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Original Article

Anti-acetylcholine receptor antibodies as a diagnostic marker for myasthenia gravis

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Abstract

Background

Myasthenia gravis (MG) is a common primary disorder of neuromuscular transmission, which is characterized by fluctuating weakness of a certain voluntary muscles, particularly those innervated by motor nuclei of the brain stem, that is, ocular and mastication muscles, and caused by antibodies binding to components in the neuromuscular junction. Most MG cases demonstrate elevated serum levels of acetylcholine receptor (ACh-R) antibodies, which cause partial or complete inhibition of receptor function and complement-mediated focal lysis of the postsynaptic membrane. ACh-R antibodies are detected in the serum of more than 80–90% patients with generalized MG, in ~50% with ocular myasthenia, and rarely in healthy people.

Aim

The aim of our study is to determine the value of anti-ACh-R antibodies in diagnosis and prognosis of MG and to evaluate their sensitivity and specificity in comparison between different types of myasthenia.

Patients and methods

All patients were recruited from the outpatient clinic of Mataria Teaching Hospital on their first visit to neuropsychiatry clinic with suspicious symptoms of MG within 3 months. Our study included 90 women, of whom 60 patients had clinical symptoms suspicious of MG. The patients were classified into five groups: four groups according to Osserman classification and the fifth group included the seronegative patients. Their age ranged from 20 to 30 years. There was another group, the sixth group, which included 30 age-matched healthy controls. All patients were subjected to full history taking, general examination, and neurological examination to facilitate clinical assessment and staging of the disease according to Osserman classification and detection of ACh-R antibodies (binding, modulating and blocking antibodies), prostigmine test, repetitive nerve stimulation, and single-fiber electromyography stimulation tests.

Results

There was no significant difference between studied groups regarding age. Moreover, we found significant differences between them and the control group regarding the levels of ACh-R antibodies (binding, blocking, and modulating antibodies), but there were no significant differences between them regarding the extent of MG. There is no correlation between the studied groups and the level of acetylcholine, except for a weak positive correlation between the Osserman class and level of blocking receptor antibodies. Receiver operating characteristic curves showed that all the three types of antibodies had poor value for discrimination between MG subgroups. Moreover, there is a significant difference between the studied groups regarding prostigmine, repetitive nerve stimulation, and single fiber electromyography tests.

Conclusion

ACh-R antibody levels are of major importance as a noninvasive sensitive and specific diagnostic test for different types of myasthenia. However, they had no role in predicting the prognosis of different classes of the disease.

Keywords: Acetylcholine receptor, antibodies, myasthenia gravis

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Introduction

Myasthenia gravis (MG) is the most common disorder of neuromuscular transmission. It is an autoimmune disease limited to specific organs in which autoantibodies attack nicotine-acetyl choline receptors in neuromuscular junctions [1]. The hypofunction of these receptors leads to neuromuscular transmission defect, which causes hypofunction, fatigue, and inflammation of skeletal muscles, resulting in weakness of the voluntary muscles, which worsens with activity and improves with rest. Its onset is usually insidious and fluctuant. The fluctuating nature of myasthenic weakness is unlike any other disease; the weakness varies in the course of a single day, sometimes within minutes, and it varies from day to day or over a longer period. The special vulnerability of certain muscles is another characteristic of MG; weakness of the elevator palpebrae or extraocular muscles is the initial manifestation of the disease in approximately half the cases, and these muscles are involved eventually in more than 90%. The muscles of the facial expression, mastication, swallowing, and speech are frequently affected in 80%, and in 5–10%, they are the first or the only muscles to be involved of ophthalmic abnormalities, such as ptosis and/or diplopia, which occur in 40–94% of cases in the early stages, and ocular muscles are affected in 97% of cases during the total morbidity period. Onset may be gradual or acute following viral infection or pregnancy [2]. Most MG cases demonstrate elevated serum levels of ACh-R antibodies, which cause loss of receptors, partial or complete inhibition of receptor function, and complement-mediated focal lysis of the postsynaptic membrane [3].

