Mechanisms of Retinal Arterial Occlusive Disease in African American and Caucasian Patients

Richard M. Ahuja, MD; Seemant Chaturvedi, MD; Dean Eliott, MD; Nishith Joshi, MD; James E. Puklin, MD; Gary W. Abrams, MD

Background and Purpose—The aim of our study was to evaluate the causes of retinal arterial occlusive disease in African American patients and to compare these etiologies with those observed in Caucasian patients with retinal ischemic symptoms.

Methods—We performed a retrospective analysis of a series of consecutive patients evaluated by both the ophthalmology department and the neurology/stroke clinic. Patients had a diagnosis of amaurosis fugax, branch retinal artery occlusion, central retinal artery occlusion, or intra-arterial retinal plaques.

Results—Twenty-nine African American patients and 17 Caucasian patients were evaluated. African American patients had a mean age of 61 years (range, 30 to 77 years) and Caucasian patients a mean age of 73 years (range, 56 to 94 years) (P < 0.003). There was no statistically significant difference between the 2 groups with respect to visible emboli on funduscopy (P = 0.462). After adjusting for age, there was also no difference between the 2 groups with regards to risk factors for arterial occlusive disease such as hypertension, coronary artery disease, hypercholesterolemia, tobacco use, and history of stroke or transient ischemic attacks. Caucasian patients had a 41% incidence (7/17) of high-grade ipsilateral internal carotid artery stenosis, measured by carotid duplex, compared with 3.4% incidence (1/29) in African American patients (P = 0.002).

Conclusions—There are racial differences in the causes of retinal arterial occlusion. African American patients have a low prevalence of moderate to severe extracranial carotid stenosis, and a high proportion of African American patients have cryptogenic retinal ischemia. In Caucasian patients there is a stronger association between extracranial carotid artery disease and retinal arterial occlusion. (Stroke. 1999;30:1506-1509.)

Key Words: amaurosis fugax ■ blacks ■ carotid stenosis ■ racial differences ■ retinal artery occlusion

Monocular visual loss, in the form of either amaurosis fugax or retinal artery occlusion, has long been recognized as a potential symptom of carotid artery disease. Patients with amaurosis fugax are at appreciable risk of developing either retinal or cerebral infarction. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), patients with transient retinal ischemia and at least 70% angiographic stenosis had a 2-year stroke risk of 17%. In a previous report, Breen reviewed several prospective and retrospective studies and found that “significant” ipsilateral carotid artery disease was present in 53% to 83% of patients with amaurosis fugax. In patients with central retinal artery occlusion (CRAO) or retinal emboli, there exists a higher mortality rate, attributed mainly to an increased incidence of cardiac disease and fatal stroke.

Racial differences in the etiologies of cerebral ischemic events have also been described. In a study of Caucasian and African American patients with symptomatic anterior circulation occlusive disease, Caplan and associates found that Caucasian patients had more internal carotid artery (ICA) origin lesions on angiography, whereas African Americans had a greater preponderance of supraclinoid ICA and middle cerebral artery (MCA) stem atherosclerotic lesions. Wityk and associates found a 2-fold higher prevalence of extracranial carotid artery lesions in Caucasian patients compared with African American patients.

Mechanisms of retinal arterial occlusive disease in African American patients have not been previously reported in great detail. It is important to determine the etiology of disease because the selection of treatment is dependent on the mechanism of retinal ischemia. Therefore, we undertook a study to evaluate the causes of retinal arterial occlusive disease in African American patients and to compare these etiologies with those observed in Caucasian patients with retinal ischemic symptoms. Our hypothesis was that moderate to severe extracranial ICA atherosclerosis would be less common in African American patients compared with Caucasian patients.
Subjects and Methods

A series of consecutive patients evaluated by the ophthalmology service and referred to the stroke clinic at a tertiary care university medical center are included in this retrospective analysis. Patients were referred to the stroke clinic with a diagnosis of either amaurosis fugax, branch retinal artery occlusion (BRAO), CRAO, or intra-arterial plaques. Systematic investigations were undertaken to determine the etiology of the retinal occlusive disease. The investigations included history and physical examination, carotid duplex ultrasound, and transthoracic echocardiography. The intracranial circulation was assessed with either magnetic resonance angiography (MRA) or conventional cerebral angiography in select patients.

