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Epidemiology of Myasthenia Gravis in Slovakia in the Years 1977–2015

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Keywords
Myasthenia gravis · Age at onset · Incidence · Prevalence · Mortality

Abstract
Purpose: The objective of the study was to evaluate changes of epidemiological parameters in patients with myasthenia gravis (MG) in Slovakia during the period 1977–2015. ***Methods:*** Data from medical records of MG patients registered in Slovakia were analyzed. Epidemiological rates (incidence, prevalence, mortality) were assessed for several periods to identify changes and drifts over the period of study. ***Results:*** Out of 2,074 patients, 892 were males (43.0%) and 1,193 were females (57.0%). The thymoma associated MG (TAMG) was diagnosed in 123 patients (5.9%). The mean age at onset shifted from 35.8 years in 1977–1989 to 60.0 years in 2010–2015. The crude incidence increased from 0.36/100,000 in 1977–1989 to 1.74/100,000 in 2010–2015. The average annual incidence of TAMG was 0.05/100,000. Maximum increase of MG incidence was registered among the elderly (≥50 years), particularly in the group of patients in the age range 70–79 years (0.34/100,000 in 1977–1989→7.10/100,000 in 2010–2015) and 80–89 years (0.00/100,000 in 1977–1989→5.31/100,000 in 2010–2015). The crude MG prevalence on December 31, 2015 was 24.75/100,000. The average MG mortality was 0.27/100,000. ***Conclusion:*** The age at onset and incidence increased significantly over the study period due to marked increase of MG incidence in elderly, particularly over 70 years. Possible reasons for this trend are discussed.

Introduction

Myasthenia gravis (MG) is an autoimmune disorder with antibodies to the acetylcholine receptor (AChR), leading to a disturbance of neuromuscular transmission [1]. The epidemiological characteristics of MG have changed evidently in the last 40 years. MG was formerly known as a disease of young females. In the last 2 decades, MG has occurred more often in older individuals and it is also more common in males than in the past [2–4].

The objective of this study was to analyze the basic epidemiological characteristics in patients with MG in Slovakia and to compare the changes of these parameters over the study period 1977–2015.

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Table 1. Diagnostic criteria of myasthenia gravis

Diagnostic criteria	
Clinical [1]	Fluctuating weakness and exhaustivity of any voluntary muscle group Worsening after physical effort Improvement after rest Positive static and dynamic load tests
Electrophysiologic [5, 6]	Repetitive nerve stimulation Pathologic decrement of CMAP amplitude/area >10% in 4th/5th answer Single fiber EMG (SFEMG) Mean jitter above upper limit of the normal value >10% of the pairs with increased jitter Blocking Reflex stapedometry Increased threshold and early decay of the stapedius reflex
Testing of anti-AChR and anti-MuSK antibodies [1]	Positive titers
Test with intravenous edrophonium/neostigmine [1]	Unequivocal improvement after application

MuSK, muscle-specific kinase; AChR, acetylcholine receptor; CMAP, compound motor action potential, SFEMG, single fiber electromyography.

Materials and Methods

The retrospective descriptive population-based nationwide epidemiologic study includes data of patients with MG registered between 1977 and 2015 in the Slovak Centre for Neuromuscular Diseases at the University Hospital Bratislava. Since its establishment in 1977 all patients suspected on MG are referred to our Centre from neurologists from whole Slovakia. The patients with confirmed MG diagnosis are subsequently treated and regularly followed up in our center. All MG cases diagnosed between 1977 and 2015 and also 30 MG cases diagnosed before the year 1977 and followed up regularly in our center since 1977 were included in the cohort.

All patients in the cohort fulfilled the diagnostic clinical criteria for MG and at least 2 of the following criteria: positive titer of antibodies to AChR or muscle-specific kinase, positive electrophysiological tests, positive reaction to anticholinesterase inhibitors (Table 1) [1, 5, 6].

We collected demographic data from all our patients and calculated crude and age-adjusted incidence and prevalence and MG mortality with the help of Slovak demographic data from the yearbooks of the National Health Information Centre for each year and each decade between 1977 and 2015.

