Chapter 5

Symptomatic and Asymptomatic Retinal Embolism Have Different Mechanisms

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Abstract

Purpose To investigate differences between symptomatic and asymptomatic retinal embolism regarding the frequency and source of cerebral microemboli.

Methods Thirty-seven patients with transient monocular blindness or retinal infarction and 27 patients (29 eyes) with asymptomatic retinal embolism were prospectively enrolled. Patients underwent a transcranial Doppler study and noninvasive imaging of the cervical internal carotid arteries (ICA). The middle cerebral artery (MCA) ipsilateral to the affected eye was monitored for 30 minutes for microembolic signals (MES), which were saved and analyzed offline. Age-matched controls (n=15) had no history of retinal or brain ischemia, <50% ICA stenosis, and normal ophthalmologic examinations.

Results MES were detected in 0/15 (0%) controls, 11/37 (30%) MCAs in the symptomatic group (*P*=0.02), and 3/29 (10%) MCAs in the asymptomatic group (*P*=0.54). Nine of 11 (82%) symptomatic eyes with MES had ipsilateral ICA stenosis of ≥ 50%, as compared with 0/3 (0%) eyes in the asymptomatic group with MES (*P*=0.03). Both MES and ICA stenosis of >50% were present in 9/37 (24%) cases in the symptomatic and in 0/29 (0%) cases of the asymptomatic group (*P*=0.0036).

Conclusions The frequency and potential source of cerebral microemboli in symptomatic and asymptomatic retinal embolism are different. Cerebral microemboli are more frequent in symptomatic patients and are associated with ICA stenosis.

Introduction

Transient monocular blindness (TMB) has been attributed to transient ischemia of the retina caused by either embolism or vascular insufficiency, and it has been associated with stenosis or occlusion of the feeding internal carotid artery (ICA).[1, 2] Retinal emboli, particularly cholesterol emboli (Hollenhorst plaques), are frequently observed in asymptomatic patients and are associated with an increased risk for stroke and vascular death, but not with ICA lesions.[3-6] Transcranial Doppler ultrasonography (TCD) studies have demonstrated microembolic signals (MES) in the basal vessels of the brain in patients with cerebral and retinal ischemia, cardioembolic lesions, and ICA stenosis.[7-10] MES are common in patients with retinal ischemia and are associated with ICA stenosis in these patients.[11] The aim of the present study was to investigate potential differences in frequency and source of MES in patients with symptomatic and asymptomatic retinal embolism.

Methods

Consecutive patients with TMB or retinal infarction and patients with asymptomatic retinal embolism were enrolled in this study. Written consent was obtained and institutional review board approval was granted. Symptomatic patients had experienced either an episode of TMB, defined as transient, painless, monocular loss of vision usually lasting for minutes, or retinal infarction. The latter was diagnosed by a history of sudden, persistent, loss of vision in part of (or the entire) visual field of 1 eye in conjunction with the characteristic findings of central or branch retinal artery occlusion on ophthalmologic examination. Asymptomatic patients had evidence of retinal emboli on routine ophthalmologic examination and no history of visual symptoms. Fundus photographs served to confirm the ophthalmologic findings.

Patients were queried about visual symptoms, medical history, and vascular risk factors by means of a standardized questionnaire. Each patient underwent a duplex or magnetic resonance angiography (MRA) study of the ICAs, an echocardiogram, and a TCD study of the intracranial arteries, including monitoring for MES. Details regarding the methods of this study have been described in a previous report.[12]

All but 1 of the TCD studies were performed on a TC-2020 instrument by 1 of 2 technicians, who saved signals suspect for MES based on their auditory or visual characteristics. Saved signals were analyzed offline and identified as MES if they satisfied criteria published by the Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium.[13] Signals reaching an intensity of 14 dB were included in this study. TCD studies were performed within 7 days

of symptom onset in symptomatic patients and within 14 days of diagnosis in asymptomatic patients. All other evaluations were completed within 14 days in both groups.

The presence of ICA stenosis was evaluated in 37 patients by either duplex ultrasound or MRA, in 24 by both studies, and in 2 by additional contrast angiography. ICA stenosis of ≥ 50% was considered significant. Forty-nine patients underwent transthoracic echocardiograms, 6 had transesophageal studies, and 7 had both. One patient refused to undergo echocardiography. The presence of a cardiac source of embolism was determined according to TOAST classification (Trial of Org 10172 in Acute Stroke Treatment).[14] Only high-risk sources were recorded. In addition, the presence of aortic arch plaque of >4-mm thickness was considered a potential source for retinal embolism.

Statistical analyses were performed using SAS/BASE and SAS/STAT software, version 8.2 of the SAS System for Microsoft Windows (Copyright 1999 to 2001, SAS Institute Inc). Group comparisons for age were made using *t* tests; all other group comparisons were made using χ^2 and Fisher exact test (2-tailed).

Results

Of the cohort of 77 patients, 63 with 66 affected eyes are included in this report.12 Ten patients (13%) had insufficient temporal bone windows for MES monitoring, and MES data could not be retrieved for offline analysis in 4 (5%). Enrollment diagnoses in the symptomatic group were TMB in 29 and central or branch retinal artery occlusion in 8. One patient in the symptomatic group had TMB and retinal emboli in the same eye. The asymptomatic group included 27 patients with 29 affected eyes with asymptomatic retinal emboli. One of the 63 patients had 1 eye in the symptomatic and 1 eye in the asymptomatic group. Fifteen age-matched controls had no history of retinal or cerebral ischemia, no retinal emboli on ophthalmologic examination, and <50% ipsilateral ICA stenosis.

