

Original Investigation | EPIDEMIOLOGY

Association Between Atopy and Herpetic Eye Disease

Results From the Pacific Ocular Inflammation Study

Durga S. Borkar, MD; John A. Gonzales, MD; Vivien M. Tham, MD; Elizabeth Esterberg, MS; Aleli C. Vinoya, BS; John V. Parker, BS; Aileen Uchida, MPH; Nisha R. Acharya, MD, MS

IMPORTANCE Immune dysregulation in patients with atopy has been hypothesized to increase susceptibility to viral infections. Herpetic eye disease (due to herpes simplex and herpes zoster) is a significant cause of visual impairment, and data on an association between this sight-threatening disease and atopy are limited.

OBJECTIVE To assess the association between atopy and herpetic eye disease, including herpes simplex virus (HSV) ocular disease and herpes zoster ophthalmicus (HZO).

DESIGN, SETTING, AND PARTICIPANTS Retrospective, population-based case-control study from January 1, 2006, through December 31, 2007, at Kaiser Permanente Hawaii, a multispecialty managed care organization serving approximately 15% of the general Hawaiian population. Participants were 217 O61 patients enrolled in the Kaiser Permanente Hawaii health plan during the study period.

MAIN OUTCOMES AND MEASURES Clinical diagnosis of HSV ocular disease or HZO during the study period determined by an initial search of the electronic medical record of Kaiser Permanente Hawaii and then confirmed through individual medical record review by a uveitis and cornea fellowship-trained ophthalmologist. Atopic disease status was determined based on *International Classification of Diseases, Ninth Revision* codes for patients with HSV ocular disease or HZO and 2 control groups, each randomly selected at a 4:1 ratio of controls to cases.

RESULTS One hundred fourteen patients with HSV ocular disease and 137 patients with HZO were identified. Using the age- and sex-matched controls, patients who had atopy had a 2.6-fold (95% CI, 1.6-4.2; $P < .001$) higher odds of having HSV ocular disease compared with patients who did not have atopy. Similarly, patients with atopy had a 1.8-fold (95% CI, 1.2-2.8; $P = .01$) increased odds of having HZO. Patients with 2 or more atopic conditions had an 8.9-fold (95% CI, 3.5-22.6; $P < .001$) higher odds of having HSV ocular disease and a 2.9-fold (95% CI, 1.1-7.7; $P = .04$) higher odds of having HZO.

CONCLUSIONS AND RELEVANCE The association between atopy and herpetic eye disease may be explained by various factors, including immunologic dysfunction in patients with atopy. Clinically, these results could help support the diagnosis of herpetic eye disease in these patients.

JAMA Ophthalmol. 2014;132(3):326-331. doi:10.1001/jamaophthalmol.2013.6277
Published online December 26, 2013.

Author Affiliations: F. I. Proctor Foundation, University of California, San Francisco (Borkar, Gonzales, Esterberg, Acharya); Department of Ophthalmology, Kaiser Permanente Hawaii, Honolulu (Tham); Center for Health Research, Kaiser Permanente Hawaii, Honolulu (Vinoya, Parker, Uchida); Department of Ophthalmology, University of California, San Francisco (Acharya).

Corresponding Author: Nisha R. Acharya, MD, MS, F. I. Proctor Foundation, University of California, San Francisco, 513 Parnassus Ave, Room S309, San Francisco, CA 94143-0412 (nisha.acharya@ucsf.edu).

Section Editor: Leslie Hyman, PhD.

Herpetic eye disease is a significant cause of sight-threatening infection worldwide.¹⁻³ Cell-mediated immunity, including the helper T cell, subtype 1 (T_H1) response, is crucial in combating herpes simplex virus (HSV) ocular disease and herpes zoster ophthalmicus (HZO).⁴⁻⁸ Several studies⁹⁻¹² have shown that atopic diseases, such as asthma, allergic rhinitis, and atopic dermatitis, heighten the T_H2 response and can weaken the T_H1 response through a complex interplay of regulatory cytokines.

Patients who develop eczema herpeticum or have bilateral HSV ocular disease frequently have a history of atopic disease.¹²⁻¹⁶ In addition, patients with atopy may develop resistant infection or require longer and higher dosages of antiviral therapy to prevent recurrences.¹⁶⁻¹⁹ The largest population-based case-control study²⁰ published on this subject to date found an association between atopy and HSV ocular disease; however, an older study²¹ did not. It is unknown if there is an association between HZO and atopy.

