Correspondence

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Autoantibodies, clinical phenotypes and quality of life in Lebanese patients with myasthenia gravis

Jihan Baalbaki[1], Mohammad Agha[2], Nisrin Jaafar[2], Bassem Yamout[2], Salim Moussa[1,*]

[1] Faculty of Health Sciences, Beirut Arab University, Beirut, Lebanon;
[2] American University of Beirut Medical Center, Beirut, Lebanon.

SUMMARY Myasthenia gravis (MG) is a rare autoimmune disease that affects the neuromuscular junction. It is characterized by the production of heterogeneous autoantibodies that bind to the neuromuscular junction and alter neural transmission. Recently, more attention was given to MG-related antibodies and their clinical influence. In Lebanon, studies about MG are very rare. To date, there is still no research on the different autoantibodies developed by Lebanese MG patients. We conducted a study aimed at detecting the prevalence of different antibodies in a group of seventeen Lebanese patients with MG, and exploring their associations with clinical phenotypes and quality of life (QOL). MG antibody test in Lebanon is restricted only to two antibodies: acetylcholine receptor (anti-AChR) and muscle-specific kinase (anti-MUSK) antibodies. Results showed that 70.6% of patients were anti-AChR positive and all of them were anti-MUSK negative. Association between MG serological profiles, clinical outcomes and QOL was not significant. Together, current findings suggest that anti-MUSK antibody is not common and difference in antibody profile may not change the clinical phenotypes and QOL of MG Lebanese patients. In the future, it is recommended to check also for autoantibodies other than anti-AChR and anti-MUSK, which may reveal new antibody profiles and possible associations with clinical outcomes.

Keywords myasthenia gravis, anti-AChR, anti-MUSK, Clinical phenotype, QOL

1. Introduction

Myasthenia gravis (MG) is a rare autoimmune disease but is the most common neuromuscular junction disorder. It can be divided into juvenile, early-onset, and late-onset MG. The annual incidence of MG was 10–29 cases per million and the prevalence was 100–350 cases per million (*1*). Autoantibodies targeted against components of the neuromuscular junction disrupt neurotransmission and lead to skeletal muscle weakness at ocular, bulbar, or general levels. The Myasthenia Gravis Foundation of America (MGFA) classified MG into five main classes according to disease severity (*2*). Anti-AChR antibody directed against the postsynaptic nicotinic acetylcholine receptor is the most common type of MG autoantibodies (*3*). It is detected in 85% of patients with generalized/bulbar MG and in 60% of ocular MG patients (*4*). The autoantibodies against muscle-specific kinase (anti-MUSK) and low-density lipoprotein receptor-related protein 4 (LRP4) are found in 6% and 2% of MG cases, respectively. Intriguingly, around 60% of anti-AChR negative cases were anti-MUSK positive. Some patients present autoantibodies against other less common neuromuscular targets such as anti-agrin, anti-collagen Q, anti-cortactin, anti-titin, or anti-ryanodine antibodies (*5*).

Some of the previous studies showed a correlation between the presence of specific autoantibodies and the onset of disease, prognosis, as well as response to treatment but no solid data supports these results (*6,7*). A Chinese study showed that the severity of double positive (anti-AChR and anti-MUSK) cases was between that of AChR-MG and MUSK-MG (*8*). Nagappa *et al.*, showed that anti-AChR positivity and clinical severity were positively correlated, and that good clinical results were associated with anti-MUSK positivity (*9*). Furthermore, the disease severity increased with the presence of anti-Agrin and anti-LRP4 antibodies in double seronegative patients (*7*). AChR antibody titer was also associated with severity (*10*). In the Middle East, few studies only had looked at MG antibodies (*11*).

Lebanese studies about MG were very rare and limited to few case reports. These works had only presented some clinical observations and operational methods to manage MG without investigating

autoantibodies (*12-15*). Therefore, the present study aimed at determining the prevalence of different autoantibodies and their association with clinical phenotypes and quality of life (QOL) in a Lebanese group with MG. It was conducted at the American University of Beirut Medical Center (AUBMC). Seventeen participants were eligible to enter the study. Pediatric patients and those who had received plasmapheresis and/or intravenous immunoglobulin (IVIG) in the preceding four weeks were excluded.

