Concomitants of Asymptomatic Retinal Cholesterol Emboli

Askiel Bruno, MD; Patrick W. Russell, DO; William L. Jones, OD; Jeffrey K. Austin, OD; Eric S. Weinstein, MD; and Susan R. Steel, RN, BSN

Background and Purpose: Asymptomatic retinal cholesterol emboli are sometimes encountered on ophthalmoscopic examination. They are associated with decreased survival, but their clinical significance is not fully known. We sought to determine which vascular risk factors are associated with such emboli.

Methods: We studied 70 consecutive men (55–84 years old) with asymptomatic retinal cholesterol emboli diagnosed in an eye clinic. Twenty-one men (57–78 years old) from the same eye clinic without retinal emboli or retinal ischemic events were randomly selected as control subjects. We determined vascular risk factors, presence of ischemic heart disease, and extracranial carotid artery disease.

Results: Patients had a higher prevalence of hypertension, smoked more, and had a higher prevalence of heterogeneous or echolucent carotid plaques on either side than did control subjects (p<0.001 for all three factors). Patients also had a higher prevalence of carotid artery stenosis ≥50% on either side and a higher prevalence of ischemic heart disease than did control subjects, but these did not reach statistical significance (p=0.06 and p=0.08, respectively).

Conclusions: Our findings suggest that hypertension and cigarette smoking may be important in the pathogenesis of asymptomatic retinal cholesterol emboli and that these emboli indicate systemic atherosclerosis rather than ipsilateral carotid artery stenosis. (Stroke 1992;23:900–902)

Key Words • embolism • retina • risk factors

Retinal cholesterol emboli are usually attributed to an atherosclerotic plaque at the common carotid artery bifurcation. These emboli can be symptomatic or asymptomatic. The relationship between asymptomatic retinal cholesterol emboli, vascular risk factors, and extracranial carotid artery stenosis has not been recently studied with the use of modern diagnostic tools. Better understanding of the factors which predispose to asymptomatic retinal cholesterol emboli may lead to a more effective prevention of vascular complications in these patients. To identify the concomitants of asymptomatic retinal cholesterol emboli we studied 70 patients and 21 control subjects.

Subjects and Methods

Between January 1989 and February 1991, we identified 70 consecutive patients with asymptomatic retinal cholesterol emboli among all patients examined in the Eye Clinic of the Albuquerque Veterans Affairs Medical Center and entered them into this study. This clinic had approximately 4,500 patient visits annually that included dilated ophthalmoscopic examination during this study. A retinal cholesterol embolus was diagnosed when an orange-, yellow-, or copper-colored fragment was seen in a retinal arteriole. An embolus was considered asymptomatic if the patient denied sudden monocular visual loss and had no monocular visual field loss on examination. Patients with symptomatic retinal emboli were excluded. Twenty-one patients of similar age without retinal emboli or ischemic ocular symptoms who were being seen in the same eye clinic during this study were randomly asked to participate as controls. All subjects were men. Patients were 55–84 (mean, 69) years old, and control subjects were 57–78 (mean, 68) years old. The reasons that patients came to the eye clinic on the day the retinal cholesterol embolus was found were as follows: for refraction, 16 patients; cataract, 15; various retinal degenerative disorders, 9; to rule out diabetic retinopathy, 8; to follow up diabetic retinopathy, 6; to follow up or rule out ocular hypertension, 4; to follow up or rule out glaucoma, 4; ocular discomfort, 3; to follow up branch retinal vein occlusion, 2; contralateral transient monocular visual loss, 1; visual fields testing after stroke, 1; and abducens nerve paresis, 1. The reasons that control subjects came to the eye clinic on the day they entered this study were as follows: cataract, 5 patients; to follow up or rule out ocular hypertension, 3; to follow up or rule out glaucoma, 3; to rule out diabetic retinopathy, 3; to rule out diabetic retinopathy, 2; refractive error, 2; macular degeneration, 1; conjunctivitis, 1; and nonspecific visual disturbance, 1.
Patients had a significantly higher prevalence of hypertension, smoked significantly more, and had a significantly higher prevalence of heterogeneous or echolucent carotid plaques on either side than did controls (p<0.001 for all three factors; Table 1). A heterogeneous or echolucent carotid plaque was seen in 52 of 55 patients (95%) whose duplex ultrasound studies were available for review; in 26 patients (47%), such abnormalities were bilateral. Patients also had a higher prevalence of carotid artery stenosis ≥50% on either side and a higher prevalence of ischemic heart disease than did controls, but this did not reach statistical significance (p=0.06 and p=0.08, respectively).

