Journal of Neurological Sciences [Turkish] **30:(1)**# 34; 135-143, 2013
http://www.jns.dergisi.org/text.php3?id=628
Research Article

Myasthenia Gravis; Single Entity, Variable Clinical Features: Ten Years of Clinical Experience in a Tertiary Care Center Ten Years Clinical Experience of a Tertiary Care Center

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Summary

Introduction: This study is a ten years experience of a tertiary care center documenting the data of 132 myasthenia gravis (MG) patients. Our aim is to review retrospectively the clinical and immunological properties and treatment responses of a heterogeneous group of MG patients. Special attention has been focused on two subgroups, thymoma associated MG and pure ocular MG patients.
Methods: Patients evaluated between 2000-2010 and followed at least two years were included. The patients who were followed-up at least 2 years in our clinic between the years of 2000-2010 were included in the study. The demographic properties, course of the disease, immunological parameters, treatment responses were reviewed. The effect of thymectomy has been retrospectively determined by Myasthenia Gravis Foundation of America (MGFA) Postintervention Status.
Results: Fifty patients (37.9 %) were presented with isolated ocular symptoms and 62 % of them were eventually generalized. The mean time to generalization was 12.67±11.9 months. 16.13 % were generalized after the second year of disease. It is noteworthy that three patients were generalized 120, 156 and 240 months after the disease onset. In the pure ocular MG subgroup, six (31.6 %) patients had thymoma whereas two (10.5 %) had thymic hyperplasia. 15.79 % of seronegative patients had thymic hyperplasia while 5% (1/19) of them had thymoma.
Conclusion: Our findings demonstrate that ocular onset MG patients can develop generalized form in an unexpected time period. The presence of thymoma and thymic hyperplasia in our seronegative and pure ocular MG patients showed the necessity to scan these groups for thymic pathology.

Key words: Myasthenia gravis, thymoma, thymectomy, Anti-muscle specific tyrosine kinase antibody, Acetylcholine receptor antibody, ocular myasthenia gravis, seronegative

Miyastenia Gravis: 3. Basamak Sağlık Merkezinin on Yıllık Tecrübeleri

Özet

Giriş: Bu çalışma, üçüncü basamak bir sağlık kuruluşu olan Hacettepe Üniversitesi'nin 10 yıl içinde değerlendirdiği 132 miyastenia gravis (MG) hastasının bilgilerini içermektedir. Çalışmanın amacı retrospektif olarak heterojen bir yapıya sahip olan miyastenia gravis hastalarının klinik ve immünolojik özelliklerini, tedavi yanıtlarını gözden geçirmektir. Timoma ilişkili MG ve oküler MG hastalarımız özel olarak ele alınmıştır.

Metot: 2000-2010 yılları arasında en az iki yıl süreyle bölümümüzde takip edilen hastalar çalışmaya dahil edilmiştir. Timektomiden faydalanma Myasthenia Gravis Foundation of America (MGFA) Postintervention Status ile retrospektif olarak değerlendirilmiştir.
Sonuçlar: Elli (% 37.9) hasta izole oküler semptomlarla başvurmuş ve bunların % 62'si izlemleri sırasında jeneralize olmuştur. Semptomların başlangıcından jeneralizasyona kadar geçen ortalama süre 12.67±11.9 aydır. Hastaların %16.13'ü izlemlerinin ikinci yılından sonra jeneralize olmuştur. Üç hastanın hastalık başlangıcından 120, 156 ve 240 ay sonra jeneralize olmaları dikkat çekici bir bulgudur. İzole oküler MG hasta grubunda 6 (% 31.6) hastada timoma, 2 (% 10.5) hastada timik hiperplazi saptanmıştır. Seronegatif hastaların %15.79'unda timik hiperplazi ve % 5'inde (1/19)ise timoma tespit edilmiştir.
Sonuç: Elde ettiğimiz bulgular oküler başlangıçlı MG hastalarının hastalığın ikinci yılından sonra da jeneralize olabileceğini göstermektedir. Seronegatif ve izole oküler MG hastalarımızda timoma ve timik hiperplazi gözlenmesi bu hasta gruplarında da timik patolojilerin araştırılması gerekliliğini ortaya koymaktadır.