Student's *t* test, Mann-Whitney U test, and chi-square test were used to compare patient groups and periods. A p value <0.01 was considered statistically significant.

Results

In all, 2,074 patients – 891 males (42.9%) and 1,183 females (57.1%; Table 2) – were registered in the Slovak Centre for Neuromuscular Diseases till the end of the year 2015. The non-thymomatous MG was diagnosed in 1,949 patients (94.1%): 845 males, 1,183 females. Thymoma associated MG (TAMG) was observed in 123 patients (5.9%): 46 males, 77 females (Table 3).

Sex Rates

Overall sex distribution (males:females) changed significantly over the study period from 1:2.38 in 1977–1989 to 1:1 at present. Table 3 shows sex differences in various age groups over the several periods. Trends remain the same over the whole study period: equal sex occurrence in children <10 years; females predominate within the range of 10–50 years and the reverse is true for the range 50–70 years. In the age group of 70–80 years, males and females are equally affected and females above the age of 80 predominate again. The preponderance of females was observed in TAMG (males: females-1:1.55; Table 3).

Age at MG Onset

Table 2 shows an increasing mean age of onset in both males and females over the whole period. In all periods, the average age of onset was higher in males than in females.

The age of onset in the different periods is given in Table 3. For the whole group over the total period, most patients (1,238, 59.5%) had their first symptoms

Table 2. MG patients according to the year of MG diagnosis and age at MG onset

	G1 1977–1989	G2 1990–1999	G3 2000–2009	G4 2010–2015	G1–G4 1977–2015	Statistic significance ($p < 0.01$)
Number of patients						
Total	304	440	776	554	2,074	
M/F	90/214	191/249	333/443	277/277	891/1,183	
Gender ratio						
M:F	1:2.38	1:1.30	1:1.33	1:1	1:1.33	G1:G2–G4
Average age at onset						
Total	35.8±2.2	46.8±1.9	52.3±1.4	60.0±1.5	50.8±0.9	G1:G2:G3:G4
M	48.5±4.1	54.6±2.4	57.4±1.8	62.7±1.7	57.6±1.1	G1:G2:G3:G4
F	30.7±2.2	40.7±2.5	48.4±2.0	57.3±2.4	45.7±1.3	G1:G2:G3:G4

G1–G4, group 1–4 MG patients registered for the first time in center for neuromuscular diseases in periods 1977–1989, 1990–1999, 2000–2009, and 2010–2015; M, males; F, females.

Table 3. Gender and age at onset of MG distribution

Age at onset categories	Number of patients			
	1977–1989 total (M/F) TAMG (M/F)	1990–1999 total (M/F) TAMG (M/F)	2000–2009 total (M/F) TAMG (M/F)	2010–2015 total (M/F) TAMG (M/F)
0–9	11 (4/7)	5 (1/4)	7 (6/1)	2 (0/2)
10–19	63 (6/57)	57 (12/45) 1 (0/1)	57 (11/46)	19 (6/13)
20–29	71 (12/59) 6 (1/5)	51 (13/38) 2 (1/1)	83 (13/70) 2 (0/2)	38 (6/32) 1 (0/1)
30–39	39 (3/36) 2 (1/1)	54 (11/43) 6 (3/3)	67 (17/50) 3 (1/2)	28 (3/25)
40–49	29 (8/21) 5 (1/4)	43 (16/27) 8 (3/5)	77 (31/46) 13 (6/7)	35 (13/22) 6 (2/4)
50–59	42 (25/17) 5 (1/4)	69 (42/27) 4 (3/1)	124 (70/54) 11 (1/10)	91 (60/31) 7 (4/3)
60–69	37 (24/13) 2 (2/0)	108 (64/44) 4 (2/2)	192 (103/89) 8 (3/5)	158 (105/53) 13 (6/7)
70–79	12 (8/4) 1 (1/0)	50 (32/18) 1 (1/0)	137 (67/70) 3 (1/2)	136 (65/71) 8 (2/6)
80–89		3 (0/3)	32 (15/17) 1 (0/1)	46 (16/30)
90–99				1 (1/0)

M, males; F, females; TAMG, thymoma associated myasthenia gravis.