Discussion

In 1961 Hollenhorst described orange-, yellow-, or copper-colored fragments seen at retinal arterial bifurcations in 31 of 228 patients with occlusive cerebrovascular disease; he suggested that these were cholesterol crystals arising from ulcerated atherosclerotic lesions of the cardiac valves, aorta, or the carotid arteries. In 1963 David et al examined similar bright plaques from the eye of a patient with a fatal ipsilateral cerebral infarct after surgical manipulation of the ipsilateral carotid artery. The plaques were composed of doubly refractile cholesterol ester crystals whose histochemical and optical characteristics were identical to those found in the patient's carotid artery atheroma and middle cerebral artery embolus. Others have also suggested that retinal cholesterol emboli arise from carotid atherosclerotic plaques.

Among Hollenhorst's initial 31 patients with retinal cholesterol emboli, 21 (68%) were asymptomatic; of the 208 patients reported subsequently, 175 (84%) were asymptomatic. Most retinal cholesterol emboli are asymptomatic, probably because of their flat shape. When these flat cholesterol crystals lodge in a retinal arteriole, they usually do not produce an occlusion unless they are associated with a thrombus.

Arterial hypertension is a well-known vascular risk factor. Hollenhorst found hypertension in 70% of his 208 patients with retinal cholesterol emboli. The prevalence of hypertension in our patients was similar (78%) and was significantly higher than in control subjects (33%, p<0.001), which suggests that hypertension may contribute to the pathogenesis of asymptomatic retinal cholesterol emboli. Most likely, hypertension enhances atherosclerosis, which predisposes an individual to cholesterol embolization.

Cigarette smoking is also a known vascular risk factor. The duration of cigarette smoking correlates with the severity of extracranial carotid atherosclerosis. In the Framingham study, the quantity of cigarettes smoked correlated directly with the risk of stroke. In our study, patients smoked significantly more than control subjects. This suggests that smoking may also contribute to the pathogenesis of asymptomatic retinal cholesterol emboli, probably by promoting atherosclerosis.

Diabetes mellitus and hypercholesterolemia are also known vascular risk factors. Among Hollenhorst's 208 patients, diabetes mellitus was present in 21%, and hypercholesterolemia (serum cholesterol >250 mg%) was also present in 21% (29 of 136 patients tested).

### Table 1. Vascular Findings in 70 Men With Asymptomatic Retinal Cholesterol Emboli and in 21 Control Subjects

<table>
<thead>
<tr>
<th>Findings</th>
<th>Patients (n=70)</th>
<th>Controls (n=21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>69</td>
<td>68</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78%</td>
<td>33%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>89%</td>
<td>95%</td>
<td>0.68</td>
</tr>
<tr>
<td>Mean pack-years smoked*</td>
<td>56</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33%</td>
<td>29%</td>
<td>0.79</td>
</tr>
<tr>
<td>Mean total serum cholesterol (mg/dl)†</td>
<td>216</td>
<td>201</td>
<td>0.24</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>58%</td>
<td>33%</td>
<td>0.08</td>
</tr>
<tr>
<td>Carotid stenosis ≥50% ipsilateral to embolus‡</td>
<td>13%</td>
<td>0%</td>
<td>0.18</td>
</tr>
<tr>
<td>Carotid stenosis ≥50% on either side‡</td>
<td>20%</td>
<td>0%</td>
<td>0.06</td>
</tr>
<tr>
<td>Heterogeneous or echolucent carotid plaque on either side</td>
<td>95%</td>
<td>60%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Quantity of smoking was determined in 64 patients and 20 control subjects.
†Total serum cholesterol was measured in 60 patients and 20 control subjects.
‡Carotid studies were performed in 56 patients and 20 control subjects.

