Journal of Neurology & Neurophysiology

Bernardo Cacho Diaz et al., J Neurol Neurophysiol
2015, 6:5
DOI: 10.4172/2155-9562.1000317

Commentary Open Access

# Myasthenia Gravis and Its Comorbidities

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**Received date:** September 16, 2015; **Accepted date:** September 22, 2015; **Published date:** September 29, 2015



## Abstract

**Background:** Myasthenia gravis (MG) is an unpredicted neurologic disorder that may cause death; previous reports have failed to find a prognostic marker for the disease.

**Aim:** To determine the impact of comorbidities in patients with Myasthenia gravis.

**Material and Methods:** From January of 2002 to February of 2008 a database was created for patients with Myasthenia gravis (MG). The following variables were studied: age at onset of MG, gender, diabetes mellitus, dyslipidemia, arterial hypertension, dysthyroidism, autoimmune disease, thymectomy procedure and histopathologic result, myasthenic crisis, emergency room visits due to weakness, use and maximum dose of pyridostigmine, prednisone and azathioprine.

**Results:** In a total of 253 patients, we found comorbidities in 73%. The most frequent associated disorders were dyslipidemia, thyroid disease, diabetes, hypertension and other autoimmune conditions. Patients with MG and thymoma, diabetes, dyslipidemia, dysthyroidism and/or hypertension had higher rates of ER visits, myasthenic crises, and required higher doses of drugs.

**Conclusions:** This study demonstrates that comorbidities are frequent in patients with MG (73%) and that they might worsen the prognosis of MG.

**Keywords:** Myasthenia Gravis, Comorbidity, Thymoma, Autoimmune, Prognosis.

## Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by fluctuating weakness of striated muscles, which can be severe enough to cause death. Several reports describe comorbidities in patients with myasthenia gravis [1-6], but most of these report autoimmune rather than metabolic diseases. The relationship between comorbidities and prognosis of MG has not yet been elucidated. Both incidence and prevalence of MG and other diseases vary according to the region of the world under study [7-11].

A history of fluctuating weakness of voluntary muscles and a detailed neurological exam are the most useful tools in diagnosing MG. It is important to confirm the clinical diagnosis with at least one lab test such as the anti-ACh receptor antibodies determination, single fibre electromyography, repetitive electrostimulation (Jolly test), ice or edrophonium test [12]. Every patient with MG should get a chest CT to rule out the presence of thymoma. Other diseases must be ruled out before confirming the diagnosis [13].

Treatment for MG includes a limited gamut of interventions and there is not a standardized scheme, so each case should be individualized according to stated recommendations [14].

Myasthenic crisis (MC) is defined as an acute exacerbation of myasthenic weakness leading to ventilatory failure often requiring mechanical support. Approximately 30% of all patients with MG develop ventilatory weakness and at least 15 to 20% suffer myasthenic crises (MC). Of patients who survive a first crisis, one third experience a second [15-16].

## Material and Methods

The objective of this study was to determine the impact of co-morbidities in patients with MG in a mestizo Hispanic population.

All patients included in this study had MG diagnosed clinically and on the basis of at least two confirmatory tests. Both main investigators (BC, GGR) met them at least once. They were seen for neurology consult at a referral center from 2002 to 2008.

The following data was obtained: age at the onset of MG, gender, results of the following tests: repetitive electrostimulation and/or single fibre electromyography, edrophonium, anti-acetylcholine receptor antibodies (Ach-R Ab), presence of ocular or systemic symptoms, thyroid function tests (TSH, T3, T4, CT3, ITL), anti-thyroid antibodies, number of visits to emergency room (ER) caused by weakness, number of myasthenic crises, maximum dose and use of pyridostigmine, prednisone and/or azathioprine. Information was obtained about whether the patients had thymectomy or not, the histopathology, and the presence or absence of comorbidities such as

diabetes mellitus, arterial hypertension, dyslipidemia, thyroid disease or any other disease.

Blood samples were obtained from patients when they were not hospitalized, had no acute disease (i.e. infection) and were not receiving high doses of steroids (>0.5mg/kg/d of prednisone or its equivalent).

Exclusion criteria: unsupported MG diagnosis or a different established diagnosis, incomplete file or medical follow-up of less than 12 months.

### Statistical analysis

Clinical and pathological manifestations in patients with MG with or without comorbidities were compared with Student T and Mann-Whitney U tests for continuous variables with or without normal distribution, respectively; ANOVA and Turkey correction were used to analyze >3 variables, odds ratio was used to compare prognostic observations.