Specific variables identified during history-taking were hypertension, diabetes, hypercholesterolemia, coronary artery disease, myocardial infarction, angina, congestive heart failure, arrhythmias, valvular heart disease, transient ischemic attack or stroke, and tobacco use. Hypertension was defined as a patient being on antihypertensive therapy or by measurements on 2 examinations of systolic pressure $\geq 140$ or diastolic pressure $\geq 90$. Diabetes and hypercholesterolemia were defined as patients being on antidiabetic therapy and history from patients or referring physicians. Coronary artery disease was defined as a patient with history of 1 of the previously stated cardiac conditions or being on appropriate therapy in addition to ECG. Cigarette smoking was recorded as pack-years. Patients also underwent laboratory testing for serum cholesterol, erythrocyte sedimentation rate, blood glucose, and complete blood count.

Etiologies for the retinal ischemic symptoms were assigned using modifications of a previously validated stroke subtype classification system used for cerebral infarction. The modifications were necessary because there were no consensus criteria for the diagnosis of small-artery disease in the retinal circulation and also to attempt to distinguish between extracranial and intracranial large artery atherosclerosis.

Univariate analyses were performed, and significance was judged based on the Student $t$ test for continuous variables, the $\chi^2$ test for categorical variables, and the Fisher exact test for instances in which individual counts were $<5$. Multivariate analyses were performed using a logistic regression model. Modeling was done using the selected factors as independent variables and age as a dependent variable. Odds ratios were calculated from the $\beta$ coefficients and their standard errors.

Results

31 African Americans and 17 Caucasian patients who were seen at the Kresge Eye Institute were referred to a subspecialist in stroke in the department of neurology. These patients were consecutively evaluated by a single stroke neurologist. Two African American patients were not included in the final analysis due to lack of follow-up for completion of testing. A total of 29 African Americans completed the testing required to be included in the study. The mean age was 61 years (range, 30 to 77 years) for the African American patients and 73 years (range, 56 to 94 years) for the Caucasian patients ($P=0.003$). The African American group included 13 men and 16 women, whereas the Caucasian group had 9 men and 8 women.

Differences in 5 primary risk factors for cerebrovascular and retinal vascular disease were examined. There were no significant differences between the 2 groups with respect to prevalence of hypertension, hypercholesterolemia, tobacco use, coronary artery disease, or prior history of stroke or transient ischemic attack (TIA). There was a significant difference between the 2 groups with respect to diabetes mellitus, with African American patients having a higher incidence of diabetes ($P=0.0273$) (Table 1). There was also no significant difference between the Caucasian and African American groups with respect to visible plaques on funduscopic examination ($P=0.462$) (Table 2).

In terms of the etiologies for the retinal ischemic symptoms, there was a statistically significant difference between the 2 groups with respect to the prevalence of moderate to severe extracranial ICA disease as measured by duplex ultrasonography. Seven of 17 Caucasian patients (41%) had $>50$% stenosis compared with only 1 of 29 African American patients (3.4%; $P=0.01$). The age-adjusted risk of carotid stenosis for Caucasian patients was 3.45 (OR, 3.45; 95% CI, 1.26 to 9.44; Table 3). Etiologies for retinal arterial occlusive disease in the African American patients were as follows: undetermined etiology (20, 69%), intracranial large-vessel atherosclerosis (5, 17%), cardioembolism (2, 7%), extracranial large-vessel atherosclerosis (1, 3.4%), and other determined cause (1, 3.4%). The corresponding etiologies for the Caucasian patients were extracranial carotid atherosclerosis (7, 41%), intracranial carotid atherosclerosis (1, 6%), and undetermined mechanism (9, 53%). The difference in extracranial carotid disease was the only mechanism that was statistically significant.