Baseline characteristics were distributed evenly between the symptomatic and asymptomatic groups as is shown in **Table 1**. MES were detected in 0/15 (0%) controls, 11/37 (30%) of symptomatic (*P*=0.022) eyes, and in only 3/29 (10%) of asymptomatic eyes (*P*=0.54). The frequency of MES in the symptomatic group was 8/29 (28%) in patients with TMB and 3/8 (38%) in those with central or branch retinal artery occlusion.

Presumed causes for retinal ischemia or embolism in the symptomatic and asymptomatic groups are shown in **Table 2**. Ipsilateral ICA stenosis was the most frequent potential source of embolism in both groups, accounting for 17/37 (46%) of eyes in the symptomatic group and in 9/29 (31%) of eyes in the asymptomatic

Table 1 Baseline Characteristics in 63 Patients (with 66 Affected Eyes) with Symptomatic Retinal Ischemia (N=37) and Asymptomatic Retinal Embolism (N=29)

Baseline Characteristic	Symptomatic Retinal Ischemia N (%)	Asymptomatic Retinal Embolism N (%)
Mean age±SD (y)	66±13	71±10
Female	8/37 (22)	2/29 (7)
Hypertension	21/37 (57)	19/29 (66)
Diabetes mellitus	9/37 (24)	12/29 (41)
Coronary artery disease	16/37 (43)	16/28* (57)
History of hyperlipidemia	25/32* (78)	17/25* (68)
Any history of smoking	33/37 (89)	21/27* (78)
Ipsilateral ICA stenosis >50%	17/37 (46)	9/29 (31)
Aortic arch lesion >4 mm	1/8* (13)	3/6* (50)
Cardioembolic lesion**	4/37 (11)	4/29 (14)
>1 Potential embolic source	3/37 (8)	3/29 (10)

*The denominators differ when information regarding a certain baseline characteristic was not available in every patient. **Determined according to the criteria used for the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Only high-risk cardioembolic sources were recorded.[14] ICA indicates internal carotid artery.

Table 2 Presumed Cause and Frequency of Cerebral Microembolic Signals in the Ipsilateral Middle Cerebral Artery in Symptomatic Retinal Ischemia (N=37) and Asymptomatic Retinal Embolism (N=29)

Cause	Symptomatic Eyes With MES N (%)	Asymptomatic Eyes With MES N (%)
ICA stenosis >50% (N=26)	9/17 (53)	0/9 (0)*
Aortic arch >4 mm (N=2)	0/0 (0)	1/2 (50)
Cardioembolism (N=4)	0/2 (0)	0/2 (0)
Other (N=5)**	0/5 (0)	0/0 (0)
No lesion identified (N=29)	2/13 (15)	2/16 (13)
Total (N=66)	11/37 (30)	3/29 (10)

*P=0.0094. **This category includes hypercoagulable states, systemic lupus erythematosus, and ophthalmic artery disease. MES indicates microembolic signals; ICA, internal carotid artery.

group. However, an association between MES and ICA disease was found only in the symptomatic group. Nine of 11 (82%) symptomatic cases with MES had ipsilateral ICA stenosis, as compared with 0/3 (0%) cases in the asymptomatic group with MES (*P*=0.03). Both MES and significant ICA lesions were present in 9/37 (24%) in the symptomatic group and 0/29 (0%) cases in the asymptomatic group (*P*=0.0036). Furthermore, within the symptomatic group, the presence of

MES was significantly associated with ICA lesions. Of the 11 eyes with MES in this group, 9 (82%) had an ipsilateral ICA stenosis as compared with only 8/26 (31%) of symptomatic eyes without MES (*P*=0.0097).

Discussion

The results of this study show that in contrast to asymptomatic retinal embolism, cerebral microembolism is relatively increased in symptomatic retinal ischemia, and it is associated with ICA stenosis. They suggest that symptomatic and asymptomatic retinal embolisms have different pathophysiologic mechanisms. The clinical correlate is the increased risk of retinal or brain infarction after TMB as compared with asymptomatic retinal embolism. These findings are consistent with the hypothesis that cerebral embolism in symptomatic patients is a more persistent process rather than a 1-time event, or that emboli in asymptomatic patients are smaller, not reaching the 14-dB threshold, and not causing retinal or cerebral symptoms. It is also possible that the composition of emboli differs between symptomatic and asymptomatic patients, and that cholesterol emboli are not detected as readily by the available TCD technology. An alternative explanation is related to the study's methodology: symptomatic patients were studied soon after symptom onset, whereas asymptomatic patients could have sustained retinal embolism weeks or months before the TCD examination. This difference in the time-to-monitoring may have affected the yield of the TCD studies in asymptomatic patients.

Retinal ischemia has been associated with various cardiac and arterial lesions, but in >40% of extensively evaluated patients no apparent cause can be detected.[12] In this study, the presence of MES in the MCA ipsilateral to the symptomatic eye was associated with an increased chance of finding a significant ICA stenosis, and it characterized this subgroup. We suspect the ICA lesions were the source of microemboli corresponding to the MES. Thus, the finding of cerebral microemboli in a symptomatic patient is clinically relevant in that it increases the likelihood that the mechanism for retinal ischemia is embolism originating from a potentially operable ICA lesion.

In the asymptomatic retinal embolism group, ICA stenosis was present in only one third of cases, and none of the 3 patients with MES in this group had substantial ICA disease. It can be argued that ICA lesions causing <50% stenosis could have served as a source for retinal emboli in these patients. Alternatively, and more likely, microemboli may have originated from more proximal large-vessel atherosclerotic lesions, such as the aortic arch.[15] An argument in favor of this hypothesis is that 3 patients (10%) in the asymptomatic group had retinal emboli affecting both eyes.

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