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Incidence and Prevalence of Myasthenia Gravis in Korea: A Population-Based Study Using the National Health Insurance Claims Database

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Background and Purpose There have been a few national population-based epidemiological studies of myasthenia gravis (MG) with wide variation of incidence and prevalence rates worldwide. Herein we report the first nationwide population-based epidemiological study of MG in Korea.

Methods We attempted to estimate the incidence and prevalence rates of MG using the Korean National Health Insurance claims database for 2010 to 2013. Cases with MG were defined as those having claim records with a principal diagnosis of MG and the prescription of acetylcholinesterase inhibitors or immunosuppressive agents including corticosteroids and azathioprine within 2 years after the diagnosis. The year 2010 was set as a washout period, such that patients were defined as incident cases if their first records of MG were observed in 2011.

Results In 2011 there were 1,236 incident cases, and the standardized incidence rate was 2.44 per 100,000 person-years. The standardized prevalence rates were 9.67 and 10.66 per 100,000 persons in 2010 and 2011, respectively. The incidence and prevalence rates peaked in the elderly population aged 60 to 69 years for both sexes.

Conclusions This is one of the largest national population-based epidemiological studies of MG, and it has confirmed the high incidence and prevalence rates of MG in the elderly population of South Korea.

Key Words myasthenia gravis, epidemiology, incidence, prevalence, Korea.

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction characterized by exertional weakness of skeletal muscles.[1] This disorder is immunologically heterogeneous, with antibodies against the nicotinic acetylcholine receptor (AChR-Ab) in most patients (85%), and antibodies against muscle-specific receptor tyrosine kinase or lipoprotein-related protein 4 in a variable proportion of AChR-Ab-negative patients.[2]

According to a recent systematic review of population-based epidemiological studies, the pooled incidence and prevalence rates of MG were estimated to be 5.4 per million person-years and 77.7 per million persons, respectively.[3] However, there were remarkable variations across different studies, with the incidence varying from 1.7 to 21.3 per million person-years, and the prevalence varying from 15 to 179 per million persons.[3] The heterogeneity of epidemiological features across studies can be attributed to differences in race, geographical regions, study period, and methodology. Reliable data on the incidence, prevalence, and clinical characteristics of MG would help facilitate health and research policy discussions on this rare disorder. To our knowledge, no population-based epidemiological data

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for MG have been reported for Korea. The aim of this study was to estimate the incidence and prevalence of MG in Korea using the National Health Insurance (NHI) claims database.

METHODS

Data source and study population

South Korea has a unique universal health-care system managed by the government. All residents must be enrolled in the NHI system, either as an NHI beneficiary or Medical Aid recipient. All types of medical institutions must mandatorily register on the NHI system. The Korean Health Insurance Review and Assessment Service maintains a database containing all the details of diagnoses, medical services, and medications for claims made. This situation means that the Korean NHI claims database provides a unique nationwide source of information on epidemiological data and health-care resource utilization. As of 2011, there were 49,299,165 (96.8%) NHI beneficiaries and 1,609,481 (3.2%) Medical Aid recipients among the total Korean population of 50,908,646.

We used the NHI claims database from 2010 to 2013 to identify patients with MG. The patients with MG were defined as those who had an outpatient visit or admission history with a principal diagnostic code of G70.0 in the Korean Standard Classification of Diseases 2015 (KCD), which is the Korean version of the International Classification of Diseases, 10th Revision. Due to the possibility of miscoding, we combined the diagnostic information with the use of MG medication. The medication records were searched for the next 2 years from the time of MG diagnosis in order to identify patients with MG more accurately. Therefore, even though we used the data obtained from 2010 to 2013, the prevalence was determined for only 2 years (2010 and 2011). As for the incidence, the 1-year period prior to 2011 was set as a "washout" period, such that patients were defined as incident cases only if their first record of an outpatient visit or admission with a principal diagnosis of MG was observed after 2010. The rate of thymoma comorbidity with MG was determined by identifying cases with thymoma (KCD codes: C37, malignant thymoma; D150, thymoma, benign; D384, thymoma, uncertain) among the incident MG cases.

Estimation of standardized incidence

Incidence was defined in this study in accordance with the definition in Medical Subject Headings (MeSH) as "the number of new cases of a given disease during a given period in a specified population." The incidence of MG in 2011 was calculated as follows:

1) 2010 was considered the washout period for calculating the annual incidence in 2011.

2) Determining the number of patients with MG who were first diagnosed in 2011 without an outpatient visit or admission history in 2010.