Serum antibody against ACh-R can be found in 80–90% of patients with generalized MG and in ~60% of those whose symptoms are restricted to the ocular muscles. Three different types of ACh-R antibodies may be involved: binding, blocking, and modulating [4]. Binding antibodies are detected in 69–82% of patients with MG with generalized disease and 59% of patients with MG with restricted ocular muscle involvement. Modulating antibodies are found at approximately the same frequency as binding antibodies. However, ~8% of patients have positive results for only one of the two tests. Modulating antibodies are found in the absence of binding antibodies in 4% of patients. Blocking antibodies, which have a similar sensitivity as modulating antibodies for MG diagnosis, are detectable in ~52% of patients with generalized disease and ~30% of patients with ocular MG. Fewer than 1% of patients have blocking antibodies without binding antibodies, and blocking antibodies are rare in non-MG disease. Therefore, blocking antibody testing may help identify false-negative binding antibody test results [5]. Other types of antibodies such as striational and muscle-specific receptor tyrosine kinase (MuSK) antibodies are also useful in MG diagnosis. Striational antibodies are found in 30% of all patients with MG, in 50% of patients with MG with late-onset disease, and in 95% of those with thymomas. These autoantibodies recognize epitopes on skeletal muscle proteins, including myosin, actin, actinin, filamin, and titin. Some types of striational antibodies, including those to titin, can provide more clinical information and aid in the diagnosis of thymoma [6]. MuSK antibodies may be useful for MG diagnosis in patients who test negative for ACh-R antibodies. Patients with antibodies to MuSK are much less likely to have a thymoma [7]. ACh-R antibodies hinder the action of acetylcholine, a chemical (neurotransmitter) that transmits messages between nerve cells. The antibodies do this in three major ways: 'binding' antibodies attach to the ACh-R on nerve cells and may initiate an inflammatory reaction that destroys them, 'blocking' antibodies may sit on the receptors, preventing acetylcholine from binding, and 'modulating' antibodies may cross-link the receptors, causing them to be taken up into the muscle cell and removed from the neuromuscular junction [8].

The diagnosis of MG is based on the clinical diagnosis confirmed by reliable laboratory methods including detection of ACh-R autoantibodies and electrophysiological studies, repetitive nerve stimulation (RNS), and single-fiber electromyography (SF-EMG). The diagnostic sensitivity of these studies varies considerably depending on whether the patient has ocular or generalized disease. Moreover, bedside tests (the prostigmine test, edrophonium test, and the ice pack test) are also used in diagnosis of MG. They are easy to perform and are sensitive [9], but they have major limitations owing to concerns about excess false-positive results.

Aim

The aim of our study is to determine the value of anti-ACh-R antibodies in diagnosis and prognosis of myasthenia types and also to evaluate the sensitivity and specificity of its different types (binding, modulating, and blocking) in differentiating between different types of myasthenia.

Patients and methods

This study conducted on 90 women, of whom 60 patients had clinical symptoms suspicious of MG, and their ages ranged from 20 to 30 years. Thirty age-matched healthy participants were taken as a control group. Patients were recruited from the outpatient clinic of Mataria Teaching Hospital on their first visit to neuropsychiatry clinic with suspicious myasthenic symptoms within 3 months of first presentation. Patients are classified into five groups: four groups according to Osserman classification and the fifth group (seronegative group) included six patients. The first group (ocular myasthenia) included 21 patients, the second group (generalized MG) 49 patients, the third group (acute fulminating MG) included six patients, the fourth group (severe MG) eight patients. All participants signed an informed written consent for acceptance to participate in the present study after explaining to them the aim and the value of our work. Patients with thyroid gland disease or with a history of congenital myasthenia at onset of birth and with a family history of MG (familial MG) were excluded from the analysis.

