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Nationwide Population-Based Epidemiological Study of Myasthenia Gravis in Taiwan

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Key Words
Myasthenia gravis, incidence/prevalence · Medical expenses · Thymus disorders · Taiwan, epidemiology

Abstract
Background: The purpose of this study is to investigate the epidemiology and medical expenses of myasthenia gravis (MG) in Taiwan. ***Methods:*** Cases of MG were identified from the National Health Insurance Research Database with corresponding codes of the International Classification of Diseases, ninth revision (ICD-9), from January 2000 to December 2007. Age- and sex-specific incidences were estimated by dividing the incidence number by population data obtained from the Department of Statistics, Ministry of the Interior. ***Results:*** During the study period, 5,211 cases were identified. The incidence ratio of males to females was 0.68. The average annual incidence rate was 2.1/100,000. MG occurred in all age groups with a higher incidence in older individuals and the lowest incidence in the 10- to 14-year-olds for both sexes. Among the 5,211 cases, 615 (12%) had a neoplasm of the thymus. The prevalence increased steadily during the study period from 8.4/100,000 in 2000 to 14.0/100,000 in 2007. ***Conclusions:*** This is the first population-based epidemiological study of MG in Taiwan. The incidence rate and prevalence were higher than in most published studies, especially in old age groups.

Introduction

Myasthenia gravis (MG) is the most common neuromuscular junction disorder, characterized by a fluctuating degree and variable combination of weakness in ocular, bulbar, limb and respiratory muscles [1]. In the majority of patients, the maximum level of severity is reached during the first 3 years. Acetylcholine esterase inhibitors and corticosteroids are the cornerstone in treating MG with satisfactory symptomatic improvement or complete remission in most cases [2].

There have been more than 50 population-based epidemiological studies of MG since the 1950s [3]. The majority of these studies were done in Europe or North America. In some large populations, surveys have been incomplete (e.g. in China and sub-Saharan Africa) or lacking (e.g. in South America and Australia). The weighted mean prevalence increased gradually from 22.2 per million in the 1950s to 93.9 per million in the 1990s [4].

This study is based in part on data from the NHI Research Database provided by the Bureau of the NHI, Department of Health, and managed by the National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of the Bureau of the NHI, the Department of Health or the National Health Research Institutes.

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The high prevalence of previously unrecognized positive acetylcholine receptor antibodies (AChR-Ab) in those older than 75 years suggests that MG might be substantially underdiagnosed in the elderly [5] or that the incidence of late-onset MG in general may be increasing [6], possibly both. A higher than expected incidence of MG in the elderly was found in a 10-year (from 1991 to 2000) prospective study of MG in Spain [7]. An increased incidence of elderly-onset MG was also noted in Japan [8]. With an aging population and advancement in immunemodulating therapy, the epidemiology of MG may be different than before, and therefore the population-based epidemiology of MG needs further investigation.

The population-based epidemiology of MG has not been reported in Taiwan before. We have previously established the population-based epidemiological data of motor neuron diseases [9], Creutzfeldt-Jakob disease, multiple sclerosis [10] and Wilson's disease [11] from the National Health Insurance Research Database (NHIRD). At least 215 studies utilizing the same database have been published. Here, we present the data of MG from the same database.

Methods

The National Health Insurance (NHI) program was initiated in Taiwan in 1995. Through risk sharing, the public has received comprehensive medical care such as preventive medicine, clinical care, hospitalization, resident care and social rehabilitation. According to the NHI Annual Statistics Report compiled by the Bureau of the NHI, the NHI coverage rate was 96.1% in 2000 and increased steadily to 98.6% in 2007.

The population in Taiwan during 2000–2007 was stable, ranging from 22.28 to 22.96 million. Population-based data were obtained by using the annual outpatient claims and hospitalization discharge claims for 2000–2007 from the Bureau of the NHI. Initially, the cases of MG were identified by all the corresponding codes of the International Classification of Diseases, ninth revision (ICD-9), in the 358 series. 99.4% of them were coded 358.0. Therefore, only ICD-9 code 358.0 was selected in the following calculation. The ICD-9 code for ocular MG and generalized MG is the same. Both ocular MG and generalized MG were included.