### Ethical aspects

The study did not raise ethical concerns and was approved by the IRB.

## Results

A total of 253 patients were included: 178 were women (70%) and 75 men (30%), with a female-to-male ratio of 2.4:1. The average age of onset of symptoms was 35 ± 17 years [31 ± 15 for women and 44 ± 18 for men (P<0.001)]. Information about the distribution and severity of weakness was obtained in 252 patients. Sixteen patients (7%) had purely ocular and 236 (93%) generalized weakness. Most patients (79%, n 200) developed symptoms before 50 years of age. Repetitive electrostimulation results (Jolly's test) were obtained in 236 patients, being positive in 219 (93%) with an average electrodecrement of 32.5% (Range: 11-118). Acetylcholine anti-receptor antibodies (AchR-ab) results were obtained in 228 patients, being positive in 199 (87%). Ninety percent of patients with systemic manifestations and 50% with purely ocular had positive AChR (p <0.001). The edrophonium test was performed in 144 patients and was reported as positive in 137 (95%).

Of the studied patients, 84 (33%) had myasthenic crisis (MC) and 150 (60%) sought assistance due to weakness. In total, 73% of our patients presented comorbidities. The prognosis according to each comorbid condition is summarized in Table 1.

| | Age (y) ± SD | Fem/Mae | MC n (%) | No. Crisis ± SD | ER n (%) | No. ER ± SD | PDM dose mg ± SD | PDN use n (%) | PDN dose mg ± SD | AZA use n (%) | AZA dose mg ± SD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Comorbidity (n 252) | | | | | | | | | | | |
| Yes 185 (73%) | 38 ± 18 | 63/37 | 64 (35) | 1.8 ± 1.2 | 118 (64) | 3.3 ± 3 | 360 ± 180 | 139 (75) | 49 ± 26 | 87 (47) | 77 ± 26 |
| No | 25 ± 9 | 91/9 | 20 (30) | 1.3 ± 0.7 | 32 (48) | 2 ± 2 | 328 ± 139 | 38 (57) | 37 ± 18 | 19 (28) | 68 ± 26 |
| P | <0.0001 | <0.0001 | NS | NS | 0.016 | 0.005 | NS | 0.004 | 0.011 | 0.006 | NS |
| OR 95% CI | | | 1.2 (0.7-2.3) | | 1.92 (1.1-3.4) | | | | | | |
| Dyslipidemia (n 234) | | | | | | | | | | | |
| Yes 140 (60%) | 39 ± 18 | 63/37 | 50 (36) | 1.7 ± 1.2 | 94 (67) | 3.4 ± 3.1 | 373 ± 182 | 106 (76) | 49 ± 27 | 70 (50) | 79 ± 27 |
| No | 31 ± 16 | 80/20 | 27 (29) | 1.7 ± 1.2 | 45 (48) | 2.8 ± 2.8 | 321 ± 148 | 60 (64) | 42 ± 21 | 32 (34) | 66 ± 24 |
| P | 0.001 | 0.004 | NS | NS | 0.003 | NS | 0.023 | 0.035 | NS | 0.011 | 0.015 |