3) Following up 2 years of medication history to identify patients with MG more accurately (we assumed that patients with MG would be treated with at least one of acetylcholinesterase inhibitors, corticosteroids, or azathioprine during the 2 years after the diagnosis).

4) Finally determining the "crude incidence," corresponding to the calculation results without any adjustment.

5) Calculating the "standardized incidence" by adjusting for sex and age using the standard population data for 2011 from the Korean Statistical Information Service in the Korea National Statistical Office.

Estimation of standardized prevalence

MeSH defines prevalence as "the total number of cases of a given disease in a specified population at a designated time." Therefore, a washout period was not needed to calculate prevalence. We used the concept of period prevalence (past 12 months, and usually 1 year) in this study. The prevalence of MG was determined as follows:

1) Determining the number of MG patients with G70.0 as a primary diagnostic code in an outpatient visit or hospital admission data in 2011 and 2012.

2) Following up 2 years of medication history to identify patients with MG more accurately (we assumed that patients with MG would be treated with at least one of acetylcholinesterase inhibitors, corticosteroids, or azathioprine during the 2 years after a diagnosis).

3) Finally determining the "crude prevalence" rates in 2010 and 2011, corresponding to the calculation results without any adjustment.

4) Calculating the "standardized prevalence" in 2010 and 2011 by adjusting for sex and age using the standard population data for 2011 from the Korean Statistical Information

Table 1. Incidence of myasthenia gravis in 2011 (per 100,000 person-years)

Age	Crude incidence			Standardized incidence*		
(years)	Subtotal	Male	Female	Subtotal	Male	Female
≤19	80	39	41	0.70	0.66	0.76
20–39	318	140	178	2.12	1.82	2.45
40–59	495	196	299	3.02	2.36	3.70
60–69	214	92	122	5.07	4.55	5.55
70–79	105	38	67	3.79	3.31	4.13
≥80	24	9	15	2.33	3.01	2.05
Total	1,236	514	722	2.44	2.02	2.85

*The overall standardized number per 100,000 persons was calculated using the standard population data for 2011 from the Korean Statistical Information Service in the Korea National Statistical Office.

Service in Korea National Statistical Office.

The prevalence was not determined for 2012 and 2013 because there was no database of 2-year medication records.

Ethics statement

This study was approved by the institutional review board of the Seoul National University Seoul Metropolitan Government Boramae Medical Center (approval number: 07-2015-4). The need to obtain informed consent was waived by the board.

RESULTS

The age- and sex-specific crude and standardized incidence rates are summarized in Table 1. In 2011 there were 1,236 incident cases, and the standardized incidence rate was 2.44 per 100,000 person-years (2.85 and 2.20 per 100,000 person-years for women and men, respectively). The standardized incidence rates peaked in elderly subjects aged 60 to 69 years for both sexes. The total number of cases was 4,907 in 2010 (61.6% women) and 5,410 in 2011 (61.5% women). The standardized prevalence rates were 9.67 and 10.66 per 100,000 persons in 2010 and 2011, respectively (Table 2). Among those 1,236 incident cases, 123 (9.95%) had a concomitant diagnosis of thymoma, most of them (88, 72.4%) after a diagnosis of MG (Table 3).

DISCUSSION

This is one of the few national population-based epidemiology studies of MG, and to our knowledge the first performed in Korea. In this study, the standardized incidence rate was estimated to be 2.44 per 100,000 person-years in 2011, and the standardized prevalence rates were 9.67 and 10.66 per 100,000 persons in 2010 and 2011, respectively. According to a recent systematic review of population-based epidemiological studies, the range of estimated pooled incidence rates were 0.17 to 2.13 per 100,000 person-years.[3] In another recent systematic literature review, the incidence rates of MG ranged between 0.3 and 3.0 per 100,000 person-years.[4] The incidence rate in our study is comparable to that reported in Taiwan,[5] but seems to be at the upper end of the ranges previously reported in other populations. These marked variations could be explained by the heterogeneity of populations in terms of ethnicity and geographical region, and also by the studies employing different methodologies and analysis periods.[3,4]

The frequency and clinical manifestations of MG seem to be influenced by onset age, sex, and ethnicity.[1] In this regard, it is notable that the incidence and prevalence rates peaked

Table 3. Number of MG patients with thymoma in 2011

Age (years)	After diagnosis of MG	Before diagnosis of MG	Total
≤19	2 (2.3%)	0 (0.0%)	2 (1.6%)
20–39	21 (23.9%)	9 (26.5%)	30 (24.4%)
40–59	41 (45.5%)	15 (44.1%)	56 (45.5%)
60–69	18 (20.5%)	9 (26.5%)	27 (22.0%)
70–79	7 (8.0%)	1 (2.9%)	8 (6.5%)
≥80	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	89 (100.0%)	34 (100.0%)	123 (100%)

MG: myasthenia gravis.