Outpatient claim files include an encrypted personal identification number, date of birth, date of service, relevant department, expenses and first 3 ICD-9 codes. The hospitalization discharge claims contain data from both acute and long-term stay hospitals. The data of the hospitalization discharge claims include an encrypted personal identification number, date of birth, length of stay, relevant department, expenses and first 5 ICD-9 codes. Multiple outpatient and hospitalization discharge claims with the same personal identification number were counted once so that only the incidence of the disease was counted. The prevalence was calculated by dividing the number of total cases for each year by the corresponding total population.

Averaged age- and sex-specific incidence rates were calculated by dividing the number of new cases in each age and sex group by the age- and sex-specific population, followed by averaging these data from 2001 to 2007. Data of these populations were derived from the Ministry of the Interior, Executive Yuan, Taiwan. Calculations were carried out using SPSS version 15.0 for Windows (SPSS Inc., Chicago, Ill., USA) and Microsoft Excel, 2003 edition.

MG is included in the list of serious accidents and diseases (SAD) published by the Department of Health, Executive Yuan, Taiwan. The approval of the SAD status is subject to evaluation and review by the Bureau of the NHI. The application of SAD is limited by board-certified specialists of a related discipline. Patients with SAD certificates are eligible for exemption from insurance premiums and copayments. Therefore, SAD patient data are highly accurate and reliable. Because of the low incidence, MG is difficult and impractical for an epidemiological approach by field community studies. The NHIRD with SAD patient data is a great resource for studying the epidemiology of MG. In this study, all of the retrieved outpatient and hospitalization data were verified by linking the encrypted personal identification number with the SAD certificate. Medical expenses were limited to those of the SAD. Confidentiality assurances were addressed by following the data regulations of the NHI Bureau. The NHIRD consists of encrypted secondary data released to the public for research purposes. Institutional review board approval was waived for this study.

Results

Sex-specific incidence and prevalence are shown in detail in table 1.

In total, there were 5,211 cases, including 3,165 females, 2,018 males (new cases during 2001–2007 plus total cases in 2000) and 28 cases without gender data: 3 in 2000, 2 in 2001, 5 in 2002, 10 in 2003, 8 in 2004 and none in 2005–2007. Therefore, the total case numbers were not equal to the sum of female and male case numbers in 2000–2004. The average incidence ratio of males to females during 2001–2007 was 0.68. The annual incidence rate ranged from 2.4 to 2.7 and 1.5 to 1.8/100,000 for females and males, respectively. The overall annual incidence rate during 2001–2007 was 2.1/100,000. Confidence intervals are not reported because these are national population data, not a sample. Age-specific incidences during 2001–2007 are listed in table 2. Detailed age-specific population information for Taiwan used in the calculation of age-specific incidences in this study can be found on the website of the Ministry of the Interior, Executive Yuan, Taiwan (http://www.moi.gov.tw/stat/english/year.asp).

The incidence was lowest in the 10- to 14-year age group and higher in the older age groups for both sexes. The incidence was significantly higher in females than in