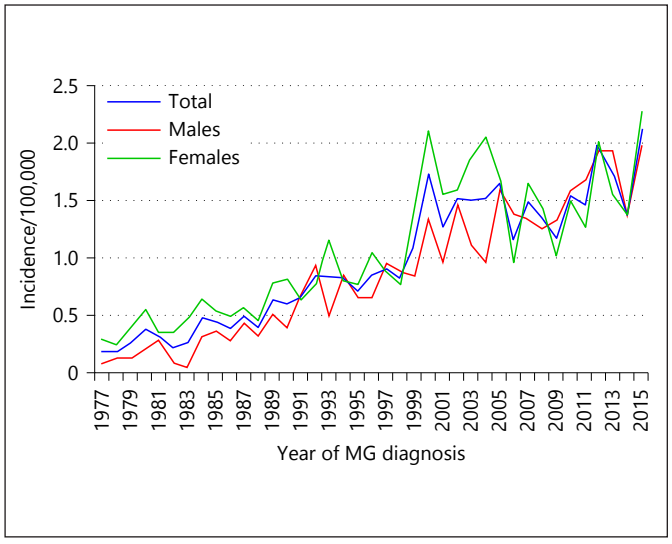

Fig. 1. Annual myasthenia gravis (MG) incidence in Slovakia.

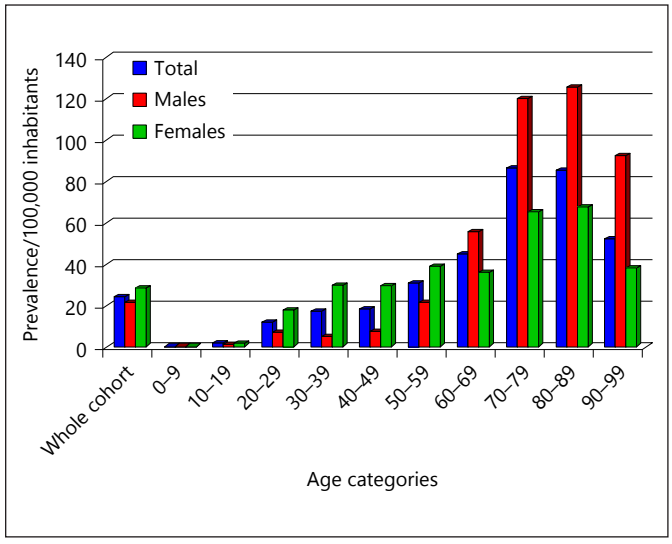

Fig. 2. Age- and sex-specific MG prevalence in Slovakia on December 31, 2015.

much after the age of 50. In the last 2 decades of the study, it was observed that most patients developed their first symptoms at the age 50–79 with considerable increase of the MG onset in the 70–79 years group. In TAMG, the first symptoms started most frequently at the age 40–59 (Table 3).

MG Incidence – Crude, Age-Adjusted

The crude MG incidence grew from 0.18 patients/100,000 in 1977 to 2.12/100,000 in 2015 (Fig. 1).

The average MG incidence increased in the whole cohort from 0.36/100,000 in 1977–1989 to 1.70/100,000 in 2010–2015 (Table 4).

The average incidence of TAMG during the study period was 0.05/100,000. The average incidence grew significantly in 2000–2009, 2010–2015, compared with 1977–1989 (Table 4).

The average age-specific incidence grew continually in all age groups ≥50 in all study periods with maximum in period 2010–2015 in age groups 60–69 (2.99/100,000) and 70–79 (3.45/100,000). In early-onset MG (<50 years), a mild decrement of average incidence rate (IR) was registered in the last study period 2010–2015 (Table 4).

MG Prevalence: Crude, Age-Adjusted

The crude MG prevalence in Slovakia has been increased continually since 1977 from 0.84/100,000 to 24.75/100,000 in 2015.

In the year 2015, we registered the highest age-specific prevalence in older age groups (>60), with peak in group 80–89 in both sexes (males 125.26/100,000, females 67.96/100,000). In older age groups (60–99), MG prevalence is clearly higher in males, whereas in young and middle age (20–59) the prevalence is higher in females (Fig. 2).