The Pacific Ocular Inflammation project is an epidemiologic study of ocular inflammatory disease in the Hawaiian Islands. Kaiser Permanente Hawaii provides an ideal setting for this because it serves more than 15% of the general Hawaiian population and has a racially diverse membership that has not been studied extensively. The objective of this specific population-based case-control study was to assess whether there is an association between atopy and herpetic eye disease, including HSV ocular disease and HZO.

Methods

Institutional review board and ethics committee approval was obtained at the University of California, San Francisco, and Kaiser Permanente Hawaii. All work was Health Insurance Portability and Accountability Act compliant and adhered to the tenets of the Declaration of Helsinki. Informed consent was not obtained because this was a study using previously collected information for standard patient care. However, all members of the Kaiser system are informed that their deidentified data may be used for research purposes. As a result, waiver of informed consent was granted by the Kaiser Permanente Hawaii Institutional Review Board and the University of California, San Francisco, Ethics Committee.

Patient encounters in the Kaiser Permanente Hawaii electronic medical record between January 1, 2006, and December 31, 2007, were queried for *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes corresponding to herpes zoster or herpes simplex with ophthalmic complications (Table 1). All diagnoses of HSV ocular disease and HZO were individually verified through electronic medical record review by a cornea and uveitis fellowship-trained ophthalmologist (N.R.A.). In addition, patients were classified as having blepharitis, conjunctivitis, dermatitis, keratitis, or uveitis based on clinical examination information. All patients with a confirmed diagnosis of HSV ocular disease or HZO who were 18 years or older as of the midpoint of the study period (January 1, 2007) were included in the study.

Table 1. International Classification of Diseases, Ninth Revision (ICD-9) Diagnosis Codes Used to Identify Herpetic Eye Disease and Atopic Disease

ICD-9 Diagnosis Code	Description
Herpetic Eye Disease	
53.20	Herpes zoster dermatitis of eyelid
53.21	Herpes zoster keratoconjunctivitis
53.22	Herpes zoster iridocyclitis
53.29	Herpes zoster with ophthalmic complications, other
54.40	Herpes simplex with unspecified ophthalmic complication
54.41	Herpes simplex dermatitis of eyelid
54.42	Herpes simplex dendritic keratitis
54.43	Herpes simplex disciform keratitis
54.44	Herpes simplex iridocyclitis
54.49	Herpes simplex with ophthalmic complications, other
Atopic Disease	
477.0-477.9	Allergic rhinitis, multiple subheadings
493.0-493.92	Asthma, multiple subheadings
691.8	Atopic dermatitis and related conditions

Two control groups were each randomly selected at a 4:1 ratio of controls to HSV ocular disease cases and to HZO cases. An ophthalmology clinic control group was selected from the population of Kaiser Permanente Hawaii patients who were 18 years or older as of January 1, 2007, and had at least 1 visit to the Kaiser ophthalmology clinic during the study period. An age- and sex-matched control group was selected from the general Kaiser Permanente Hawaii population having at least 1 physician visit during the study period. Age was matched within 5 years.

A diagnosis of atopic disease was determined based on an ICD-9 diagnosis code related to atopy before or during the study period (Table 1). Patients with atopic disease were classified as having asthma, atopic dermatitis, or allergic rhinitis based on specific ICD-9 diagnosis codes. Additional demographic data were collected electronically for cases and controls. Smoking status for cases and controls was determined based on electronic data obtained at physician office visits. A patient's smoking status closest to the midpoint of the study period was used for cases and controls.

Demographic data were compared between cases and controls using Fisher exact test and *t* test for categorical and continuous variables, respectively. The association between atopy and herpetic eye disease was assessed using a logistic regression with herpetic eye disease (herpes simplex or herpes zoster) as the outcome. A conditional logistic regression was used when comparing cases with the age- and sex-matched controls. Age and sex were included as covariates for analyses using the ophthalmology clinic controls. Additional analyses were performed to assess the effect of race and smoking status on the association.

P < .05 was considered statistically significant. All analyses were performed using statistical software (STATA 11.0; StataCorp LP).

