Higher Risk of Myasthenia Gravis in Patients With Thyroid and Allergic Diseases

A National Population-Based Study

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Abstract: The aim of this study was to determine the risk of myasthenia gravis (MG) in patients with allergic or autoimmune thyroid disease in a large cohort representing 99% of the population in Taiwan.

Data from the Taiwan National Health Insurance Database were used to conduct retrospective analyses. The study comprised 1689 adult patients with MG who were 4-fold frequency matched to those without MG by sex, age, and assigned the same index year. Multivariate logistic regression models were used to calculate the odds ratios and 95% confidence intervals for the association between allergic or autoimmune thyroid disease and MG.

An increased subsequent risk of MG was observed in the patients with allergic conjunctivitis (AC), allergic rhinitis, Hashimoto thyroiditis, and Graves disease. The adjusted odds ratios (aORs) were 1.93 (1.71–2.18), 1.26 (1.09–1.45), 2.87 (1.18–6.97), and 3.97 (2.71–5.83), respectively. The aORs increased from 1.63 (1.43–1.85) in a patient with only 1 allergic or autoimmune thyroid disease to 2.09 (1.75–2.49) in a patient with 2 thyroid or allergic diseases to 2.82 (2.19–3.64) in a patient with ≥3 thyroid or allergic diseases. MG was associated with the cumulative effect of concurrent allergic and autoimmune thyroid disease with combined AC and Hashimoto thyroiditis representing the highest risk (aOR = 15.62 [2.88–87.71]).

This population-based case-control study demonstrates the association between allergic or autoimmune thyroid disease and the risk of MG. The highest risk of subsequent MG was associated with combined AC and Hashimoto thyroiditis.

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Abbreviations: AC = allergic conjunctivitis, AD = atopic dermatitis, AR = allergic rhinitis, CI = confidence interval, DM = diabetes mellitus, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, Ig = immunoglobulin, MG = myasthenia gravis, NHIRD = National Health Insurance Research Database, OR = odds ratio.

INTRODUCTION

Based on the presence of thyroid autoimmunity in children affected by allergic diseases, allergy and autoimmunity are 2 potential outcomes of dysregulated immunity.[1] Myasthenia gravis (MG) is an acquired autoimmune disease caused by autoantibodies against the nicotinic acetylcholine receptor on the postsynaptic membrane at the neuromuscular junction.[2] Thyroid autoimmunity, a well documented comorbidity among patients with myasthenia, was noted in 10% of the MG patients in Taiwan.[3] MG-associated allergic diseases have not been comprehensively established among hospital-based studies, except for allergic conjunctivitis (AC) in a single study.[4] A nationwide population study to investigate the onset of MG in children with preexisting allergic diseases found that children with allergic diseases were at an increased subsequent risk of MG, especially those children with AC and atopic dermatitis (AD).[5] However, this study focused only on pediatric patients, which excluded a possibly associated thyroid disorder and most generalized MG, which is uncommon among pediatric patients in Taiwan.[6] We used a large cohort representing 99% of the population in Taiwan to determine the risk of MG in adult patients with thyroid or allergic diseases.

MATERIALS AND METHODS

Data Source

The National Health Insurance Research Database (NHIRD) is a nationwide database containing claims records

from Taiwan's mandatory National Health Insurance program. The National Health Insurance program was initiated in 1995. By the end of 2007, 22.60 of the 22.96 million people residing in Taiwan were covered by this insurance program (http://w3.nhri.org.tw/nhird//date_01.html). The NHIRD contains a patient's sex, date of birth, dates of clinical visits, details of prescriptions, and diagnoses of diseases coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Medical reimbursement specialists and peer review should scrutinize all insurance claims. The diagnoses in this study were based on the ICD-9 codes that were judged and determined by related specialists and physicians according to the standard criteria. Therefore, the diagnoses and codes in this study should be correct and reliable. Every individual has a unique personal identification number. To protect privacy, data on patient identities are encrypted in the NHIRD. In this study, we used datasets of the Registry for Longitudinal Health Insurance Database and Catastrophic Illness Patient Database. All datasets can be interlinked through individual personal identification numbers. This study was approved by the institutional review board of China Medical University (CMU-REC-101-012).