The diagnosis of MG was based on three or more of the following: (a) full history taking. (b) Full medical and neurological examination. (c) Clinical evidence of fatigability with recovery on rest. (d) Osserman classification: ocular myasthenia class I (15–20%); mild generalized myasthenia

class IIa, with slow progression but no crises, with drug responsive (30%); moderately severe generalized myasthenia class IIb; severe skeletal and bulbar involvement but no crisis with drug response less than satisfactory (25%); acute fulminating myasthenia class III, rapid progression of severe symptoms with respiratory crisis and poor drug response, high incidence of thymoma, and high mortality (15%); and late severe myasthenia class IV, symptoms like class III but resulting in steady progression over 2 years from class I to class II (10%). (e) Prostigmine test: definite clinical improvement after intramuscular injection of neostigmine methyl sulfate in the dose of 1.5 mg was regarded as a positive prostigmine test result. Atropine sulfate should be given several minutes in advance to counteract muscarinic effects. A negative test result does not exclude MG but is a strong point against the diagnosis. (f) SF-EMG is a quantitative and most sensitive clinical measure of dysfunctional neuromuscular transmission and an accurate electrical correlate of the fiber-type grouping by demonstrating increased variability of the interpotential interval (Jitter) or blocking of successive discharges from single muscle fibers belonging to the same motor unit (normal Jitter <35 s). (g) RNS test was done at a stimulation rate of 3 Hz. It was considered positive when the decrement exceeded 10% between first and fourth response. If the initial resting RNS test result was negative, then postexercise RNS was done (normal RNS difference between first and fourth response is <10%). (h) Detection of ACh-R antibodies (binding, modulating, and blocking antibodies using enzyme-linked immunosorbent assay technique) (SinoGenClon Biotech Co. Ltd, 333 O'farrel street San Francisco-USA). (i) Exclusion of alternative relevant diagnosis (some thymomas) in people who are being treated with drugs such as penicillamine, with some small cell lung cancers, with autoimmune liver disease, and with Lambert–Eaton myasthenic syndrome (a condition associated with interference with the release of acetylcholine from the nerve ending).

Statistical analysis

Data were analyzed using SPSS Statistics, version 23 (IBM Corp., Armonk, New York, USA) and MedCalc, version 15.8 (MedCalc Software bvba, Ostend, Belgium). Normality of numerical data distribution was examined using the Shapiro–Wilk test. Non-normally distributed numerical data were presented as median and interquartile, and intergroup differences were compared using the Mann–Whitney test (for two-group comparison) or the Kruskal–Wallis test (for multiple-group comparison). The Conover test was used for post-hoc comparison after the Kruskal–Wallis test, if needed, with application of the Bonferroni's correction. Categorical data were presented as number (%), and differences were compared using Fisher's exact test. Correlations were tested using the Spearman rank correlation. Receiver operating characteristic (ROC) curve analysis was used to examine the diagnostic accuracy of ACh-R antibodies. *P* values less than 0.05 were considered statistically significant.

Results

A total of 90 adult women were enrolled in this study, of whom 60 patients had suspicious symptoms of MG within 3 months. Their ages ranged from 20 to 30 years. Thirty age-matched healthy participants were taken as a control group. Patients were classified into five groups: four groups according to Osserman classification and the fifth group included the seronegative patients. The first group (ocular myasthenia) included 21 patients, the second group (generalized MG) included 49 patients, the third group (acute fulminating MG) included six patients, the fourth group (severe MG) included eight patients, and the seronegative group included six patients. Insignificant differences were found between the studied groups regarding age ($P = 0.854$) (Table 1). Significant differences were found between four studied groups of patients and the control group regarding the prostigmine, RNS, and SF-EMG test results ($P < 0.001$) (Tables 2 and 3). Concerning the levels of ACh-R antibodies (binding, blocking, and modulating antibodies) in the four studied groups of patients, we found significant differences between them as compared with the control group ($P < 0.001$) (Table 4), but there were no significant differences between them regarding Osserman classification of myasthenia types ($P = 0.946$, 0.221, and 0.631, respectively) (Table 5). Figs. 1–3 show the level of ACh-Rs binding, blocking, and modulating antibodies in patients with ocular and generalized MG, respectively. Fig. 4 showed ROC curves for discrimination between ocular or generalized MG using binding, blocking, and modulating type of ACh-R antibodies, which revealed that all the three types of antibodies had poor value for discrimination between MG subgroups (area under the curve = 0.505, 0.590, and 0.535, respectively) (Table 6). Moreover, the correlation between the Osserman class and level of ACh-R antibodies showed that there was a weak positive correlation between the Osserman class and level of blocking antibodies (Spearman's rho = 0.236, $P = 0.031$) (Table 7). There was a significant difference between the studied groups regarding prostigmine, RNS, and SF-EMG test results.

