Retinal Ischemia and Embolism

Causes and outcomes

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Retinale Ischemie en Embolieën
Oorzaken en prognose
(met een samenvatting in het Nederlands)

Proefschrift

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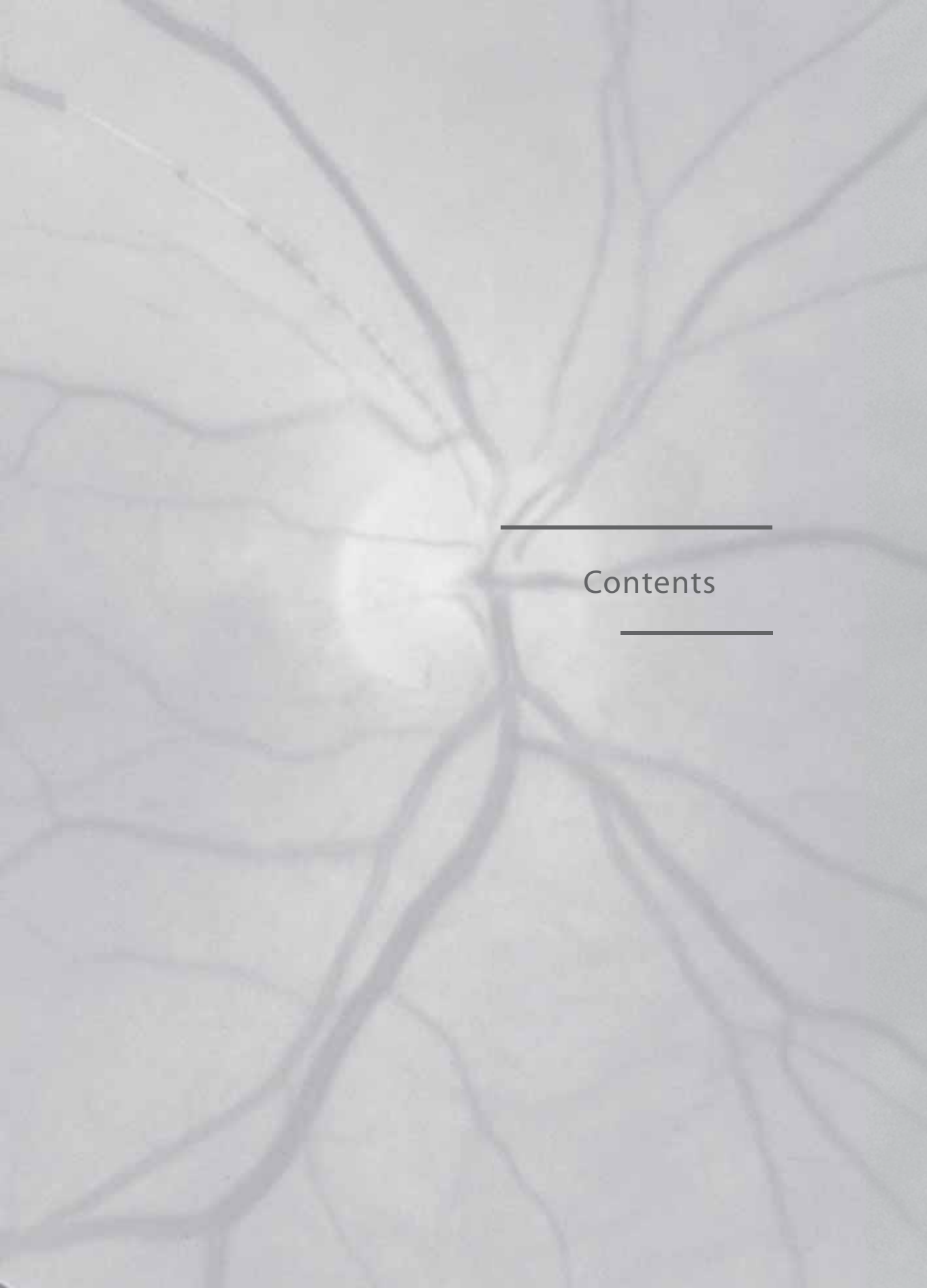
Christine Anne Cunegonde Wijman
geboren op 8 juli 1965
te Amsterdam

Promotoren: Prof. dr. L.J. Kappelle
Prof. dr. J. van Gijn
Prof. V.L. Babikian

To David, Fred, Anna, and my parents



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Introduction

Adapted from: Christine A.C. Wijman, Viken L. Babikian, Ippolit C. Matjucha. Monocular visual loss and platelet fibrin embolism to the retina.

J Neurol Neurosurg Psychiatry. 2000;68:386-387.

