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Research Article

Thyroid Eye Disease not Associated with the Risk for Uveitis: A 13-Year Nationwide Population-Based Cohort Study in Taiwan

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ABSTRACT

Purpose: To investigate whether patients with thyroid eye disease (TED) are at increased risk of uveitis.

Methods: Data was collected from the Taiwan National Health Insurance system and included patients newly diagnosed with TED from 2000 to 2012. The endpoint of interest was a diagnosis of uveitis.

Results: 444 patients with TED yielding1,776 matched comparisons revealed that patients with TED were found to have no significantly higher risk for developing uveitis. When comparison of TED and non-TED group was stratified by gender, and age, the association of TED and uveitis was also not significant.

Conclusion: TED is characterized as an extraocular inflammatory disease and uveitis is an intraocular inflammation. In the largest study of TED in uveitis to date, our findings indicate that TED are not associated with (the risk for) uveitis. Different autoimmune mechanisms could explain the unique condition. The present data warrant further exploration that different auto antibodies may be involved in the immunopathology of TED and uveitis.

Keywords: Age; Gender; Ocular inflammation; Thyroid eye disease; Uveitis

INTRODUCTION

Thyroid eye disease (TED) is a complex orbital inflammatory disease causing inflammation in the extraocular muscles, eyelids, lacrimal glands, and surrounding connective and adipose tissue, which could be sight-threatening and disfiguring [1]. TED is also known as Graves' ophthalmopathy, named after Robert J. Graves [2]. Most patients with TED have biochemical evidence of hyperthyroidism. TED may also occur in patients who have hypothyroidism or euthyroidism [3,4].

Uveitis is characterized by intraocular inflammation that might result from various systemic diseases. Patients of uveitis comorbidant with thyroid disease have been reported since 1915 [5-7] and the association of thyroid disease with uveitis has recently received more attention [8]. As the uvea is rich in blood vessels, immune system activation in one organ can result in hematogenous spread of inflammatory cells and cytokines into the eyes. Common pathophysiological mechanisms may be responsible for immune dysregulation in both thyroid disease and uveitis in certain individuals [9].

Immune dysregulation can lead to extraocular TED or intraocular uveitis. Studies have focused on the association between thyroid disease and uveitis [8,10-15]. However, no study has so far investigated TED and uveitis. Therefore, we conducted a nationwide cohort study by analyzing the claims data from the Taiwan National Health Insurance Research Database (NHIRD) during a follow-up period from 2000 to 2012 with ICD-9 codes to investigate whether there is an association between uveitis and TED in the Taiwanese population. We furthermore review some

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of the common biomarkers involved in TED and ocular inflammation.

MATERIALS AND METHODS

Datasource

Taiwan's Bureau of National Health Insurance set up the NHIRD based on the single-payer National Health Insurance program. This program was inaugurated on March 1, 1995 and provides coverage to over 99% of all residents in Taiwan. We obtained a Longitudinal Health Insurance Database (LHID), a part of the NHIRD, which includes one million insurants randomly selected from the 2000 Registry for Beneficiaries. All medical claims included both inpatient and outpatient visits and medical treatment for each insurant from the start of 1996 to the end of 2012 that were contained in the LHID. To comply with the Personal Information Protection Act, the identification of each insurant in the LHID was re-coded. This study was also approved by the Institutional Review Board of China Medical University Hospital, Taiwan.

Study subject

We collected patients who were newly diagnosed with TED [the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) 376.21] from 2000 to 2012. Patients with at least three medical visits for thyroid disease were defined as new cases and the first visit date for thyroid disease was defined as the index date. Those with a diagnosis of thyroid disease prior to 2000 were excluded. The endpoint was a new diagnosis of uveitis (ICD-9-CM 360.00, 360.11, 360.12, 362.18, 363.00, 363.01, 363.03, 363.05, 363.08, 363.1x, 363.20, 363.21, 363.4x, 364.00, 364.02, 364.04, 364.1x, 364.3x). The end date of follow-up was December 31, 2013.

