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.

INTRODUCTION

Based on the presence of thyroid autoimmunity in children affected by allergic diseases, allergy and autoimmunity are 2 potential outcomes of dysregulated immunity. Myasthenia gravis (MG) is an acquired autoimmune disease caused by autoantibodies against the nicotinic acetylcholine receptor on the postsynaptic membrane at the neuromuscular junction. Thyroid autoimmunity, a well-documented comorbidity among patients with myasthenia, was noted in 10% of the MG patients in Taiwan. MG-associated allergic diseases have not been comprehensively established among hospital-based studies, except for allergic conjunctivitis (AC) in a single study. 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). 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. 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: 372.05, 372.10, and 372.14), Hashimoto thyroiditis (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).

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, 20.28 years) in the MG group and 51.28 years (standard deviation, 20.27 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).

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).
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 1. Demographic Characteristics and Results of Multiple Logistic Regression Models Showing the Odds Ratio and 95% Confidence Interval in Myasthenia Gravis and Control Groups |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | No N = 6756     | Yes N = 1689    | P Value         | Crude OR (95% CI) | Adjusted OR (95% CI) |
| Sex                             |                 |                 |                 |                 |                 |
| Women                           | 3832            | 958             | 0.99            | 1.00            | 1.00            |
| Men                             | 2924            | 731             |                 |                 |                 |
| Age                             |                 |                 | 0.99            |                 |                 |
| 20–34                           | 1252            | 313             |                 |                 |                 |
| 35–49                           | 1928            | 482             |                 |                 |                 |
| 50–64                           | 2108            | 527             |                 |                 |                 |
| ≥65                             | 1468            | 367             |                 |                 |                 |
| Mean (SD)                       | 51.28 (16.29)   | 51.41 (16.16)   | 0.78            |                 |                 |
| Allergic disease                |                 |                 |                 |                 |                 |
| AC                              |                 |                 | 0.001           |                 |                 |
| No                              | 5232            | 1041            | 1.00            | 1.00            | 1.00            |
| Yes                             | 1524            | 648             | 2.14 (1.91–2.39)** | 1.93 (1.71–2.18)*** |
| AR                              |                 |                 | 0.001           |                 |                 |
| No                              | 5454            | 1274            | 1.00            | 1.00            | 1.00            |
| Yes                             | 1302            | 415             | 1.37 (1.20–1.55)*** | 1.26 (1.09–1.45)** |
| Asthma                          |                 |                 | 0.01            |                 |                 |
| No                              | 6207            | 1516            | 1.00            | 1.00            | 1.00            |
| Yes                             | 549             | 173             | 1.29 (1.08–1.55)** | 1.07 (0.85–1.35) |
| AD                              |                 |                 | 0.95            |                 |                 |
| No                              | 6566            | 1641            | 1.00            | 1.00            | 1.00            |
| Yes                             | 190             | 48              | 1.01 (0.73–1.39) | 0.85 (0.61–1.20) |
| Urticaria                       |                 |                 | 0.02            |                 |                 |
| No                              | 6026            | 1472            | 1.00            | 1.00            | 1.00            |
| Yes                             | 730             | 217             | 1.22 (1.04–1.43)** | 1.06 (0.89–1.26) |
| Autoimmune thyroid disease      |                 |                 |                 |                 |                 |
| Hashimoto thyroiditis           |                 |                 | 0.003           |                 |                 |
| No                              | 6744            | 1678            | 1.00            | 1.00            | 1.00            |
| Yes                             | 12              | 11              | 3.68 (1.62–8.36)** | 2.87 (1.18–6.97)* |
| Graves disease                  |                 |                 | 0.001           |                 |                 |
| No                              | 6697            | 1631            | 1.00            | 1.00            | 1.00            |
| Yes                             | 59              | 58              | 4.04 (2.80–5.82)*** | 3.97 (2.71–5.83)*** |
| Comorbidity                     |                 |                 |                 |                 |                 |
| Malignancies                    |                 |                 | 0.001           |                 |                 |
| No                              | 6559            | 1592            | 1.00            | 1.00            | 1.00            |
| Yes                             | 197             | 97              | 2.03 (1.58–2.60)*** | 1.36 (1.03–1.81)* |
| DM                              |                 |                 | 0.001           |                 |                 |
| No                              | 6635            | 1421            | 1.00            | 1.00            | 1.00            |
| Yes                             | 121             | 268             | 10.34 (8.28–12.92)*** | 9.51 (7.54–11.98)*** |
| CVD                             |                 |                 | 0.001           |                 |                 |
| No                              | 5790            | 1383            | 1.00            | 1.00            | 1.00            |
| Yes                             | 96              | 1430            | 1.33 (1.15–1.53)*** | 0.92 (0.79–1.09) |
| Chronic pulmonary disorders     |                 |                 | 0.01            |                 |                 |
| No                              | 5011            | 1200            | 1.00            | 1.00            | 1.00            |
| Yes                             | 1745            | 489             | 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.

1 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.
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 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) |
| Yes | No  | Yes                    | No             | 437   | 198 | 2.42 (1.97–2.96)*** |
| Yes | No  | No                     | Yes            | 2     | 5   | 15.62 (2.88–87.71)*** |
| Yes | No  | No                     | Yes            | 7     | 12  | 9.29 (3.50–24.69)*** |
| Yes | Yes | No                     | Yes            | 1     | 2   | 12.26 (1.11–135.57)*** |
| Yes | No  | Yes                    | Yes            | 12    | 5   | 2.19 (0.74–6.52)  |
| Yes | 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   | –           |
| Yes | Yes | Yes                    | Yes            | 1     | 0   | –           |
| Yes | Yes | Yes                    | Yes            | 0     | 0   | –           |

**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)) |
|-------------|------------------|---------------------|---------------------|---------------------|------------------|
| 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)*** |

\(\text{OR} = \text{odds ratio}\)

\(\text{CI} = \text{confidence interval}\)

\(\text{Model adjusted for sex, age, malignancies, DM, CVD, and chronic pulmonary disorders.}^{10,11}\)

\(\text{Model adjusted for sex, age, malignancies, DM, CVD, and chronic pulmonary disorders.}^{11}\)
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 became 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 (FcεRII 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. Second, 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 particular lymphoid malignancy in myasthenia gravis patients: A population-based cohort study.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.

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