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Prevalence and associations of asymptomatic retinal emboli in Latinos: The Los Angeles Latino Eye Study (LALES)

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Abstract

Purpose—To study the prevalence and associations of asymptomatic retinal emboli in a cohort of Latinos, and compare these findings to those of previous population studies.

Design—Population-based cross-sectional study

Methods—All participants in this study underwent a comprehensive eye exam, including fundus photography. Photographs were graded by trained masked graders. Lifestyle factors and medical history were obtained during extensive interviews. Blood pressure, serum glucose, and glycosylated hemoglobin were measured. Age and gender-specific prevalence rates were calculated. Odds Ratios (OR) were calculated using stepwise logistic regression analyses to identify independent risk factor associations with asymptomatic retinal emboli.

Results—Photographs gradable for retinal emboli were obtained from 5959 participants. For all participants, the prevalence of definite asymptomatic retinal emboli was 0.4% (n=26). Stepwise logistic regression analyses identified smoking (>5 pack years) (OR=4.3) and history of coronary artery disease (OR=2.8) to be independently associated with retinal emboli ($P<0.05$).

Conclusion—We found a lower prevalence of asymptomatic retinal emboli compared to previous population-based studies. This could be secondary to the LALES population being younger, having

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lower blood pressure, and fewer smokers than other studies. As in other studies, smoking emerges as the strongest association with retinal emboli.

INTRODUCTION

Retinal emboli are discrete plaque-like deposits located at the lumen of retinal vessels, found along or at the bifurcation of retinal arteries. Early descriptions by Hollenhorst categorized these plaques as bright or dull in appearance on funduscopic exam.^{1,2} The bright or reflective emboli are believed to contain cholesterol and to stem from atherosclerotic plaques of carotid or cardiac origin.^{1,3,4} Dull or creamy appearing plaques are believed to contain fibrin or platelet material. Other studies have shown an increased mortality in patients found to have retinal emboli compared with the general population of the same age and sex distribution.^{2,5,6} Many retrospective studies have since linked retinal emboli to stroke and cardiovascular risk factors such as male gender, increasing age, smoking, hypertension, and diabetes.^{7,8}

Two previous population-based studies have focused on the significance of asymptomatic retinal emboli findings in middle-aged to elderly cohorts. Mitchell et al of the Blue Mountains Eye Study (BMES) and Klein et al of the Beaver Dam Eye Study (BDES) found a similar prevalence of retinal emboli, 1.4% and 1.3%, respectively.^{9–11} After controlling for age and sex, the BMES researchers found that the prevalence of retinal emboli was associated with hypertension, smoking, and vascular disease.^{9,10} In the BDES, researchers found that independent factors for retinal emboli prevalence included age, history of smoking, diabetes, and hypertension.¹¹

Both the BMES and the BDES examined cohorts of primarily non-Hispanic white populations. No clinic or population-based studies of retinal emboli in a Latino population have been described. The Los Angeles Latino Eye Study (LALES) is a population-based study of Latino patients in Los Angeles County that was undertaken to develop a better understanding of health care and eye disease in Latino Americans.¹² As the Latino population is the largest and fastest growing minority group in the US,^{13,14} it is important that we better understand the characteristics of disease in this group. Data strongly suggests that, compared to non-Hispanic whites, Latinos have an increased prevalence of vascular risk factors, such as diabetes.^{15–17} There is conflicting evidence as to whether this increase results in a higher risk for stroke and other complications of diabetes and hypertension in Latinos.^{15–16,18–21} It is unclear whether increased diabetes or possible differences in other vascular risk factors in Latinos may be associated with an increased prevalence in retinal emboli. The objectives of this paper are to describe the prevalence and associations of asymptomatic retinal emboli in a Latino population-based cohort and to compare our findings with those of previous studies. Additionally, we sought to summarize the significance and management of asymptomatic retinal emboli based on our findings and those of other studies.