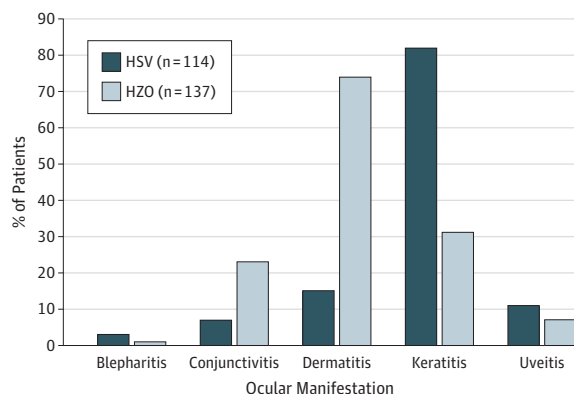
Results

The midpoint population of Kaiser Permanente Hawaii on January 1, 2007, was 217 061 patients. Of this population, 114 adult patients had a confirmed diagnosis of HSV ocular disease, and 137 adult patients had a confirmed diagnosis of HZO. Ocular manifestations for each type of herpetic eye disease are shown in the **Figure**. For the ophthalmology clinic controls, 456 patients and 548 patients were randomly selected for compar-

son with the patients having HSV ocular disease and the patients having HZO, respectively. When selecting the age- and sex-matched controls, there were 4 patients with HSV ocular disease and 7 patients with HZO for whom only 3 controls could be matched. As a result, 452 patients and 541 patients comprised the HSV ocular disease and HZO age- and sex-matched controls, respectively.

Demographic data, atopic disease, and smoking status were compared between patients with HSV ocular disease and both control groups (**Table 2**). Using the ophthalmology clinic controls, patients who had atopic dermatitis had a 3.9-fold (95% CI, 1.8-8.5; $P = .001$) higher odds of having HSV ocular disease compared with patients who did not have atopic dermatitis (**Table 3**). Similarly, patients who had asthma had a 1.8-fold (95% CI, 1.1-3.1; $P = .03$) higher odds of having HSV ocular disease compared with patients who did not have asthma. This association was strengthened for both conditions using the age- and sex-matched controls. Furthermore, patients who had a diagnosis of any atopic disease had a 2.6-fold (95% CI, 1.6-4.2; $P < .001$) higher odds of having HSV ocular disease compared with patients who did not have atopic disease. An association was also found between allergic rhinitis and HSV ocular disease (odds ratio, 2.2; 95% CI, 1.1-4.6; $P = .04$) using this control group. If allergic rhinitis was omitted as an atopic diagnosis to allow for comparison with a prior case-control study²⁰ investigating the association between atopy and HSV ocular disease, patients who had atopic disease had a 3.5-fold (95% CI, 2.1-5.8; $P < .001$) increased odds of having HSV ocular disease

Figure. Ocular Manifestations of Patients With Herpetic Eye Disease



Patients with more than 1 ocular manifestation were counted in each category. HSV indicates herpes simplex virus; HZO, herpes zoster ophthalmicus.

Table 2. Demographic Data for Patients With HSV Ocular Disease and Controls

Variable	Cases, No. (%) (n = 114)	Ophthalmology Clinic Controls, No. (%) (n = 456)	P Value	Age- and Sex-Matched Controls, No. (%) (n = 452)	P Value
Atopic disease	33 (28.9)	109 (23.9)	.27	62 (13.7)	<.001
Atopic dermatitis	14 (12.3)	16 (3.5)	.001	11 (2.4)	.001
Asthma	26 (22.8)	61 (13.4)	.02	36 (8.0)	<.001
Allergic rhinitis	12 (10.5)	52 (11.4)	.87	23 (5.1)	.047
Female sex	54 (47.4)	248 (54.4)	.21	214 (47.3)	>.99
Age, mean, y	53	63	<.001 ^a	52	.74 ^a
Race ^b	(n = 83)	(n = 389)	<.001	(n = 335)	.31
Alaskan/Native American	1 (1.2)	5 (1.3)		7 (2.1)	
Asian	26 (31.3)	179 (46.0)		138 (41.2)	
Black	2 (2.4)	1 (0.3)		4 (0.9)	
Pacific Islander	28 (33.7)	79 (20.3)		78 (23.3)	
White	26 (31.3)	125 (32.1)		108 (32.2)	
Ever smoker	48 (42.1)	158 (34.6)	.16	178 (39.4)	.60

Abbreviation: HSV, herpes simplex virus.

