=0.22).

Regarding the contributing factors for exacerbation, infection (chest infection in most of them) was the most responsible factor (56.7% of cases), and this result was similar to previous studies by Thomas et al. and Gummi et al. which found that infection was the most common precipitant for myasthenia exacerbation; and the most frequent was bacterial pneumonia, followed by a bacterial or viral upper respiratory tract infection, this result may be explained by myasthenic patients are chronically immunocompromised and had increased risk of aspiration pneumonia (14,15).

Non-compliance to treatment was found in (26.7%) of our patients, which was higher than the previous study of Gummi et al. (8%) this difference may be attributed to a lower socioeconomic state in our patients (15).

Patients with unknown causes of exacerbation were (20%) of cases, lower than the previous study of Thomas et al., in which thirty percent of cases were with no obvious precipitant (14), this result may be explained by the smaller sample size in this study.

There were (16.7%) of patients exposed to medications that may worsen MG. These medications are mainly beta blockers and antibiotics. This percentage was close to Gummi et al. that found (19%) of documented exacerbations were attributed to exposure to these medications, Azithromycin was the drug most frequently linked to an aggravation, followed by fluoroquinolones and beta blockers (15).

Myasthenic crisis was the initial presentation in some patients, (10%) of cases in this study. Schroeter et al. state that the crisis manifests as the disease's earliest symptom in (20%) (16).

When comparing the predisposing factors between patients with exacerbation and myasthenic crisis, the results were statistically insignificant.

As an outcome of patients, most of them improved and two patients died. In those who died the predisposing factor was an infection, which conforms with the previous study done by, Nelke et al. which stated that an infectious trigger for exacerbation was associated with an unfavorable outcome (17).

Conclusion

MG exacerbations generally occur in the first few years after diagnosis. Infection is the most common predisposing factor for disease exacerbation.

Recommendations

Factors predisposing to myasthenia exacerbation should be identified to improve preventive measures, with the administration of vaccines, advising MG patients to adhere to their treatment, and avoiding drugs that may worsen their disease.

Funding

This research did not receive any specific fund.

Conflict of Interest

Authors declare no conflict of interest

Data availability

Data are available upon reasonable request

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To cite this article: Al Dulaimy, A. A., Al-Mashtah, S. A. R., & Ahmed, M. H. Factors associated with Exacerbation of Myasthenia Gravis in a Group of Iraqi Patients . AL-Kindy College Medical Journal, 2023; 19(2), 218–222.