METHODS

PARTICIPANTS

LALES was a population-based prevalence study of eye disease in Latino residents of six census tracts in the city of La Puente, located in the county of Los Angeles. The study design, sampling plan, and baseline data have been described previously.¹² In brief, Latinos 40 years and older, primarily of Mexican ancestry and living in the designated area were eligible to participate in the study. All participants were informed of the goals, requirements, and procedures of the study. Prior to any data collection, a written informed consent was obtained from each study participant. Approval to conduct the study was obtained from the Los Angeles County/University of Southern California Medical Center Institutional Review Board. All

study procedures adhered to the principles outlined in the Declaration of Helsinki for research involving human subjects.

INTERVIEW AND EXAMINATION OF PARTICIPANTS

All interview, examination, and clinical techniques used in LALES have been described previously.^{12,22} Participants completed questionnaires and interviews conducted in their homes by trained interviewers. Those able to take part in in-clinic exams also completed in-clinic questionnaires and interviews. Participants answered questions about systemic and ocular disease history, current symptoms, and estrogen use in females. Social history, including an extensive history of tobacco and alcohol use, was also obtained. Random serum glucose and glycosylated hemoglobin were measured using the Hemocue B-Glucose Analyzer (Hemocue, Inc., Lake Forest, Calif) and the DCA 2000+ System (Bayer Corporation, Tarrytown, N.Y.), respectively. Blood pressure measurements were taken by trained medical staff. Trained ophthalmologists performed detailed eye exams, either in the clinic or in the participants' homes.

DEFINITIONS OF DISEASE CHARACTERISTICS

Diabetes was categorized as either definite or probable. Definite diabetes was defined as meeting at least one of the following criteria: (1) a previous diagnosis of diabetes and treatment with oral medication, insulin, or diet control; (2) glycosylated hemoglobin level of 7.0% or higher; or (3) a random serum glucose of 200 mg/100 ml or higher. Probable diabetes was defined as a self-reported history of diabetes without treatment, or a glycosylated hemoglobin level greater than or equal to 6.5% and less than 7.0% with a random glucose below 200 mg/100 ml. Any diabetes was defined as having either definite or probable diabetes.

Two blood pressure and pulse measurements were taken while each participant was sitting. The mean values of these measurements were used in the statistical analysis.

Cardiovascular history was obtained by self-report. Participants were instructed to answer either yes or no to questions about any personal history of stroke (ischemic or hemorrhagic), angina, heart attack, or heart failure. A history of coronary artery disease was defined as having a history of angina, myocardial infarction, or congestive heart failure.

LIFE STYLE RISK FACTORS

Information about each participant's smoking history was obtained during the in-home interview. Participants were asked the age at which they began and stopped smoking, as well as an estimate of the number of cigarettes smoked per day. Number of cigarettes smoked per day was divided by 20 and multiplied by years of smoking to calculate pack years smoked. Alcohol use was determined from an interviewer-administered questionnaire asking participants how many days per month they drank alcohol and how many drinks (volume and type of beverage) were consumed on each occasion. From these estimates, average grams of alcohol per week were calculated.

IDENTIFYING ASYMPTOMATIC RETINAL EMBOLI

Similar to the Beaver Dam Study, three stereoscopic fundus fields were photographed on all nondiabetic persons, and seven stereoscopic fundus fields were photographed on all diabetic persons in each eye. Disc photographs were taken of all participants as well. Retinal emboli were identified in a manner described previously by Klein et al as part of the Wisconsin Age-Related Maculopathy grading scheme.^{11,23,24} Trained, masked graders examined all fields photographed to detect retinal emboli, which were defined as reflective bright or nonreflective dull lesions of rhomboidal, rectangular, or round shape lodged in retinal arterioles. Participants

were classified as having definite, questionable, or absent emboli, with questionable emboli defined as 50% to 90% grader confidence in the presence of emboli. Only definite emboli were included in the study, with the number per eye counted, and classified as either bright or dull. Cases of questionable and definite emboli were reviewed by one of the authors (R.K.). Participants complaining of transient monocular loss of vision, as well as those with history of or exam showing retinal artery occlusion, were considered symptomatic and excluded.