| OR 95% CI | | | 1.4 (0.8-2.4) | | 2.2 (1.3-3.8) | | | | | | |
| Dysthyroidism (n 233) | | | | | | | | | | | |
| Yes 45 (19%) | 37 ± 17 | 76/24 | 15 (33) | 2 ± 1.4 | 35 (78) | 3.8 ± 3.1 | 374 ± 204 | 33 (73) | 49 ± 31 | 20 (44) | 73 ± 21 |
| No | 34 ± 17 | 70/30 | 61 (32) | 1.6 ± 1 | 109 (58) | 2.8 ± 2.8 | 348 ± 162 | 132 (70) | 46 ± 24 | 82 (44) | 76 ± 28 |
| P | NS | NS | NS | NS | 0.01 | NS | NS | NS | NS | NS | NS |
| OR 95% CI | | | 1.0 (0.5-2.1) | | 2.5 (1.2-5.4) | | | | | | |
| Diabetes mellitus (n 252) | | | | | | | | | | | |
| Yes 50 (20%) | 46 ± 17 | 56/44 | 24 (48) | 1.7 ± 0.9 | 40 (80) | 3.6 ± 3.6 | 410 ± 204 | 34 (68) | 52 ± 21 | 27 (54) | 82 ± 28 |
| No | 32 ± 16 | 74/26 | 60 (30) | 1.7 ± 1.2 | 110 (55) | 2.8 ± 2.6 | 337 ± 158 | 143 (71) | 45 ± 26 | 79 (39) | 73 ± 25 |
| P | <0.0001 | 0.012 | 0.012 | NS | 0.001 | NS | 0.006 | NS | 0.029 | 0.041 | NS |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| OR 95% CI | | | 2.2 (1.2-4.1) | | 3.4 (1.6-7.1) | | | | | | |
| Hypertension (n 252) | | | | | | | | | | | |
| Yes 39 (15%) | 54 ± 15 | 51/49 | 17 (44) | 1.9 ± 1.2 | 31 (80) | 3.4 ± 2.7 | 366 ± 203 | 33 (85) | 48 ± 18 | 22 (56) | 81 ± 31 |
| No | 31 ± 15 | 74/26 | 67 (31) | 1.6 ± 1.1 | 119 (56) | 2.9 ± 2.9 | 349 ± 164 | 144 (68) | 46 ± 26 | 84 (39) | 74 ± 25 |
| P | <0.0001 | 0.005 | NS | NS | 0.004 | NS | NS | 0.022 | NS | 0.037 | NS |
| OR 95% CI | | | 1.7 (0.8-3.4) | | 3.1 (1.4-7) | | | | | | |
| Autoinmune desease (n 253) | | | | | | | | | | | |
| Yes 17 (7%) | 30 ± 12 | 94/6 | 2 (12) | 1 ± 0 | 7 (41) | 2.4 ± 2.6 | 367 ± 219 | 13 (77) | 43 ± 14 | 6 (36) | 92 ± 34 |
| No | 35 ± 17 | 69/31 | 82 (35) | 1.7 ± 1.1 | 143 (61) | 3.1 ± 2.9 | 351 ± 167 | 164 (70) | 46 ± 26 | 100 (43) | 74 ± 26 |
| P | NS | 0.018 | 0.039 | NS | NS | NS | NS | NS | NS | NS | NS |
| OR 95% CI | | | 0.3 (0.1-1.1) | | 0.5 (0.2-1.2) | | | | | | |
| Thymoma (n 199) | | | | | | | | | | | |
| Yes 30 (15%) | 44.5 ± 14 | 30/70 | 16 (53) | 1.6 ± 0.7 | 21 (70) | 2.9 ± 2.3 | 405 ± 253 | 27 (90) | 48 ± 27 | 17 (57) | 72 ± 23 |
| No | 29.5 ± 13 | 82/18 | 50 (30) | 1.8 ± 1.3 | 95 (56) | 3.3 ± 3.3 | 368 ± 154 | 115 (68) | 46 ± 27 | 64 (38) | 78 ± 28 |
| P | <0.0001 | < 0.0001 | 0.011 | NS | NS | NS | NS | 0.009 | NS | 0.043 | NS |
| OR 95% CI | | | 2.7 (1.2-6) | | 1.8 (0.8-4.2) | | | | | | |