Discussion

MG is a common primary neuromuscular disorder. World incidence has increased in the last decades going from 2–5/1 000 000 to 9–21/1 000 000. It is a rare disease among Africans, but the prevalence among white adults varies from

Table 1: Comparison between ages in the five studied groups

Variables	Control ($n=30$)	Ocular myasthenia ($n=21$)	Generalized MG ($n=29$)	Acute fulminant MG ($n=6$)	Severe MG ($n=8$)	*P*[a]
Age (years)	26.0 (23.0-28.0)	25.0 (23.0-28.0)	25.0 (24.0-28.0)	24.5 (22.0-26.0)	25.5 (23.0-27.0)	0.854

Data are median (interquartile range). MG, myasthenia gravis. [a]Kruskal-Wallis test.

Table 2: Comparison between results of prostigmine test in different Osserman classes of myasthenia

Variables	Ocular myasthenia (*n*=21)	Generalized MG (*n*=49)	Acute fulminant MG (*n*=6)	Severe MG (*n*=8)	*P*[a]
Osserman class					<0.001
Class I	21 (100.0)	0 (0)	0 (0)	0 (0)	
Class IIa	0 (0)	39 (79.6)	0 (0)	0 (0)	
Class IIb	0 (0)	10 (20.4)	0 (0)	0 (0)	
Class III	0 (0)	0 (0)	6 (100)	0 (0)	
Class IV	0 (0)	0 (0)	0 (0)	8 (100)	
Prostigmine test					<0.001
Negative	5 (23.8)	34 (69.4)	3 (50.0)	0 (0)	
7	16 (76.2)	15 (30.6)	3 (50.0)	8 (100)	

Data are *n* (%). MG, myasthenia gravis. [a]Fisher's exact test.

Table 3: Comparison between results of repetitive nerve stimulation and single-fiber electromyography stimulation tests in different Osserman classes of myasthenia

Variables	Control (*n*=30)	Ocular myasthenia (*n*=21)	Generalized MG (*n*=29)	Acute fulminant MG (*n*=6)	Severe MG (*n*=8)	*P*[a]
RNS test						<0.001
Negative	30 (100)	0 (0)	0 (0)	0 (0)	5 (62.5)	
Positive	0 (0)	21 (100)	49 (100)	6 (100)	3 (37.5)	
SF-EMG test						<0.001
Normal jitter	30 (100)	18 (85.7)	0 (0)	0 (0)	0 (0)	
Increased jitter	0 (0)	3 (14.3)	49 (100)	6 (100)	8 (100)	

Data are *n* (%). MG, myasthenia gravis; RNS, repetitive nerve stimulation; SF-EMG, single-fiber electromyography stimulation. Fisher's exact test.

Table 4: Comparison between acetylcholine receptor antibodies levels in different Osserman classes of myasthenia

Variables	Control (*n*=30)	Ocular myasthenia (*n*=21)	Generalized MG (*n*=49)	Acute fulminant MG (*n*=6)	Severe MG (*n*=8)	*P*[a]
Binding antibodies (nmol/l)	0.18 (0.08-0.24)	1.32 (0.85-2.61)[b]	1.17 (0.87-2.32)[b]	2.15 (0.96-6.09)[b]	1.26 (1.03-3.14)[b]	<0.001
Blocking antibodies (%)	8.04 (4.52-11.87)	38.65 (30.58-45.26)[b]	39.99 (31.87-46.31)[b]	45.38 (32.45-56.07)[b]	50.42 (42.26-63.84)[b]	<0.001
Modulating antibodies (%)	12.85 (7.32-24.76)	53.45 (37.30-58.26)[b]	52.22 (48.27-61.43)[b]	62.90 (47.33-71.32)[b]	56.63 (28.47-63.07)[b]	<0.001

Data are median (interquartile range). Reference ranges: Binding antibodies: 0.0-0.4 nmol/l (positive >0.4). Blocking antibodies: 0-26% (intermediate=26-41, positive >42). Modulating antibodies: 0-45% (positive >45). MG, myasthenia gravis. [a]Kruskal-Wallis test. [b]Statistically significant difference (<0.005) versus control group (Conover post-hoc test).