MG Mortality

In all, 734 out of 2074 MG patients (35.4%) died. MG patients numbering 26 (1.3%) died due to myasthenic crisis, 3 of them in combination with cholinergic crisis. Only 7 out of them died in the last 30 years. Six patients with TAMG died due to malignant thymoma dissemination. While the overall mortality is increasing significantly over the study period (0.07/100,000 in 1977–1989→0.75/100,000 in 2010–2015), the mortality due to myasthenic crisis is gradually decreasing (0.029/100,000 in 1977–1989→0.00/100,000 in 2010–2015; Table 5).

Discussion

A distinct advantage of our MG patients' cohort is that the diagnostics and management of MG for the whole population of Slovakia was provided in 1 myasthenic center.

MG was diagnosed in 891 males and 1,183 females. The significant increase of MG incidence was observed during

Table 4. Average annual MG incidence according to age at onset

Age at onset categories	Average incidence/100,000					Statistic significance ($p < 0.01$)
	G1 (1977–1989) total TAMG	G2 (1990–1999) total TAMG	G3 (2000–2009) total TAMG	G4 (2010–2015) total TAMG	G1–G4 (1977–2015) total TAMG	
0–9	0.07±0.07	0.07±0.08	0.12±0.10	0.06±0.12	0.08±0.04	
10–19	0.43±0.10	0.63±0.20 0.01±0.02	0.75±0.12	0.54±0.18	0.59±0.18 0.003±0.004	G1:G3
20–29	0.43±0.14 0.04±0.03	0.63±0.14 0.02±0.05	0.91±0.21 0.02±0.03	0.79±0.35 0.02±0.04	0.69±0.10 0.03±0.04	G1:G3+G4
30–39	0.29±0.10 0.01±0.02	0.67±0.16 0.07±0.07	0.84±0.19 0.04±0.04	0.52±0.18	0.58±0.10 0.03±0.04	G1:G2+G3
40–49	0.35±0.17 0.05±0.05	0.58±0.18 0.11±0.08	0.98±0.10 0.16±0.06	0.78±0.35 0.14±0.12	0.68±0.13 0.1±0.04	G3:G1+G2
50–59	0.58±0.22 0.05±0.05	1.34±0.31 0.08±0.06	1.81±0.46 0.16±0.11	2.0±0.40 0.15±0.17	1.43±0.24 0.1±0.04	G1:G2+G3+G4
60–69	0.66±0.24 0.03±0.03	2.48±0.59 0.09±0.10	4.31±0.41 0.18±0.13	4.5±0.66 0.37±0.19	2.99±0.55 0.12±0.05	G1:G2–G4; G2:G3+G4 G1:G4
70–79	0.34±0.18 0.02±0.04	1.89±0.38 0.03±0.06	4.47±0.84 0.1±0.10	7.10±0.97 0.42±0.30	3.45±0.77 0.09±0.06	G1:G2:G3:G4
80–89		0.31±0.41	2.81±0.91 0.09±0.17	5.31±2.68	2.11±0.54 0.02±0.04	G2:G3+G4
90–99				1.00±1.70	0.25±0.24	
Whole cohort (0–99)	0.36±0.07 0.02±0.01	0.82±0.09 0.05±0.02	1.44±0.12 0.08±0.02	1.70±0.24 0.11±0.04	1.08±0.17 0.05±0.01	G1:G2–G4; G2:G3+G4 G1:G3+G4

G1–G4, group 1–4 MG incidence in periods 1977–1989, 1990–1999, 2000–2009, 2010–2015; TAMG, thymoma associated myasthenia gravis.