Ethical boards at American University of Beirut (AUB) and Beirut Arab University (BAU) approved the present study that is conformed to the provisions of the Declaration of Helsinki (IRB BAU approval code: 2020-H-0104-H5-R-0375 and AUB approval code: BIO-2020-0011). All informed consent was obtained from the subject(s) and/or guardian(s).

2. Clinical data

Around 70% (n = 12) were males and 30% (n = 5) females. Most of the patients (around 78%, n = 13) had late-onset MG at an age > 50 years. Participants were from all Lebanese districts (South Lebanon, North Lebanon, Bekaa, Baalbeck, Akkar, Mount Lebanon, and Beirut). Two patients were diagnosed in 2021 and the rest between 2018 and 2020.

Only two antibodies (anti-AChR and anti-MUSK) were investigated in our group of MG patients. Tests for other antibodies are not routinely performed in Lebanese hospitals. All participants were anti-MUSK negative and the majority were anti-AChR positive (n = 12). Subsequently, MG patients were classified into two groups: group I (anti-AChR negative; anti-MUSK negative) and group II (anti-AChR positive; anti-MUSK negative). Of these, 35.3 % of participants (n = 6) had ocular MG, 5.9 % (n = 1) had bulbar MG, and 17.7 % (n = 3) belonged to ocular-bulbar MG class. The others were diagnosed with generalized MG 41.2% (n = 7). According to MGFA classification, MG classes of patients were distributed as follows: 35.3% (n = 6) were class I, 17.7 % (n = 3) were class II (33% class II a and 67% class II b). In addition, 23.5% (n = 4) were class III with 50% class III a and 50% class III b, 17.7 % (n = 3) belonged to class IV, with 67% to class IV a and 33% to class IV b and 5.9% (N=1) belonged to class V.

Interestingly, 17.7 % (n = 3) of patients underwent thymectomy, while 82.3 % (n = 14) showed no evidence of thymoma. One patient only had a respiratory crisis after thymectomy. The majority were on Mestinon and azathioprine (around 29.4%, n = 5), 23.5% (n = 4) received IVIG at certain point of time, 29.4% (n = 5) were on Mestinon alone, and 11.8% (n = 2) were on Mestinon and steroids.

For the quality-of-life characteristics, we used the questionnaire (MG-QOL15r) that checks for difficulties in eating, speaking, eye-opening, mood, independence, and ambulation (*16*). A higher score indicates a more severe case of MG. The mean score (MG-QOL15r) of group I patients was 12.8/30 at baseline, 8.2/30, and 7/30 at three and six months; respectively. On the other hand, group II had a mean score (MG-QOL15r) of 13.3/30 at baseline, 8.3/30, and 5.08/30 at 3 and 6 months respectively (Table 1).

Both groups I and II showed similar clinical phenotypes and QOL patterns ($p > 0.05$) (Table 2). This indicates that there was no significant association between difference in these two antibody profiles and clinical phenotype, and QOL.

3. Discussion

Today, autoantibody testing became essential for the diagnosis and management of MG. However, very little research on antibody profiles and their possible association with clinical outcomes was conducted in the Middle East. In Lebanon, this was the first study looking at MG-related antibodies. Based on PubMed search with the combination of the keywords "Myasthenia Gravis" and "Lebanon", less than twenty articles only had been identified between 1991 and 2023. Most of studies were case reports. None had aimed to investigate the MG autoantibodies. They had mainly described clinical observations like a paraneoplastic MG with central nervous system lymphoma (*12*), an association of MG with polyarteritis nodosa (*13*), and a thymoma accompanied by MG, PRCA, and Good's syndrome (*14*). Other discussed management of MG like the radiotherapy for thymoma resection (*15*), the safety of cardiopulmonary bypass

Table 1. Clinical phenotypes of MG Lebanese cohort

Characteristics	Frequency	Percentage (%)
MG category		
Ocular	6	35.3
Bulbar	1	5.9
Ocular-bulbar	3	17.7
Generalized	7	41.2
MGFA Class		
I	6	35.3
II	3	17.7
III	4	23.5
IV	3	17.7
V	1	5.9
Thymus condition		
Thymectomy	3	17.7
Absence of thymoma	14	82.3
Severe respiratory crisis		
Yes	1	5.9
No	16	94.1
Treatment		
Mestinon	5	29.4
Mestinon + Steroid	2	11.8
Azathioprine	1	5.9
Mestinon + Azathioprine	5	29.4
IVIG	4	23.5
Rituximab	0	0

Table 2. Association between antibodies profiles, clinical phenotypes, and QOL.