Population

We constructed a population-based case-control study during the period from January 1, 2008, to December 31, 2011. We identified 1689 patients with newly diagnosed MG (ICD-9-code: 358.0) ≥20 years who were registered through the dataset of Catastrophic Illness Patient Database. The date of the application of a catastrophic illness certificate in the approved patient was the index date. For each patient with MG, 4 study participants without a history of MG were randomly selected from the registry of Longitudinal Health Insurance Database, frequency-matched by sex, age (every 5 years), and index year. Overall, the MG and control groups comprised 1689 and 6756 enrollees, respectively (Figure 1).

The risk factors included in this study were those that have been found to be associated with or possibly related to the development of MG. We recorded disease histories before the index date, including allergic diseases [AC (ICD-9-code: 372.05, 372.10, and 372.14), allergic rhinitis (AR) (ICD-9-code: 477), asthma (ICD-9-code: 493 and 434), AD (ICD-9-code: 691.8), urticaria (ICD-9-code: 708)], and autoimmune thyroid diseases [Hashimoto thyroiditis (ICD-9 code: 245.2) and Graves disease (ICD-9 code: 242.0)] (supplemental data, http://links.lww.com/MD/A280).

In addition to sex and age (in groups ages 20–34, 35–49, 50–64, and ≥65 years), comorbidities were also analysed. The pre-existing comorbidities include malignancies (ICD-9-code: 140-208), diabetes mellitus (DM, ICD-9-code: 250), cardiovascular diseases (ICD-9-code: 410-414), and chronic pulmonary disorders (ICD-9-code: 490-496).

Statistical Analysis

Differences in demographic factors between 2 study populations were compared using a *t*-test for continuous variables and a chi-squared test for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using a multiple logistic regression model and were used to estimate the association between allergic or autoimmune thyroid diseases and risk of MG. We also assessed the relation between MG and MG-associated diseases, including AC, AR, Hashimoto thyroiditis, and Graves disease. Finally, we estimated and compared the age-specific risk of MG between patients with and without diseases (allergic or autoimmune thyroid diseases). SAS version 9.3 (SAS Institute, Cary, NC) was used for data analyses; two-sided tests were performed, and $P < 0.05$ was considered statistically significant.

RESULTS

We selected 1689 patients with MG and a control group of 6756 members. The proportion of sex and age at entry distribution was similar in both groups. The mean age was 51.41 years (standard deviation, 16.16 years) in the MG group and 51.28 years (standard deviation, 16.29 years) in the control group (Table 1). Compared with the control group, the MG group tended to have AC (38.37% vs 22.56%), AR (24.57% vs 19.27%), asthma (10.24% vs 8.13%), urticaria (12.85% vs 10.81%), Hashimoto thyroiditis (0.62% vs 0.18%), Graves disease (3.43% vs 0.87), malignancies (5.74% vs 2.92%), DM (15.87% vs 1.79%), cardiovascular diseases (18.12% vs 14.30%), and chronic pulmonary disorders (28.95% vs 25.83%). In multiple logistic regression models, patients with AC, AR, Hashimoto thyroiditis, Graves disease, malignancies, or DM were associated with an increased risk of MG compared with patients with no counterpart disease [adjusted odds ratio (aOR) = 1.93, 95% CI = 1.71–2.18 for AC; 1.26, 1.09–1.45 for AR; 2.87, 1.18–6.97 for Hashimoto thyroiditis; and 3.97, 2.71–5.83 for Graves disease]. Among the comorbidities, patients that presented a previous history of malignancies and DM exhibited the risk of developing MG (aOR = 1.36, 95% CI = 1.03–1.81 for malignancies; and 9.51, 7.54–11.98 for DM).
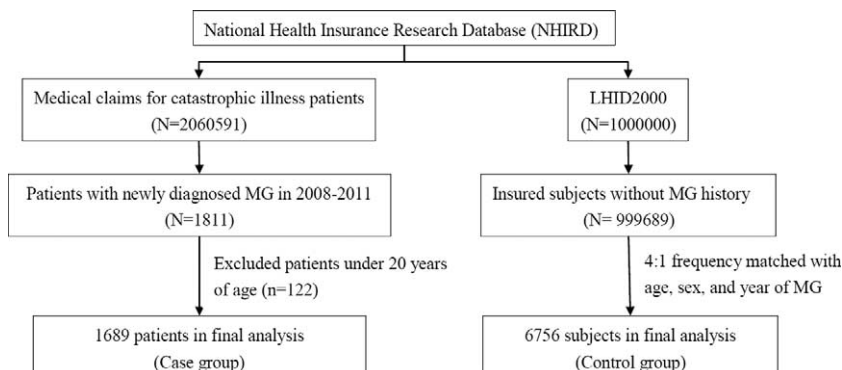