^a By 2-sample mean comparison *t* test. Other *P* values were obtained by Fisher exact test.

^b Percentages for each race subgroup are listed in parentheses using the number of patients reporting race as the denominator.

Table 3. Logistic Regression Models Predicting HSV Ocular Disease^a

Variable	Cases vs Ophthalmology Clinic Controls ^b Odds Ratio (95% CI)	P Value	Cases vs Age- and Sex-Matched Controls Odds Ratio (95% CI)	P Value
Atopic disease	1.3 (0.8-2.1)	.26	2.6 (1.6-4.2)	<.001
Atopic dermatitis	3.9 (1.8-8.5)	.001	5.6 (2.5-12.7)	<.001
Asthma	1.8 (1.1-3.1)	.03	3.4 (2.0-6.0)	<.001
Allergic rhinitis	0.9 (0.5-1.8)	.78	2.2 (1.1-4.6)	.04

Abbreviation: HSV, herpes simplex virus.

^a Each row represents a unique regression model predicting HSV ocular disease.

^b Odds ratios are adjusted for age and sex.

Table 4. Demographic Data for Patients With HZO and Controls

Variable	Cases, No. (%) (n = 137)	Ophthalmology Clinic Controls, No. (%) (n = 548)	P Value	Age- and Sex-Matched Controls, No. (%) (n = 541)	P Value
Atopic disease	36 (26.3)	115 (21.0)	.21	89 (16.5)	.01
Atopic dermatitis	9 (6.6)	24 (4.4)	.27	18 (3.3)	.09
Asthma	22 (16.1)	62 (11.3)	.15	50 (9.2)	.03
Allergic rhinitis	13 (9.5)	47 (8.6)	.74	31 (5.7)	.12
Female sex	74 (54.0)	296 (54.0)	>.99	290 (53.6)	>.99
Age, mean, y	62	62	.72 ^a	62	.62 ^a
Race ^b	(n = 116)	(n = 458)	.74	(n = 410)	.30
Alaskan/Native American	2 (1.7)	2 (0.4)		6 (1.5)	
Asian	52 (44.8)	212 (46.3)		180 (43.9)	
Black	1 (0.9)	8 (1.7)		6 (1.5)	
Pacific Islander	22 (19.0)	83 (18.1)		75 (18.3)	
White	39 (33.6)	153 (33.4)		143 (34.9)	
Ever smoker	51 (37.2)	193 (35.2)	.69	181 (33.5)	.42

Abbreviation: HZO, herpes zoster ophthalmicus.

^a By 2-sample mean comparison t test. Other P values were obtained by Fisher exact test.

^b Percentages for each race subgroup are listed in parentheses using the number of patients reporting race as the denominator.

Table 5. Logistic Regression Models Predicting HZO^a

Variable	Cases vs Ophthalmology Controls ^b		Cases vs Age- and Sex-Matched Controls	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Atopic disease	1.3 (0.9-2.1)	.18	1.8 (1.2-2.8)	.01
Atopic dermatitis	1.5 (0.7-3.4)	.30	2.0 (0.9-4.7)	.09
Asthma	1.5 (0.9-2.5)	.13	1.9 (1.1-3.2)	.02
Allergic rhinitis	1.1 (0.6-2.1)	.72	1.7 (0.9-3.4)	.11

Abbreviation: HZO, herpes zoster ophthalmicus.

^a Each row represents a unique regression model predicting HZO.

^b Odds ratios are adjusted for age and sex.

compared with patients who did not have atopic disease using the age- and sex-matched controls.

Similarly, HZO cases were compared with both control groups (Table 4). Using the age- and sex-matched controls, patients who had any type of atopic disease had a 1.8-fold (95% CI, 1.2-2.8; $P = .01$) higher odds of having HZO compared with patients who had no atopic disease (Table 5). A significant association was also found specifically in patients with asthma for this control group. Patients who had asthma had a 1.9-fold (95% CI, 1.1-3.2; $P = .02$) higher odds of having HZO compared with patients who did not have asthma. Controlling for race or smoking status did not affect the results for HSV ocular disease or HZO.

