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Myasthenia Gravis and Associated Diseases

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Abstract

BACKGROUND: Myasthenia gravis (MG) is an autoimmune disease caused by the action of specific antibodies to the postsynaptic membrane of the neuromuscular junction, leading to impaired neuromuscular transmission. Patients with MG have an increased incidence of other autoimmune diseases.

AIM: to determine the presence of other associated diseases in patients with MG.

METHOD: A group of 127 patients with MG followed in 10 years period, in which the presence of other associated diseases has been analysed.

RESULTS: The sex ratio is in favour of the female sex, the average age of the initial manifestation of the disease is less than 50 years, 65.4% of the patients with MG have another disease. 15.0% patients have associated another autoimmune disease. Thyroid disease is the most common associated with MG, rarely rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other autoimmune diseases. Other diseases include hypertension, heart disease, diabetes, respiratory diseases, dyslipidemia. 10.2% of the patients are diagnosed with extrathymic tumours of various origins.

CONCLUSION: Associated diseases are common in patients with MG, drawing attention to the possible common basis for their coexistence, as well as their impact on the intensity and treatment of the disease.

Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by a variety of complex mechanisms of action of specific antibodies to the postsynaptic membrane, leading to impairment of the function of the neuromuscular junction (NMJ) and neuromuscular transmission.

Cardinal clinical features are the weakness and fatigue of different, specific muscle groups with characteristic distribution, which increase with activity, and are improved with rest [1] [2].

The thymus plays a central role in the pathophysiology of MG due to the presence of the key elements of the myasthenic autoimmune process, such as antigen presenting cells, T and B cells. Approximately 80% of patients with MG have thymic abnormalities; up to 70% of patients have thymic hyperplasia, 10 - 15% of thymomas, and in 15 – 20% thymus is normal or regressive, i.e. atrophic and replaced with fat tissue [3] [4] [5].

Current trends in the treatment of MG arise from the pathogenesis of the disease and provide satisfactory control in most patients. However, the course of the disease and the outcome of the treatment may be affected by other conditions:

associated autoimmune diseases (AD), diseases common in the general population or tumours [2] [4].

In some patients, these diseases occur before, and in others after the manifestation of MG.

This study is aimed to assess the frequency and type of comorbidity in the examined group of patients with MG.

Methods

An observational study of 127 patients with MG monitored retrospectively and prospectively on the Neurology Clinic in 10 years period. The demographic characteristics of patients, the clinical manifestation of the disease, thymectomy, thymic pathology and the presence of associated diseases have been analysed.

The diagnosis of MG was confirmed by clinical examination, by the positive response to Prostigmin, specific antibody testing, neuromuscular weakness response to repetitive nerve stimulation test, computed tomography (CT) on the anterior mediastinum.

The severity of the disease was defined according to the classification of Osserman-Jankins, modified by Abt PL et al. (2001) [6] [7].

Patients with MG were monitored with regular neurological examinations, and other investigations were performed depending on the clinical manifestation of the associated conditions.

The diagnosis of thyroid disease is based on clinical features, examination, laboratory findings and ultrasound examination.

The diagnosis of Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) is set according to the Criteria of the American College of Rheumatology (ACR) [8] [9].

Statistics: Statistical analysis is made in statistical programs: STATISTICA 7.1; SPSS 17.0 (Difference test, Pearson Chi-square).

Results

All 127 patients included in the study have a confirmed diagnosis of MG. The basic demographic and clinical characteristics of patients are shown in Table 1; average age in MG patients with or without associated autoimmune disease is shown in Table 2, and Table 3 presents the characteristics of patients with MG and associated disease.