A 61-year-old woman was admitted to the hospital because of recurrent episodes of loss of vision affecting the right eye. Six months earlier she had sustained a retinal artery branch occlusion of the right eye, which had caused a persistent small scotoma in the inferior nasal visual field, and two corresponding areas of scarring of the superior temporal arteriole (**Figure 1**, panel D arrow heads). In the month before admission she experienced five episodes of sudden, painless, loss of vision affecting the upper half, the lower half, or the entire field of vision of the right eye, lasting 45 minutes to several hours. Vision was described as dark grey, black or absent, and occasionally accompanied by small bright moving dots. During her stay in the hospital another episode occurred. Funduscopic examination during the episode showed white, not shiny, intravascular material, typical of platelet-fibrin embolism that occupied the proximal portions of the retinal arterioles on the optic disc. Forty-five minutes later, the material broke up and advanced slowly and intermittently downstream predominantly in the superior temporal arteriole (**Figure 1**, panels A, B, C, and D black arrows). Three hours later vision had returned to baseline, and the embolic material had resolved, but a new area of arteriolar sheathing or stationary platelet-fibrin embolic material was seen in the proximal superior arterioles (**Figure 1**, panel E open arrow heads). An extensive investigation for a source of embolism including a transesophageal echocardiogram, and a contrast angiogram of the aortic arch, the carotid arteries, and the intracranial carotid system, including the ophthalmic artery, was unrevealing. She was discharged home and treated for 3 months with warfarin, followed by aspirin. She remained asymptomatic during 18 months of follow-up.

Platelet-fibrin emboli typically appear as dull, grey-white, mobile intravascular material, occupying a long arteriolar segment before breaking up. As illustrated by this case, recurrent platelet-fibrin embolism does occur in the absence of an evident source of embolism. This raises the possibility of local formation of fibrin-platelet embolic material due to an increased tendency for platelet aggregation.

Transient monocular blindness (TMB) or amaurosis fugax denotes an attack of sudden, painless, monocular loss of vision, typically lasting for minutes. TMB is often attributed to a transient episode of retinal ischemia and has been associated with atherosclerotic disease of the internal carotid artery and future cerebral and retinal ischemic events.[1-7] A common mechanism underlying TMB is thought to be retinal embolism, resulting in transient interruption of blood flow as was witnessed and photographed in the patient described above.[1] Miller Fisher was the first to describe mobile intravascular embolic material traveling through the retinal vasculature during an episode of monocular visual loss in a patient with internal carotid artery disease.[8] Since then retinal embolism has been recognized as an important cause not only of transient retinal ischemia, but also of retinal infarction in patients with

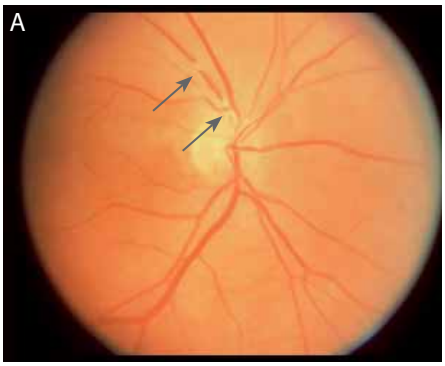
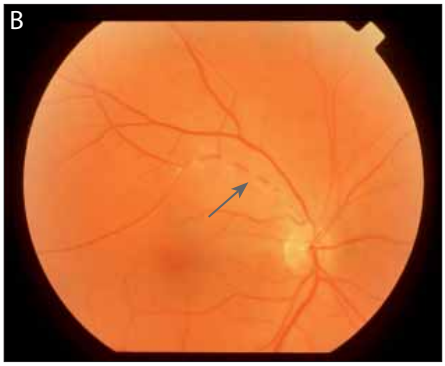
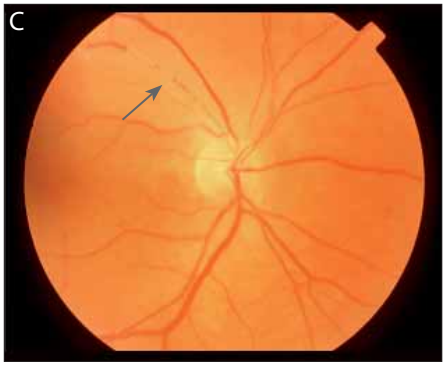
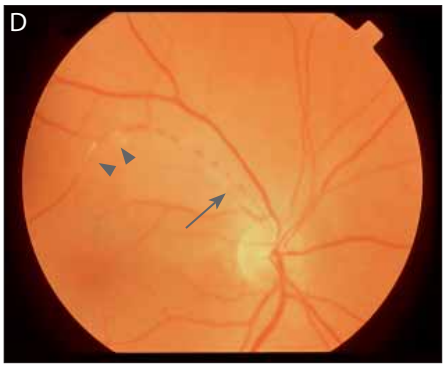
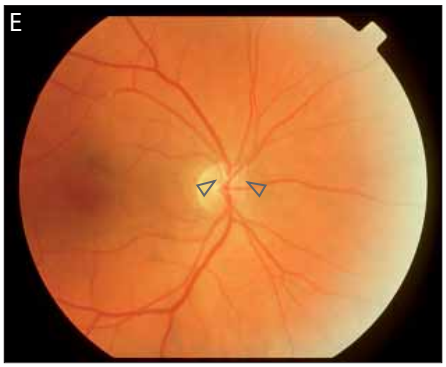