For HSV ocular disease and HZO, having 2 or more atopic conditions had an even stronger association with herpetic eye disease compared with having fewer than 2 atopic conditions. Specifically, patients who had 2 or more atopic conditions had a 2.9-fold (95% CI, 1.4-6.1; $P = .01$) higher odds of having HSV ocular disease and a 1.7-fold (95% CI, 0.7-4.2; $P = .25$) higher odds of having HZO compared with patients who had fewer than 2 atopic conditions using the ophthalmology clinic controls and adjusting for age and sex. Using the age- and sex-matched controls, patients who had multiple atopic diseases had an 8.9-fold (95% CI, 3.5-22.6; $P < .001$) higher odds of having HSV ocular disease and a 2.9-fold (95% CI, 1.1-7.7; $P = .04$) higher odds of having HZO compared with patients who had one or no atopic disease.

Discussion

Before this study, evidence suggested that patients with atopy are more likely to develop eczema herpeticum, have bilateral HSV ocular disease, and require antiviral therapy for longer durations.¹²⁻¹⁸ A previous study²⁰ showed an association between atopy and HSV ocular disease. Similarly, this study found that patients with atopic disease were more than twice as likely to have HSV ocular disease. An association between atopic disease and HZO has not been previously described to our knowledge. We found that patients with atopy were almost twice as likely to have HZO. Furthermore, having more than 1 atopic condition increased the odds of having herpetic eye disease for HSV ocular disease and for HZO.

Like an earlier population-based case-control study²⁰ researching this question, we observed an association between HSV ocular disease and atopic disease. In our study, we found a 2.6-fold increased odds of having HSV ocular disease for patients with atopy using the age- and sex-matched controls. This is similar to the 1.9-fold higher odds of having HSV ocular disease for patients with atopy that was found in the earlier study. We also included patients with allergic rhinitis in our analyses, while the prior study did not because it may be a nonspecific diagnosis. In a sensitivity analysis, we excluded allergic rhinitis as an atopic condition, and our association became even stronger.

In our study, atopic dermatitis had the strongest association with HSV ocular disease, followed by asthma. Of the prior smaller investigations on this topic, studies^{12,13,17,22} have also reported an association with atopic dermatitis, in particular, and with ocular disease. In addition, studies^{12,23} in the systemic literature have noted that patients with atopic dermatitis may have a predisposition to more severe HSV infection. There may be some explanation for this specific association at the cellular level. For example, it is well known that mutations in several genes associated with skin barrier dysfunction are found in patients with atopic dermatitis.^{24,25} As a result, colonization of several pathogens, including HSV, is facilitated in these patients.²⁶

While an association between HSV ocular disease and atopy has been described, information on HZO and atopy is lacking. In this study, we found that patients who had atopic disease had an almost 2.0-fold increased odds of having HZO compared with patients who did not have atopic disease using age- and sex-matched controls. A prior study²⁷ has shown a protective effect of primary varicella zoster virus infection on the subsequent development and severity of atopic dermatitis in children. Further study is needed to determine if children with primary varicella zoster virus infection who eventually manifest atopic conditions are more likely to develop herpes zoster compared with those who do not manifest atopic conditions. In addition, patients who had asthma had an almost 2.0-fold increased odds of having HZO compared with patients who did not have asthma in our study. It is possible that the association between asthma and HZO could in part be due to the immunosuppressant medications that are used to treat asthma, such as corticosteroids. However, a prior study²⁸ has shown no association between inhaled corticosteroid use, one of the most common immunosuppressant treatments for asthma, and the development of herpes zoster.

The association between atopy and both HSV ocular disease and HZO can potentially be explained by the immune system dysregulation observed in patients with atopy. Specifically, these patients have been shown to have a predominance of T_H2 cells, leading to increased levels of interleukin 4 and IgE.²⁹ These immune system modulators can prevent differentiation of T_H1 cells that stimulate production of key cytokines, including interferon- γ , for combating viral infections.^{30,31} In this study, we found that having more than 1 atopic condition significantly increased the odds of having herpetic eye disease. Prior studies³²⁻³⁴ have shown a positive association between severity of atopic conditions and serum IgE levels. Therefore, it is possible that multiple atopic conditions could correlate with increased immune dysregulation, explaining the stronger association with HSV ocular disease and HZO that we found in patients with at least 2 atopic conditions.