Table 1: Characteristics of the total number of patients with MG in the study

Gender	*N*	*%*
Female	81	63.8
Male	46	36.2
Age (years)	*N*	
≥ 50	70	55.1
< 50	57	44.9
Age at diagnosis (years)	*Average*	*N*
Female	44.5	81
Male	56.5	46
n=127	48.8	127
Age at onset (years)	*Average*	*N*
Female	43.3	81
Male	55.7	46
N=127	47.8	127
Comorbidity	*N*	*%*
Yes	83	65.4
No	44	44.6
Associated autoimmune disease	*N*	*%*
No	108	85
Yes	19	15
Hypothyroidism		*%*
Yes	12	9.4
Hyperthyroidism		
Yes	4	3.1
Sle		
Yes	1	0.8
Ra		
Yes	2	1,6
Vasculitis		
Yes	1	0.8
Thrombocytopenia		
Yes	1	0.8
Heart disease		
Yes	31	24.4
Hypertension		
Yes	60	47,2
Diabetes mellitus		
Yes	18	14,2
Dyslipidaemia		
Yes	14	11
Respiratory disease		
Yes	17	13.4
Tumors		
Yes	13	10.2

*SLE -systemic lupus erythematosus; *RA-rheumatoid arthritis.

The sex ratio is 1.9: 1 in favour of the female sex, statistically significant, p = 0.0001.

The difference in the average age at the first symptoms, which is higher in men, is statistically significant, p = 0.001564 (Table 1).

MG with late onset (over 50 years) have 55.1%, and with early onset (under 50) have 44.9% of the patients, statistically non-significant, p = 0.1040 (Table 1).

Majority of 83 (65.4%) patients with MG have another disease, p = 0.0009 (Table 1).

Older than 50 years are 81.9%, younger than 50 years, are 18.1 % of patients with comorbidity, p = 0.0001, (Table 2 and 3).

Table 2: Mean age in patients with MG with/without associated autoimmune disease

Without	With	t-value	Df	P	Without	With	Sd-without	Sd- with
47.25	51.0	-0.712645	125	0.477394	108	19	21.55329	18.58614

A subgroup of 73 from a total of 83 (88%) patients with comorbidity present a generalised form of the disease, while 10 (12%) have an ocular form of the disease.

Table 3: Characteristics of patients with MG with associated disease

Gender	*N=83*	*%*
Female	51	61.4
Male	32	38.6
Age (years)	*N*	
≥ 50	68	81.9
< 50	15	18.1
Age at diagnosis (years)	*Average*	*N*
Female	55.8	51
Male	67.6	32
Age at onset (years)	*Average*	*N*
Female	54.8	51
Male	66.7	32
Associated autoimmune disease	*N=19*	*%*
≥ 50	11	57.9
< 50	8	42.1
Hypothyroidism	*N=12*	
≥ 50	7	58.3
< 50	5	41.7
Hyperthyroidism	*n=4*	
≥ 50	2	50
< 50	2	50
Sle		
≥ 50	1	100
Ra		
≥ 50	2	100
Vasculitis		
≥ 50	1	100
Thrombocytopenia		
≥ 50	1	100
Heart disease	*N=31*	*24,4%*
≥ 50	30	96.8
< 50	1	3.2
Hypertension	*N=60*	*47,2%*
≥ 50	57	95
< 50	3	5
Diabetes mellitus	*N=18*	*14,2%*
≥ 50	17	94.4
< 50	1	5.6
Dyslipidaemia	*N=14*	*11%*
≥ 50	11	78.6
< 50	3	21.4
Respiratory disease	*n=17*	*13,4%*
≥ 50	17	100
Tumors	*N=13*	*10,2%*
≥ 50	11	84.6
< 50	2	4

*SLE -systemic lupus erythematosus; *RA-rheumatoid arthritis.

Associated autoimmune diseases (AD)

Nineteen (15.0%) patients have associated another AD, 11 (57.9%) are older than 50 years. (≥ 50 years), and 8 (42.1%) are younger than 50 years. (< 50 yrs) (Table 3). In 14 (73.7 %) of them, the associated AD was diagnosed before MG. Fifteen 15 (78.94 %) are women; 8 (53.3%) are younger, and 7 (46.7%) are older than 50 years. Men are 4 (21.06%), and all have late-onset MG (≥ 50 years). Sixteen (12.6 %) have thyroid disease (Table 3).

The generalised form of MG have 14 patients (87.5%) (11 with hypo-, 3 with hyperthyroidism), and with ocular form, there are 2 patients (one with hypo and hyperthyroidism). Two (1.6%) of the patients have rheumatoid arthritis (RA) and a generalised form of MG (Table 1). One patient (0.8%) is with SLE, with a generalised form of MG. One patient (0.8%) is with vasculitis and a generalised form of MG, and one (0.8%) with thrombocytopenia and ocular MG (Table 1).