FIGURE 1. Flowchart showing selection of study participants. LHID = Longitudinal Health Insurance Database, MG = myasthenia gravis.

TABLE 1. Demographic Characteristics and Results of Multiple Logistic Regression Models Showing the Odds Ratio and 95% Confidence Interval in Myasthenia Gravis and Control Groups

| | **Myasthenia Gravis** | | | | | | |
| | No N = 6756 | | Yes N = 1689 | | | | |
	n	**%**	**n**	**%**	***P* Value**	**Crude OR (95% CI)**	**Adjusted[†] OR (95% CI)**
Sex					0.99		
Women	3832	56.72	958	56.72			
Men	2924	43.28	731	43.28			
Age					0.99		
20–34	1252	18.53	313	18.53			
35–49	1928	28.54	482	28.54			
50–64	2108	31.20	527	31.20			
≥65	1468	21.73	367	21.73			
Mean (SD)	51.28	(16.29)	51.41	(16.16)	0.78		
Allergic disease							
AC					<0.001		
No	5232	77.44	1041	61.63		1.00	1.00
Yes	1524	22.56	648	38.37		2.14 (1.91–2.39)***	1.93 (1.71–2.18)***
AR					<0.001		
No	5454	80.73	1274	75.43		1.00	1.00
Yes	1302	19.27	415	24.57		1.37 (1.20–1.55)***	1.26 (1.09–1.45)**
Asthma					0.01		
No	6207	91.87	1516	89.76		1.00	1.00
Yes	549	8.13	173	10.24		1.29 (1.08–1.55)**	1.07 (0.85–1.35)
AD					0.95		
No	6566	97.19	1641	97.16		1.00	1.00
Yes	190	2.81	48	2.84		1.01 (0.73–1.39)	0.85 (0.61–1.20)
Urticaria					0.02		
No	6026	89.19	1472	87.15		1.00	1.00
Yes	730	10.81	217	12.85		1.22 (1.04–1.43)*	1.06 (0.89–1.26)
Autoimmune thyroid disease							
Hashimoto thyroiditis					0.003		
No	6744	99.82	1678	99.35		1.00	1.00
Yes	12	0.18	11	0.62		3.68 (1.62–8.36)**	2.87 (1.18–6.97)*
Graves disease					<0.001		
No	6697	99.13	1631	96.57		1.00	1.00
Yes	59	0.87	58	3.43		4.04 (2.80–5.82)***	3.97 (2.71–5.83)***
Comorbidity							
Malignancies					<0.001		
No	6559	97.08	1592	94.26		1.00	1.00
Yes	197	2.92	97	5.74		2.03 (1.58–2.60)***	1.36 (1.03–1.81)*
DM					<0.001		
No	6635	98.21	1421	84.13		1.00	1.00
Yes	121	1.79	268	15.87		10.34 (8.28–12.92)***	9.51 (7.54–11.98)***
CVD					<0.001		
No	5790	85.70	1383	81.88		1.00	1.00
Yes	966	14.30	306	18.12		1.33 (1.15–1.53)***	0.92 (0.79–1.09)
Chronic pulmonary disorders					0.01		
No	5011	74.17	1200	71.05		1.00	1.00
Yes	1745	25.83	489	28.95		1.17 (1.04–1.32)**	0.86 (0.74–1.00)