Figure 1 Consecutive funduscopic photographs of the right eye of a 61-year-old woman during an episode of transient monocular blindness. She had previously sustained a branch retinal artery occlusion, which had caused two areas of scarring of the superior temporal arteriole (panel D arrow heads). Dull, white, slowly advancing intravascular material, typical of platelet-fibrin embolism, is seen predominantly in the superior temporal arteriole (panels A, B, C, and D black arrows). After the attack the embolic material has vanished, but a new area of arteriolar sheathing or stationary platelet-fibrin embolic material is seen in the proximal superior arterioles (panel E open arrow heads). (*For full color photographs see inside front cover*).









central or branch retinal artery occlusions.[9, 10] Another important vascular cause of TMB is retinal hypoperfusion, caused either by vasospasm (retinal migraine) or by chronic narrowing or occlusion of its feeding blood vessels.[11] Other, less common causes of TMB include states of altered coaguability, inflammatory disorders, and non-vascular conditions.[12] Elucidating the cause of retinal ischemia in the individual patient is important, because it may affect treatment decisions and help assess the risk of future cerebral or retinal ischemic events.

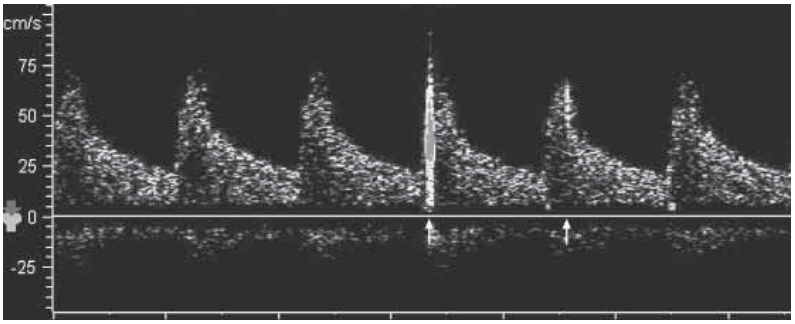
Retinal emboli may be composed of atheromatous material containing cholesterol, also called Hollenhorst plaques, platelet-fibrin material, or calcium. Cholesterol emboli in the retina are frequently observed in asymptomatic individuals during routine ophthalmologic examination and have been associated with an increased risk of stroke and vascular death.[13, 14] In patients with symptoms caused by retinal ischemia, the presence of retinal emboli has been associated with an increased risk of stroke and death when compared to symptomatic patients without retinal emboli.[15, 16] Most retinal emboli are thought to originate from atherosclerotic lesions of the ipsilateral carotid artery, but they can also originate from atheromatous disease of the aortic arch or one of its major branches, and from cardiac lesions.[17]

Emboli that travel to the retina via the internal carotid artery may be accompanied by emboli that travel to the brain, as has been confirmed by pathological studies.[18] However, since embolism is a process that tends to occur intermittently and transiently and that may occur in the absence of symptoms, it may be difficult to detect on clinical grounds alone.

The introduction of transcranial Doppler ultrasound allows non-invasive monitoring of *in vivo* embolism in the cerebral arteries. High-intensity transient signals, so called microembolic signals, can correspond to microemboli composed of thrombus, platelet-rich aggregates, atheromatous material, cholesterol, fat, and gaseous material as demonstrated by laboratory and pathological studies (**Figure 2**).[19, 20] By means of this technology, asymptomatic cerebral embolism has been demonstrated in the cerebral arteries of patients with internal carotid artery lesions, aortic arch plaque, and patients with a cardio-embolic source.[21]

In the studies described in this thesis we aimed to unravel the causes, mechanisms, and outcome of retinal ischemia and embolism in several populations. In addition to a retrospective cohort of patients with cerebral and retinal ischemia, we prospectively studied and followed a cohort of 77 patients with symptoms of retinal ischemia or with documented retinal embolism (or both). We also studied the outcome of symptoms of retinal ischemia in a cohort of patients with systemic lupus erythematosus and of migraine equivalents in the general population.

Figure 2 Transcranial Doppler ultrasonographic recording of the middle cerebral artery showing a large and a small microembolic signal within the Doppler spectrum (white arrows). (*For full color image see inside back cover*).



The specific aims of each of the studies were the following:

- To determine whether cerebral microembolism as detected by transcranial Doppler ultrasonography (TCD) in patients with cerebral ischemia identifies patients at increased risk for early, recurrent cerebral or retinal ischemic events (chapter 2).

- To investigate the frequency and source of cerebral microembolism as detected by TCD in patients with symptoms of retinal ischemia, and to assess its correlation with carotid artery stenosis (chapter 3).

- To identify the most likely causes of retinal ischemia and embolism in a prospective cohort of patients, and to determine the frequency of recurrent vascular events (chapters 4 and 6).

- To investigate differences between symptomatic and asymptomatic retinal embolism regarding the frequency and source of cerebral microemboli as detected by TCD (chapter 5).

- To investigate the relationships between emboli characteristics, visual symptoms, source, and recurrent vascular events in patients with symptomatic or asymptomatic retinal emboli (chapter 7).

