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### Authors

Lin, Tiffany Y  
Li, Ning  
Yeh, Michael W  
et al.

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Original research

## Prognostic indicators for the development of strabismus among patients with graves' ophthalmopathy

Tiffany Y. Lin<sup>a</sup>, Ning Li<sup>b</sup>, Michael W. Yeh<sup>c</sup>, Angela M. Leung<sup>d,e,\*</sup>, Daniel B. Rootman<sup>f,g</sup><sup>a</sup>UCLA David Geffen School of Medicine, Los Angeles, CA 90024, USA<sup>b</sup>Department of Biomathematics, UCLA David Geffen School of Medicine, Los Angeles, CA 90024, USA<sup>c</sup>Section of Endocrine Surgery, Department of Surgery, UCLA David Geffen School of Medicine, Los Angeles, CA 90024, USA<sup>d</sup>Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, UCLA David Geffen School of Medicine, Los Angeles, CA 90024, USA<sup>e</sup>Division of Endocrinology, VA Greater Los Angeles Healthcare System, Los Angeles, CA 90024, USA<sup>f</sup>Jules Stein Eye Institute, Division of Orbital and Ophthalmic Plastic Surgery, UCLA David Geffen School of Medicine, Los Angeles, CA 90024, USA<sup>g</sup>Doheny Eye Center, Division of Orbital and Ophthalmic Plastic Surgery, UCLA David Geffen School of Medicine, Los Angeles, CA 90024, USA

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## ABSTRACT

**Objective:** Thyroid eye disease (TED), an autoimmune inflammatory process involving the orbital tissues around the eye, is the most common extra-thyroidal manifestation of Graves' disease (GD). Due to changes in the patient's appearance, TED is a socially and visually disabling condition with significant impacts on quality of life. The aim of this study is to assess predictors of strabismus, a severe manifestation of TED.

**Design:** Single-institution retrospective case-control study. Cases of Graves' ophthalmopathy patients with strabismus were matched 1:1 to controls of Graves' ophthalmopathy patients without strabismus by age and sex.

**Patients:** Patients  $\geq 18$  years old with severe Graves' ophthalmopathy who received their medical care at UCLA with strabismus between 2012 and 2015.

**Measurements:** Eligibility criteria for cases was a diagnosis of Graves' ophthalmopathy with a subsequent diagnosis of strabismus. Using conditional logistic regression, the odds ratios of developing strabismus following the diagnosis of Graves' disease were assessed. The prognostic indicators assessed include race, ethnicity, cigarette smoking (active), serum thyroid peroxidase (TPO) antibody positivity, serum thyroglobulin (Tg) antibody positivity, antithyroidal medication use, and steroid use.

**Results:** The study sample (45 cases 1:1 matched against 45 controls) was comprised primarily of non-Hispanic, non-Latino Caucasian women with TED (mean  $\pm$  SD age  $63.0 \pm 13.1$  years). There were no significant predictors for the development of strabismus, including cigarette smoking (active), serum thyroid peroxidase (TPO) antibody positivity, serum thyroglobulin (Tg) antibody positivity, antithyroidal medication, and steroid use.

**Conclusions:** No significant predictors of strabismus, a severe manifestation of Graves' ophthalmopathy, were identified following a diagnosis of TED in this study.

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## Introduction

Approximately 50% of patients with Graves' disease have signs and/or symptoms of Graves' ophthalmopathy, and 5% have severe thyroid eye disease (TED) [1]. TED is an immunomediated inflammatory disorder characterized by a diverse set of well-described signs and symptoms, which range from extremely common

(i.e. eyelid retraction) to relatively rare (i.e. dysthyroid optic neuropathy) [2]. Each of these physical effects can occur along a scale of severity, affecting quality of life variably. One of the most common and severe physical sequelae of TED is strabismus. Diplopia is well known to significantly affect quality of life [3] and may lead to disability in life functioning.

Although strabismus is a well characterized aspect of TED, predicting and preventing its occurrence has proven to be challenging. Although major modifiable risk factors associated with the development of in TED patients such as cigarette smoking, exposure to radioactive iodine (RAI), and thyroid dysfunction have

\* Corresponding author at: Division of Endocrinology (111D), VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd, Los Angeles, CA 90073, USA.

E-mail address: [amleung@mednet.ucla.edu](mailto:amleung@mednet.ucla.edu) (A.M. Leung).

been identified, none have been specifically associated with strabismus [4]. Additionally, a recent report has demonstrated that thyroidectomy or statin use may significantly reduce the relative risk of developing TED, while increased serum thyrotropin levels and exposure to RAI increased this risk [5]. Such risk factors have not been specifically associated with the development of more severe manifestations of TED, such as strabismus. This case-control study investigates demographic, medication, and laboratory-based prognostic indicators of strabismus, a severe manifestation of TED.

## Materials and methods

In this case-control study, patients with TED who received care from the University of California Los Angeles (UCLA) from 2012 to 2015 were screened for study entry utilizing data from a health system wide electronic medical record database.

Inclusion criteria for subjects was a diagnosis of TED with a subsequent diagnosis of strabismus according to International Classification of Diseases, Ninth Revision (ICD-9) codes.

