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Association Between Thyroid Disease and Uveitis
Results From the Pacific Ocular Inflammation Study

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IMPORTANCE Common pathophysiological mechanisms may be responsible for immune dysregulation in both thyroid disease and uveitis. Studies investigating a possible association are limited.

OBJECTIVE To determine the association between thyroid disease and uveitis.

DESIGN, SETTING, AND PARTICIPANTS A retrospective, population-based case-control study was conducted from January 1, 2006, to December 31, 2007, among 217 061 members of the Kaiser Permanente Hawaii health system during the study period. A clinical diagnosis of uveitis was determined through a query of the electronic medical record followed by individual medical record review for confirmation by a uveitis specialist. Thyroid disease was determined based on *International Classification of Diseases, Ninth Revision*, coding. Two control groups were chosen at a 4:1 ratio for comparison with patients with uveitis. A logistic regression analysis was performed with uveitis as the main outcome variable and thyroid disease as the main predictor variable, while adjusting for age, sex, race, smoking status, and history of autoimmune disease. Data analysis was conducted between 2014 and 2016.

MAIN OUTCOMES AND MEASURES A diagnosis of thyroid disease among patients with uveitis and respective controls.

RESULTS Of the 224 patients with uveitis (127 women and 97 men; mean [SD] age, 54.1 [17.8] years) identified during the study period, 29 (12.9%) had a diagnosis of thyroid disease, compared with 62 of 896 patients (6.9%) in the control group ($P = .01$) and 78 of 896 patients (8.7%) in the ophthalmology clinic control group ($P = .06$). Using the general Kaiser Permanente Hawaii population control group, patients who had thyroid disease had a 1.7-fold (95% CI, 1.03-2.80; $P = .04$) higher odds of having uveitis compared with patients who did not have thyroid disease when controlling for age, sex, race, smoking status, and autoimmune disease. A similar association was found using the ophthalmology clinic control group (odds ratio, 1.8; 95% CI, 1.1-2.9; $P = .02$) while adjusting for these factors.

CONCLUSIONS AND RELEVANCE These findings suggest that a history of thyroid disease has a weak to moderate association with uveitis. Similar autoimmune mechanisms could explain the pathogenesis of both conditions. If future studies corroborate these findings, they may have further clinical implications in the laboratory workup of uveitis.

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Uveitis is a diverse set of conditions characterized by intraocular inflammation and is responsible for an estimated 10% of cases of legal blindness in the United States.[1-4] Patients with uveitis often have other autoimmune diseases, raising the question of whether widespread immune dysregulation is the common mechanism behind this association. Although case reports, case series, in vitro studies, and animal studies have suggested a potential association between uveitis and thyroid disease,[5-13] to our knowledge, a larger clinical study investigating this association has not been performed.

In particular, prior studies have highlighted possible associations between human T-lymphotropic virus type 1 uveitis and Graves disease,[8,14-16] tubulointerstitial nephritis and uveitis and hyperthyroidism,[10,17,18] juvenile idiopathic arthritis-associated uveitis and Graves disease,[13] and Vogt-Koyanagi-Harada syndrome and hypothyroidism.[19,20] The oldest case series suggesting an association between uveitis and thyroid disease dates back to 1915, when thyroid extract was reported to effectively treat uveitis.[5] Although they raise important questions, these studies are limited by their relatively small sample sizes and lack of control groups. The aim of this population-based case-control study was to investigate whether there is an association between uveitis and thyroid disease using data from the Pacific Ocular Inflammation Study.[21]

Key Points

Question Is there an association between thyroid disease and uveitis?

Findings In a population-based case-control study of a Hawaiian managed care organization, patients with thyroid disease had a 1.7-fold higher odds of having uveitis compared with patients who did not have thyroid disease, when controlling for age, sex, race, smoking status, and autoimmune disease. A similar association was found using an ophthalmology clinic control group.

Meaning The weak to moderate association between thyroid disease and uveitis in this cohort might be explained by similar pathophysiological mechanisms of immune dysregulation.

Table 1. *ICD-9* Diagnosis Codes Used to Identify Thyroid Disease

Diagnosis Codes	Description
240.0-241.9	Goiter
242.0-242.9	Thyrotoxicosis
243	Congenital hypothyroidism
244.0-244.9	Hypothyroidism
245.0-245.9	Thyroiditis
246.0-246.9	Other diseases of the thyroid

Abbreviation: *ICD-9*, *International Classification of Diseases, Ninth Revision*.