Table 1. Incidence and prevalence of MG in Taiwan

	Total population, × 10^6			New cases			Total cases			Incidence rate per 10^5/year			Prevalence per 10^5			M/F ratio of incidence
	F	M	T	F	M	T	F	M	T	F	M	T	F	M	T	
2000	10.9	11.4	22.3				1,200	672	1,875				11.0	5.9	8.4	
2001	11.0	11.4	22.4	273	191	466	1,283	738	2,025	2.5	1.7	2.1	11.7	6.5	9.0	0.67
2002	11.0	11.5	22.5	297	182	484	1,421	826	2,255	2.7	1.6	2.1	12.9	7.2	10.0	0.59
2003	11.1	11.5	22.6	268	196	474	1,538	920	2,475	2.4	1.7	2.1	13.9	8.0	10.9	0.70
2004	11.1	11.5	22.7	265	178	451	1,643	986	2,645	2.4	1.5	2.0	14.7	8.5	11.7	0.65
2005	11.2	11.6	22.8	272	195	467	1,755	1,065	2,820	2.4	1.7	2.1	15.7	9.2	12.4	0.69
2006	11.3	11.6	22.9	298	195	493	1,916	1,120	3,036	2.6	1.7	2.2	17.0	9.7	13.3	0.64
2007	11.3	11.6	23.0	292	209	501	1,996	1,209	3,205	2.6	1.8	2.2	17.6	10.4	14.0	0.70

F = Female; M = male; T = total.

Table 2. Averaged age-specific incidence of MG in Taiwan during 2001–2007

Age group	Cases			Averaged incidence per 10^5/year			F/M incidence rate p value
	F	M	T	F	M	T	
0–4	50	27	77	1.21	0.60	0.89	0.003
5–9	43	30	73	0.84	0.54	0.69	n.s.
10–14	23	19	42	0.42	0.32	0.37	n.s.
15–19	63	33	96	1.14	0.55	0.83	0.001
20–24	146	61	211	2.27	0.90	1.60	<0.001
25–29	173	82	265	2.59	1.19	1.95	<0.001
30–34	161	83	249	2.54	1.28	1.94	<0.001
35–39	178	109	291	2.73	1.63	2.21	<0.001
40–44	181	117	298	2.74	1.73	2.23	<0.001
45–49	205	146	351	3.32	2.34	2.83	0.001
50–54	173	114	287	3.28	2.17	2.72	0.001
55–59	125	119	245	3.52	3.41	3.48	n.s.
60–64	112	97	209	3.93	3.59	3.77	n.s.
65–69	110	109	219	4.31	4.65	4.47	n.s.
70–74	107	87	194	5.28	4.13	4.69	n.s.
75–79	73	84	157	4.98	4.86	4.92	n.s.
≥80	42	29	72	2.90	2.04	2.51	n.s.

F = Female; M = male; T = total; n.s. = not significant.

males in age groups of 0–4 and 15–54 years. The prevalence increased steadily from 8.4/100,000 in 2000 to 14.0/100,000 in 2007.

The 5,211 patients utilized 174,876 outpatient services and 4,976 inpatient services. On average, each patient utilized 8.6 outpatient services and 0.24 hospitalizations per year. The average length of stay in an acute ward was 15.6 days. The majority of the medical services were provided by department of neurology (77.3%). Other departments that provided more than 1% of the services included departments of pediatrics (4.3%), Chinese medicine (3.9%), internal medicine (3.5%), family medicine (1.8%), ophthalmology (1.8%), physical medicine and rehabilitation (1.5%) and surgery (1.1%).

The average expense was 1,616 New Taiwan Dollars (NTD, 1 USD = 30–34 NTD) for each outpatient service and 118,514 NTD for each hospitalization. The detailed annual expenses and numbers of outpatient visits and hospitalizations are listed in table 3. The medical expenses only represented SAD-related direct costs. Indirect

Table 3. Medical expenses of MG in Taiwan

Year	Number of outpatient services	Sum of outpatient expenses, NTD	Average expense per outpatient service, NTD	Number of inpatient services	Sum of inpatient expenses, NTD	Average expense per inpatient service, NTD	Average of total yearly expenses per patient, NTD
2000	15,207	21,728,813	1,429	516	57,718,087	111,857	42,372
2001	17,110	24,122,669	1,410	508	54,752,072	107,780	38,950
2002	19,307	28,794,079	1,491	539	57,853,271	107,334	38,425
2003	19,549	32,677,873	1,672	593	79,914,665	134,763	45,492
2004	22,694	37,655,926	1,659	645	78,352,052	121,476	43,859
2005	25,111	38,666,583	1,540	695	90,523,313	130,249	45,812
2006	27,454	45,013,512	1,640	730	89,630,524	122,782	44,349
2007	28,444	53,882,037	1,894	750	80,981,698	107,976	42,079