STATISTICAL ANALYSIS

Age- and gender-specific prevalence rates were calculated. The relationship between retinal emboli and demographic and clinical characteristics was evaluated using the chi-square test or Fisher exact test for discrete variables, and the Student t-test for continuous variables. Univariate logistic regression was used to assess the association of demographic and clinical characteristics with retinal emboli. Multiple logistic regression analyses with forward stepwise selection were used to identify the independent relationships of risk factors. The Statistical Analysis System 9.1 (SAS Institute Inc., Cary, N.C.) was used for statistical analyses. All analyses were conducted at the 0.05 significance level.

RESULTS

A total of 6028 participants completed interviews and clinical exams, and had fundus photographs taken. Of these, 68 participants were excluded because graders were unable to grade their fundus photographs for definite retinal emboli. One participant with definite retinal emboli was considered symptomatic and was excluded secondary to a history of central retinal artery occlusion. This rendered a base cohort of 5959 participants for this study. The overall prevalence of asymptomatic retinal emboli in our study was 0.4% (26 of 5959 participants). Prevalence was higher in men (0.6%) than in women (0.3%) and increased somewhat with age, with the highest prevalence (1.4%) seen in males aged 70 years and older. However, these trends did not reach statistical significance.

Demographic and clinical characteristics in patients with and without at least one definite retinal emboli are listed in Tables 1 and 2. Of the 5959 participants, 2479 (42%) were male and 3480 (58%) were female. The mean age was 58.5 years in those with retinal emboli and 54.7 years in those without. The criteria for definite diabetes were met by 1208 (20%) participants; 185 (3%) people reported a history of ischemic or hemorrhagic stroke; and 195 (3%) had a history of myocardial infarction.

All 26 participants with retinal emboli had unilateral definite retinal emboli on photographic grading, 12 in the right eye and 14 in the left. Four participants had more than one unilateral emboli. Sixteen emboli in 12 patients were classified as bright, and 17 emboli in 16 patients were classified as dull, with two having both bright and dull emboli. As shown in Tables 1 and 2, factors significantly associated with retinal emboli on univariate analysis included (1) a history of smoking ($P<0.002$); (2) a history of myocardial infarction ($P<0.05$); (3) a history of coronary artery disease ($P<0.01$); (4) higher systolic blood pressure ($P<0.03$).

Participants with a history of stroke or congestive heart failure were two to three times more likely to have retinal emboli, but the results were not statistically significant. Although the prevalence of emboli was higher with older age, male gender, and the presence of diabetes, these relationships were also not statistically significant. Significant associations identified on univariate regression analysis did not change with the exclusion of participants 80 years of age and older. Elevated glycosylated hemoglobin results, a history of alcohol consumption, elevated body mass index, and a history of estrogen use were not associated with retinal emboli.

Multivariable stepwise analysis was performed using a model that included age, gender, and the likely candidates for risk indicators found on univariate analysis: systolic blood pressure, smoking, coronary artery disease, heart attack history (Table 3). As a result, a history of smoking ($P<0.006$) and a history of coronary artery disease ($P<0.05$) were shown to be independent risk indicators for asymptomatic retinal emboli.

DISCUSSION

In our study of middle-aged to elderly Latinos of primarily Mexican ancestry, we found the overall prevalence of asymptomatic retinal emboli to be 0.4%. This was lower than the prevalence found by either BMES (1.4%) or BDES (1.3%)^{9–11} Although the LALES cohort was younger than either the BMES or BDES cohorts, there was a trend for lower prevalence even when examining by age groups (Table 4). All three population studies had similar proportions of women. One explanation for the lower prevalence found in LALES may be that fundus photos were taken in only three fields per eye for nondiabetic participants (seven fields in diabetic participants), whereas in the Blue Mountains group, photos were taken in six fields per eye.⁹ However, the Beaver Dam Study used the same methods and number of fundus photos as our study used, but had a similar retinal emboli prevalence compared to the Blue Mountains Study.^{9,11} Another possibility for a lower prevalence is that the blood pressures of the BMES participants were higher (mean systolic and diastolic blood pressures of 145.6 mmHg and 83.8 mmHg, respectively) than those of our cohort (mean systolic and diastolic blood pressures of 123.3 mmHg and 75.7, respectively).²⁵ The higher prevalence of retinal emboli in BDES can be explained, in part, by the higher percentage of smokers (18.1% females, 22.3% males) compared to that in LALES (13.8% overall).²²