Table 5: Comparison of acetylcholine receptor antibodies levels between ocular and other classes of myasthenia regarding their prognosis

Variables	Ocular myasthenia (*n*=21)	Generalized MG (*n*=63)	*P*[a]
Binding antibodies (nmol/l)	1.32 (0.85-2.61)	1.18 (0.90-2.64)	0.946
Blocking antibodies (%)	38.65 (30.58-45.26)	43.36 (32.45-49.06)	0.221
Modulating antibodies (%)	53.45 (37.30-58.26)	52.82 (47.39-63.27)	0.631

Data are median (interquartile range). MG, myasthenia gravis. [a]Mann-Whitney test.

1 in 10 000 to 1 in 50 000, with a male predilection after 50 years of age [10]. The peak of onset is between 20 and 30 years in woman younger than 40 years. Women are affected two to three times more often than men; however, later in life between 50 and 60 years, the incidence in men is higher. There is also a genetic predisposition in cases where disease onset is before 40 years as thymoma-female preponderance and increased association with HLA A1, B8, and DRW3 antigens. Pregnancy, emotional stress, surgeries, trauma, and use of antibiotics were suggested as predisposing factors [11]. The aim of our study was to display the value of anti-ACh-R antibodies in diagnosis and prognosis of MG and also to evaluate the sensitivity and specificity of their different types in differentiating between localized and generalized MG.

In the present study, we found no significant difference between the studied patients groups regarding their age. There was a significant difference in levels of anti-ACh-R binding, blocking, and modulating antibodies in the studied patients groups as compared with the control group ($P < 0.001$), but there was no significant difference between them regarding MG subgroups ($P = 0.946$, 0.221, and 0.631, respectively).

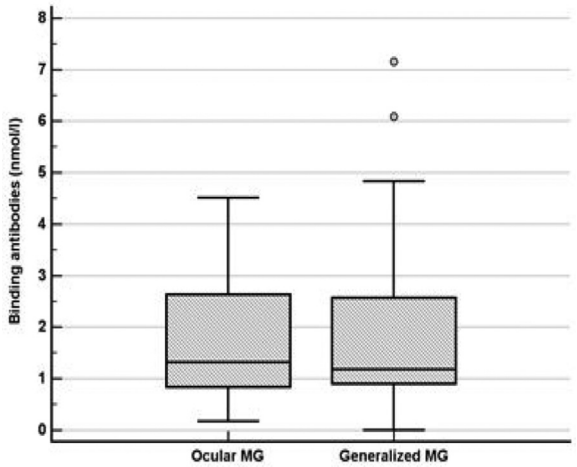

Figure 1: Box plot showing the level of acetylcholine receptor-binding antibodies in patients with ocular or generalized MG. MG, myasthenia gravis.

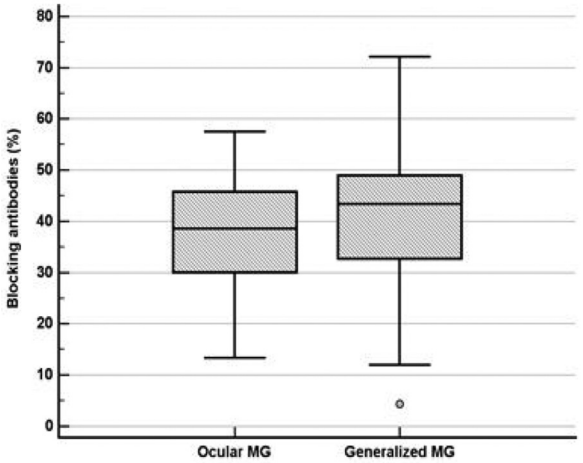

Figure 2: Box plot showing the level of acetylcholine receptor-blocking antibodies in patients with ocular or generalized MG. MG, myasthenia gravis.

