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Extrathymic malignancies in a defined cohort of patients with myasthenia gravis

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ABSTRACT

Introduction: Myasthenia gravis (MG) may be associated with extrathymic malignancies, especially in patients with thymoma.
Aim: To determine the frequency and type of extrathymic malignancies in MG patients from the Belgrade area, and to identify potential risk factors associated with tumors.
Patients and method: The study comprised 390 patients with MG. Different sociodemographic and clinical variables potentially associated with extrathymic neoplasms were analyzed.
Results: Extrathymic malignancies were present in 42 (10.8%) MG patients — 22 (52.4%) males and 20 (47.6%) females. The most frequently detected were breast (40%) and lung (40%) neoplasms. The tumors appeared with similar frequency before (45.2%) and after the onset of MG (42.9%). Significant predictors for the development of extrathymic malignancies were current age ($p = 0.001$) and immunoglobulin (IVIg) therapy ($p = 0.021$). On the other hand, current age ($p = 0.001$), longer MG duration ($p = 0.001$) and generalized form of MG ($p = 0.002$) were significant predictors of malignancy occurring after the MG onset.
Conclusion: Our study revealed that older MG patients, as well as those with longer duration of the disease, and those who received IVIg therapy had a higher oncogenic risk for the development of extrathymic malignancies.

1. Introduction

Acquired autoimmune myasthenia gravis (MG) is an organ-specific autoimmune disease characterized by the production of autoantibodies against different neuromuscular junction antigens, typically against the nicotinic acetylcholine receptor (nAChR). These autoantibodies cause damage to neuromuscular transmission on postsynaptic level, which clinically manifests as weakness and fatigue in the skeletal muscles with improvement after rest or administration of anticholinesterase therapy [1].

MG is associated with thymoma in 10–15% of patients, and therefore classified as an atypical paraneoplastic neurological disorder [2]. According to the literature, MG may be associated with secondary, extrathymic malignancies, especially in a group of patients with thymoma [3–6]. Increased frequency of malignancies has also been observed in several other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythomatosus, inflammatory myopathies, scleroderma, Sjogren's syndrome and thyroiditis, suggesting that impairment of the immune response may lie at the core of this phenomenon [7,8]. Nevertheless, this association may also be explained by genetic predisposition, as well as by the influence of different exogenous factors, such as prolonged immunosuppressive therapy [9,3]. However, risk factors that could be associated with the neoplasms developing in MG patients remain unclear.

This study aimed to assess the frequency and type of extrathymic malignancies in all MG patients within the defined population of Belgrade area, Serbia, as well as to identify potential risk factors associated with extrathymic neoplasms in this cohort.

2. Patients and method

This retrospective study was conducted using the data obtained from MG registry on patients from all neurology departments in Belgrade from 1 January 1992 to 31 December 2008 [10]. In all 390 patients, the diagnosis of MG was based on typical clinical findings confirmed by positive response to neostigmine and/or decremental response to repetitive nerve stimulation or increased *jitter* on single fiber electromyography (SFEMG) [11]. The severity of the disease was defined according to the classification recommended by the Myasthenia Gravis Foundation of America (MGFA) [12]. Patients were divided into two groups depending on the severity of disease, as follows — mild

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form (MGFA I, IIa, IIb, IIIa) and severe form of MG (MGFA IIIb, IVa, IVb, V). The level of antibodies against nAChR was detected using a radioimmunoassay (RIA) commercial kit (RsR, Cardiff, UK) in 268 patients who were diagnosed with MG in the last ten years, since this diagnostic tool was not available in our country before. The analysis of MuSK antibodies was performed in 54 seronegative patients using a commercial RIA kit (RsR, Cardiff, UK). All living patients were clinically reexamined during 2012, while family members of deceased patients were contacted.

Two separate analyses were performed in this study. The first analysis included all patients with MG and extrathymic neoplasms, while the second one included only patients with extrathymic tumors occurring after MG onset, since we tended to assess if prolonged immunosuppressive therapy contributed to cancer development and also to provide more information about the association of MG and extrathymic malignancies. The controls were MG patients with no secondary tumors at the last follow-up. The demographic and clinical variables (gender, current age, age at MG onset, disease duration, severity of the disease at nadir, seropositivity to AChR and MuSK, thymectomy and thymus pathology as well as type of immunosuppressive therapy) were analyzed as factors potentially associated with extrathymic neoplasms.

The study was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade.

The statistical analysis included descriptive statistics, univariate and multivariate logistic regression analyses. The variables at the minimum significance level of 0.05 were entered in multivariate logistic regression models. The relative risk (OR — odds ratio) was estimated for each selected variable with 95% confidence interval (95% CI). A value of $p < 0.05$ was considered statistically significant. SPSS 17.0 statistical software package (SPSS Inc., Chicago, IL, U.S.A.) was used in statistical analysis.

3. Results

Baseline demographic and clinical characteristics of 390 MG patients upon entry to the study are presented in Table 1.