- To determine the frequency, characteristics, and occurrence of stroke in patients with migrainous visual accompaniments in the Framingham cohort (chapter 8).

- To determine the incidence and prognosis of transient monocular blindness in a cohort of patients with systemic lupus erythematosus (chapter 9).

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Chapter 2

Cerebral Microembolism and Early Recurrent Cerebral or Retinal Ischemic Events

Viken L. Babikian, Christine A. C. Wijman, Charles Hyde, Nancy L. Cantelmo, Michael R. Winter, Errol Baker, Val E. Pochay

Stroke. 1997;28:1314-1318.

Abstract

Background and Purpose We investigated whether cerebral microembolism as detected by transcranial Doppler ultrasonography (TCD) identifies patients at an increased risk for early, recurrent cerebral or retinal ischemic events.

Methods Records of consecutive patients examined during a 40-month period in the Neurovascular Laboratory were reviewed for the presence of cerebral microembolism. Of the original 302 patients, 229 with 310 arteries met inclusionary criteria. Follow-up information was obtained from the laboratory's database as well as the hospital records. Microembolus detection studies were performed on TC-2000 or TC-2020 instruments equipped with special software, and criteria established a priori were used for microembolus selection. TCD testing was performed a median interval of 9 days after the initial symptoms of cerebral ischemia. Severity of arterial stenosis was determined by cerebral angiography or noninvasive methods.

Results Microembolic signals were detected more frequently in symptomatic (40/140; 28.6%) than asymptomatic (21/170; 12.4%) arteries ($P<0.001$). Ten recurrent ischemic events occurred during a median follow-up of 8 days after TCD examination, all in the territories of symptomatic arteries. Nine events occurred in the territories of microembolic signal–positive arteries (9/61; 14.8%) and one in the territory of a microembolic signal–negative artery (1/249; 0.4%) ($P<0.001$). No association was detected in the subgroup with known cardiac lesions. Microembolic signals were more frequent in arteries with lesions causing 70% or more stenosis or occlusion (26/99; 26.3%) than in those with a degree of stenosis less than 70% (17/126; 13.5%) ($P=0.016$).

Conclusions In this retrospective study, microembolic signals were more common in the territories of symptomatic arteries and particularly those with severely stenotic lesions. During a short follow-up, recurrent ischemic events were more common along the territories of arteries with TCD-detected microembolism and previous symptoms of cerebral or retinal ischemia.

Introduction

The increased incidence of recurrent cerebral ischemic events during the days and weeks after a transient ischemic attack or a cerebral infarct has long been recognized.[1] "Stroke in evolution," "progressive stroke," and early "recurrent stroke" are terms frequently used to describe the development of new neurological symptoms and imply the extension of ischemia to previously spared cerebral regions.[2,3] Clinically identified conditions such as atrial fibrillation and severe, extracranial internal carotid artery stenosis increase the risk of early recurrent events.[4,5] It is, however, frequently impossible for the treating physician to identify or monitor intravascular flow changes and embolism that may be the immediate cause of recurrent ischemia in an individual patient. Available techniques, such as cerebral angiography, are associated with a risk of complications. Brain CT or MR imaging and angiography are almost always in use. Still, these methods do not show direct, real-time evidence of microembolism. The ability to diagnose the latter is of clinical interest since its identification may potentially be helpful in selecting specific treatment modalities.

High-intensity transient signals are frequently detected during TCD testing in patients with symptoms of cerebral ischemia.[6-8] These signals, also called microembolic signals, have also been observed during operative procedures.[9,10] Laboratory and animal models suggest that they correspond to microbubbles or formed element particles composed of platelet-rich aggregates, atheromatous material, or fat.[11] Examination of carotid endarterectomy specimens shows that they may correspond to platelet and fibrin particles originating at stenotic lesions of the cervical carotid artery.[12] The ability to detect these signals is a relatively new development of TCD technology and provides a means to monitor cerebral microembolism in vivo.

In this study we investigated whether in patients with cerebrovascular disease, the presence of microembolic signals along the internal carotid or basilar artery territories was associated with new or recurrent cerebral ischemic events.

Subjects and Methods

Patients

The records of consecutive patients examined between March 29, 1993, and July 31, 1996, at the Neurovascular Laboratory of our hospital were reviewed. Three hundred two patients with 404 arteries had adequate ultrasonic windows and were examined during the study period. Most of these patients were either

hospitalized (Stroke or Vascular Surgery Services) or were followed at the outpatient Stroke Clinic. Ninety-four arteries were excluded for the following reasons: incomplete TCD data sheets or unavailable medical records (n=17), clinical and laboratory data complete but insufficient to establish diagnosis of ischemic cerebrovascular disease with reasonable certainty (n=35), follow-up duration of less than 24 hours (n=14), arterial territory of transient ischemic attack (TIA) not determined with reasonable certainty (n=10), and recent carotid endarterectomy or angioplasty ipsilateral to the insonated side (n=9). In addition, 9 arteries were excluded because of the diagnosis of concomitant neurological or hematologic diseases including subdural hematoma (n=5), giant cell arteritis (n=1), hypercoagulable state (n=1), migraine (n=1), and intracranial asymptomatic aneurysm (n=1). The remaining 310 arteries in 229 patients constituted the study sample. The study population had a mean age of 67.7 years (range, 30 to 87 years) and consisted of 223 men and 6 women. Patients were diagnosed with TIAs (n=28 arteries), transient monocular blindness or other retinal ischemic syndromes (n=36 arteries), or cerebral infarction (n=76 arteries). One hundred seventy arteries were asymptomatic.