Methods

International Classification of Diseases, Ninth Revision (*ICD-9*) diagnosis codes that could be associated with a diagnosis of uveitis were used to broadly search all patient encounters between January 1, 2006, and December 31, 2007, in the Kaiser Permanente electronic medical records. The study objectives and design for this study were determined in 2011 along with the other objectives for the Pacific Ocular Inflammation Study, and this specific analysis was completed between 2014 and 2016. A comprehensive list of the diagnosis codes used in the Pacific Ocular Inflammation Study has been described previously.[21] A uveitis and cornea fellowship-trained ophthalmologist (N.R.A.) subsequently verified all uveitis diagnoses based on results of documented clinical examinations. All incident and prevalent cases of uveitis during the study period were included in this study. Institutional review board and ethics committee approval was obtained at the University of California San Francisco and Kaiser Permanente Hawaii for all aspects of this study involving retrospective review of patient data. Both the University of California San Francisco and Kaiser Permanente Hawaii institutional review boards allowed for a waiver of patient consent. All work was compliant with the Health Insurance Portability and Accountability Act.

In this retrospective case-control study, patients with uveitis were compared with 2 control groups. Each control group was randomly selected at a 4:1 ratio to patients with uveitis. A general Kaiser Permanente control group was composed of a random sample of the general Kaiser Permanente population who had at least 1 visit during the study period, while an ophthalmology control group was composed of a random sample of adult Kaiser Permanente Hawaii members who had at least 1 visit to the ophthalmology clinic during the study period.

A diagnosis of thyroid disease was based on an electronic search for *ICD-9* codes related to thyroid disease (**Table 1**) during the study period. Use of thyroid medication was determined by a search for relevant Generic Product Identification codes in the Kaiser Permanente Hawaii pharmacy database. Demographic data, comorbid diagnoses, and smoking status were also collected electronically. For patients with uveitis, the smoking status closest to the diagnosis date was used for incident cases and the smoking status closest to the first related visit during the study period was used for prevalent cases. For patients in a control group, the smoking status closest to the midpoint of the study period, January 1, 2007, was used. In addition, infectious and noninfectious cases of uveitis were noted. Infectious cases were those in patients who had an associated diagnosis of herpes simplex virus or herpes zoster virus, histoplasmosis, toxoplasmosis, human immunodeficiency virus, Bartonella, tuberculosis, syphilis, cytomegalovirus retinitis, or Lyme disease documented electronically or during individual medical record review.

Data analysis was conducted between 2014 and 2016. Clinical and demographic characteristics were compared using the Fisher exact test for continuous variables or a 2-sample *t* test for categorical variables. A logistic regression analysis was conducted with uveitis as the main outcome variable and thyroid disease as the main predictor variable,

Table 2. Demographic Data for Patients With Uveitis and Controls

Characteristic	No./Total No. (%)		P Value	Ophthalmology Controls, No./Total No. (%)	P Value
	Patients With Uveitis	General Controls			
Female sex	127/224 (56.7)	511/896 (57.0)	.94[a]	497/896 (55.5)	.76[a]
Age, mean (SD), y	54.1 (17.8)	51.6 (18.6)	.06[b]	62.6 (17.7)	<.001[b]
Race					
Alaskan/ Native American	5/185 (2.7)	15/732 (2.0)	.03[a]	8/742 (1.1)	.11[a]
Asian	70/185 (37.8)	271/732 (37.0)		347/742 (46.8)	
African American	4/185 (2.2)	4/732 (0.5)		7/742 (0.9)	
Pacific Islander	37/185 (20.0)	217/732 (29.6)		135/742 (18.2)	
White	69/185 (37.3)	225/732 (30.7)		245/742 (33.0)	

[a] Obtained by Fisher exact test.

[b] Obtained by 2-sample mean comparison test.