Anahtar Kelimeler: Miyastenia gravis, timoma, timektomi, anti-muscle specific tyrosine kinase antikoru, asetilkolin reseptör antikoru, oküler miyastenia gravis, seronegatif

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease of neuromuscular junction. Its incidence is 3-30 per 100.000.[12] Although the immunopathogenesis is well known, there are still some difficulties in treatment of some particular patients. Therefore, long -term and detailed follow-up of myasthenia gravis patients is valuable for the clinicians.

The purpose of this study is to review the immunological, clinical properties and treatment responses of a heterogeneous group of MG patients. This is a ten years experience of a tertiary care center documenting the data of 132 MG patients. Special attention has been focused on two subgroups, thymoma associated MG and pure ocular MG patients.

MATERIAL AND METHODS

Myasthenia Gravis patients who were evaluated between January 2000 and December 2010 and followed at least for two years in our center were included. The diagnosis was made on the basis of clinical findings and confirmed by single fiber electromyography (SFEMG). Tensilon, ice or pyridostigmine tests were performed when necessary. All patients underwent measurement of acetylcholine receptor antibody (AchR-ab). AchR-ab negative patients were tested for anti-muscle specific tyrosine kinase antibody (anti-MuSK-ab). Thorax computerized tomography (CT) was performed for all patients.

The disease severity has been retrospectively determined by Myasthenia Gravis Foundation of America (MGFA) clinical classification and the effect of thymectomy has been evaluated by MGFA Postintervention Status.[8] The follow-up period after thymectomy was at least two years.

Responses to medical treatments were assessed by improvement in objective and subjective complaints within expected time of onset of the agent/procedure effect.

The data were recorded to SPSS version 15.0. The relations between age, sex and thymus pathology were analyzed with Mann-Whitney and ki-square test. Statistical significance was accepted if $p<0.05$.

RESULTS

1. Demographics

Between January 2000 and December 2010, 197 MG patients were evaluated in our center. 132 patients who had adequate

information and follow-up were included. The demographic properties, course of the disease, immunological parameters, treatments and treatment responses were documented. The mean age of onset was 38.64±17.61 (10-75) years. Seventy-nine of 132 (59.8%) patients were female. The mean age of onset was 35.06±16.61 in female and 43.96±17.86 years in male patients. Female patients were younger than male patients (p= 0.004).

2. Clinical features

2.a. Age of onset according to the antibody status:

The mean age of onset was 38.37±17.9 (11-75) years in acetylcholine receptor antibody (AchR-ab) positive patients and 28.70±11.7 (10-52) years in anti-muscle specific tyrosine kinase antibody (anti-MuSK-ab) positive patients.

2.b. Symptom of onset:

2.b.1. How ocular onset disease behave?

Fifty patients (37.9 %) were presented with isolated ocular symptoms (ptosis or/and diplopia). Thirty-one of these patients (62 %) were eventually generalized. The mean time to generalization was 12.67±11.9 months. 16.13 % were generalized after the second year of disease. It is noteworthy that three patients generalized in a time period as 120, 156 and 240 months.

2.b.2. Pure Ocular MG patients

Nineteen of our patients had pure ocular symptoms during the clinical course. Twelve (63.15 %) of them were male. The mean age of onset was 41±18.3 (15 -73). Thirteen patients (68.4 %) were seropositive for AchR-ab, whereas five patients (26.3 %) were seronegative and the other one was seropositive for anti-MuSK-ab.

Six of pure ocular MG patients had thymoma while two had thymic hyperplasia.

Fifteen patients had corticosteroid treatment and two had also azathioprine due to thymoma. Four patients were followed without any immunosuppressive treatment.

2.b.3. Rest of the patients presented with isolated bulbar (17/82; 20.73%), bulbar plus ocular symptoms (19/82; 23.17%) or generalized weakness (46/82; 56.1%). During this study these patients are classified as generalized MG.

