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THE CONCOMITANT ASSOCIATION OF THYROID DISORDERS AND MYASTHENIA GRAVIS

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Abstract

Background: Some of the thyroid disorders (TD) and Myasthenia gravis (MG) are autoimmune related disease. The purpose of the study to evaluate the relationship of MG with all morphological and functional thyroid disorders.
Methods: We constructed a population-based cohort study during the period from January 2000–December 2002 by using reimbursement data from the Bureau National Health Insurance (NHI) system in Taiwan. Patients with TD and MG were identified by referring to the ICD-9-CM codes. (ICD-10-CM as reference) .The association of TD with MG occurred only in the same person within the study period. The Q value was used to measure the strength of disease–disease associations.
Results: We obtained 520628 TD and 7965 MG records for analysis. Diffuse toxic goiter had highest association rate, followed by nontoxic nodular goiter, simple goiter, chronic lymphocytic thyroiditis, thyroid cancer, and toxic nodular goiter. Female and older patients had a higher rate than their male and younger counterparts, respectively. Functional abnormalities revealed higher incidence of thyrotoxicosis and hypothyroidism in both sexes. We also found the strongest association in men with chronic thyroiditis, diffuse toxic goiter, thyrotoxicosis, acquired hypothyroidism, thyroid cancer, and simple goiter. While an intermediate association was observed in female with diffuse toxic goiter, in a male with toxic and nontoxic nodular/multinodular goiters, in female with thyrotoxicosis, thyroid cancer and acquired hypothyroidism.
Conclusion: This population based cohort study showed potential association of all types of TD with MG, and observed a higher association rate in female autoimmune TD whereas males showed a higher strength of association.

Keywords

• Autoimmune thyroid disease • chronic lymphocytic thyroiditis • Graves' disease • hypothyroidism • myasthenia gravis

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Introduction

Myasthenia gravis (MG) is a rare antibody-mediated autoimmune disease of the neuromuscular junctions which affects the neuromuscular junction, blocking synaptic neurotransmissions, and clinically symptomatic muscle weakness [1]. According to McGoogan et al. [2] MG 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. A systemic review mentioned that incidence and prevalence rates of MG were estimated to be 5.4 per million person years and 77.7 per million persons, respectively [3]. Although there were remarkable variations among different studies, and the incidence varying from 1.7 to 21.3 per million person years, and the prevalence varying from 15 to 179 per million persons [3-6].

Autoimmune thyroid diseases (ATDs) are a heterogeneous group of disorders; the three major phenotypes such as patients with hyperthyroidism due to Graves' disease (GD), patients with hypothyroidism due to Hashimoto's thyroiditis (HT); and euthyroid patients with positive anti-thyroid autoantibodies. In 1908, Rennie first time reported the association of MG with Graves' disease, an autoimmune thyroid disease (AITD) that are responsible for ocular myopathy and exophthalmos [7]. On the other hand, McEachern study suggested that there is no considerable evidence for the relationship between two diseases [8]. To find out the association between thyroid disease with MG; Sahay et al. found eight patients with MG of which 5 were of hypothyroidism and 3 of hyperthyroidism patients [9]. However, a study confirmed the coexistence of autoimmune diseases with MG and it was noticeable that AITD seemed to be more frequent compared with other autoimmune conditions. They mentioned AITD occurred more often in female and AChRAb serology-positive MG patients [10] . In the same vein Bollaert et al. [11] noted that the frequency of coexistence of autoimmune disease in patients with GD and Hashimot's disease was reported to be 9.67% and 14.3%, respectively.

Recently, literature has emerged that offers contradictory findings about the association of thyroid diseases with myasthenia gravis.

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But this paper attempt to show the association of myasthenia gravis with thyroid disorders through a large population cohort study. Moreover, this study also evaluated the co-occurrence rate of these two diseases and the strength of association.

Methods

In this study, we used data from the Taiwan's National Health Insurance (NHI) database, comprising 782 million out-patient claims records including 10.8 million males and 10.6 million females from January 2000 to December 2002. We identified all patients with MG and thyroid disorders by referring to the International Classification of Disease, Clinical Modification, Ninth Revision [ICD-10-CM] codes (MG: code 358 / G70.01). We only consider MG patients associated with thyroid disorders only if patients occurred within the 3-year study period. Moreover, all of the records were stratified by sex and ages at a 20-year interval. Further, we divided thyroid disorders into 1. Morphological diseases: simple goiter (code 240, 240.0 / E04.9; E04.0) and non-toxic nodular/multinodular goiter (code 241, 241.0, 241.1, 241.9 / E04.1 / E04.2) 2. Coexisting functional and morphological diseases: diffuse toxic goiter (code 242.0, 242.00, 242.01 / E05.00 E05.01) and toxic nodular/multinodular goiter (code 242.1, 242.10, 242.11, 242.2, 242.20, 242.21, 242.3, 242.30, 242.31 / E05.10 E05.11 E05.20 E05.21) 3. Chronic lymphocytic thyroiditis (code 245.2 / E06.3) (4) thyroid cancer (code 193 / C73). Also, thyroid dysfunctions were collected separately according to code for further analysis: thyrotoxicosis (code 242.9, 242.90, 242.91 / E05.90 E05.91) and acquired hypothyroidism (code 244, 244.0, 244.1, 244.2, 244.3, 244.8, and 244.9 / E03.2 E03.8 E03.9 E89.0). In our study, each sub-set of thyroid disease used separately to quantify the strength of disease-disease association (co-occurrence). To measure the association between two diseases, we also calculate Q value. In this analysis we categorized Q value into three different groups such as strong (Q>10), Intermediate (Q=5-10) and weak (Q= 1-4.99). A Q value has been used to measure strength of the associations between diseases

