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Epidemiologia i leczenie miastennii w Polsce

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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ABSTRACT

Epidemiology and treatment of myasthenia gravis in Poland

Myasthenia gravis (MG) is a rare autoimmune disorder of the neuromuscular junction causing skeletal muscles weakness and fatigability. Approximately 90% of MG patients have pathogenic antibodies against acetylcholine receptor (anti-AChR) or muscle-specific tyrosine kinase (anti-MuSK).

MG is a rare disease and the available epidemiological data are sparse, based on a variety of methodologies and small patient populations, resulting in significant discrepancies in the results. In recent years, pyridostigmine prescription databases have been used as a tool for epidemiological studies of symptomatic MG in Norway, Portugal, Colombia, Chile and Australia. Epidemiology and treatment of MG have not been studied in the Polish population so far.

MG is a chronic disease, in some patients - severe. Symptomatic treatment of MG is based on the acetylcholinesterase inhibitors: pyridostigmine bromide and ambenonium chloride. Some of the patients require also immunosuppressive treatment, multiple hospitalizations and specialist care. There is a risk of life-threatening exacerbation of symptoms called myasthenic crises, defined as an acute respiratory failure caused by muscle weakness due to MG.

The aims of the study are:

1. Assessment of the epidemiology of symptomatic MG in Poland,
2. Assessment of the methods of treatment of MG, the number of hospitalizations, the occurrence of myasthenic crisis and deaths as indirect measures of the severity of this disease in the entire Polish population.

Material and methods:

During the study period, pyridostigmine bromide and ambenonium chloride were reimbursed in Poland only in MG. Using the database of the National Health Fund (NFZ), we have identified all prescriptions for pyridostigmine bromide and ambenonium chloride prescribed between January 1, 2012 and December 31, 2018. MG patient was defined as a person with

at least one medical service coded in ICD-10 as MG (G70) who received at least 2 prescriptions for pyridostigmine bromide or ambenonium chloride in two consecutive years.

Results:

The first stage of the study was to assess the epidemiology of symptomatic MG, to investigate its incidence and prevalence in Poland, as well as to assess the incidence and prevalence trends during observation period.

In 2018, the incidence of MG was 2.36 / 100,000 inhabitants, 2.54 for women and 2.16 for men with a predominance in women up to 50 years of age, a small peak in the incidence in women between 20 and 29 years of age and low incidence up to 60 years of age in women and 50 years of age in men. Marked increase in the incidence was observed in both sexes over 60 years of age. The incidence of early-onset myasthenia gravis (EOMG) was significantly higher in women ($p < 0.001$), while the incidence of late-onset MG (LOMG) was significantly higher in men ($p < 0.005$). In the period 2013-2018, an increase in the incidence was observed, caused by the increase in the incidence of LOMG.

In 2018, we have identified 8702 patients with MG in Poland, F: M 1.65: 1. Prevalence ratio was 22.65/100,000 inhabitants, 27.30 for women and 17.69 for men ($p < 0.001$). The average age of the MG patient in 2018 was 58.54 years for women and 65.13 years for men ($p < 0.001$). The point prevalence in the age group < 50 was 9.21/100,000 inhabitants, while since the age of 50 it increased to 45.36/100,000 inhabitants. In women < 50 years of age, the prevalence was more than three times higher than in men ($p < 0.001$); since the age of 50, no significant gender differences were observed. The peak prevalence was 71.45 patients/100,000 inhabitants and was observed in patients aged 80-89 (59.65/100,000 for women and 96.25/100,000 for men). In the period 2013-2018 there was a discernible increase in MG prevalence, noted in the population aged 50 and more.

In the second stage of the study, I have assessed the treatment of patients with symptomatic MG: the use of immunosuppressants, the number of hospitalizations, including treatment with intravenous immunoglobulins (IVIg) or plasmapheresis (PE), hospitalizations in intensive care units (ICU) and the mortality of patients with MG. The study included the entire cohort of patients identified in the epidemiological MG study.

To date, the literature data on the treatment of MG mostly come from the single-center analyzes or hospital registries, which may cause bias towards the patients with more severe course of the disease, as they more often require hospitalization or care in referral centers.

On January 1, 2019, 33.7% of MG patients were treated with glucocorticosteroids (CS) or other immunosuppressive drugs (IS). There was significantly higher percentage of patients treated with CS or IS in men than in women ($p < 0.001$); 66.3% of MG patients received only symptomatic treatment. In 2018, 42.3% of MG patients required at least one hospitalization due to any indication, and 13.7% required hospitalization due to MG. In 2018, 1.3% of patients were hospitalized more than twice due to MG, in the period 2013-2018 it was 1.3-1.6%; a small percentage (0.09%, $N = 8$) of patients required multiple (10 or more) hospitalizations per year due to cyclical IVIG or PE treatment. Patients requiring multiple hospitalizations (more than two per year) were significantly younger and more often treated with CS or IS ($p < 0.01$); no gender differences were observed. Average length of hospitalization of a MG patient in 2018 was 8.34 ± 10 days per person and was significantly longer if the hospitalization was due to MG than other indications ($p < 0.01$). Hospitalizations in patients with myasthenic crisis (MC; defined as hospitalization in ICU with the main diagnosis of MG (G70), respiratory failure (J95, J96), asphyxia (R09), other and unspecified breathing disorders (R06.8)), were significantly longer (mean 21 ± 21.9 days per person) in comparison with the other hospitalizations due to MG ($p < 0.01$). Patients treated with PE were hospitalized significantly longer than patients treated with IVIG (with the exception of 2015).

In 2018, 11.86% of the patients hospitalized due to MG (1.63% of all MG patients) were treated with PE, and 16.95% (2.33% of all MG patients) – with IVIG. Overall, 26.6% of patients hospitalized due to MG required IVIG or PE treatment (2.1% of all MG patients). Patients requiring multiple (more than 2 per year) cycles of IVIG or PE treatment were significantly younger and more often treated with CS or IS ($p < 0.01$).

In 2013-2018, 16.4 to 21.2% of patients hospitalized due to MG required ICU stay, 15.25% of patients hospitalized due to MG had MC, according to the criteria described above.

The mean age at death of patients with MG was 75.7 years and was not lower than in the general population. The overall mortality in patients with MG in the Polish population in 2013-2018 was 3.1-3.5% per year and was significantly higher in men than in women ($p < 0.01$). Mortality of patients hospitalized in ICU was high and ranged from 17.2 to 22%, which stands for

2.0-4.4% of patients hospitalized due to MG. The in-hospital mortality of patients in MC ranged from 10.6 to 18.5% per year and did not differ significantly between the sexes.

Conclusions: MG requiring symptomatic treatment is a rare disease, with an increasing incidence and prevalence, especially in the group of the patients over 50 years of age.

Despite the relatively small number of patients, the burden on the healthcare system caused by MG is significant, especially due to high need of immunosuppressive therapy, inpatient treatment, severe exacerbations in the course of the disease, and the risk of death due to MC.