3.Antibodies

AchR antibody was positive in 103 (78.03 %) of patients. Twenty-nine AchR-ab-negative patient sera were evaluated for anti-MuSK antibody. As a result, ten of them found to be positive for anti-MuSK antibody (Table 1).

4. Crisis:

53.1 % (60/113) of generalized MG patients had at least one myasthenic crisis. The incidence of myasthenic crisis in relation to different antibodies was given in Table 2.

5. Thymus pathology

Thymectomy was performed to patients with thymus pathology such as thymoma or thymic hyperplasia suspected by thorax computerized tomography and/or unresponsive to all therapies. Finally, 54.55 % (72/132) of patients had thymectomy. The thymus pathology showed thymoma in 30 (41.67 %) and thymic hyperplasia in 24 (33.33 %) patients. 19 (79.2%) of patients with thymic hyperplasia and 17 (56.7%) of patients with thymoma were female. Thymectomy could not be performed in 5 patients as the tumour infiltrated to the mediastinal great vessels. These patients had chemotherapy and radiotherapy.

The mean age of disease onset was 43.93±14.7 (18-73) years in patients with thymoma and 27.21±10.7 (14-54) years in patients with thymic hyperplasia ($p<0.001$).

Neither thymic hyperplasia nor thymoma were found in the limited number of anti-

MuSK-ab-positive patients. 15.79 % of seronegative patients had thymic hyperplasia while 5.26% (1/19) of them had thymoma (Table 3). The seronegative patient with thymoma was female. She had diplopia and ptosis at the age of 30 and she developed generalized disease at the age of 32. AchR-ab and MuSK-ab were found to be negative in two repeated determinations. The thymus pathology showed thymoma type B1 according to WHO classification.[20] After the thymectomy, she had only mild weakness under pyridostigmine treatment (MM-3).

In the pure ocular MG subgroup, six patients had thymoma whereas two had thymic hyperplasia (Table 4).

6. Thymectomized MG patients with thymoma

Twenty-five patients with thymoma had thymectomy. The mean age of onset of these patients was 42.92±15.0 (18-73). Twelve of them were female. The mean age of onset was 39.33±15.9 (18-73) in females and 46.23±13.9 (22-70) in males ($p>0.05$).

After the thymectomy, the patients were followed-up at least two years. According to MGFA Postintervention Status 11 patients (44 %) were evaluated as “Minimal Manifestations-3” (MM-3); 4 (16 %)patients were accepted as ”Pharmacologic Remission” (PR) and 2 (8 %) patients were accepted as “Complete Stable Remission” (CSR). Three patients (12 %) were evaluated as “Unchanged” (U) and the rest five (20 %) patients were accepted as “Worse” (W).

7. Other Laboratory Findings and associated conditions

Antinuclear antibody (ANA) was positive in eleven AchR-ab-positive patients; five of them had also systemic lupus erythematosus and one of them had mixed connective tissue disease. Antithyroid peroxidase antibody (Anti-TPO-ab) was positive in five patients (one of them is seronegative MG). Thyroid stimulating hormone (TSH) receptor antibody was positive in one and anti-thyroglobulin antibody was positive in three patients (one of them is seronegative MG).

Eleven patients had hyperthyroidism (one of them is seronegative MG) and three patients had hypothyroidism.

8. Treatment

Oral corticosteroid (CS), immunosuppressants (azathioprine, methotrexate and cyclophosphamide), mycophenolate mofetil (MM), intravenous immunoglobulin (IVIG) and plasma exchange (PE) were used. The dosage was 1-1.5 mg/kg/day for CS; 100-150 mg/day for azathioprine (AZA), 7.5 mg/week for methotrexate (Mtx); 150 -200 mg/day for cyclosporine (CP); 1500-2500 mg/day for MM. PE was used 5-10 times for crisis and twice a week for the clinical worsening. IVIG was given 2 gr/kg for crisis and 0.4 gr/kg/month in a single day for clinical maintenance in unresponsive patients (Table 5).

Responses to treatments were assessed by improvement in objective and subjective complaints within expected time of onset of the agent/procedure effect (Table 6).