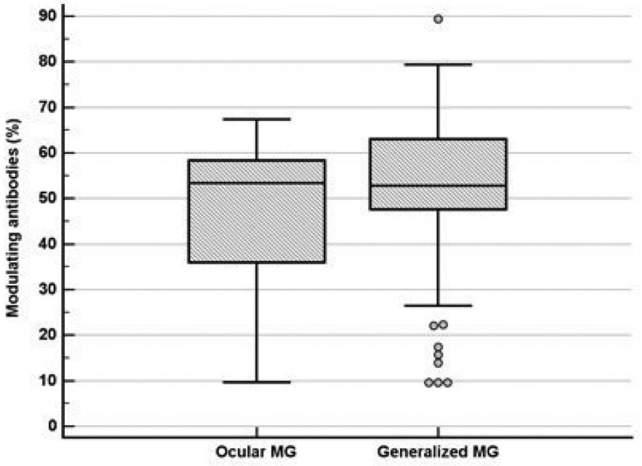

Figure 3: Box plot showing the level of acetylcholine receptor-modulating antibodies in patients with ocular or generalized MG. MG, myasthenia gravis.

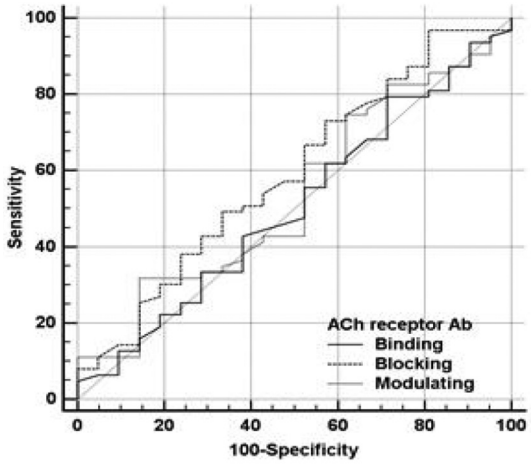

Figure 4: Receiver operating characteristic (ROC) curves for discrimination between ocular or generalized MG using binding, blocking, or modulating type of acetylcholine receptor antibodies. All three types of antibodies had poor value for discrimination between both MG subgroups (AUC = 0.505, 0.590, and 0.535, respectively). AUC, area under the curve; MG, myasthenia gravis.

In accordance with our results, Jung *et al*. [12] found an abnormal increase in anti-ACh-R antibodies level in more than 90% of cases of MG and in 45–65% of ocular myasthenia. However, contrary to our results, they found that in OM cases accompanied by high titer, systemic MG is more likely to occur. Moreover, Matthew and Donald, found an elevated level of anti-ACh-R antibodies in 80–85% in patients with generalized MG and 50–75% of patients with OM. Moreover, Bindu *et al*. [13] found that the serological prevalence of ACh-R antibody in different series was varied, being in the 67–93% range, and these antibodies are virtually absent in normal controls or in patients with other neurological or immunological diseases and admitted the usefulness of this simple diagnostic tool in the evaluation of patients with myasthenia.

In our study, we found a nonsignificant correlation between Osserman patient groups and ACh-R antibodies, except for a significant positive correlation between the Osserman class and level of blocking antibodies ($P = 0.031$). Our results are in accordance with Sidra *et al*. [14], who revealed that serum concentration of ACh-R antibodies do not correlate with the severity of MG. Moreover, Abbas and Nicholas [15] found that ACh-R antibodies titer does not correlate with disease severity; their significance is mainly in the initial diagnosis or in case of modulating antibodies as a potential marker for thymoma. Moreover, Matthew and Donald revealed that in spite of an elevated level of anti-ACh-R binding antibodies in patients with compatible clinical features of MG, the absolute concentration of antibodies does not precisely predict disease severity in all patients with MG or their therapeutic response concentration. In contrary to our results, Tindall [16] reported serum ACh-R antibody titers in patients with MG according to disease severity as measured by the Osserman

Table 6: Receiver operating characteristic curve analysis for discrimination between ocular or generalized myasthenia gravis using the level of binding, blocking, or modulating type of acetylcholine receptor antibodies

ROC curve parameter	Marker		
	Binding antibody	Blocking antibody	Modulating antibody
AUC	0.505	0.590	0.535
SE	0.074	0.074	0.073
95% CI	0.394-0.616	0.477-0.696	0.423-0.645
z statistic	0.066	1.216	0.482
P	0.947	0.224	0.630
Youden index J	0.079	0.159	0.175
Cutoff criterion	>0.85	>20.42	>58.39
Sensitivity (%)	79.4	96.8	31.8
Specificity (%)	28.6	19.1	85.7

95% CI, 95% confidence interval; AUC, area under the ROC curve; ROC, receiver operating characteristic.