Results

We collected 7965 MG (4803 female and 3162 males) and 520628 cases of thyroid disorders (421512 female and 99116 male; female to male ratio= 4.3:1.0) for final analysis. Table 1 shows the association rate of MG and subset of thyroid disorders. It is apparent from Table 1 that toxic diffuse goiter had highest rate of 4.37%(348/7965female 4.96%, male 3.48%),that is followed by non-toxic nodular goiter 1.46% (116/7965; female 1.98%, male 0.66%), simple goiter1.19% (95/7965;female 1.46%, male 0.79%), chronic lymphocytic thyroiditis 0.60% (48/7965; female 0.67%, male 0.51%), thyroid cancer 0.34% (27/7965; female 0.42%, male 0.22%) and toxic nodular goiter 0.25% (20/7965; female 0.33%, male 0.13%). It is observed that every subset female patient's rate had higher compared with male patients. From the data in table 1, it can also seen that in the case of functional disorders-thyrotoxicosis had 7.51% (598/7965;female 8.91%, male 5.38%) and hypothyroidism had 2.79% (222/7965; female 3.52%, male 1.68%) association rate. Interestingly, there were also differences in the ratio of male and female patients. The most striking result to emerge from the data is that 60-79 year-old patients observed higher association rate of 2.4% (168/7003) and then 20-39,40-59 and younger patients saw 0.75% (1627/215786),

Table 1. Association rates of 520628 cases of thyroid disorders (421512 female and 99116 male cases) and 7965 cases of myasthenia gravis (4803 female and 3162 male cases); the strength of association values (Q values) are listed.

Thyroid disorder	Gender	No.	Co- occurrence No.	Association Rate (%)	Q value
Simple goiter	Female	34488	70	1.46	4.51
	Male	7649	25	0.79	11.2
Non-toxic nodular/multinodular goiter	Female	72695	95	1.98	2.90
	Male	11644	21	0.66	6.19
Diffuse toxic goiter	Female	61899	238	4.96	8.54
	Male	16165	110	3.48	23.4
Toxicnodular/multinodular goiter	Female	7224	16	0.33	4.92
	Male	1798	4	0.13	7.63
Chronic lymphocytic thyroiditis	Female	15401	32	0.67	4.62
	Male	1830	16	0.51	30.0
Thyroid cancer	Female	7483	20	0.42	5.94
	Male	1940	7	0.22	12.4
Thyrotoxicosis	Female	156197	428	8.91	6.09
	Male	43809	170	5.38	13.3
Acquired Hypothyroidism	Female	66125	169	3.52	5.68
	Male	14281	53	1.68	12.7

0.3% (571/189793), and 0.26% (105/40669) respectively. A Q value of greater than 1 indicated a significant association between two diseases. Table 2 shows the strength of association betweem two diseases. It is noted that in male patients chronic lymphocytic thyroiditis Q value (30) had highest, and other conditions of this group are diffuse toxic goiter (Q=23.4), thyrotoxicosis (Q= 13.3), acquired hypothyroidism (Q=12.7), thyroid cancer (Q=12.4), and simple goiter (Q= 12.2). On the other hand, Toxic nodular/multinodular goiter and non-toxic nodular/multinodular goiter in male patients Q value had 7.6 and 6.2,; as well as diffuse toxic goiter, thyrotoxicosis, thyroid cancer and acquired hypothyroidism of the female patients observed Q value 8.5, 6.1,5.9 and 5.7 respectively. Simillarly only female patients with toxic nodular/multinodular goiter (Q=4.9), chronic lymphocytic thyroiditis (Q=4.6), simple goiter (Q=4.5), and non-toxic nodular/ multinodular goiter (Q=2.9) included in weak association group.