Arteries were considered "symptomatic" when symptoms of cerebral or retinal ischemia had occurred along their territories during the 6-month period preceding TCD testing. They were otherwise labeled "asymptomatic." Arteries associated with silent infarcts detected by brain CT or MRI were considered asymptomatic.

Follow-up information was obtained from the Neurovascular Laboratory's patient records. The latter are routinely completed for each patient within 24 hours of the study and, for hospitalized patients, are updated as needed throughout the hospital stay. They contain summaries of each patient's neurological diagnoses, other medical conditions, follow-up information, and neuroradiological and TCD test results. In addition, the medical record or, for hospitalized cases, the dis-charge summary of each patient was reviewed to complete information regarding follow-up events. These documents were reviewed by two of the investigators (V.L.B., C.A.C.W.) using a structured protocol.

A diagnosis of recurrent event was made when a focal deficit of abrupt onset was detected during the period after TCD testing; when applicable, it was confirmed by neuroimaging studies to rule out cerebral edema or bleeding. For patients who had more than one follow-up cerebrovascular event, the dates of only the first event and that of the last follow-up visit were extracted for analysis. Diagnoses were established by the treating physician, almost always either a stroke neurologist or an experienced, board-certified neurology consultant. Each case was reviewed at the time of data collection to confirm the initial clinical impression.

The diagnosis of cardiac disease was based on clinical histories and electrocardiograms in all patients and either transthoracic or transesophageal echocardiograms in 120 patients. Sonos 1000 or Sonos 1500 instruments (Hewlett Packard) were used for echocardiographic testing. With the exception of one patient with atrial fibrillation and severe extracranial carotid stenosis who had recurrent, stereotypical TIAs ipsilateral to the stenosed carotid and whose TIAs resolved after carotid endarterectomy, arteries in patients with atrial fibrillation (n=34), prosthetic heart valves (n=20), ventricular aneurysms (n=9), left ventricular thrombi (n=4), and severe akinetic segments of the left ventricle (n=13) were considered "cardiac" for the purpose of analysis in this study. There were no patients with infective endocarditis, recent myocardial infarction, atrial septal defect, or left atrial myxoma in the study group.

At the time of TCD testing, most patients were receiving antiplatelet or anticoagulant therapy, in addition to their regular medications. Analyses probing the possible effect of treatment on clinical outcome or the prevalence of microembolism were not performed.

TCD Studies

TCD studies were performed on either a TC-2000 or a TC-2020 instrument (Nicolet/EME) equipped with special software for microemboli detection. With the help of a specially designed headband, a 2-MHz probe was immobilized against the temporal bone of each patient, and the distal internal carotid artery or proximal middle cerebral artery was insonated. For studies of the basilar artery, the probe was handheld. The technique of TCD testing has been described before.13 Each microemboli detection study lasted 30 minutes. An experienced technologist monitored the patient as well as the instrument throughout each study and kept a log of potential sources of artifact. Potential microembolic signals were identified as they occurred and were saved on floppy disk for subsequent analysis.

Criteria for microembolic signals were established before data collection. Accepted signals were more than 25 milliseconds in duration, most lasting less than 100 milliseconds; they had an intensity of at least 9 dB above that of the background blood flow, were unidirectional within the Doppler velocity spectrum, and were accompanied by a "chirp" on the audio output. In individuals with more than one TCD examination, only the findings of the first study were included for data analysis.

Cerebrovascular Imaging Studies

The carotid arteries and intracranial vessels were imaged by contrast cerebral angiography in 93 arteries, Duplex ultrasonography in 154, and MR angiography in 43. Imaging studies were not obtained in 20 arteries. With the exception of 35 cases in which the original films could not be located, all imaging studies were reviewed. The original radiology report was used when films could not be located.

The severity of arterial stenosis, when determined by cerebral angiography or MR angiography, was based on a formula modified from Wiebers et al[14] and presented in another report.[8] It was divided into four categories: mild (0% to 29%), moderate (30% to 69%), and severe (70% to 99%) stenosis and complete occlusion. A 1.5-T Signa unit (General Electric Medical Systems) was used for MRI. An Ultramark 9-HDI instrument (Advanced Technology Laboratories) was used for duplex imaging. The severity of stenosis determined by ultrasound studies was based on the criteria published in 1996 by Hood et al,[15] and studies performed before that date were reread.