History of hypertension, diabetes mellitus, and ischemic heart disease was determined by patient interview and review of medical records. Ischemic heart disease was diagnosed if it was confirmed by a physician; if the electrocardiogram demonstrated myocardial infarction; or if other cardiac tests, when available, suggested ischemic heart disease. Quantity of cigarettes smoked was determined by patient interview. Each subject was referred for a carotid duplex ultrasound, total serum cholesterol determination, and an electrocardiogram if it had not been performed within the past 12 months. An Ultrasonix SD 750 duplex scanner (Yonkers, New York) with a 5-mHz Doppler probe was used. Carotid stenosis was classified as <50%, 50–79%, 80–99%, or occlusion based on the spectral analysis. We chose ≥50% stenosis as the threshold for serious carotid artery disease because the severity of carotid stenosis correlates with the risk of stroke and because at our medical center this degree of stenosis on duplex ultrasound correlates best with severity of angiographic stenosis. Homogeneous plaques were characterized by predominantly moderate-to-high, uniform echogenicity and heterogeneous plaques by predominantly echolucent or mixed echogenicity. One author read all the carotid duplex ultrasound studies unaware of whether they were from patients and which were from control subjects. Two-sided Fisher's exact test and two-sided t test were used to compare patients with controls.

Results

Results are summarized in Table 1. Carotid artery stenosis ≥50% ipsilateral to the embolus was found in 7 of 56 patients (13%); six of the patients had 50–79% stenosis, and one had occlusion. Carotid artery stenosis ≥50% contralateral to the embolus was found in 5 of 56 patients (9%); three of the patients had 50–79% stenosis, and two had occlusion. One of the patients had bilateral 50–79% carotid stenosis. All control subjects had <50% carotid stenosis on either side.
The prevalence of these vascular risk factors in our patients is similar and not significantly different from that in our control subjects. Diabetes mellitus and hypercholesterolemia do not appear to play an important role in the pathogenesis of asymptomatic retinal cholesterol emboli.

The prevalence of ischemic heart disease in our patients is similar to that in Hollenhorst's 208 patients (58% and 59%, respectively). Although in our study this is not significantly different from the prevalence in control subjects, there appears to be a trend toward an association between asymptomatic retinal cholesterol emboli and ischemic heart disease (p=0.08; Table 1).

Attention has focused on extracranial carotid atherosclerosis in patients with retinal cholesterol emboli. It has been suggested that retinal cholesterol emboli indicate an unstable carotid atherosclerotic plaque.1-7 Although asymptomatic retinal cholesterol emboli have been documented after carotid manipulation,2 arteriography,3 and carotid endarterectomy,4,6 in previous reports the carotid arteries were not studied systematically. In our study, the prevalence of carotid stenosis \( \geq 50\% \) ipsilateral to the embolus is relatively low in patients (15%) and not significantly different from that in control subjects (Table 1). However, carotid stenosis \( \geq 50\% \) on either side is more common in patients than control subjects and is nearly statistically significant (p=0.06; Table 1).

In contrast to the degree of stenosis, carotid plaque morphology is significantly different between patients and control subjects. Patients have a higher prevalence of heterogeneous or echolucent plaques on either side than do control subjects (p<0.001; Table 1). Carotid plaque morphology determined by ultrasound imaging correlates with plaque pathology15,16 and ischemic symptoms.15-19 Heterogeneous echogenicity or echoluency of a carotid plaque correlates with intraplaque hemorrhage and ischemic symptoms, whereas homogeneous medium-to-high echogenicity correlates with fibrotic, collagenous, or fibrocalcific plaque and no ischemic symptoms. Asymptomatic retinal cholesterol emboli may be a presymptomatic manifestation of heterogeneous or echolucent carotid plaques. The high prevalence of bilateral heterogeneous or echolucent carotid plaques among patients (47%) suggests systemic atherosclerosis in addition to carotid artery disease ipsilateral to the cholesterol embolus.

Our study demonstrates that asymptomatic retinal cholesterol emboli are associated with hypertension, cigarette smoking, and presence of a heterogeneous or echolucent carotid plaque on ultrasound. Carotid studies and the prevalence of ischemic heart disease suggest that asymptomatic retinal cholesterol emboli reflect systemic atherosclerosis and not ipsilateral carotid artery stenosis \( \geq 50\% \). Extracranial carotid artery plaque is a likely source of asymptomatic retinal cholesterol emboli, but the main source has not been proven. Whether such emboli are an independent risk factor for symptomatic cerebrovascular and cardiovascular disease, and how serious a risk, remains to be determined.

Acknowledgment

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References

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