Discussion

The present study was designed to determine Myasthenia gravis (MG) correlate with the different thyroid disorder. In this large population-based study, we found myasthenia moderately associated with thyroid disorders. It is interesting to note that all subcategories of thyroids had an association with myasthenia gravis, and its rate had 0.25-4.37 percent. Thyroid disease in patients must be categorized into functional disorder, morphological disorder and or combined disorder. For example, Graves' disease is diffuse toxic goiter. Toxic means hyper function and Diffuse means morphological enlargement. Therefore, we tried to classify accordingly shown in the study. For example, simple goiter is enlargement of thyroid but within normal thyroid function range. While Fang et al. [12] recently published an article that showed higher rate of association than our study result. In addition, previous studies also support our result and mentioned the significance relationship between thyroid disorders and myasthenia gravis [9, 13-15]. The association of MG and AITD has been identified in autoimmune polyendocrine syndrome type II (APS-II), which comprises Addison's disease, AITD (GD and hypothyroidism caused by chronic lymphocytic thyroiditis), MG, type 1 diabetes, and others [16]. In 2009, Martignago et al. [17] mentioned this major study; The AChR-Ab seropositive MG is associated with thymoma or thymic hyperplasia and thyroid disease. So, it is clear to understand that autoimmunity always plays a critical role in the association of MG and thyroid disorders.

Our study reveals that AI-related thyroid disorders including diffuse toxic goiter, chronic lymphocytic thyroiditis had the higher number of female patients. This result is accord with previous studies indicating that diffuse toxic goiter is greater in female [18-20]. It is somewhat surprising that male patients with diffuse toxic goiter and chronic lymphocytic thyroiditis had a strong association with myasthenia gravis. On the contrary, the female patient with these two thyroid diseases showed an intermediate and weak association. Although we observed that female had a higher number in case of all thyroid diseases, but male patients with thyroid conditions showed strong association with myasthenia gravis. In fact, the prevalence rate of thyroid disease is most common in females. However, if male suffer with thyroid disease, we assume that it is usually more serious and not easy to treat. Mostly thyroid disease are more common in females than male including morphological and functional thyroid disorders. If a man has thyroid disease such as Graves' disease, the symptoms and signs are more serious in male than female based on clinical experience .Also the prognosis is worse in males compared to females [21, 22].

In our study, we tried to figure out the reason for higher strength of association in male when compare with female. Q value of chronic lymphocytic thyroiditis had 30 which is much higher than any other thyroid diseases. The result of this study also showed that male patients with diffuse toxic goiter, thyrotoxicosis, acquired hypothyroidism, thyroid cancer, and simple goiter had a strong association with myasthenia gravis. These results seem to be consistency with other results which found this thyroid disease is related to myasthenia gravis [23-25]. It is, therefore, likely that such connections exist between thyroid disorders and myasthenia gravis. Mao ZF et al. [10] showed that autoimmune thyroid disease is more coexisted with myasthenia gravis. Similarly, Tamer et al. [26] has confirmed this view and mentioned, autoimmune thyroid disease (16%) are associated with myasthenia gravis. Simple goiter, alternatively termed diffuse non-toxic goiter, mostly affects female and is caused by the inability of the thyroid to produce a sufficient amount of hormones for body requirement, resulting in the enlargement of the thyroid (goiter) and eventually euthyroid. The considered etiologies were mainly due to inadequate iodine intake or people living in an endemic iodine deficiency area (endemic goiter), the ingestion of goitrogenic food, drugs or chemicals, smoking, stress, and heredity. Non-toxic nodular/multinodular goiter is functionally euthyroid and benign in the nodules histopathology. They are the most common morphological thyroid disorders that consist of the pure cyst, colloid nodules, adenoma, granulomatous disease or focal thyroiditis.

Table 2. Strength of the association values of thyroid disorders and MG.

Q value	Thyroid disorders (M=male, F=female) (Q value)
>10 (strong)	chronic lymphocytic thyroiditis of M (30.0) diffuse toxic goiter of M (23.4) thyrotoxicosis of M (13.3) acquired hypothyroidism of M (12.7) thyroid cancer of M (12.4) simple goiter of M (11.2)
5-10 (intermediate)	diffuse toxic goiter of F (8.5) toxic nodular/multinodular goiter of M (7.6) non-toxic nodular/multinodular goiter of M (6.2) thyrotoxicosis of F (6.1) thyroid cancer of F (5.9) acquired hypothyroidism of F (5.7)
1-4.9 (weak)	toxic nodular/multinodular goiter of F (4.9) chronic lymphocytic thyroiditis of F (4.6) simple goiter of F (4.5) non-toxic nodular/multinodular goiter of F (2.9)

Conclusions

This study has identified, Myasthenia is positively associated with all thyroid disorders. We observed a higher association rate of autoimmune thyroid disease in females but in older males had a higher strength of association. The result of this study also indicates that the co-existence of autoimmunity play significant roles in the pathogenesis. Further studies need to be carried out to validate the association between two diseases.

Conflict of interest

None

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