Table 2. Prevalence of myasthenia gravis (per 100,000 persons)

Year	Age (years)	Crude prevalence			Standardized prevalence*		
		Subtotal	Male	Female	Subtotal	Male	Female
2010	≤19	322	140	182	2.84	2.36	3.36
	20–39	1,196	444	752	7.98	5.76	10.34
	40–59	2,117	824	1,293	12.93	9.94	16.00
	60–69	744	310	434	17.64	15.35	19.75
	70–79	441	143	298	15.91	12.47	18.35
	≥80	87	24	63	8.43	8.02	8.60
	Total	4,907	1,885	3,022	9.67	7.42	11.93
2011	≤19	329	137	192	2.90	2.31	3.54
	20–39	1,281	494	787	8.55	6.41	10.83
	40–59	2,329	908	1,421	14.22	10.95	17.58
	60–69	847	347	500	20.09	17.18	22.76
	70–79	506	162	344	18.26	14.12	21.18
	≥80	118	36	82	11.43	12.02	11.19
	Total	5,410	2,084	3,326	10.66	8.20	13.13

*The overall standardized number per 100,000 persons was calculated using the standard population data for 2011 from the Korean Statistical Information Service in the Korea National Statistical Office.

in elderly subjects aged 60 to 69 years in our study. The high prevalence in the elderly might be related to the low mortality rate associated with MG and lengthening lifespans in general.[6] The increasing incidence with age in males is in accordance with the pattern found in most previous studies.[7-15] However, a bimodal distribution of the incidence in females, which is a frequently reported pattern,[8,9,11,14,15] was not observed in our population; instead there was a trend for the incidence to increase with age, which has also been found in other populations.[10,12,13] The high incidence of MG in the elderly of our population may be explained by the increasing incidence of late-onset MG.[11,16-20] It also may reflect improved awareness of the disease and a high index of suspicion in the elderly patients in our country. Childhood MG, mostly with purely ocular manifestation, was reported to be much more common in Chinese,[21,22] but this was not the case in our population, with the incidence being lowest in subjects younger than 20 years. Thymoma is the most wellknown comorbidity in MG, but its frequency of association has varied widely across studies.[23] The association rate in the present study (9.95%) was at the lower end of the previously reported range (10−30%), which might be attributable to differences in study populations and methodologies.[23]

Several methodological issues should be addressed regarding the NHI claims database utilized in this study. First, the validity of the MG diagnosis could be questioned because the claims data might contain miscoding errors. For this reason, we used information on both diagnosis and treatment rather than simply relying on the diagnostic code for case identification. However, the possibility of overestimation could remain. In clinical practice, medications for treating MG as well as diagnostic coding could be given to patients in order to check therapeutic response, but the diagnosis might turn out to not be MG. The incidence and prevalence rates would be lower if a criterion for the duration of MG medications had been applied for case identification. However, it should be a challenging task to determine a reasonable cutoff duration for such a criterion. Furthermore, the risk of underestimation would be increased if more strict criteria were applied, because patients with mild MG would be excluded. Second, not all patients with MG have access to a hospital, and so patients with mild symptoms might have been missed, thereby leading to the incidence and prevalence rates being underestimated. Third, although we set a washout period of 1 year to define incident cases, those patients who had relapsed after complete stable remission might have been counted erroneously as incident cases. Lastly, the incidence data obtained from the NHI claims database do not specify the age at onset, but rather the age at diagnosis. Despite these abovementioned limitations, the NHI claims database has merits of complete coverage of the entire population of the country. Other sources of data such as the nationwide MG registry would be valuable in complementing the NHI claims database, and also to elucidate the clinical characteristics of MG in Korea.

In summary, this is the first national population-based epidemiological study of MG in Korea that has utilized the NHI claims database. The incidence of MG was found to increase with age in both sexes, peaking in elderly subjects aged 60 to 69 years. We hope that this study will help raise the awareness of this rare disorder, and increase research into the diagnosis and effective treatment of MG.

Conflicts of Interest

The authors have no financial conflicts of interest.