Table 3. Clinical Characteristics of Patients With Uveitis and Controls

Characteristic	No. (%)		P Value[a]	Ophthalmology Controls, No. (%) (n = 896)	P Value[a]
	Patients With Uveitis (n = 224)	General Controls (n = 896)			
Thyroid disease	29 (12.9)	62 (6.9)	.01	78 (8.7)	.06
Thyroid medications	23 (10.3)	57 (6.4)	.06	64 (7.1)	.13
Current smoker	36 (16.1)	129 (14.4)	.53	83 (9.3)	.01
Chronic conditions					
Lipid metabolism disorders	100 (44.6)	381 (42.5)	.60	474 (52.9)	.03
Type 1 and 2 diabetes	38 (17.0)	176 (19.6)	.39	205 (22.9)	.06
Hypertension	88 (39.3)	367 (41.0)	.70	461 (51.5)	.001
Autoimmune diseases[b]	27 (12.1)	25 (2.8)	<.001	42 (4.7)	<.001

[a] Obtained by Fisher exact test.

[b] Includes reactive arthritis, sarcoidosis, Behcet disease, multiple sclerosis, polyarteritis nodosa, granulomatosis with polyangiitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease, juvenile idiopathic arthritis, and systemic lupus erythematosus.

while adjusting for age, sex, race, smoking status, and history of autoimmune disease. $P < .05$ was considered statistically significant. All analyses were conducted with STATA, version 12.0 (StataCorp).

Results

Of the total Kaiser Permanente membership (N = 217 061 at the midpoint of the study period), 224 cases of uveitis were confirmed during the study period. Detailed clinical characteristics for these cases are presented separately.[21] Briefly, most of these patients (162 [72.3%]) had anterior uveitis. The disease course was acute in 96 patients (42.9%), recurrent in 59 (26.3%), and chronic in 57 (25.4%). Forty-seven patients (21.0%) had an associated infectious disease. Demographic characteristics of patients with uveitis and control groups are shown in **Table 2**.

Twenty-nine patients with uveitis (12.9%) had a diagnosis of thyroid disease during the study period, compared with 62 of 896 individuals (6.9%) in the general population control ($P = .01$) and 78 of 896 individuals (8.7%) in the ophthalmology clinic control ($P = .06$) (**Table 3**). Compared with the general population control group, a similar proportion of patients with uveitis had lipid metabolism disorders (100 [44.6%] vs 381 [42.5%]), type 1 and 2 diabetes (38 [17.0%] vs 176 [19.6%]), and hypertension (88 [39.3%] vs 367 [41.0%]). A significantly higher percentage of patients in the ophthalmology clinic control group had lipid metabolism disorders (474 [52.9%]) and hypertension (461 [51.5%]) compared with the patients with uveitis (Table 3); however, this difference was not significant after adjusting for age. Compared with both control groups, patients with uveitis had a higher proportion of autoimmune diseases (27 [12.1%]) (Table 3).

In a multivariate logistic regression controlling for age, sex, race, smoking status, and autoimmune disease, patients with thyroid disease had a 1.7-fold higher odds of having uveitis compared with the general population control group (95% CI, 1.03-2.80; $P = .04$) (**Table 4**). Similarly, patients with thyroid disease had a 1.8-fold higher odds of having uveitis compared with the ophthalmology clinic control group when adjusting for these factors (95% CI, 1.1-2.9; $P = .02$).

Additional sensitivity analyses were performed to evaluate this association for subgroups of patients with uveitis. Using only noninfectious cases of uveitis and controlling for age, sex, smoking status, and autoimmune disease, patients with thyroid disease had a 1.7-fold higher odds of having uveitis (95% CI, 0.97-2.9; $P = .06$). A similar significant association was found using the ophthalmology clinic control group and controlling for the same demographic and clinical characteristics (odds ratio, 1.8; 95% CI, 1.1-3.1; $P = .03$).

Table 4. Logistic Regression Model for Uveitis Diagnosis

Characteristic	Cases vs General Controls		Cases vs Ophthalmology Controls	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Thyroid disease	1.7 (1.03-2.80)	.04	1.8 (1.1-2.9)	.02
Current smoker	1.2 (0.8-1.9)	.33	1.7 (1.1-2.6)	.02
Age (by decade)	1.0 (0.95-1.10)	.42	0.8 (0.7-0.8)	<.001
Female sex	0.9 (0.7-1.3)	.79	1.1 (0.8-1.4)	.73
Race (reference: white)				
Alaskan/Native American	1.2 (0.4-3.4)	.78	1.4 (0.4-4.5)	.59
Asian	0.9 (0.6-1.3)	.60	0.8 (0.5-1.1)	.17
African American	2.6 (0.6-11.4)	.21	1.1 (0.3-4.1)	.86
Pacific Islander	0.6 (0.4-0.9)	.02	0.8 (0.5-1.3)	.36
Unknown	0.9 (0.5-1.4)	.54	0.7 (0.4-1.1)	.09
Autoimmune disease	4.4 (2.4-7.8)	<.001	3.0 (1.7-5.1)	<.001

Abbreviation: OR, odds ratio.