Seven Caucasian patients were referred for carotid endarterectomy, and the only African American patient with severe extracranial carotid stenosis was also referred for carotid endarterectomy. The mean angiographic percentage stenosis in the Caucasian patients referred for surgery was 73%, and it was 95% in the only African American patient referred for carotid endarterectomy.

| TABLE 1. Comparison of Risk Factors for Retinal Arterial Occlusive Disease |
|--------------------------|--------------------|----------------|
| Risk Factor                | African American (n=29) | Caucasian (n=17) | $P$ |
| Hypertension               | 79                  | 53              | 0.11 |
| Coronary artery disease    | 24                  | 24              | 0.83 |
| Diabetes mellitus          | 35                  | 6               | 0.02 |
| Hypercholesterolemia       | 14                  | 18              | 0.56 |
| Tobacco use                | 62                  | 53              | 0.83 |

n indicates number of patients.

*Adjusted for age.

| TABLE 2. Types of Retinal Arterial Occlusive Disease |
|--------------------------|--------------------|----------------|
|                         | African American (n=29) | Caucasian (n=17) |
| Amaurosis fugax          | 24                  | 24              |
| BRAO without emboli      | 10                  | 29              |
| BRAO with emboli         | 3                   | 29              |
| CRAO without emboli      | 48                  | 18              |
| CRAO with emboli         | 3                   | 0               |
| Emboli alone             | 10                  | 0               |

n indicates number of patients.
TABLE 3. Degree of ICA Stenosis Measured by Duplex Ultrasound

<table>
<thead>
<tr>
<th>Degree of Stenosis</th>
<th>African Americans (n=29)</th>
<th>Caucasians (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Minimal stenosis (1–15%)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Mild stenosis (16–49%)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Moderate stenosis (50–69%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Severe stenosis (70–99%)</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

n indicates number of patients; age-adjusted P=0.01.

Discussion

The objectives of our study were to define the etiologies of retinal arterial occlusive disease in African American patients and to compare these causes with those in a Caucasian population. We found that African American patients have a high percentage of retinal arterial occlusion of undetermined etiology and a low prevalence of moderate to severe extracranial ICA stenosis. The relationship between extracranial ICA atherosclerosis was much stronger for Caucasian patients. After correcting for age, Caucasian patients still had a 3.5-fold higher degree of carotid stenosis than African American patients. We do not feel that this substantial difference in the prevalence of extracranial carotid artery disease (41% versus 3.4%) can be explained by the baseline imbalance of age between the 2 groups, because one would not expect such a large increase in carotid stenosis over the course of a decade. Therefore, this finding is clinically important.

With regards to methodological points, our results may have been influenced by selection bias in the distribution of African American and Caucasian patients. However, the patient population from which the study groups were drawn consisted of self-referral, outside ophthalmologist referral, and general practice physician referral. Although the study was conducted in an inner-city setting with a predominantly African American population, there was no difference in referral pattern between the Caucasian and the African American patients.

Our study has certain limitations. For example, it is possible that the number of patients assigned to the undetermined etiology group may be too high because of incomplete testing. We did not obtain transesophageal echocardiography in all cryptogenic patients, and it is conceivable that occult cardiac lesions or atheromatous lesions in the ascending aorta may have been missed. Studies have described the detection of cardiac abnormalities by transesophageal echocardiography previously undetected by transthoracic echocardiography in patients with retinal arterial obstructive disease.

Second, it was not our practice to subject patients with <50% ultrasound stenosis to conventional angiography. It is possible that some patients may have had carotid plaques with mild to moderate narrowing of 30% to 49% with significant ulceration. This would not have changed the etiologic classification system, however.

Some patients had the intracranial vasculature investigated with MRA only, and MRA is not ideally suited for evaluation of the ophthalmic artery. Ophthalmic artery disease may at times be the causative factor in patients with amaurosis fugax. Finally, in our study African American patients had a higher incidence of hypertension than Caucasian patients, but this was not statistically significant, possibly because of our small sample size. However, this finding is agreement with widely published data indicating that African Americans have an increased prevalence of hypertension relative to non-Hispanic white patients.