Those with a history of uveitis (ICD-9-CM 360.00, 360.11, 360.12, 362.18, 363.00, 363.01, 363.03, 363.05-363.08, 363.1x, 363.20, 363.21, 363.4x, 364.00-364.02, 364.04 and 364.1x-364.3x) prior to 2000were excluded. Patients with viral hepatitis (ICD-9-CM code 070), cirrhosis (ICD-9-CM code 571, A347), interferon treatment, human immunodeficiency virus (HIV) infection (ICD-9-CM code 042-044, 795.8, V08),tuberculosis (ICD-9-CM code 010-012), syphilis (ICD-9-CM code 091.0, 095.4, 095.8), systemic malignancy (ICD-9-CM code 140-208), autoimmune diseases (ICD-9-CM code 135, 279.49, 283, 443, 571.42, 696, 710, 714, 715) were also excluded. Subjects without medical visit for eye diseases were also excluded.

Controls were randomly selected from people without histories of thyroid disease, viral hepatitis, interferon treatment, HIV infection, tuberculosis, syphilis, or uveitis history. They were frequency-matched by age group (<20, 20-39, 40-64 and 65+years old), gender, ophthalmologic outpatient department (OPD) before the index date, and index-year at a ratio 4:1. We include only patients with at least one medical visit for ophthalmology before enrolling into the study.

End-point, demographic characteristics and TED

The clinical endpoint was a diagnosis of uveitis. Patients with at least two medical visits for uveitis, which were separated for at least 7 days, were defined as the end point to ensure the validity. All study subjects were followed from the index date until the endpoint. Those without endpoint development were followed until the date of withdrawal from the program or the end of 2012, whichever occurred first. In this study, the demographic characteristics included age group (<20, 20-39, 40-64 and 65+years old), and gender before the index date.

Statistical analysis

A chi-square test was used for the difference of demographic characteristics between the TED cohort and comparison cohort from 2000 to 2012. Continuous variable, such as age and follow-up time was showed as mean and standard deviation (SD) and analyzed using Wilcoxon rank sum test. A multivariable Cox model was adjusted for continuous age, and gender for ophthalmology before the index date. Univariate and multivariable cox proportional regression analysis measuring hazard ratio (HR) and 95% confidenceinterval (CI) to assess the association between TED and the risk of developing uveitis. The incidence density rate of uveitis (per-1,000 years) was calculated for TED cohort and comparison cohort. The risk of uveitis in TED cohort comprised with comparison cohort was stratified by age group and gender, using Cox proportional hazard regression. All analyses were performed using SAS statistical software, version 9.4 for Windows (SAS Institute, Cary, NC). The level of significance was set at $p<0.05$ at two-tailed test. Wilcoxon rank-sum test was used for verification of average age and follow-up time.

RESULTS

In this retrospective cohort study, we selected 444 patients with TED and 1,776 age, gender, and index-year matched comparisons. Among patients with TED, there were more women than men (73% vs. 27%) and the mean age was 39.1 ± 13.7 (mean ± standard deviation) years old (Table 1). The mean follow-up periods were 6.85 ± 3.87 and 6.83 ± 3.83 years in the TED and comparison cohorts, respectively; there was no significant difference of mean follow-up years between the two cohorts.

During the follow-up period, patients with TED were found to have no significantly higher incidence of uveitis when compared to the control cohort from Cox regression analysis (Table 2), as the hazard ratios in both cohorts were not significantly different. After age and gender were adjusted for, the risk was still not significantly higher in the TED group.

Table 1: Baseline characteristics of patients.

	Thyroid eye disease (n=444)		Comparison group (n=1776)		*p value
	n	%	n	%	
Gender					>0.99
Female	324	73	1296	73	
Male	120	27	480	27	
Age, years					>0.99
<20	28	6.31	112	6.31	
20-39	228	51.4	912	51.3	
40-64	166	37.4	664	37.4	
≥ 65	22	4.95	88	4.95	
Mean (SD)†	39.1 (13.7)		39.0 (13.8)		0.92
Follow-up time, year†	6.85 (3.87)		6.83 (3.83)		0.88

* p value using chi-square for the comparisons between with and without thyroid eye disease.

†Average age and follow-up time using Wilcoxon rank-sum test for verification.

Table 2: Cox model measured hazard ratios and 95% confidence interval of thyroid eye disease associated with gender and age.