Statistical Methods

All data were stored on a personal computer with the use of Microsoft Excel software (version 5.0). Group comparisons were made with the χ^2 test, Fisher's exact test (two-tailed), or the Wilcoxon rank sum test. Statistical analyses were performed at the Data Coordinating Center of the Boston University School of Public Health.

Results

Microembolic signals were detected in 61 of 310 arteries (19.7%). They were more frequent in symptomatic (40/140; 28.6%) than asymptomatic (21/170; 12.4%) vessels. The difference between the two groups was significant (P<0.001). Further analyses showed that this association did not reach statistical significance in patients with identified cardiac lesions (**Table 1**).

Table 1 Frequency of Microembolic Signal–Positive Arteries in Symptomatic and Asymptomatic Subgroups

Subgroup	Symptomatic	Asymptomatic	P	RR	95% CI
All arteries	40/140 (28.6%)	21/170 (12.4%)	<0.001	2.3	1.4-3.7
All except cardiac arteries	33/104 (31.7%)	10/126 (7.9%)	<0.001	4.0	2.1-7.7
Cardiac arteries only	7/36 (19.4%)	11/44 (25.0%)	0.554	. . .	. . .

Two cerebral infarcts and 8 transient cerebral or retinal ischemic events occurred along the territories of 10 arteries within 30 days after the TCD testing. All of these recurrent events occurred in the territories of symptomatic arteries. Nine events occurred in the territories of 61 microembolic signal–positive arteries and 1 in the territory of 1 of the 249 microembolic signal–negative arteries. The latter, a TIA, occurred along the distribution of an internal carotid artery with a severe extracranial stenosis. The difference between microembolic signal–positive and –negative arteries with regard to recurrent events after TCD testing was significant (P<0.001; RR, 36.7; 95% CI, 4.7 to 284.5). Additional analyses of subgroups of the study sample are summarized in **Table 2**. No significant association was found between the presence of microembolic signals and recurrent ischemic events in patients with identified cardiac lesions.

Table 2 Frequency of Recurrent Ischemic Events in Microembolic Signal–Positive and –Negative Arteries

Subgroup	No. (%) of Arteries		P	RR of Recurrent Event	95% CI
	MS+	MS-			
All arteries	9/61 (14.8)	1/249 (0.4)	<0.001	36.7	4.7-284.5
All except cardiac arteries	8/43 (18.6)	1/187 (0.5)	<0.001	34.8	4.7-270.9
Cardiac arteries only	1/18 (5.6)	0/62 (0)	0.062	. . .	. . .
Symptomatic arteries only	9/40 (22.5)	1/100 (1)	<0.001	22.5	3.0-171.9

MS+ indicates microembolic signal–positive arteries; MS-, microembolic signal–negative arteries

The median follow-up after TCD testing for microemboli was 8 days for the group of 310 arteries; it was 3 days for the subgroup of arteries with recurrent events and 8 days for those without recurrence. TCD testing was performed a median interval of 9 days after the initial symptoms of cerebral ischemia.

The relationships between the severity of arterial stenosis, the presence of microembolism, and recurrent clinical events were studied in patients who did not have identified cardiac lesions. Two hundred thirty arteries were designated as "noncardiac"; in 5, imaging studies of the cerebral vasculature were not obtained. The remaining 225 were divided into the following categories: mild stenosis (n=60 arteries), moderate stenosis (n=66 arteries), severe stenosis (n=76), and occlusion (n=23). The frequency of microembolic signals was significantly higher in the groups with occlusion or stenosis equal to or exceeding 70% (26/99; 26.3%) than in the groups with stenosis less than 70% (17/126; 13.5%) (P=0.016; RR, 1.95; 95% CI, 1.1 to 3.4). Further analyses regarding the effect of increasing degrees of stenosis on microembolic signals are presented in **Table 3**.

Table 3 Frequency of Microembolic Signal–Positive Arteries by Degree of Luminal Stenosis

Degree of Luminal Stenosis	No. (%) of MS+ Arteries	Group Comparison	P	RR	95% CI
Group A (<70%)	17/126 (13.5)	. . .	. . .	. . .	. . .
Group B (70-99%)	22/76 (29.0)	Groups A vs B	0.007	2.2	1.2-3.8
Group C (70-100%)	26/99 (26.3)	Groups A vs C	0.016	2.0	1.1-3.4

MS+ indicates microembolic signal–positive arteries.

No significant association was found between the degree of arterial stenosis and recurrent cerebral or retinal ischemic events.

Discussion

The findings of this study indicate that in patients without cardiac embolic sources, microembolic signals in the territory of a symptomatic cerebral artery can be precursors of recurrent ischemic cerebrovascular events in the distribution of that artery. In addition, the findings show that microembolic signals are more prevalent along the territories of cerebral arteries with severely stenotic lesions.