Discussion

Although prior case reports, as well as in vitro and animal studies, have suggested an association between thyroid disease and uveitis,[5-13] to our knowledge, a large, population-based case-control study investigating such an association has not been performed. In our study, patients with a history of thyroid disease had a weak to moderate association with uveitis using both a general Kaiser Permanente population control group and an ophthalmology clinic control group. In addition, this association persisted when considering only noninfectious cases of uveitis.

Autoimmunity is a biologically plausible mechanism that may explain the association between uveitis and thyroid disease. Autoimmune thyroid disease has been associated with several other autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.[22-25] Similarly, the link between thyroid disease and uveitis may be explained by an underlying predisposition to immune dysregulation in certain individuals.

Other shared pathophysiological mechanisms between the 2 disease entities may further explain the association observed in this study. Specifically, 1 animal study using a rat model of endotoxin-induced acute anterior uveitis found increased signs of oxidative stress in the anterior segment of rats with both endotoxin-induced acute anterior uveitis and thyroid dysfunction, either hypothyroid or hyperthyroid, as compared with euthyroid mice with uveitis.[12] In addition, studies suggest that both experimental autoimmune uveitis and autoimmune thyroiditis are T-cell-dependent disease processes, particularly implicating T helper 1 and T helper 17 cells.[26,27]

Limitations

There are a few limitations of this study to acknowledge. In some cases, *ICD-9* codes may not capture sufficient detail. For example, thyroid disease was identified based on the codes listed in Table 1, which did not include codes for thyroid cancer. The most common code was unspecified hypothyroidism (21 of 29 patients [72%] with uveitis, 52 of 62 individuals [84%] in the general control group, and 60 of 78 individuals [77%] in the ophthalmology control group), followed by codes for Hashimoto thyroiditis and Graves disease. Thus, specifics regarding autoimmune thyroid disease or thyroid eye disease cannot be ascertained on the basis of *ICD-9* coding; however, patients with these diagnoses would have been included in our study based on the more general *ICD-9* codes used. Since common autoimmune mechanisms between uveitis and thyroid disease likely explain the association described, identification of patients with autoimmune thyroid disease would be helpful to perform further sensitivity analyses to ascertain the association between uveitis and autoimmune thyroid disease specifically. These analyses would further corroborate the hypothesis that autoimmunity is the common link between the 2 disease processes. Also, it is possible that cases of thyroid disease were missed owing to miscoding. However, it is unlikely that there would be differential miscoding of thyroid disease between patients with uveitis and members of the control groups.

In addition, it is possible that confounding factors could have contributed to the association found in this study. However, several known confounders were adjusted for in the statistical analyses. Prior studies have shown that tobacco use may be associated with both thyroid disease, particularly with orbital involvement, and uveitis, suggesting smoking could be a possible confounder.[28-31] Similarly, multiple autoimmune diseases have been connected to both uveitis and thyroid disease.[22-25] Autoimmune disease and smoking status were controlled for in the primary regression models and the results remained significant, suggesting an independent association between thyroid disease and uveitis. In this study, we included all confirmed cases of uveitis, including infectious, during the study period. It is possible that infectious uveitis could have a different underlying mechanism than noninfectious cases. However, a sensitivity analysis using only noninfectious cases demonstrated an association with the same effect size.

Although this study has some limitations, there are also several strengths including its large size and population-

based, case-control design. Although uveitis studies performed in tertiary care referral centers often have limited generalizability owing to referral bias, the population-based design of this study helps to broaden its applicability. The incidence of thyroid dysfunction in our general population control was 6.9%, which is similar to prior population-based estimates[32] of approximately 6%. Furthermore, the cases of uveitis included in this study were each reviewed by a single uveitis specialist to adjudicate the diagnosis. Since 95% of Kaiser Permanente Hawaii patients had the Kaiser Permanente health plan as their only insurance plan, the Kaiser Permanente Hawaii electronic medical record provides a comprehensive health profile for almost all its members. Although the association in any case-control study is subject to the effect of confounders, it is notable that the association in this study persisted despite controlling for multiple confounders.