AC = allergic conjunctivitis, AD = atopic dermatitis, AR = allergic rhinitis, CI = confidence interval, CVD = cardiovascular disease, DM = diabetes mellitus, OR = odds ratio, SD = standard deviation.

[†] Adjusted for AC, AR, asthma, AD, urticaria, Hashimoto thyroiditis, Graves disease, malignancies, DM, CVD, and chronic pulmonary disorders in multiple logistic regression model. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Compared with patients without any AC, AR, Hashimoto thyroiditis, or Graves disease, patients with only AC (aOR = 2.12, 95% CI = 1.83–2.64), only AR (1.31, 1.09– 1.57), only Graves disease (4.74, 2.82–7.97), AC and AR (2.42, 1.97–2.96), AC and Hashimoto thyroiditis (15.62, 2.88–87.71), AC and Graves disease (9.29, 3.50–24.69), AR

TABLE 2. Joint Effect Between Allergic Diseases and Autoimmune Thyroid Disease in Association With MG in Study Population

AC	AR	Hashimoto Thyroiditis	Graves Disease	Non-MG	MG	OR[†] (95% CI)
No	No	No	No	4335	803	1.00
Yes	No	No	No	1071	421	2.12 (1.83–2.46)[***]
No	Yes	No	No	844	200	1.31 (1.09–1.57)[**]
No	No	Yes	No	6	2	2.30 (0.476–11.45)
No	No	No	Yes	32	29	4.74 (2.82–7.97)[***]
Yes	Yes	No	No	437	198	2.42 (1.97–2.96)[***]
Yes	No	Yes	No	2	5	15.62 (2.88–87.71)[**]
Yes	No	No	Yes	7	12	9.29 (3.50–24.69)[***]
No	Yes	Yes	No	1	2	12.26 (1.11–135.57)[*]
No	Yes	No	Yes	12	5	2.19 (0.74–6.52)
No	No	Yes	Yes	1	0	–
Yes	Yes	Yes	No	1	0	–
Yes	Yes	No	Yes	6	10	10.44 (3.76–28.98)[***]
Yes	No	Yes	Yes	0	2	–
No	Yes	Yes	Yes	1	0	–
Yes	Yes	Yes	Yes	0	0	–

AC = allergic conjunctivitis, AR = allergic rhinitis, CI = confidence interval, MG = myasthenia gravis, OR = odds ratio.
[†] Model adjusted for sex, age, malignancies, DM, CVD, and chronic pulmonary disorders. [*]P < 0.05, [**]P < 0.01, [***]P < 0.001.

and Hashimoto thyroiditis (12.26, 1.11–135.57), and AC, AR, and Graves disease (10.44, 3.76–28.98) were significantly associated with an increased risk of MG, after adjustment for sex, age, and comorbidities (Table 2).

Overall, the likelihood of MG increased as the number of diseases increased from 1.63 (95% CI = 1.43–1.85) for patients with only 1 disease to 2.09 (1.75–2.49) for those with 2 diseases to 2.82 (2.19–3.64) for those with ≥3 diseases (P for trend < 0.001) (Table 3). Additionally, we found that the association between the number of diseases and MG was similar in the age groups of 20 to 34, 35 to 49, 50 to 64, and ≥65 years.