Table 4. Top 20 common coexisting ICD-9 codes

ICD-9 code	Disease	Frequency
401.9	Essential hypertension	12,199
465.9	Acute upper respiratory infections of unspecified site	7,905
250.00	Diabetes mellitus, type II, adult onset	5,902
729.1	Myalgia and myositis, unspecified	5,318
536.9	Unspecified functional disorder of stomach	5,042
164.0	Malignant neoplasm of thymus	3,965
460	Acute nasopharyngitis	3,942
780.52	Other insomnia	2,896
300.9	Unspecified neurotic disorder	2,628
401.1	Benign essential hypertension	2,555
784.0	Headache	2,487
300.00	Anxiety state	2,337
272.4	Other and unspecified hyperlipidemia	2,291
733.00	Osteoporosis, unspecified	2,247
212.6	Benign neoplasm of thymus	2,243
242.90	Thyrotoxicosis	2,108
780.4	Dizziness and giddiness	2,026
780.50	Sleep disturbances, unspecified	1,822
710.0	Systemic lupus erythematosus	1,714
786.2	Cough	1,632

costs, such as time lost from work or disability, were not included. Direct medical cost not paid by the NHI, such as that for a single room, was not included either.

Among these 5,211 cases, 615 (12%) had a concomitant diagnosis of neoplasm of the thymus. The top 20 common coexisting ICD-9 codes among these 174,876 outpatient and 4,976 inpatient services are shown in table 4. We also evaluated the coexisting frequency of various autoimmune diseases. In addition to systemic lupus erythematosus which ranked 19, 710.2 'sicca syndrome' (747 services) and 714.0 'rheumatoid arthritis' (661 services) were also relatively common.

Discussion

The present study is not only the first population-based epidemiological study on MG in Taiwan, but also the largest epidemiological study that has ever been conducted on MG in the world, and one of very few with entire national data. The annual incidence rates were stable (2.0–2.2/100,000/year) throughout the study period. This might reflect the quality of the SAD data of the NHIRD as well as the stability of the disease.

Case ascertainment was based on clinical coding in the present study and may raise the question of diagnostic accuracy. However, in Taiwan's medical environment, we believe the diagnosis of MG is reliable in most cases due to the following reasons. First, an assay of AChR-Ab, which is present in 85% of individuals with MG [12, 13], is available in Taiwan. Although no data on AChR-Ab are available in our database, AChR-Ab is almost routinely checked for patients with suspected MG in clinical practice. Second, single-fiber electromyography, which is the most sensitive diagnostic tool for MG, is available in many hospitals in Taiwan. It is positive in more than 95% of those with generalized MG and 90–95% of those with ocular MG [12, 14]. In clinical practice in Taiwan, the patients with suspected MG without positive AChR-Ab are usually referred to hospitals with facilities for single-fiber electromyography. The patients can also directly visit medical centers for diagnosis and treatment without referral. Third, no matter the disease severity, MG is included in the list of SAD, which has economic factors ren-