Variable	Uveitis			Adjusted	
				Crude HR	HR
	Event	PY	IR	(95%CI)	(95%CI)
Thyroid eye disease					
No	34	12132	2.8	1(reference)	1(reference)
Yes	9	3045	2.95	1.05	1.06
				(0.50-2.19)	(0.51-2.21)
Gender					
Female	35	11009	3.17	1(reference)	1(reference)
Male	8	4168	1.91	0.6	0.48
				(0.28-1.30)	(0.22-1.06)
Age, years					
<20	1	1102	0.9	1(reference)	1(reference)
20-39	14	8027	1.74	1.92	2.04
				(0.25-14.6)	(0.26-15.5)
40-64	24	5447	4.4	4.9	5.24
				(0.66-36.3)	(0.70-38.8)
≥65	4	601	6.65	7.64	9.8
				(0.85-68.5)	(1.07-89.2)*

PY: Person-Years; IR: Incidence Rate: per 1000 Person-Years; HR: Hazard Ratio; CI: Confidence Interval; HR adjusted for gender and age.*p<0.05, ** p<0.01, ***p<0.001

DISCUSSION

The changes associated with TED can be classified into two subtypes: congestive ophthalmopathy, in which inflammatory changes in the periorbital tissues predominate, and ocular myopathy, in which eye muscle damage is the main feature [16]. The timing of TED presentation may differ between patients. There are patients in whom thyroid dysfunction precedes TED development; and there are patients in whom thyroid dysfunction and TED present at the same time, and there are patients in whom TED is the first clinical manifestation, preceding thyroid dysfunction [3,4].

Antibodies against the 67-kDa flavoprotein (Fp) subunit of the mitochondrial enzyme succinate dehydrogenase (SDH); G2s, a 141 amino acid fragment of the winged-helix transcription factor; calsequestrin, a 63-kDa calcium-binding protein; and collagen XIII, a connective tissue protein that is closely linked to the congestive ophthalmopathy subtype of TED have been found as the markers of TED [16-19].

G2s and antibodies against the Fp subunit of SDH, a thyroid and eye muscle shared protein, are good markers of eye muscle cell damage in patients with ocular myopathy. Another antigen associated with ophthalmopathy is the flavine adenine nucleotide (FAD) cofactor of several mitochondrial enzymes, including SDH [20].

Uveitis is a remitting-relapsing autoimmune disease characterized by breakdown of the blood-retinal barrier, infiltration by inflammatory cells, and tissue destruction. The development, progression, and recurrence of uveitis are frequently driven by a group of participatory autoantigens [21]. The human major histocompatibility complex (MHC) class I HLA-B27 is associated with an estimated 50% of acute anterior uveitis (AAU) cases and is one of the most identifiable causes for AAU. Heterogeneous nuclear ribonucleoprotein H3 (Hnrph3) had also been characterized for AAU relevance and independently verified by Western blot [22].

Intraocular anti-peptide neurofilament medium (NF-M) IgM and cellular retinaldehyde binding protein (CRALBP) auto antibodies have been found to occur with high prevalence in the vitreous of patients with spontaneous equine recurrent uveitis [21,23]. The presence of cellular CRALBP auto antibodies in about half of uveitis patients supports CRALBP as a possible autoantigen in human autoimmune uveitis [24]. Tubulin beta chain, vimentin, ATP synthase subunit beta, actin, and L-lactate dehydrogenase B chain, heat shock cognate 71 kDa protein and keratin, were also found to be bound by juvenile idiopathic arthritis-associated uveitis patient sera [25].

TSHR autoantibody is the hallmark of TED and relates to the immunological derangement. A postulated mechanism is that TSHR-reactive T cells and B cells induce activation of thyroid eye disease. Under activation, the B cells secrete TSHR antibodies and induce T cells to secrete pro-inflammatory cytokines [26]. Both B cells and T cells play a key role in mediating the chronic inflammatory changes of the autoimmune diseases seen in the thyroid gland, in the retro-orbit, and in the skin. Carbonic anhydrase 1 (CA1) and alcohol dehydrogenase 1B (ADH1B) of orbital fat tissue in thyroid orbitopathy have been noted in our previous studies [27]. These two autoantigens have also been found significantly in other autoimmune diseases, such as autoimmune pancreatitis, Sjogren's syndrome, and rheumatoid arthritis (RA) [28]. However, these TED-associated auto antibodies are not related to uveitis.

CONCLUSION

Although the serum auto antibodies that bind to ocular antigens discussed above are not disease-specific, a significant diversity of auto antibodies against a broad range of antigens has been detected in TED and uveitis patients. This nationwide cohort study also suggests that a history of TED is not significantly associated with uveitis. Different autoimmune mechanisms could explain the unique pathogenesis of both conditions. The present data warrant further exploration that different auto antibodies may be involved in the immunopathology of TED and uveitis.

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