DISCUSSION

This nationwide population-based case-control study shows that MG is associated with autoimmune thyroid disease and allergic disease in 1689 adult Taiwanese patients with MG. In this study, thyroid disease was most strongly associated with the subsequent development of MG. Autoimmune thyroid disease has been found to be associated with common allergic diseases including urticaria[7,8] and AC[9] and higher levels of

immunoglobulin (Ig) E[10] and autoantibodies.[1] The mechanisms of these associations are unknown.[10] The association between urticaria and thyroid disease might be due to a shared susceptibility to autoimmune or chronic inflammatory processes.

AC was first reported to be associated with MG in a hospital-based report in 2004.[4] This study reported a significant association of AC with subgroups of MG, including ocular, seronegative, and patients without thymoma. A nationwide population study on the same issue confirmed that AC was associated with a higher subsequent risk of MG in pediatric patients.[5] However, the study focused on pediatric patients exclusively, and thus did not cover most generalized MG, which is uncommon among pediatric patients in Taiwan.[11] This study extended the target population to adults with MG using the same methodology and found an increase of the ORs for an association with AC in MG from 1.60 (1.20–2.15) in the pediatric group to 1.93 (1.71–2.28) in the adult counterpart. Although this study could not explore the ocular or generalized phenotypes of MG in the NHIRD data, the ocular form predominated in the pediatric group (about 75%) and accounted for 50% of cases in the adult group based on clinical observation.[11]

TABLE 3. Association Between the Number of Diseases and Myasthenia Gravis among Age Group

Age (years)	All OR[†] (95% CI)	20–34 OR[‡] (95% CI)	35–49 OR[‡] (95% CI)	50–64 OR[‡] (95% CI)	≥65 OR[‡] (95% CI)
Number of diseases[*]					
0	1.00	1.00	1.00	1.00	1.00
1	1.63 (1.43–1.85)[***]	1.67 (1.26–2.23)[***]	1.73 (1.36–2.20)[***]	1.74 (1.38–2.21)[***]	1.29 (0.95–1.75)
2	2.09 (1.75–2.49)[***]	2.21 (1.48–3.30)[***]	2.84 (2.05–3.92)[***]	1.78 (1.28–2.48)[**]	1.69 (1.17–2.44)[**]
>3	2.82 (2.19–3.64)[***]	3.08 (1.68–5.66)[***]	4.82 (2.81–8.27)[***]	1.92 (1.19–3.08)[**]	2.45 (1.52–3.96)[***]
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001

CI = confidence interval, OR = odds ratio.
[*] Diseases including allergic diseases and autoimmune thyroid disease.
[†] Model adjusted for sex, age, malignancies, DM, CVD, and chronic pulmonary disorders.
[‡] Model adjusted for sex, malignancies, DM, CVD, and chronic pulmonary disorders. [**]P < 0.01, [***]P < 0.001.

Therefore, AC also seemed to be significantly associated with the general type of MG in this study.

Association with AD was found in pediatric patients with MG (ORs 1.88 with CI 1.19–2.99), but not in the adult counterpart (ORs 0.85 with CI 0.61 to 1.20). By contrast, the ORs representing the association between AR and MG become statistically significant from 1.25 (0.93–1.69) in the pediatric group to 1.26 (1.09–1.45) in the adult counterpart. Interestingly, urticaria, which is commonly associated with thyroid disease, was not determined to be associated with MG in this study.

The ORs increased from 1.63 (1.43–1.85) in patients with only 1 thyroid or allergic disease to 2.09 (1.75–2.49) in patients with ≥2 thyroid or allergic diseases. MG was determined to be associated with the cumulative effect of the concurrent thyroid and allergic diseases, with a highest risk of MG among those with combined Hashimoto thyroiditis and AC (ORs 15.62 with CI 2.88–87.71). The aforementioned findings support that allergy and autoimmunity can be 2 potential outcomes of dysregulated immunity.[1]

IgE is the central player in the allergic response.[12] The low-affinity IgE receptor (FceRII or CD23) has long been proposed to be a natural regulator of IgE synthesis.[13] CD23 was strongly and diffusely expressed in the whole area of germinal centers of MG thymi.[14] Higher levels of IgE were found in the patients with autoimmune thyroid disease.[1] The above findings support the IgE might play a major role in the link between allergy and autoimmunity.