Several limitations must be taken into consideration when the results of this study are interpreted. First, the retrospective nature of the investigation may have affected the data. The need for a prospective investigation is recognized. Second, the selection of a microembolic signal intensity of 9 dB probably introduced a bias in the study sample toward large particles. Third, the majority of patients were receiving some form of antiplatelet or anticoagulant therapy at the time of TCD testing and during the follow-up period. These medications may have affected the rate of both recurrent ischemic events and microembolic signals and may have introduced an unmeasurable error in the study's findings. Fourth, multiple imaging modalities were used to measure the severity of arterial stenosis, introducing a degree of inconsistency to our methods. However, even when a relatively crude measure of stenosis based on the criterion of 70% was used rather than stratified values based on small, incremental increases, a significant association was found. The need to complete a similar study using one imaging technology is also recognized.

The finding of a significant association between microembolic signals and recurrent cerebral ischemia in symptomatic patients without clinically detected cardiac sources for embolism considerably extends the observations of previous studies. Although other investigators have found an association between microembolic

signals and symptoms of cerebral ischemia, in most studies TCD testing was performed after these symptoms were clinically evident,[7, 8, 16] an observation confirmed by this investigation. Two published studies present data about patients who were prospectively monitored after TCD testing for microembolism. Siebler et al[17] followed 48 asymptomatic patients with severe carotid stenosis after TCD testing and found that a middle cerebral artery microembolic rate of 2 or more per hour is associated with an increased risk of developing cerebral ischemia in the territory of the ipsilateral internal carotid artery. Tegeler et al[18] reported a trend toward an increased risk for recurrent cerebral ischemic events among those of the 66 patients with cerebral infarction who had positive microemboli studies at baseline. An association between microembolic signals during carotid endarterectomy and perioperative cerebral infarction has also been reported,[9] and microembolic signal counts have been linked to the neuropsychological deficit after cardiopulmonary bypass surgery.[10] When our observation is reviewed in conjunction with those of the preceding studies, it indicates that the presence of microembolic signals may have diagnostic value by identifying patients at an increased risk for early, recurrent cerebral or retinal ischemia.

Worsening of the neurological condition during the days after the initial symptoms of cerebral ischemia can be seen in 4% to 50% of patients.[1, 2, 19-23] Recurrent cerebral embolism,[21, 22] impaired collateral flow,[24] and other factors[20] can contribute to further progression of the original neurological deficit. The exact impact of each of these factors in an individual patient is often not known. In this study, 9 of 10 recurrent ischemic events occurred along the distribution of arteries with ultrasonic evidence of microembolism, suggesting that the latter has a high prevalence in this setting. However, given the study's technical limitations and the small number of recurrent events during the follow-up period, a cause and effect relationship between microembolism and recurrent cerebral ischemia could not be proven. In addition, although the association's RR values were high, wide 95% confidence intervals did not establish reliable estimates of these values.

The 4% incidence of new cerebrovascular events during follow-up in this study is low compared with the results of investigations referenced above. It is not unexpected, because only retinal or cerebral ischemic events occurring after TCD testing were included in this analysis. TIAs and cerebral or retinal infarcts that occurred during the 9-day interval between the onset of symptoms and TCD testing were excluded, thus limiting the total number of recurrences. In addition, only recurrent ischemic events that occurred in the territories of insonated arteries were taken into account, and patients with clinical diagnoses

of neurological worsening secondary to other causes were excluded. Because this is a retrospective study and not all patients were monitored for prolonged periods of time, it is possible that some recurrent events were not detected. Given the exhaustive nature of our review, we doubt that this limitation had a severe impact on the main findings.

Extensive clinical experience provides support to the notion of a cause and effect relationship between severe arterial stenosis and cerebral infarction.[4, 25-28] Severe arterial stenosis was associated with microembolic signals in this study, suggesting that microembolism can be considered a link in the cause and effect chain. Pathological examination of specimens obtained at carotid endarterectomy consistently shows that atheromatous debris and intraluminal thrombi are regularly present in these lesions.[26, 29] Plaque ulceration and lumen thrombus are also the main sources of microembolic signals in high-grade internal carotid artery stenosis.[30] The lack of association between severity of stenosis and recurrent events in this study is to be noted. Taken in conjunction with the significant association between microembolic signals and recurrent events, it supports the previously established notion of embolism as a risk factor for ischemic events irrespective of the severity of stenosis. Its exact causes remain undetermined.

The clinical relevance of microembolic signals in patients at an increased risk for cardioembolic stroke remains unknown. Although microembolic signals have predictive value in subjects with left ventricular assist devices,[31] in patients with prosthetic cardiac valves they are not associated with stroke.[6] No significant association was detected in cardiac patients in this investigation either; however, the number of studied arteries was too small to derive any conclusions. The reasons for this apparent disparity between patients with or without cardiac sources for embolism are undetermined. Cardiac lesions form a heterogeneous group, with subgroups associated with microemboli of variable composition.[6, 7, 32] The potential for cerebral ischemic damage from microembolism may vary among these subgroups.

In summary, microembolic signals are more common in the territories of symptomatic cerebral arteries, particularly those with severely stenotic lesions, and are associated with an increased risk of recurrent ischemic events. The exact extent of this risk and other specific features of microembolism, such as emboli count or particle size, remain unknown.