Extrathymic malignancies were registered in 42 (10.8%) MG patients — 22 (52.4%) males and 20 (47.6%) females. The frequency, type and treatment of extrathymic tumors are shown in Table 2. The most common type of malignancy in male patients was lung (40%) and colon (20%) carcinoma, while in females the breast (40%) and uterus (20%) carcinomas were the most frequently detected.

According to the period of appearance, malignant tumors occurred in 19 (45.2%) patients before the first MG symptoms, in 18 (42.9%) cases after the diagnosis of MG, while neoplasm and MG simultaneously occurred in only 5 (11.9%) patients.

Having analyzed the impact of different variables as risk factors for developing secondary malignancies in the whole group of MG patients, we noted that current age ($p = 0.003$), age at onset ($p = 0.031$) and IVIg therapy ($p = 0.042$) were significant risk factors for the cancer occurrence (Table 3). The influence of thymoma on the neoplasm development was on the border of statistical significance ($p = 0.054$) (Table 3).

After observing only a group of patients with malignant tumors occurring after MG onset, we found that current age ($p = 0.011$), duration of the disease ($p = 0.003$) and generalized form of MG ($p = 0.019$) were significantly associated with the presence of malignancy (Table 4). The presence of thymoma as well as the immunosuppresive therapy had no effect on the tumor occurrence in patients with neoplasms appearing after the diagnosis of MG (Table 4).

Multivariate regression analysis revealed that current age ($p = 0.001$) and IVIg treatment ($p = 0.021$) were significant independent predictors for the development of secondary malignancies in the whole group of MG patients (Table 5). However, significant predictors for the development of secondary tumors in patients with neoplasms detected after MG onset, as shown by multivariate analysis, were the current age ($p = 0.001$), MG duration ($p = 0.001$) and a generalized form of the disease ($p = 0.002$) (Table 5).

Table 1
Baseline demographic and clinical features of analyzed MG patients (n = 390).

Variable	Value
Gender (males)	181 (46.4%)
Current age (mean years ± SD)	58.3 ± 18.5
Age at onset (mean years ± SD)	49.0 ± 20.4
Disease duration (mean years ± SD)	9.3 ± 7.8
Age at cancer diagnosis (mean years ± SD)	54.9 ± 16.4
MGFA at nadir of disease	
I	57 (14.7%)
IIa	96 (24.8%)
IIb	125 (32.3%)
IIIa	4 (1.0%)
IIIb	78 (20.2%)
IVa	1 (0.3%)
IVb	14 (3.6%)
V	12 (3.1%)
Seropositivity [a]	
AchR	214 (79.9%)
MuSK	6 (2.3%)
Seronegative	29 (17.8%)
Thymectomy	157 (40.0%)
Hyperplasia/thymus persistens	130 (82.8%)
Thymoma	27 (17.2%)
Autoimmune disorders	69 (17.7%)
Hashimoto thyroiditis	32 (46.4%)
Systemic lupus erythematosus	6 (8.7%)
Rheumatoid arthritis	3 (4.3%)
Other [b]	31 (40.6%)
Therapy	
Acetylcholinesterase inhibitors	390 (100.0%)
Corticosteroids	355 (91.0%)
Azathioprine	201 (51.5%)
Cyclosporine	12 (3.1%)
IVIg	9 (2.3%)
TIP	17 (4.4%)

[a] Serum antibody analysis was performed in 268 patients.
[b] Other autoimmune disorders included idiopathic thrombocytopenic purpura, vasculitis, Sjogren's syndrome, pernicious anemia, vitiligo, psoriasis, and pemphigus.

4. Discussion

Previous studies reported conflicting results on the incidence of secondary, extrathymic malignancies in patients with MG. Some studies reported reduced risk of cancer (1.7–2.8%) in MG patients, while other studies showed that the risk was higher than in healthy population (7.5%) [4,5,8,9,13,14]. The highest frequency of extrathymic neoplasms (15.4%) in patients with MG was reported by Levin et al. [8]. On the other hand, the majority of authors registered that the frequency of malignant tumors in patients with MG was similar to the frequency observed in other autoimmune diseases, suggesting that primary immune dysregulation may be responsible for both — autoimmunity and tumorogenesis [3,8,9,15–17]. In a comprehensive Italian study including 2479 MG patients, extrathymic tumors were found in 8.9% of cases [3], which is similar to the frequency of neoplasms found in our investigation (10.8%). Since environmental factors may strongly influence carcinogenesis, a comparison of tumor frequencies in patients from different regions may further shed light on the development of neoplasms in MG. Regarding the design of our study, the influence of particular environmental factors could not be assessed, thus future studies analyzing this issue may be of interest.

Regarding the types of neoplasms that are registered in our cohort of patients with MG, the breast (40%) and uterus (20%) carcinomas were the most common malignancies among women, while men usually had lung (40%) and colorectal (20%) cancers. This is in agreement with the distribution of malignant tumors in the general population of Serbia, according to the latest data from the Cancer Registry of Central Serbia [18]. In the Serbian general population, the most common