Table 1: Prognosis of patients with Myasthenia gravis according to the presence or absence of comorbidities: Dyslipidemia, Thyroid disease, Diabetes, Hypertension, Autoimmune disease, Thymoma. AZA = Azathioprine, SD = Standard deviation, ER = Emergency Room visits, Fem= Female, Masc = Male, MC = Myasthenic crisis, No. = number, NS= Non significant, PDM = pyridostigmine, PDN = prednisone, OR= Odds ratio, CI = confidence interval

Almost 200 patients were submitted to thymectomy and the histopathology of the thymus was available in 199, 30 (15%) were positive for thymoma (MGT). Of the MGT group (n 30), the onset of MG was between 30-70 years, 16 (53%) had at least one MC, 70% required ER services; for the 169 patients without thymoma (MGNT), the age at onset ranged from 10-40 years, 50 (30%) had MC and 56% required ER services. MGT patients showed a higher frequency of autoimmune diseases (10 vs 7%).

Thyroid function test results were obtained in 233 patients and alterations were found in 45 (19%), indicating hyperthyroidism in 14 (31%) and hypothyroidism in 31 (69%). In the overall cohort, 13% presented hypothyroidism and 6% presented hyperthyroidism; of the patients with dysthyroidism, 98% presented a generalized form of MG and only one case presented with a pure ocular form, of the 15 patients with purely ocular symptoms, only one presented dysthyroidism. A lipid profile was obtained in 234 patients and dyslipidemia was diagnosed in 60%. Glucose levels or glucose tolerance tests were performed in 252 patients and diabetes mellitus (DM) was diagnosed in 20%. Blood pressure levels were determined at least twice in 253 patients; hypertension (AH) was diagnosed in 16%. All patients were questioned and examined to identify concomitant autoimmune diseases (AD); 21 ADs were found in 17 patients, including 6 with rheumatoid arthritis, 3 autoimmune thrombocytopenic purpura, 2 systemic lupus erythematosus, 2 anti-phospholipid syndrome, 2 vitiligo, 2 neuromyelitis optica, 1 uveitis, 1 pemphigus foliaceus, 1 cyclic autoimmune neutropenia, and 1 with Sjögren's syndrome.

In 6 patients we found 7 cases of non-thymic neoplasia, breast cancer being the most frequent (n=3); followed by non-Hodgkin lymphoma, prostatic, thyroid or bladder cancer (one case each). Other diseases found in our patients were: stroke (2), hyperparathyroidism (2), interventricular communication, asthma, acromegaly, congenital lymphangioma and hyperprolactinemia (one case each).

## Discussion

All patients included in the present study (n 253) had a definite diagnosis of MG. Few reports and series mention how their diagnoses were made; for this reason, in this study, we decided that every patient should fulfil well-defined and accepted diagnostic criteria [12] with the purpose of having solid results.

The average age of onset and the relation women: men of MG in this study (7:3) are similar to previous studies [17]. In regard to the affection form, 93% of the patients manifested a generalized presentation and only 7% a pure ocular form of the disease; this could be explained by a reference systematic error. However, other authors have found a similar proportion in the affection degree (Grob [17] et al 86% vs 14% and Kuks [7] et al 90% vs 10%).

The AchR-Abs were positive in 87% of all patients and were more frequently positive in those with generalized (90%) than in purely ocular presentations (50%).

## Thymoma

Of patients submitted to thymectomy, 15% had thymoma, for a total of 30 cases (12%) of the whole cohort. The frequency of MC was higher in our studied population than in earlier reports (33 vs 15-20%), regardless of thymic pathology [15]. The MGT group had a later age at onset (45 ± 14 years) than those without thymoma (MGNT) (30 ± 13 y) ($p<0.0001$), similar to previous reports [7]. The presence of thymoma seems to be an important risk factor for MC; in the present study 53% of MGT had MC OR of 2.7; 95% CI, 1.2-6; others [7] also have associated a higher incidence of MC and a more aggressive disease in patients with thymoma.

## Co-morbidities

Co-morbidity (concomitant disease besides MG) was found in 185 patients (73%), the most common associations being: dyslipidemia 60% (MGD), diabetes mellitus 20% (MGDM), dysthyroidism 19% (MGTD), hypertension 16% (MGAH) and autoimmune diseases 7% (MGAD). Having a comorbid disease was associated more frequently with MC (OR 1.2) and ER visits (OR 1.92).

## Thyroid function and steroids in Myasthenia gravis

Thyroid hormones have an influence on neuromuscular junction (NMJ); alterations have been demonstrated in 79% of hypothyroid and 67% of hyperthyroid patients with clinical weakness in 38% and 62% respectively [18]. These clinical manifestations significantly improve after thyroid function correction. The diagnosis of thyroid disease (TD) must be carefully considered and under certain conditions, not all alterations in thyroid function tests imply a diagnosis of TD [19].

TD is one of the most frequent comorbidities associated with MG, with a prevalence varying from 5% to 10%, and MG is present in 0.2% of the patients diagnosed with autoimmune thyroid disease [4].

Acute disease and the use of steroids affect thyroid function, but steroids have a beneficial effect on MG and are used as treatment [20] due to its immunoregulator function and associated proliferation of Ach receptors [21].

Thyroid function tests were abnormal in 19% of the 233 studied patients; hypothyroidism was more frequent (69%) than hyperthyroidism (31%), different from previous data [17]. The reason for this high occurrence of thyroid alterations is unknown, but a systemic reference bias may play an important role. The diagnosis of TD was meticulous, making sure they were not hospitalized; on a high steroid dose or in acute conditions at the time the samples were taken. Patients studied showed higher frequency of TD than the general population [22] 19 vs. 5%, meaning it is five times more common to find TD in patients with MG.