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REFERENCES

1. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurol* 2009;8:475-490.
2. Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B. Diagnostic and clinical classification of autoimmune myasthenia gravis. *J Autoimmun* 2014;48-49:143-148.
3. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. *BMC Neurol* 2010;10:46.
4. McGrogan A, Sneddon S, de Vries CS. The incidence of myasthenia gravis: a systematic literature review. *Neuroepidemiology* 2010;34:171-183.
5. Lai CH, Tseng HF. Nationwide population-based epidemiological study of myasthenia gravis in taiwan. *Neuroepidemiology* 2010;35:66-71.
6. Phillips LH 2nd, Torner JC. Epidemiologic evidence for a changing natural history of myasthenia gravis. *Neurology* 1996;47:1233-1238.
7. Storm-Mathisen A. Epidemiology of myasthenia gravis in Norway. *Acta Neurol Scand* 1984;70:274-284.
8. Ferrari G, Lovaste MG. Epidemiology of myasthenia gravis in the province of Trento (northern Italy). *Neuroepidemiology* 1992;11:135-142.
9. Christensen PB, Jensen TS, Tsiropoulos I, Sørensen T, Kjaer M, Højer-Pedersen E, et al. Incidence and prevalence of myasthenia gravis in western Denmark: 1975 to 1989. *Neurology* 1993;43:1779-1783.
10. Somnier FE, Engel PJ. The occurrence of anti-titin antibodies and thymomas: a population survey of MG 1970-1999. *Neurology* 2002;59:92-98.
11. Vincent A, Clover L, Buckley C, Grimley Evans J, Rothwell PM; UK Myasthenia Gravis Survey. Evidence of underdiagnosis of myasthenia gravis in older people. *J Neurol Neurosurg Psychiatry* 2003;74:1105-1108.
12. Wirtz PW, Nijnuis MG, Sotodeh M, Willems LN, Brahim JJ, Putter H, et al. The epidemiology of myasthenia gravis, Lambert-Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland. *J Neurol* 2003;250:698-701.
13. Aragonès JM, Bolíbar I, Bonfill X, Bufill E, Mummany A, Alonso F, et al. Myasthenia gravis: a higher than expected incidence in the elderly. *Neurology* 2003;60:1024-1026.
14. Casetta I, Fallica E, Govoni V, Azzini C, Tola M, Granieri E. Inci-

dence of myasthenia gravis in the province of Ferrara: a community-based study. Neuroepidemiology 2004;23:281-284.
15. Lavrnic D, Basta I, Rakocevic-Stojanovic V, Stevic Z, Peric S, Nikolic A, et al. Epidemiological study of adult-onset myasthenia gravis in the area of Belgrade (Serbia) in the period 1979-2008. *Neuroepidemiology* 2013;40:190-194.
16. Casetta I, Groppo E, De Gennaro R, Cesnik E, Piccolo L, Volpato S, et al. Myasthenia gravis: a changing pattern of incidence. *J Neurol* 2010; 257:2015-2019.
17. Pallaver F, Riviera AP, Piffer S, Ricciardi R, Roni R, Orrico D, et al. Change in myasthenia gravis epidemiology in Trento, Italy, after twenty years. *Neuroepidemiology* 2011;36:282-287.
18. Pakzad Z, Aziz T, Oger J. Increasing incidence of myasthenia gravis among elderly in British Columbia, Canada. *Neurology* 2011;76:1526-1528.
19. Somnier FE. Increasing incidence of late-onset anti-AChR antibody-seropositive myasthenia gravis. *Neurology* 2005;65:928-930.
20. Matsui N, Nakane S, Nakagawa Y, Kondo K, Mitsui T, Matsumoto T, et al. Increasing incidence of elderly onset patients with myasthenia gravis in a local area of Japan. *J Neurol Neurosurg Psychiatry* 2009;80: 1168-1171.
21. Yu YL, Hawkins BR, Ip MS, Wong V, Woo E. Myasthenia gravis in Hong Kong Chinese. 1. Epidemiology and adult disease. *Acta Neurol* Scand 1992;86:113-119.
22. Zhang X, Yang M, Xu J, Zhang M, Lang B, Wang W, et al. Clinical and serological study of myasthenia gravis in HuBei Province, China. *J Neurol Neurosurg Psychiatry* 2007;78:386-390.
23. Mao ZF, Mo XA, Qin C, Lai YR, Hackett ML. Incidence of thymoma in myasthenia gravis: a systematic review. *J Clin Neurol* 2012;8:161-169.