More significant associations were found between atopy and both HSV ocular disease and HZO using the age- and sex-matched control group. This may in part be explained by differences between the 2 control groups. Patients in the ophthalmology clinic control group may have been more likely to have diseases diagnosed because of increased interaction with physicians for existing comorbidities, such as diabetes mellitus. In contrast, the age- and sex-matched controls needed only

one physician visit during the study period to be included. A similar difference in results using a clinic-based control group and a population-based control group was noted in the prior study²⁰ that investigated the association between atopy and HSV ocular disease.

There are some limitations of the study. Demographic differences may affect the applicability of our results to the Hawaiian population. Based on the most recent census data, the age and sex distribution of Kaiser Permanente Hawaii is comparable to that of the general Hawaiian population; however, Kaiser Permanente Hawaii has a larger percentage of Pacific Islanders.³⁵ Similarly, differences in demographic factors, such as racial distribution, may affect the generalizability of this study to other populations outside of Hawaii. However, an association between HSV ocular disease and atopy has been found in a different population,²⁰ suggesting that the findings in our study may not be unique to the present study population. It is also possible that certain cases or controls may have been diagnosed as having an atopic condition by a physician outside of the Kaiser system, but only approximately 5% of the Kaiser Permanente Hawaii membership has dual insurance that would facilitate receiving health care outside of the Kaiser system.

In addition, there are some diagnostic considerations. While misdiagnosis of herpetic eye disease is possible, all patients were seen by a Kaiser Permanente Hawaii ophthalmologist, and cases of herpetic eye disease were individually verified through medical record review by a uveitis and cornea fellowship-trained ophthalmologist (N.R.A.), decreasing the likelihood of misdiagnosis. A diagnosis of atopic disease was determined based on ICD-9 diagnosis codes alone. Although this could potentially lead to misdiagnosis, the same method was used to determine an atopic diagnosis for both cases and controls. The temporal association of atopic disease and a herpetic eye disease diagnosis should also be considered. It is possible that some patients were diagnosed as having atopic disease after their initial diagnosis of herpetic eye disease. However, this would be unlikely because atopic diseases are generally more chronic and diagnosed at a young age. The mean age of the patients with herpetic eye disease in this study is older than 50 years for HSV ocular disease and for HZO, and more than 80% of these patients were incident cases. Theoretically, it is possible that ophthalmologists were diagnosing patients having HSV ocular disease with atopic conditions because of their knowledge of an association that was published during the study period.²⁰ However, our medical record review demonstrated that this was not the case. In addition, no association was known between HZO and atopy before the present study, so it would be unlikely for a diagnostic bias to exist.

In conclusion, we found an almost 2.0-fold increased odds of having HZO and a more than 2.0-fold increased odds of having HSV ocular disease for patients who had atopic disease compared with patients who had no atopic disease. Specific diagnoses, such as atopic dermatitis, as well as the presence of more than 1 atopic condition increased the odds of having herpetic eye disease. While an association between atopy and HSV ocular disease has been shown in a prior study,²⁰ no association between atopy and HZO has been described. The results of this

study are novel and should be validated in other populations. Knowledge of this association could help support the diagnosis of herpetic eye disease in patients with atopy.

These findings also raise questions about whether there are common pathophysiological mechanisms behind both of these conditions.

ARTICLE INFORMATION

Submitted for Publication: May 6, 2013; final revision received July 25, 2013; accepted July 26, 2013.

Published Online: December 26, 2013.
doi:10.1001/jamaophthalmol.2013.6277.

Author Contributions: Dr Acharya had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Borkar and Gonzales contributed equally to the manuscript.

Study concept and design: Borkar, Gonzales, Acharya.

Acquisition of data: Tham, Esterberg, Vinoya, Parker, Uchida.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Borkar, Gonzales, Acharya.

Critical revision of the manuscript for important intellectual content: All authors.

Conflict of Interest Disclosures: None reported.

Funding/Support: The University of California, San Francisco, Department of Ophthalmology is supported by grant EY06190 from the National Eye Institute, by That Man May See Foundation, and by an unrestricted grant from Research to Prevent Blindness. Dr Acharya is supported by grant K23EY017897 from the National Eye Institute, by a Research to Prevent Blindness Career Development Award, and by a University of California, San Francisco, Research Evaluation and Allocation Committee Award.

Role of the Sponsor: The sponsors or funding organization had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentation: The results of this study were presented in part at the 2012 Association for Research in Vision and Ophthalmology Annual Meeting; May 10, 2012; Fort Lauderdale, Florida.

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