Data pooled from the Atherosclerosis Risk in Communities Study and Cardiovascular Health Study, with participants 45 years and older, showed a retinal emboli prevalence of 0.2%.²⁶ While this prevalence is closer to that found in our study, it is difficult to compare results given significant differences in methodology. For example, only one 45 degree photograph centered on the disc and macula of one randomly selected eye was taken.²⁶ As cautioned previously, any estimate of retinal emboli prevalence or incidence in our study or others is likely an underestimate secondary to the transient nature of emboli and selective survival of participants.^{9,11,27,28}

Retinal emboli have been associated with cardiovascular risk factors.^{1–3,5–11,27, 28} Univariate analysis showed a significant association in our participants between retinal emboli and a history of smoking, coronary artery disease or myocardial infarction or a finding of increased systolic blood pressure. A history of smoking or of coronary artery disease were found to be independent associations on multivariate analysis. These findings are similar to those of BMES, which found hypertension, smoking, vascular disease (hypertension, angina, myocardial infarction, or stroke) and past vascular surgery (coronary, carotid, or femoropopliteal) to be significant associations, independent of age and gender.^{9,10} Similarly, BDES found hypertension, smoking, cardiovascular disease, myocardial infarction, coronary bypass surgery, and age to be independently associated with retinal emboli.¹¹ Our results showed a higher prevalence of retinal emboli in older Latinos, as well as a higher prevalence in males, but this result did not reach significance on univariate or multivariate analysis, perhaps as a result of the infrequency of retinal emboli cases.

Previous studies have demonstrated a strong correlation between retinal emboli and ischemic stroke.^{1,2,8,27} In BDES, those with retinal emboli in prevalence studies were about three times as likely to have stroke listed as a cause of death, after controlling for systemic factors.¹¹ In our population, those with asymptomatic retinal emboli were more likely to have reported a history of stroke, although this finding did not reach statistical significance (OR 2.6, CI 0.6–

11.2, $P < 0.12$). This is consistent with previous studies: a history of stroke was more common in those with retinal emboli in both BMES and BDES, but the association was not significant in either study,^{9–11} again perhaps due to sample size.

In summary, asymptomatic retinal emboli are a relatively infrequent finding on fundus exam that signals the likelihood of increased cardiovascular risk factors and increased risk of stroke. The prevalence and associations of asymptomatic retinal emboli in our Latino population of primarily Mexican ancestry is lower than that of other primarily white population studies. However, as in other studies, a history of smoking tobacco is the strongest associated risk factor for having retinal emboli. For ophthalmologists who diagnose a patient with asymptomatic retinal emboli, management may include referral to a primary care physician and counseling of smoking cessation if applicable.

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Table 1

Demographic and Clinical Characteristics of Participants in the Los Angeles Latino Eye Study by Status of “Definite Retinal Emboli” Obtained by History

Variable	No Emboli (n = 5933)	Definite Emboli (n = 26)	P value ⁺
Age (mean, years)	54.7(10.8)	58.5 (11.9)	0.08
Gender			0.20
Male	2465 (41.6%)	14 (53.9%)	
Female	3468 (58.5%)	12 (46.1%)	
Smoking in pack years			0.002
None	3661 (62.2%)	9 (36.0%)	
≤ 5 pack years	1029 (17.5%)	4 (16.0%)	
> 5 pack years	1193 (20.3%)	12 (48.0%)	
Alcohol Consumption			0.67
None	2308 (39.0%)	8 (30.8%)	
Ex-drinker	1087 (18.4%)	5 (19.2%)	
Current drinker	2519 (42.6%)	13 (50.0%)	
Stroke History *			0.19
No	5748 (96.9%)	24 (92.3%)	
Yes	183 (3.1%)	2 (7.7%)	
Angina History			0.62
No	5708 (96.4%)	25 (96.1%)	
Yes	214 (3.6%)	1 (3.9%)	
Myocardial Infarction History			0.05
No	5736 (96.8%)	23 (88.5%)	
Yes	192 (3.2%)	3 (11.5%)	
Heart Failure History			0.17
No	5753 (97.2%)	24 (92.3%)	
Yes	168 (2.8%)	2 (7.7%)	
Coronary Artery Disease History *			0.01
No	5489 (92.6%)	20 (76.9%)	
Yes	442 (7.4%)	6 (23.1%)	
Hormone Replacement Therapy (> 12 months)			0.36
No	1640 (81.7%)	8 (100%)	
Yes	368 (18.3%)	0 (0%)	