Patients with TD did not show worse prognosis overall, however, those without TD sought less attention due to weakness 78vs58% OR of 2.5; 95% CI, 1.2-5.4. A pure ocular form was found in only 2% of the TD group vs 7% without TD, unlike previously reported [4]. Further investigations must be made to answer the role of TD on the prognosis of MG.

## Diabetes mellitus

The association of Diabetes Mellitus (DM) and MG was first described in 1950 by Perry [23]. Since then, several authors have confirmed their coexistence [24-25]. The ADA (American Diabetes Association) has established criteria for the diagnosis and treatment [26]. DM was identified in 20% of our patients, three times higher than in the general population (7%) [27]. Patients with MGDM had later age of onset, than those without DM. Men were more likely to develop DM than women (29 vs 16%, p 0.012). Patients with MGDM: a) had higher frequency of MC (48 vs 29.7%, OR of 2.2; 95% CI, 1.2-41, b) required more attention from the ER services (80 vs 54.5%) OR of 3.4; 95% CI 1.6-7.1, c) required higher mean dose of PDM (410 vs 337 mg/day, p 0.006), d) higher mean dose of prednisone (52 vs 45 mg/day, p 0.029), and e) were prescribed with azathioprine more often (54 vs 39%) (p 0.041); than those without DM. No differences in frequency of DM were found between patients using steroids or not; however, this relation cannot be dismissed by the present study.

## Arterial Hypertension

This disease is the main risk factor for mortality in the world. Fifteen percent of our patients with MG were diagnosed with AH (MGAH); the prevalence of AH in patients with MG was half lower than in the general population (15 vs 30%) [28]. Mean age of onset of MG symptoms was higher for patients with HT (54 vs 31 years) ($p<0.0001$). Males presented AH more frequently (25 vs 11%). Patients with MG and AH required more services from the ER than patients without AH (80 vs 56%, OR 3.1) and had more MC (44 vs 31%, OR 1.7). The use of steroids was higher in patients with MGAH (85 vs. 68%) (p 0.022). Whether or not, the use of steroids is related to the presence of AH is a conclusion that this study cannot presume to reach.

## Dyslipidemia

Dyslipidemia is one of the main risk factors for the development of cardiovascular diseases. The impact of this disorder in patients with MG has not yet been studied; however, it is known that treatment with statins is associated with the development or exacerbation of MG [29-31].

Dyslipidemia was diagnosed in 60% of the patients (MGD), more frequent in men (73% vs 54%) (p 0.004). Patients with MGD needed more ER services (68 vs 32%) OR od 2.2; 95% CI, 1.3-3.8 and had more MC (36 vs 29%) OR 1.4, used higher mean dose of PDM (373 vs 321 mg/d) and were more often prescribed azathioprine (69 vs 31%). This study does not discard that steroids are a risk factor for the presence of dyslipidemia; however, the occurrence of dyslipidemia in those without steroid treatment seems to be an independent factor associated with MG.

Mean age of symptom onset was greater in MGD (39 vs 31 years) (p 0.001). Higher prevalence of dyslipidemia was found for patients with MG than in the general population (60 vs 27%) [28], even for patients that were not receiving steroids (50%).

## Other autoimmune diseases

Seventeen patients (7%) presented a non-thyroid related autoimmune disease (MGAD). Women presented higher frequency of AD (9% vs 1%), p 0.018. MGAD patients had less MC (12 vs 35%, OR 0.3) and required less ER visits (41 vs 61%, OR 0.5); the etiology of this finding cannot be explained by the present study; further investigations should be performed to answer the association. No other differences were found between MGAD vs MG without AD. Our MG population had a similar prevalence of AD to those reported in other studies [7].

## Conclusions

The present study demonstrates the elevated occurrence of comorbidities (73%) in patients with MG. The presence of dysthyroidism, dyslipidemia and diabetes mellitus was more frequent in patients with MG than in the general population, and the prevalence of AH was slightly lower.

Patients with MG should be screened for thyroid function, diabetes, hypertension, dyslipidemia, autoimmune diseases and thymoma. We found a 15% frequency of MGT in our patients. The frequency of other neoplastic disorders (non thymoma) seems to be increased in patients with MG.

According to the variables studied, we could assume that the prognosis of the MG worsens in the presence of thymoma, thyroid disease, DM, dyslipidemia and/or AH. This is the first investigation analysing concomitant metabolic diseases as prognostic factors in patients with MG.

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