Table 5. Epidemiological studies of MG in different countries

First author	Year	Region	Cases	Population	Incidence per million/year	Prevalence per million
Storm-Mathisen [16]	1912–1952	Norway	90	3,700,000	1	21
Garland [17]	1955	Yorkshire, UK	60	3,500,000	5	26
Giagheddu [18]	1961	Sardinia, Italy	110	1,500,000	2.6	7.7
Oosterhuis [19]	1965	Amsterdam, The Netherlands	73	850,000	3.1	53
Giagheddu [18]	1971	Sardinia, Italy	110	1,500,000	2.6	17.6
Pirskanen [20]	1976	Finland	264	4,700,000	n.a.	5.6
Storm-Mathisen [21]	1981	Norway	458	3,700,000	4	90
Phillips [22]	1984	Virginia, USA	112	550,000	9.1	142
Giagheddu [18]	1986	Sardinia, Italy	110	1,500,000	2.6	45
Somnier [23, 24]	1970–1988	Eastern Denmark	229	2,320,000	4.4	77
Yu [25]	1987	Hong Kong	262	5,610,000	4	53.5
Christensen [26]	1990	Western Denmark	290	2,800,000	5	78
Lavrnic [27]	1992	Belgrade, Yugoslavia	124	1,495,000	7.1	121.5
Tola [28]	1994	Emilia Romagna, Italy	86	2,925,000	14.7	n.a.
Robertson [29]	1997	Cambridgeshire, UK	100	685,000	11	150
Poulas [15]	1992–1997	Greece	843	10,475,878	7.4	70.63
Oopik [30]	1997	Estonia	70	1,462,130	n.a.	78
Somnier [6]	1995–1999	Eastern Denmark	241	2,300,000	3.5 vs. 20.8[1]	n.a.
Lai (present study)	2000–2007	Taiwan	5,211	22,958,360	21	140

n.a. = Not available. [1] Early and late onset, respectively.

dering the data highly reliable as described in the Methods section.

There are also other limitations in the present study. The age of symptom onset was not available in the database. Although it is convenient and affordable to seek medical help in Taiwan, it is not always prompt for SAD approval, because SAD will not be approved until firm evidence has been obtained, and atypical symptoms in some MG patients make the diagnosis challenging. Therefore, the annual incidence of MG in this study represents the yearly number of new SAD approvals for MG, and the prevalence of MG represents the yearly number of total MG cases with approval of SAD. The age of age-specific incidence in the present study represents that of the confirmed diagnosis and was approved by SAD. The age approved by SAD is definitely older than that of symptom onset.

We modified the work of Poulas et al. [15] and reviewed epidemiological studies of MG done in the past (table 5). Compared with previous studies, a few features were noted in the present study, including the high annual incidence rate and prevalence. There is a trend of increasing incidence and prevalence over calendar time.

The typical bimodal age distribution of an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decades (male predominance) [1, 15, 31] observed in Caucasian populations was not observed in the present study, nor was it seen in another 3 MG studies in Chinese populations [25, 32, 33]. Several reports have noted that the incidence of elderly-onset patients with MG has been increasing in the USA, European countries and Japan [5–8, 22, 26, 29, 34]. Our study showed an older-age predominance distribution, which is similar to that in Japan from 1997 to 2001 [8] and suggests that the incidence of elderly-onset patients with MG is probably also increased in Chinese. A recently published systematic literature review about the incidence of MG showed that the most accurate estimate of incidence of MG was around 30/1,000,000/year and the incidence in children and adolescents was between 1 and 5/1,000,000/year [35]. Our results are similar to the estimation.

Neoplasm of the thymus, thyrotoxicosis and systemic lupus erythematosus need special attention.

In the present study, 12% of the patients had a malignant or benign neoplasm of the thymus, and this is similar to other studies [1, 8, 32]. Mediastinum image evaluation is necessary for MG patients. Thyroid function tests are also needed in patients suspected of having MG due to the frequently coexisting thyrotoxicosis. Paying attention to other autoimmune diseases is recommended due

to relatively common coexisting systemic lupus erythematosus, sicca syndrome and rheumatoid arthritis.

Compared with similar studies we have done on motor neuron diseases [9], Creutzfeldt-Jakob disease and multiple sclerosis [10], the average annual medical expense per patient associated with MG is much lower due to the availability of effective and inexpensive medications for the condition.

Conclusions

This study presents the first epidemiological data of MG in Taiwan. The incidence and prevalence of MG in Taiwan were higher than those in most published studies. The phenomenon was most significant in the elderly. A neoplasm of the thymus was present in 12% of MG cases.

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