Conclusions

This case-control study supports a weak to moderate association between uveitis and thyroid disease, which has been suggested anecdotally for a century. When controlling for multiple relevant demographic and clinical characteristics, patients with thyroid disease were nearly twice as likely to have uveitis as individuals in the control groups. These results suggest that thyroid disease has an important association with ocular inflammation and raises questions regarding whether they share common pathophysiological mechanisms. If these results are further corroborated by future studies, this finding may have implications for clinical care, particularly in the laboratory evaluation of patients with uveitis who have signs and symptoms of thyroid dysfunction.

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Acquisition, analysis, or interpretation of data: All authors.
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Invited Commentary

Autoimmune Thyroid Disease and Uveitis

Sunir J. Garg, MD

Although most ophthalmologists are familiar with Graves disease, some may be less familiar with the role that immune regulation plays in thyroid disease. Often associated with hyperthyroidism, Graves disease occurs because of antibodies binding to and activating the thyroid-stimulating hormone receptor. The most common cause of hypothyroidism is Hashimoto thyroiditis, which is also the most common autoimmune disease. It is characterized by autoantibodies to thyroid antigens such as thyroperoxidase and thyroglobulin. Together, Hashimoto thyroiditis and Graves disease constitute autoimmune thyroid disease (AITD),[1] which occurs more commonly in women than in men. Both genetic and environmental factors affect the development of AITD. Genetic polymorphisms for several human leucocyte antigens, various proteins including cytokines, thyroid-stimulating hormone receptor, and cytotoxic T lymphocyte–associated factor 4 play a role.[2] Environmental exposure to toxins may lead to the development of AITD, but even this possibility is not fully understood. For example, while smoking exacerbates Graves disease, multiple studies have suggested that it reduces the risk of developing autoantibodies and hypothyroidism.

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Because AITD affects approximately 5% of the population, it becomes less surprising that it may be associated with other autoimmune diseases. Several studies during the past 20 years have found an association between AITD and other autoimmune conditions such as type 1 diabetes, celiac disease, vitiligo, alopecia, scleroderma, and Sjögren syndrome.[3] However, thyroid disease does not affect the eye in the way that other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus do. This fact makes it challenging to determine the effect these types of studies might have on what to look for on examination, what tests to order, and how to treat our patients.

In this issue of *JAMA Ophthalmology*, Borkar et al[4] studied patients who belonged to a large health network in Hawaii. The authors found a nearly 2-fold higher incidence of uveitis in patients who had thyroid disease compared with patients who had no evidence of thyroid disease. An association between thyroid disease and uveitis has been described before; tubulointerstitial nephritis and uveitis syndrome has been associated with hyperthyroidism.[5] However, prior to the study by Borkar et al,[4] there had been no large cross-sectional or case-controlled studies that found an association between uveitis and AITD.

This article also ties into other recent developments. Studies on environmental triggers have identified low levels of both selenium and vitamin D in patients with AITD, and deficiency of these vitamins appears to influence both the development and severity of the disease.[6] Vitamin D deficiency also occurs in patients with other autoimmune diseases such as Behcet disease, rheumatoid arthritis, and multiple sclerosis. Interestingly, recent work has shown that lower levels of vitamin D were associated with noninfectious anterior uveitis.[7] A potential common mechanism may be the importance of vitamin D to Th1 and Th17 cell development.

The study by Borkar et al[4] is important for hypothesis generation, and will help guide future research projects. However, it is not designed to change how we manage our patients with uveitis. At this time, ordering tests to evaluate patients with uveitis for AITD is not likely to be clinically useful or cost-effective. Similarly, the presence of AITD should not influence treatment, particularly systemic immunosuppression, for patients with uveitis. From a clinician's perspective, knowing that an association exists between uveitis and other conditions such as AITD may help to provide a greater understanding as to why a patient develops uveitis. Patients often want to know the reason they developed ocular inflammatory disease and, unless we find an association with a specific disease such as sarcoidosis or the HLA-B27–associated diseases, many times we tell the patients that "we don't know why." Although this fact remains true to some degree, we can at least counsel our patients that we are making progress in understanding the complex relationships between our organs, the immune system, and environmental influences.