Patients with vasculitis and thrombocytopenia are considered separately from other patients with the confirmed associated AD. In these patients, the aetiology of the condition has not been confirmed with certainty, but according to immunological tests, the probability of their immunological basis is high.

One patient has MG and two associated AD - RA and hypothyroidism. From the 19 patients with the associated AD, 15 (78.9%) were generalised, and 4 (21.1%) had an ocular disease. There is no significant association between the clinical form of MG and the associated AD (Table 4).

Table 4: Association between the clinical form of MG and the associated AD

Associated autoimmune disease	Pearson Chi-square	p
Hypothyroidism	0.546045	0.45994
Hyperthyroidism	0.291224	0.58944
SLE	0.185305	0.66685
RA	0.375129	0.54022
Vasculitis	0.185305	0.66685
Thrombocytopenia	5.52734	0.01872

In patients with MG and associated AD, AChR antibody tests were done on 6: the results were positive on 4 patients, from which 2 were non - thymectomized with Graves's disease and 2 thymectomized patients were with hypothyroidism (Hashimoto thyroiditis), with micro microthymoma B1B2, thymic hyperplasia. The other 2 patients with rheumatoid arthritis and hyperthyroidism (Graves's disease) were negative for the antiAChRat.

Other associated diseases

All patients have a generalised form of the disease, and most are older than 50 years (Table 1 and 3). There is no significant association between severity of MG and associated disease (Table 5).

Table 5: Association between severity of MG and other diseases

Another disease	Pearson chi-square	P
Hypertension	0.036403	0.84869
Diabetes mellitus	0.797006	0.37199
Heart disease	5.63665	0.01759
Dyslipidaemia	0.455038	0.49995
Respiratory disease	1.49967	0.22072

Tumors

Thirteen (10.2%) patients were diagnosed with extrathymic tumours of different origin (Table 1), 11 (84.6%) were with late-onset MG (Table 3 and 6).

Table 6: MG patients with extrathymic tumours

MG/tumor N=13	
Before MG dg	*After MG dg*
Prostate cancer 1	Malignant melanoma 2
Breast cancer 1	Adrenal tumour 1
Kidney cancer 1	
Basocellular skin cancer 1	
Uterine tumour 2	
Tonsil tumour 1	
Parotid gl. tumour 1	
Breast fibroid tumour 1	
Brain meningioma	

Some patients with extrathymic tumours, also have associated autoimmune disease other than MG - rheumatoid arthritis, hypothyroidism, vasculitis.

Thymectomy

A group of 23, from a total of 83 patients (27.7%), are thymectomized (Table 7).

Table 7. Thymus histology

Thymus histology	N = 23
Thymic hyperplasia	15 (65.2%)
Thymoma (3 malignant t, thymoma AB 1, thymoma B1B2 1)	5 (2.7%)
Thymic atrophy/fatty replacement	2 (8.7%)
Persistent thymus	1 (4.3%)

From the 19 patients with the associated autoimmune disease, 7 (36.8%) underwent thymectomy; 5 (71.4%) had thymic hyperplasia, all women, with an average age of 32.8 years. (min 20, max 56), and only one had positive antiAChRat.

In these 5 patients with thymic hyperplasia and associated autoimmune disease, 4 were with hypothyroidism, and one patient with SLE.

Two of the operated patients with hypothyroidism (Hashimoto thyroiditis) had thymoma, and late-onset MG, average age - 64 years, one patient had + antiAChRat, and the other was not tested.

Other patients with thymus pathology had hypertension, heart and respiratory diseases, diabetes, dyslipidemia.

Discussion

Autoimmune diseases are a heterogeneous group of diseases caused by loss of immune tolerance to their antigens in which multiple alterations to the immune system result in a spectrum of syndromes that either target specific organs or the whole body [10].

The incidence is approximately 80/100,000 inhabitants per year, approximately 5% of the population is affected by one or more autoimmune diseases, and the prevalence is higher in women than men. In patients with one AD, there is a greater risk of developing another AD, or more. The common influence of the genetic, immunological, hormonal and environmental factors is considered to be the cause of these diseases [5] [10] [11] [12] [15].