9. Mortality

Five of our patients died during the follow up. The cause of death was sepsis in all patients. All had severe bulbar symptoms, required ventilator support, unresponsive to treatments and could not be extubated. Four were seropositive for AchR antibody and one patient had anti-MuSK antibody. One of the AchR-ab-positive patients had an inoperable invasive thymoma; another one had SLE.

Table 1: The frequency of different autoantibodies in relation to sex (AchR-ab: Acetylcholine receptor antibody, Anti-MuSK-ab: Anti-muscle specific tyrosine kinase antibody)

Sex	**AchR antibody(+)**	**Anti-MuSK (+)**	**Seronegative**
Female	62.1 %	60 %	47.4 %
(n=79)	(n= 64)	(n= 6)	(n= 9)
Male	37.9 %	40 %	52.6 %
(n=53)	(n= 39)	(n= 4)	(n= 10)
Total	(n=103)	(n=10)	(n=19)

Table 2: Number of generalized MG patients who experienced at least one crisis during the course of the disease in relation to different antibodies (AchR-ab: Acetylcholine receptor antibody, Anti-MuSK-ab: Anti-muscle specific tyrosine kinase antibody)

Antibody positivity in generalized MG patients (n=113)	**At least one crisis**
Seronegative	28.6 %
(n=14)	(n=4)
AchR-ab (+)	55.55 %
(n=90)	(n=50)
Anti-MuSK-ab (+)	66.67 %
(n=9)	(n=6)

Table 3: Thymus pathology in relation to different antibodies (AchR-ab: Acetylcholine receptor antibody)

Antibody	**Thymic hyperplasia**	**Thymoma**
Seronegative	3	1
(n= 19)	(15.79%)	(5.26%)
AchR ab(+)	21	29
(n= 103)	(20.39%)	(28.16%)
MuSK ab (+)	0	0
(n= 10)		

Table 4: Thymus pathology according to the disease subgroups

Type	Thymic hyperplasia	Thymoma
Pure Ocular	2	6
(n= 19)	(10.5%)	(31.6%)
Generalized	22	24
(n= 113)	(19.5%)	(21.2%)

Table 5: Number of patients under treatment (CS: Corticosteroid; IS: Immunosuppressants; PE: Plasma exchange; IVIG: Intravenous immunoglobulin; MM: Mycophenolate mofetil; AchR-ab: Acetylcholine receptor antibody, Anti-MuSK-ab: Anti-muscle specific tyrosine kinase antibody)

Patients	CS	IS	PE	IVIG	MM
Seronegative	84.21%	36.84%	36.84%	36.84%	5.3%
(n=19)	(n=16)	(n=7)	(n=7)	(n=7)	(n=1)
AchR antibody (+)	84.47%	30.1%	41.75%	43.69%	6.8%
(n=103)	(n=87)	(n=31)	(n=43)	(n=45)	(n=7)
Anti-MuSK (+)	100%	50%	70%	70%	30%
(n=10)	(n=10)	(n=5)	(n=7)	(n=7)	(n=3)

Table 6: Patient responses to treatments (*All responders were under cyclosporine) (CS: Corticosteroid; IS: Immunosuppressants; PE: Plasma exchange; IVIG: Intravenous immunoglobulin; MM: Mycophenolate mofetil; AchR-ab: Acetylcholine receptor antibody, Anti-MuSK-ab: Anti-muscle specific tyrosine kinase antibody)

	CS (%)	IS (%)	PE (%)	IVIG (%)	MM (%)
Seronegative	68.8	57.14	100	85.7	100
AchR antibody (+)	86.2	87	93	91.1	85.7
Anti-MuSK (+)	40	40*	71.43	57.14	33.3