The following diagnosis title was used to determine a diagnosis of Graves' eye disease: thyrotoxic exophthalmos. The following diagnoses titles were used for a diagnosis of strabismus: diplopia – primary, esotropia, exocyclotropia, eye motility disorder, hypotropia, mechanical strabismus. There were no exclusion criteria for this study.

Cases of TED patients with strabismus were 1:1 matched against TED patients without strabismus by age and gender. Prognostic indicators assessed were race, ethnicity, cigarette smoking (active), serum thyroid peroxidase (TPO) antibody positivity, serum thyroglobulin (Tg) antibody positivity, antithyroidal medication use, and steroid use. The status of these prognostic indicators was evaluated at any date following the diagnosis of TED.

Conditional logistic regression was used to estimate the odds ratios (OR) and its 95% confidence intervals (CI) of strabismus in patients with TED related strabismus. P-values < 0.05 were considered significant. The study was approved by the UCLA Institutional Review Board (IRB).

## Results

The study cohort consisted of 45 cases with TED who were subsequently diagnosed with strabismus during the study period (Table 1). Mean (SD) age for the cohort was 63.0 (13.1) years and the cohort was 62.2% female and 68.9% Caucasian. 5.6% of the cohort reported being active cigarette smokers, 5.6% reported using steroid medications, and 5.6% reported using antithyroidal medications. Controls were matched by age and gender. Race and ethnicity were self-reported, as recorded in the medical record.

**Table 1**  
Subject Demographics.

	Strabismus Patients (N = 45)	Matched TED Patients Without Strabismus (N = 45)
Age (yrs), Mean ± SD	63.0 ± 13.1	63.1 ± 12.9
Age Range	23.4–89.4	21.3–90.3
Female, N (%)	28 (62.2%)	28 (62.2%)
Race, N (%)		
White or Caucasian	31 (68.9%)	28 (62.2%)
Asian	3 (6.7%)	3 (6.7%)
Other	11 (24.4%)	14 (31.1%)
Ethnicity, N (%)		
Not Hispanic or Latino	41 (91.1%)	33 (73.3%)
Hispanic and Other	4 (8.9%)	12 (26.7%)

**Table 2**  
Multivariate Conditional Logistic Regression.

	Odds Ratio	95% CI	p-Value
Hispanic and Other Ethnicities	Reference	–	–
Non-Hispanic Ethnicity	6.91	(1.20, 39.70)	0.0301
Cigarette Smoking (Former)	Reference	–	–
Cigarette Smoking (Active)	0.15	(0.01, 2.16)	0.1621
Cigarette Smoking (Other)	0.63	(0.18, 2.21)	0.4676
Serum TPO Ab Positivity	1.40	(0.26, 7.62)	0.6982
Serum Tg Ab Positivity	1.38	(0.15, 12.68)	0.7756
Antithyroidal Medication Use	0.32	(0.04, 2.62)	0.2856
Steroid Use	2.81	(0.29, 27.24)	0.3716

\* Other includes never, not asked, and passive.

In logistic regression analysis, no significant predictors for the development of strabismus were identified. Among the predictors assessed were: cigarette smoking (active), serum thyroid peroxidase (TPO) antibody positivity, serum thyroglobulin (Tg) antibody positivity, antithyroidal medication use, and steroid use, with the exception of non-Hispanic, non-latino ethnicity (Table 2).

## Discussion

Strabismus impacts quality of life through both functional and psychosocial factors [3] and thus is considered a severe manifestation of thyroid eye disease.

This case-control study of subjects with TED seen over a 13-year period at a large, urban academic medical center was not able to elucidate clinically meaningful prognostic indicators for the development of strabismus after a diagnosis of TED.

In contrast to previous studies linking active cigarette smoking to increased rates of strabismus surgery [6,7], active cigarette smoking was not found to be a significant predictor within this study population. However, many previous studies compare such outcomes to the general GD population [8], while this study matches against TED subjects specifically in order to focus on the population as they present with TED. As such, the discrepancy in findings may be attributed to the association between GD and the development of thyroid eye disease that includes strabismus, rather than the development of strabismus within the more narrow restriction of TED patients specifically. However, it may also be due to the smaller cohort of smokers in this population of this study. In the study from Moorfields Eye Hospital, more than 50% were active smokers [6] whereas in our cohort this proportion was closer to 5%.

Other risk factors for severe disease have been discussed in the literature. For instance, men are more highly represented in population of TED patients with severe disease [9]. Dysthyroid optic neuropathy has additionally been associated with lower socioeconomic status in Great Britain [10] and type II diabetes mellitus in Italy [11]. These studies did not specifically examine the relationship with strabismus, and we did not demonstrate such associations.

This study demonstrates no clinically meaningful significant risk factors for the development of strabismus in patients with TED, a severe manifestation of thyroid eye disease, following the diagnosis of TED. This finding tends to confirm clinical experience in that it is often difficult to identify individuals who will be at risk of developing strabismus and fibrotic restrictive disease before they demonstrate clinical findings. Further research into potential blood borne, genetic and/or proteomic biomarkers may be an interesting area of research. Identification of reliable indicators may provide guidance for how aggressively to treat patients with GD with or without associated TED, as well as modifiable targets for potential intervention earlier in these disease courses.

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