Patients with MG have an increased incidence of other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, Graves' disease and pernicious anemia, and the frequency varies widely: from 8.7 to 25%, 13 to 22%, while the rates of association in the Norwegian and Danish studies are 22.9%, i.e., 9.4% [13][14][15][16].

In MG with the associated AD, the female patients, with early - onset and generalised MG are predominant, although the other group, late-onset MG, exhibits an increased risk of associated AD compared with the general population [17].

Associated AD varies among different MG subgroups. Thymus hyperplasia is considered to be at greater risk for the associated AD, unlike MG with other than antiAChR types of antibodies (to titin, or to a ryanodine receptor) are associated with a lower risk [17].

Thyroid disease is the most common AD associated with MG, with a prevalence of 5 – 10%, while MG is present in 0.2% of the patients with diagnosed autoimmune thyroid disease [14].

Acute disease and the use of corticosteroids affect the thyroid function, but at the same time, corticosteroids have a positive effect due to their immune - regulatory function associated with the proliferation of AChR (acetylcholine receptors) [18] [19].

In various studies, these diseases are differently represented, but the most common is the hypothyroidism (Hashimoto thyroiditis) about hyperthyroidism (Graves' disease) [20] [21]. MG - associated autoimmune thyroid disease is considered to have a milder form, and the ocular form has a special relationship with it [22]. The explanations for this association are: a) ocular and generalised MG are considered as two different diseases that may be associated with various other autoimmune conditions; b) cross - immune response to epitopes or autoantigens common to thyroid and eye muscles; c) genetic basis [23] [24].

The prevalence rate of coexistence of SLE and MG in published studies is usually around 2.6%, but in the study of Sthoeger Z. et al. on 78 patients, the rate rises to 7.7%, with greater prevalence of women [25] [26] [27].

MG is organ - specific (antibodies to AChR), while SLE is a systemic autoimmune disease affecting multiple organs, producing a wide spectrum of antibodies (targeted mainly to nuclear antigens and ds - DNA) and impaired T and B cell function [28].

Autoantibodies are the basis of immunopathogenesis for both diseases, and molecular mimicry, as a potential mechanism for initiating and/or maintaining the production of autoantibodies, is related to the association of MG and SLE. Also, there is a similarity among the segment of AChR for U1, the nuclear ribonucleoprotein that is an autoantigen marker for SLE, and a mixed connective tissue disease. Most of the antibodies in MG are targeted to a small region of the alpha subunit of the AChR, called the major immunogenic region. Various autoimmune diseases begin with a wide range of reactivity towards multiple autoantigens, and in MG, according to such structural similarities, the response to the main immune region of the acetylcholine receptor is polyreactive [28] [29].

Almost equal is the number of patients where MG is initially diagnosed, and thymectomy has been performed, and the same number of patients in whom SLE occurs after thymectomy, which imposes the dilemma about the role of thymectomy [30] [31].

Rheumatoid arthritis occurs in 4–7% of patients with MG, and after thyroid autoimmune disease, RA is frequently present [13] [14] [17] [18] [25]. Patients with MG as a result of RA treated with d-penicillamine [33] have also been described. None of our patients has been treated with d - penicillamine. Similarly, with the findings of the patients with SLE, RA manifestations are also less pronounced than those of MG.

It has been observed that the frequency of heart disease or increased mortality due to heart disease in patients with MG is equal to the prevalence of the general population [34].

The most common are cardiac rhythm disorders, sympathetic destabilisation, and especially parasympathetic function [35]. Particular attention deserves patients with MG and severe cardiomyositis, where the heart muscle can be the target of autoimmune inflammation in MG (antibodies to titin, striated muscles, ryanodine receptors which are detected in thymoma and elderly patients react with the heart muscle) [36] [37].

DM prevalence among MG patients varies from 2 – 3 % to 20 % in different studies [18].