⁺ P value obtained by chi-square test, Fisher’s exact test (discrete variables), and Student t-test (continuous variables)

* Refer to Methods section for disease definitions.

Table 2

Demographic and Clinical Characteristics of Participants in Los Angeles Latino Eye Study by Status of “Definite Retinal Emboli” Obtained by Examination.

Variable	No Emboli (n = 5933)	Definite Emboli (n = 26)	P value ⁺
Systolic Blood Pressure (mean, mmHg)	123.3 (19.3)	129.2 (22.8)	0.13
Systolic Blood Pressure (median, mmHg)			0.03
SBP < 121 mmHg	2959 (49.9%)	7 (28.0%)	
SBP ≥ 121 mmHg	2966 (50.1%)	18 (72.0%)	
Diastolic Blood Pressure (mean, mmHg)	75.7 (11.0)	76.9 (12.4)	0.60
Diastolic Blood Pressure (median, mmHg)			0.54
DBP < 76 mmHg	2972 (50.2%)	11 (44.0%)	
DBP ≥ 76 mmHg	2953 (49.8%)	14 (56.0%)	
Hemoglobin A1c, (mean, per unit)	6.04 (1.6)	6.18 (1.4)	0.65
Body Mass Index (mean, per unit)	31.3 (10.8)	30.3 (5.4)	0.38
Definite Diabetes[*]			0.18
No	4733 (79.8%)	18 (69.2%)	
Yes	1200 (20.2%)	8 (30.8%)	
Definite or Probable Diabetes[*]			0.38
No	4545 (76.6%)	18 (69.2%)	
Yes	1388 (23.4%)	8 (30.8%)	

* Refer to Methods section for disease definitions.

⁺ P value obtained by chi-square test, Fisher's exact test (discrete variables), and Student t-test (continuous variables).

Table 3
Stepwise Multivariable Analysis of Risk Factors for Definite Retinal Emboli

Variables	OR (95% CI)	<i>P</i> value*
Smoking (pack years)		0.006
None	1.0	
≤ 5 pack years	1.8 (0.5, 6.0)	
> 5 pack years	4.3 (1.7, 10.6)	
History of Coronary Artery Disease		< 0.05
No	1.0	
Yes	2.8 (1.1, 7.6)	

Note: Variables included in the multivariate model were: age, gender, systolic blood pressure, history of smoking (pack years), history of myocardial infarction, history of coronary artery disease.

* *P* values obtained by stepwise logistic regression.

Table 4
Comparison of Retinal Emboli Prevalence stratified by Age Groups in different population-based studies

Age Group	Los Angeles Latino Eye Study	Blue Mountains Eye Study ^{*,†}	Age Group	Los Angeles Latino Eye Study	Beaver Dam Eye Study [*]
<60	0.3%	0.8%	40–49	0.3%	0.1% ⁺
60–69	0.5%	1.4%	50–59	0.3%	0.7%
70–79	1.1%	2.1%	60–69	0.5%	1.6%
≥ 80	0%	1.5%	≥ 70	0.9%	2.0%

^{*} Blue Mountains Eye Study data from Mitchell et al⁸ and Beaver Dam Eye Study data obtained from Ronald Klein (Personal Communication).

⁺ Age range 43–49 years.