There are some limitations in this study. Firstly, we do not provide diseases' severity because some data (including laboratory, pathological, and imaging information) are not available in the database. Secondly, because this study is not a randomized clinical trial, it could lose some confounding factors for adjustments. Thirdly, the database and diagnose are majorly for billing and do not validate for research uses. Fourthly, because of the law to protect personal privacy, it is impossible to do individual study participants' medical record review. Finally, the patients with MG were associated with a previous history of malignancies and DM noted in this study, which were documented and discussed in detail in previous studies.[15,16]

This population-based retrospective study demonstrates the association between thyroid or allergic diseases and the risk of MG. The highest risk of subsequent MG was associated with combined thyroid disease and AC.

REFERENCES

1. Pedullà M, Miraglia Del Giudice M, Fierro V, et al. Atopy as a risk factor for thyroid autoimmunity in children. *J Biol Regul Homeost Agents.* 2012;26:S9–S14.

2. Vincent A, Waters P, Leite MI, et al. Antibodies identified by cell-based assays in myasthenia gravis and associated diseases. *Ann N Y Acad Sci.* 2012;1274:92–98.

3. Chen YL, Yeh JH, Chiu HC. Clinical features of myasthenia gravis patients with autoimmune thyroid disease in Taiwan. *Acta Neurol Scand.* 2013;127:170–174.

4. Murai H, Osoegawa M, Ochi H, et al. High frequency of allergic conjunctivitis in myasthenia gravis without thymoma. *J Neurol Sci.* 2004;225:27–31.

5. Tsai JD, Lin CL, Shen TC, et al. Increased subsequent risk of myasthenia gravis in children with allergic diseases. *J Neuroimmunol.* 2014;276:202–206.

6. Chiu HC, Vincent A, Newsom-Davis J, et al. Myasthenia gravis: population differences in disease expression and acetylcholine receptor antibody titers between Chinese and Caucasians. *Neurology.* 1987;37:1854–1857.

7. Confino-Cohen R, Chodick G, Shalev V, et al. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol.* 2012;129:1307–1313.

8. Gangemi S, Saitta S, Lombardo G, et al. Serum thyroid autoantibodies in patients with idiopathic either acute or chronic urticaria. *J Endocrinol Invest.* 2009;32:107–110.

9. Tesse R, Spadavecchia L, Fanelli P, et al. New insights into childhood Vernal keratoconjunctivitis-associated factors. *Pediatr Allergy Immunol.* 2012;23:682–685.

10. Sato A, Takemura Y, Yamada T, et al. A possible role of immunoglobulin E in patients with hyperthyroid Graves' disease. *J Clin Endocrinol Metab.* 1999;84:3602–3605.

11. Chen WH, Chiu HC, Hseih RP. Association of HLA-Bw46DR9 combination with juvenile myasthenia gravis in Chinese. *J Neurol Neurosurg Psychiatry.* 1993;56:382–385.

12. Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol.* 2008;8:205–217.

13. Conrad DH, Ford JW, Sturgill JL, et al. CD23: an overlooked regulator of allergic disease. *Curr Allergy Asthma Rep.* 2007;7:331–337.

14. Murai H, Hara H, Hatae T, et al. Expression of CD23 in the germinal center of thymus from myasthenia gravis patients. *J Neuroimmunol.* 1997;76:61–69.

15. Yeh JH, Lin CC, Chen YK, et al. Excessive risk of cancer and in particular lymphoid malignancy in myasthenia gravis patients: A population-based cohort study. *Neuromuscul Disord.* 2014;24:245–249.

16. Yeh JH, Chen HJ, Lin CC, et al. Risk of diabetes mellitus among patients with myasthenia gravis. *Acta Neurol Scand.* 2015. [Epub ahead of print].