Characteristics	Group I (AChR negative; MUSK negative)	Group II (AChR positive; MUSK negative)	*p* value
Gender			0.117
Male	2	10	
Female	3	2	
MG Category			0.879
Generalized	1	6	
Ocular	2	4	
Bulbar	1	0	
Ocular-bulbar	1	2	
MGFA Class			1.00
Class I	2	4	
Class II	1	2	
Class III	1	3	
Class IV	1	2	
Class V	0	1	
Thymus status			0.515
Absence of thymoma	5	9	
Thymectomy	0	3	
History of severe respiratory crisis			1.00
No	5	11	
Yes	0	1	
Treatment			1.00
Mestinon	2	3	
Mestinon+Steroids	1	1	
Mestinon+Azathioprine	1	4	
IVIG	1	3	
Azathioprine	0	1	
Response to treatment			0.413
No/Poor	2	2	
Complete Remission	1	1	
Partial remission	2	9	
MG-QOL15 r score (Baseline)			1.00
0 to 10/30	2	5	
11/30 to 20/30	2	5	
21/30 to 30/30	1	2	
MG-QOL15 r score (3 months)			1.00
0 to 10/30	2	6	
11/30 to 20/30	3	6	
21/30 to 30/30	0	0	
MG-QOL15 r score (6 months)			1.00
0 to 10/30	4	8	
11/30 to 20/30	1	4	
21/30 to 30/30	0	0	

Fisher's exact test ($p < 0.05$ is considered statistically significant).

(*17*), new anesthetics conditions and treatments (*18,19*).

In our group, antibody testing had included only anti-AChR and anti-MUSK antibodies. Antibody test of other MG-related autoantibodies such as LRP4, agrin, collagen Q, titin *etc.* is not prescribed in Lebanon. Therefore, Lebanese MG patients can be divided into two groups based on serological findings: anti-AChR negative/anti-MUSK negative and anti-AChR positive/anti-MUSK negative groups. Results showed that most Lebanese patients with MG were anti-AChR positive like the other MG populations worldwide (*20*). However, all patients were anti-MUSK negative. Thus, it becomes of interest to check also for the other MG antibodies that may reveal new antibodies profiles and possible effects. Results showed no significant association between the different serological profiles and gender, MGFA Class, MG category, thymus status, history of respiratory crisis, choice of treatment, and response to treatment. However, three patients who underwent thymectomy belonged to the seropositive group with titers higher than the rest of the patients. Interestingly, patients with MGFA class I and II had a lower titer of anti-AChR antibodies compared to other classes and patients that went into remission showed lower titers of anti-AChR antibodies. Two patients went into total remission after around a year of diagnosis. One of them was seronegative and had remission following resection of a lung adenocarcinoma and the other had a low anti-AChR titer. Importantly, some patients had other diseases prior to MG such as lung cancer and Systemic Lupus Erythematosus. This supports the idea that other diseases may trigger

autoimmune disorder. Results showed no significant association between serological profiles and QOL. However, all participants presented an overall improvement in the QOL at 3 months and 6 months after starting treatment.

Based on this study, we conclude that MG patients in Lebanon should not only be tested for anti-MUSK and anti-AChR antibodies but also for the other types of MG autoantibodies. This is essential in order to set up all antibody profiles and their possible associations with clinical phenotypes and QOL.

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**Address correspondence to:*
Salim Moussa, Faculty of Health Sciences, Beirut Arab University, 11 5020 Beirut, Lebanon.
E-mail: s.moussa@bau.edu.lb