Previous studies have attempted to correlate carotid artery disease and a variety of ocular ischemic symptoms. Sandok et al analyzed 43 patients with amaurosis fugax studied with arteriography. Only 1 patient had a normal carotid system on the symptomatic side. In the remaining patients, 42 of 43 had either stenosis (30 patients, 70%) or occlusion (12 patients, 28%) of the ipsilateral common carotid or extracranial ICA or both. In a study from Norway, 53 consecutive patients with amaurosis fugax were evaluated with ultrasound and angiography. Atherosclerotic lesions were detected in 63% of the ICA vessels on the symptomatic side, and 53% of these lesions were >75% in terms of diameter reduction. A study by Hankey and colleagues prospectively examined 98 patients with retinal infarction referred primarily from Oxford Eye Hospital, England. Of the 55 patients who underwent carotid angiography, atheromatous disease of varying severity was detected at the origin of the ipsilateral ICA in 47 patients (85%). Owing to demographic factors, it is likely that all of these studies were done in predominantly, if not exclusively, Caucasian patients.

With regard to retinal artery occlusions, Hollenhorst et al have written that “embolism is responsible for 98% of branch artery occlusions and an unknown percentage of central retinal artery occlusions.” In a study that evaluated 201 cases of BRAO for “etiology, natural history, and treatment,” no statement was made regarding the findings on carotid artery testing in the entire group. It was mentioned that carotid bruits were found in fewer than half of patients with visible retinal emboli. The presence of emboli may be important in decreasing patient life expectancy. Savino et al reported a 4- to 5-fold increase in stroke mortality in patients with visible symptomatic retinal emboli. In our study there was no significant difference between the Caucasian and African American groups with respect to visible plaques on funduscopy.

As for intra-arterial plaques, a study from the United Kingdom retrospectively analyzed 48 patients with evidence of retinal emboli on funduscopic examination who were evaluated with angiography. In this sample of 48 patients, 39 had abnormalities of the ipsilateral ICA, with the most common findings being stenosis (15 patients, degree not specified), “irregularity” (14 patients), or occlusion (7 patients).

Previous studies of retinal arterial occlusion and carotid disease have not provided sufficient detail regarding etiologies of symptoms in different racial groups. Hurwitz et al performed a comparison of amaurosis fugax patients and those with cerebral TIA and found that operable atherosclerotic lesions of the carotid arteries were more common in amaurosis fugax patients (66%) than in patients with cerebral
TIA (51%). However, only 3 of 93 patients (3%) in the amaurosis fugax group were of African American background, limiting any conclusion on causes of amaurosis fugax in African American patients. Wijman and associates found a 73.3% incidence of high-grade stenosis in ipsilateral ICA of patients diagnosed with retinal ischemia. The patient population in this study, however, was predominantly composed of elderly Caucasian males.

The relatively high percentage of retinal arterial occlusive episodes in African American patients that are classified as cryptogenic in our study is not unprecedented. Smit et al evaluated 41 patients with a clinical diagnosis of retinal embolism with a battery of tests including ECG, Holter monitoring, transcranial echocardiography, and carotid ultrasound. No cause was identified for the retinal symptoms in 27 of 41 patients (66%), a figure virtually identical to the 69% cryptogenic rate reported for African American patients in our study. The study of Smit and colleagues was done in the Netherlands, however, on a population likely to be almost entirely Caucasian.

It is possible that some of the African American patients in our study classified as cryptogenic may have had primary thrombosis in the retinal arteries. Hollenhorst et al have identified hypertensive arteriosclerosis as a cause of primary thrombosis, and hypertension does disproportionately affect African American patients. It is possible that some African American patients experience greater arteriolar damage due to hypertension, and this could lead to arterial occlusions in the presence of microemboli. Glaser has also pointed out that primary thrombosis in the retinal arterial circulation perhaps deserves reinvestigation.

In conclusion, we performed an analysis in African American patients with retinal arterial occlusive disease to examine the prevalence of moderate to severe extracranial carotid stenosis in these patients. We found a very low prevalence rate of such carotid stenosis (3%). We also found that cryptogenic arterial occlusive events (69%) were common in African American patients. In contrast, the relationship between extracranial ICA disease and retinal arterial occlusion was much stronger for Caucasian patients. Our findings are preliminary due to the limited sample size and require confirmation from other centers. Future studies should also attempt to better characterize the cohort of African American patients with cryptogenic retinal arterial occlusion in terms of causative mechanisms.

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References

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