Table 7: Correlation between the Osserman class and level of acetylcholine receptor antibodies

Variables	Osserman class	
	Spearman's rho	*P*
Binding antibodies level	0.083	0.453
Blocking antibodies level	0.236*	0.031
Modulating antibodies level	0.053	0.634

*$P = 0.031$

MG classification and found a correlation between antibody titers and disease severity.

In a population of 865 patients with MG, from a single academic center, there was a correlation between anti-ACh-R antibody levels and maximum disease severity per Myasthenia Gravis Foundation of America disease classification [17], but with many outliers and exceptions. This lack of a precise correlation is likely explained by many factors, including differences in the specificities of ACh-R antibodies, immunoglobulin subclass, and their ability to activate complement, as well as differences in serum and tissue antibody [18]. In our study, ROC curves revealed that although binding and blocking ACh-R antibodies provide a sensitive diagnostic test (79.4–96.8%, respectively) and modulating antibodies provide a specific diagnostic test (85.7%), the three types of antibodies had poor value for discrimination between MG subgroups (area under the curve = 0.505, 0.590, and 0.535, respectively). Our results confirm the findings of Mathew and Donald [19] who found that in ~85% of patients with MG, circulating antibodies against ACh-R are not only immune molecules but also provide a sensitive and specific noninvasive diagnostic test on suspected cases of MG. Moreover, our results are in agreement with Gilhus and Verschuuren [20] who found that sensitivity and specificity of binding and blocking antibody levels together are 99.6% and hence they are the tests of choice, and the positive modulating antibodies in patients negative for above antibodies are less than 0.4%

In our study, 10% of the patients were seronegative (OM and GM class IIa). Moreover, Bindu *et al*. [13] found that 12–17% of patients with generalized MG lack demonstrable serum ACh-R antibodies, and they are referred to as the seronegative group. Soliven *et al*. [21] reported that there was no difference in the age of onset, sex, duration of symptoms, or frequency of crises between the seropositive and seronegative patients. Sanders *et al.*, 2003, observed that seronegative patients were more likely to be males and have milder disease, ocular myasthenia, and fewer thymomas. The newly discovered autoantibodies to MuSK antibodies were reported to be present in two-thirds of the ACh-R antibody-negative patients [22]. In our study, the MuSK antibody status could not be assessed and so a comparison between the two groups could not be made. Moreover, we found a significant difference between the studied groups regarding prostigmine, RNS, and SF-EMG tests and also found that SF-EMG was abnormal in all patients with MG at the time of initial examination which came in the view of several studies [23]. Two muscles studied for jitter analysis were abnormal in 98% of all patients with MG, and this far exceeds the sensitivity of all diagnostic tests for MG with RNS, which was found at 77% as testing multiple muscles.

SF-EMG was sensitive regardless of whether the disease was ocular or generalized; the yield was more than 90% even in ocular muscles. Mostafa *et al*. [24] reported that the sensitivity of SF-EMG was 90%, of RNS was 70%, and of prostigmine was 45% and a negative ACh-R antibodies which is a common occurrence in patients with MG either with recent onset or with symptoms restricted to ocular muscles. Regarding treatment, plasma exchange and intravenous immunoglobulin are recommended, where the removed plasma is replaced with albumin and saline, which lead to the reduction in the circulating antibodies, especially binding and blocking types also there is increase in the degree of clinical improvement, as the exchange will remove 80% of circulating antibodies.

Conclusion

Our study concluded the importance of using different measures in the diagnosis of myasthenia and its leveling. These measures include clinical, neurophysiologic, and laboratory investigations, especially ACh-Rs antibodies. Antibody levels were of major importance as a noninvasive sensitive and specific diagnostic test for different types of myasthenia than other neurophysiological tests, where the procedures might be more difficult and need expensive and computerized equipment. However, ACh-R antibodies had no role in predicting the prognosis of different classes of the disease. Further research study is recommended to evaluate other types of antibodies in the diagnosis and prognosis of myasthenia.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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