Table 5. Average annual mortality of MG patients

Study periods	Mortality/100,000		
	Overall	Myasthenic crisis	Malignant thymoma dissemination
G1 (1977–1989)	0.07±0.03	0.029±0.022	0.00
G2 (1990–1999)	0.10±0.05	0.006±0.006	0.002±0.004
G3 (2000–2009)	0.41±0.08	0.004±0.005	0.00
G4 (2010–2015)	0.75±0.14	0.00	0.02±0.01
G1–G4 (1977–2015)	0.27±0.08	0.012±0.008	0.003±0.003
	$p < 0.01$	$p < 0.01$	$p < 0.01$
	G1:G2:G3:G4	–	–

G1–G4, group 1–4 MG mortality in periods 1977–1989, 1990–1999, 2000–2009, 2010–2015.

the study period in both sexes. We found a preponderance of males at the age of 50–70 (1.5:1). In the age group 70–79, the sex ratio is almost equal and the preponderance of females is observed in the age over 80. The equalization of sex rates after the age over 70 is explainable by better life expectancy of females compared to males.

The occurrence of TAMG differs according to different authors between 4.9 and 20.0% [7]. The TAMG occurrence in our cohort is 5.9%. This proportion was constant during the whole study period.

The MG IR in Slovakia (Table 4) is growing continually during the study period. The average values of crude MG incidence in Slovakia and the increase of MG occurrence in the higher age groups (70–99) are consistent with the findings of other authors [8–13].

The continual growth of MG IR in Slovakia reflects several factors. The first one is an improved case finding generally and mainly in elderly people, which reflects better understanding of disease, increasing knowledge of MG among neurologists in Slovakia, and improvement of diagnostic approaches (routine examination of anti-AChR and anti-muscle-specific kinase antibodies titers, implementation of electrophysiological tests into routine praxis, e.g., single fiber electromyography). This led to the constant growth of myasthenia IR particularly in the first 3 study periods (Fig. 1). The ageing of population is another factor leading to considerable increase of MG incidence in higher age groups (>50 and especially >70), particularly in the last 2 study periods (Table 4). It is likely that in the age >70, the immune system is more harmful to immune tolerance breakdown leading towards easier development of MG in predisposed people (e.g., with certain human leukocyte antigen pattern, gene polymorphisms) under appropriate environment circumstances at this age [14]. Nowadays more predisposed people can achieve this risk, with the age reflecting the rise of life-expectancy in many populations worldwide. The highest crude MG incidence (2.12/100,000) in 2015 could point to the third factor of MG incidence increase – the real biological increase as the population structure and diagnostic algorithms have not changed dramatically in the past years. However, further studies evaluating the trends in MG incidence are needed in order to confirm or refuse this hypothesis.

The actual MG prevalence rate in Slovakia at the end of 2015 (24.75/100,000) was high. Only Breiner et al. [8] referred higher crude prevalence (32.0/100,000) in Ontario, Canada in year 2013. The high MG prevalence in Slovakia reflects the (1) overall rise of mean life-expectancy in whole Slovak population due to improvements in healthcare generally, (2) centralization of MG management with quick MG diagnostics, early start of adequate immunotherapy and intensive follow up of MG patients resulting in good surviving of MG patients, and (3) gradual and significant increase of MG incidence during the study period.

The overall MG mortality increased during the study period (Table 5) due to ageing of myasthenic population. The death causes are in most cases the same as in general population (cardiac diseases, cancer, bronchopneumonia, pulmonary artery embolism). Only a small group of 26 MG patients died in myasthenic crisis and since 2004, no patient died in crisis. The immediate death causes were severe respiratory failure, aspiration bronchopneumonia, and suffocation. The severe life-threatening myasthenic symptomatology developed because of delayed MG diagnosis, inadequate MG treatment, and inappropriate time indication of thymectomy in MG patients not adequately prepared for total anesthesia. A marked decrease of MG mortality due to myasthenic crisis in Slovakia during the last 25 years is a consequence of significant improvements in overall MG management. Six patients died due to malignant thymoma dissemination despite of complex oncologic treatment (radiotherapy, chemotherapy).

Conclusion

The MG prevalence has increased continually since the year 1977 in both genders, mostly in older age groups (>60), reflecting the rise in late-onset MG with preponderance of males. Higher occurrence of MG is a consequence of good established MG diagnostics and centralization of MG patients with adequate therapy and follow-up. Consistent centralization has an important impact on growing MG prevalence rate over the last 40 years.

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Disclosure Statement

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