In these patients, late MG is more frequent, unlike those without DM. It is more frequent in men than women (29 vs 16 %). Patients with MG and DM may have positive more organ-specific antibodies (with DM type 1), or onset of DM during corticosteroid therapy (DM type 2) [38]. Doses of prednisolone higher than 30 mg/day increase the level of glycaemia in patients who already have DM, and can cause glucose intolerance or diabetes in previously normoglycaemic subjects [39]. Therefore, it is unclear when corticosteroid therapy directly induces DM, or only accelerates the manifestation of the disease.

In most of the patients with MG, respiratory symptoms are manifested in the advanced stage of the disease, but in some patients, depending on the intensity of the weakness and fatigue, it can be acutely manifested. Chronic respiratory diseases and infections are the most common precipitating factor for severe respiratory muscle weakness [40] [41]. Thirty nine percentage (39%) of the patients have reduced vital capacity, and 19 % with severe generalised MG have experienced a myasthenic crisis with the need for assisted ventilation [34] [40].

A higher prevalence of dyslipidemia in MG was found in the general population - 60 vs 27%, even in patients who do not receive steroids (50%). It is more common in men, with late-onset MG. Treatment with statins preparations may cause exacerbations of MG [18] [42].

Hypertensive disease in patients with MG is less than half (15 vs 30%) in the general population, more commonly in men with late-onset MG, and with higher administered doses of corticosteroids [18].

The increased frequency of neoplasms in MG and other autoimmune diseases has long been detected. In older studies, the risk for neoplasms in MG is three times higher than expected and with a higher frequency of occurrence in the first year after diagnosis and before thymectomy. After surgery, the risk is reduced and is similar to that of the general population [43].

According to recent reports, the risk of an extrathymic tumour is higher in MG with thymoma [44] [45] [46], and reported prevalence rate is between 3 and 12% [46] [47] [48].

The nature and origin of tumours are different. According to some reports, solid tumours are most common, according to others, autoimmune diseases treated with immunosuppressive therapy are associated more often with the tumour of hematopoietic organs and skin [17] [47] [50].

The increased risk is explained by 1. the role of immune mechanisms in MG in the appearance of extrathymic tumours, especially after the diagnosis of MG, as a result of impaired immune response and immunosuppressive therapy; 2. common genetic predisposition to thymomas and other tumours; 3. exogenous factors [50].

According to the results of our analysis, majority of the malignancies have been diagnosed before MG and patients were not treated with immunosuppressive therapy for MG, the histological type, the late onset of the disease, disagree with those in studies in which the onset of malignancy is more common after the diagnosis of MG [49].

Patients with late-onset MG have an increased risk of malignant disease; have a more severe form of MG, probably due to the weakness and dysregulation of the immune system [47].

The role of thymectomy as a therapeutic modality in MG in the onset of associated autoimmune disease has not yet been fully clarified.

The thymectomy alone does not seem to affect the development of associated AD, but it can cause a decrease in tolerance to its antigens and be a risk factor for its occurrence through the lack of thymic hormones that cause disruption of the function of suppressor cells, and their substitution can lead to a partial return to their function. Experimental studies of the SLE model do not show either clinical or changes in antibody concentrations, so that thymectomy may not be the precipitating factor for the development of associated AD [17] [28] [29] [30] [32]. Studies in which the occurrence of the associated AD is before MG and thymectomy, explain it with the pathogenic effect of myasthenic thymus [31].

Only in one patient in this study, the associated AD occurs after the thymectomy, which supports the consideration of genetic predisposition to autoimmune diseases.

In conclusion, the significance of this study is that this research has been done for the first time in Macedonia. By using our materials, we have researched the occurrence and prevalence of other diseases in patients with MG. The results are mainly in line with the overall prevalence of all associated autoimmune diseases, and the most common autoimmune diseases of the thyroid gland are 12.6 %, but the rates of SLE, RA, thrombocytopenia, vasculitis are lower.

From the other associated diseases, the most frequent one is hypertensive disease; diabetes is in line with the published rates, and the least represented are dyslipidemia and respiratory diseases. The frequency of tumours of extrathymic origin is equal to the referenced publications but before the diagnosis of MG. The origins, character and severity of the conditions, which can occur with MG (before or after), impose the need to consider their influence on the clinical manifestation and treatment of the disease.

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