DISCUSSION

Our clinical data about the age of onset of disease according to the antibody status showed that anti-MuSK-ab-positive patients had a tendency to be younger. Stickler et al found the mean age of onset in anti-MuSK-ab-positive patients as 27.[19] Another noticeable point about anti-MuSK-ab-positive patients was their

higher myasthenic crisis rates when compared with AchR-ab-positive and seronegative subgroups. Sixty percent of our anti- MuSK-ab positive patients experienced at least one crisis during the course of the disease. In the literature, the risk of crisis has been documented between 23-46% in anti-MuSK positive-patients.[1,3,6] Deymeer et al noticed the high rate of crisis in the first two years of disease in anti-MuSK-ab-positive MG patients.[1]

Our study especially focused on the pure ocular MG patients. In the literature the risk of generalization in ocular onset MG patients is highest within the first year and is not greater than 7% after three years.[4] Our retrospective analysis showed that the mean time to generalization was 12.67±11.9 months. 16.13 % were generalized after the second year of disease. It is noteworthy that three patients generalized in a time period as 120, 156 and 240 months.

Paraneoplastic MG is a particular subgroup of MG and there are limited numbers of studies about the effect of thymectomy on the course of the disease.[18] Thymus pathologies such as follicular hyperplasia and thymoma were commonly reported in AchR-ab-positive patients.[10] In our series, 28.16 % of AchR-ab-positive patients had thymoma. Furthermore, 20.39 % of AchR-ab-positive patients and 15.79 % of seronegative patients had thymic hyperplasia. We have not detected any thymus pathology in our anti-MuSK antibody positive patients similar to the literature.[2,16] Interestingly, although we could not rule out the presence of low affinity antibodies, one of our seronegative patients tested for antibodies in two different occasions had thymoma. She was accepted as generalized MG and type B1 thymoma was demonstrated. She improved and stayed in MM-3 after thymectomy. It is noteworthy to underline this patient as there are only limited number of seronegative MG patients with thymoma in the literature.[11,14] Maggi et al. reported two seronegative MG patients whose outcome was PR after thymectomy.[11] These findings indicate that thymus pathologies should be searched in seronegative patients.

In patients with thymoma the main aim is to treat the tumour rather than for any effect on the MG. Few studies have evaluated the effect of thymectomy on disease course. Li et al. reported that MG symptoms relieved in 33.3% and improved in 20.5% of patients after thymoma resection.[10] In our series, 44% of patients were evaluated as MM-3 while 16 % of patients were accepted as PR and 8 % of patients were accepted as CSR. Thymoma or thymic hyperplasia has been reported in pure ocular MG patients before.[17] Six of our 19 pure ocular MG patients had thymoma while two patients had thymic hyperplasia. In our knowledge, this is the highest rate of thymoma in pure ocular MG patients.[7,9,15,17] Thymectomy had been performed in ten of these 19 pure ocular MG patients and none of them developed generalized disease. This data emphasizes that pure ocular patients should be examined for the presence of thymus pathology.

Four of our anti-MuSK-ab-positive patients unresponsive to any treatment had thymectomy. In the follow-up we did not observe any clinical improvement associated with the operation. Evoli et al also did not demonstrate the efficacy of thymectomy in anti -MuSK- ab-positive patients.[5]

We retrospectively evaluated treatment responses for different immunosuppressive treatments in different MG subgroups. It is noteworthy to report our clinical observation about the clinical response of anti-MuSK-ab-positive MG patients to cyclosporine. The PE and IVIG responses of seronegative and AchR-ab-positive patients were similar. In anti-MuSK-ab-positive patients the best outcome was obtained with PE.

Depending on the heterogeneous trait of MG based on their different antibodies, it is sometimes hard to estimate the prognosis. Our observations in 132 cases indicate that; majority of ocular onset patients can develop generalized form within two years, however there are three cases longer than expected time window, as 120, 156 and 240 months. Thymoma was found in one of 19 seronegative patients, 6 of 19 with pure ocular MG and 29 of 103 with AchR-ab. None of 10 anti-MuSK-ab-positive patients had thymoma. The presence of thymoma and thymic hyperplasia in our seronegative and pure ocular MG patients showed the necessity to scan these groups for thymic pathology.

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Received by: 28 July 2012
Accepted: 05 November 2012

The Online Journal of Neurological Sciences (Turkish) 1984-2013
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

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