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Chapter 3

Cerebral Microembolism in Patients with Retinal Ischemia

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Abstract

Background and Purpose We investigated the frequency of cerebral microembolism detected by transcranial Doppler ultrasonography in patients with clinical evidence of retinal ischemia, including transient monocular blindness, central and branch retinal artery infarction, and ischemic oculopathy, and assessed its correlation with carotid artery stenosis.

Methods Records of 331 consecutive patients examined during a 47-month period at the Neurovascular Laboratory were reviewed. Of the original 453 intracranial arteries, 186 middle cerebral arteries (MCAs) satisfied qualifying criteria that excluded patients with cardiac embolic sources. Forty-five MCAs ipsilateral to the symptomatic eye constituted the study group. The control group consisted of 141 asymptomatic MCAs. Microembolus detection studies were performed on transcranial Doppler instruments equipped with special software, and the degree of carotid artery stenosis was measured by cerebral or MR angiography or by color duplex studies.

Results Microembolism was detected in 40.0% of study MCAs and 9.2% of controls ($P<0.001$). In the study group, microembolic signals were detected in 61.9% of MCAs tested within a week of symptom onset and 20.8% of those tested afterward ($P<0.001$). Severe (≥70%) carotid stenosis or occlusion was more frequent in the study group ($P<0.001$). Microembolic signals were detected in 25.3% and 11.2%, respectively, of MCAs distal to carotid arteries with 70% to 100% and 0% to 69% stenosis ($P=0.013$).

Conclusions In patients without cardiac embolic sources, cerebral microembolism is frequently present on the side of retinal ischemia, particularly during the week after onset of symptoms. It is often associated with severe stenosis or occlusion of the ipsilateral carotid artery.

Introduction

Transient monocular blindness (TMB) is recognized as a warning sign for retinal and cerebral infarction[1-4] and is associated with internal carotid artery (ICA) disease. [5-7] Common mechanisms of TMB are embolism, causing transient occlusion of retinal arterioles, and retinal vascular insufficiency secondary to a hemodynamically significant stenosis of feeding arteries.[8] Other less common etiologies include vasospasm, states of altered coagulability, and thrombocytosis.[9] Since treatment strategies may be influenced by the mechanism of TMB, identification of the cause in an individual patient is of considerable clinical importance.

The notion of retinal embolism as an important cause of not only TMB but also of other forms of retinal ischemia, such as central or branch retinal artery occlusion, is predominantly based on clinical observations.[10-15] In some patients, embolic material has been observed to course through retinal arterioles during episodes of transient monocular visual loss.[10, 11] However, retinal embolism tends to occur transiently and intermittently16 and thus cannot be excluded on clinical grounds alone.

Emboli that originate from ICA or more proximal vascular lesions can travel not only to the retina but also to cerebral branches of the ICA,[11, 17] and pathological evidence of cerebral emboli originating from ICA plaques has been demonstrated in this context.[18] In addition, clinically undetectable cerebral embolism has been shown with cerebral angiography and indirectly with cerebral blood flow studies and electroencephalography in patients with transient retinal ischemia.[19] However, these studies are not routinely obtained because of their invasiveness or lack of sensitivity. Therefore, the frequency of in vivo cerebral embolism in patients with retinal ischemia is presently unknown.

High-intensity transient signals detected by transcranial Doppler ultrasonography (TCD) have been identified in the intracranial vasculature of asymptomatic individuals as well as in patients with symptoms of cerebral ischemia associated with cardiac lesions[20-22] or high-grade ICA stenoses.[23-25] Laboratory models and pathological studies show that these signals can correspond to microemboli composed of thrombus, platelet-rich aggregates, atheromatous material, cholesterol, fat, and gaseous material.[26, 27] The ability to detect these signals provides a means to monitor cerebral microembolism in vivo.

In this study we investigated the frequency of cerebral microembolism in patients with clinical evidence of retinal ischemia, including TMB, central and branch retinal artery infarction, and ischemic oculopathy, and assessed its correlation with carotid artery stenosis.

Subjects and Methods

Subjects

The records of consecutive patients who were examined between March 29, 1993, and February 21, 1997, at the Neurovascular Laboratory of this tertiary care medical center were reviewed. During this time period, 453 intracranial arteries in 331 patients were examined for the presence of microembolic signals. Of these, all middle cerebral arteries (MCAs) in patients with clinical evidence of ipsilateral retinal ischemia with or without associated symptoms of cerebral ischemia (n=51) and all asymptomatic MCAs (n=198) were selected for the purpose of this study. MCAs on the side of a recent carotid endarterectomy (n=10), arteries with incomplete data sheets or missing medical records (n=6), and arteries in patients with other concomitant cerebrovascular diagnoses (n=7) were excluded.

Clinical evidence of retinal ischemia included patients with TMB and patients with retinal infarction (central and branch retinal artery occlusion and ischemic oculopathy). TMB was defined as painless, transient, monocular visual loss, with complete resolution usually within minutes of symptom onset. Its diagnosis was clinically verified by one of the authors, a neurologist. Cases of central or branch retinal artery occlusion were confirmed by formal ophthalmologic examination. Chronic ocular ischemia was diagnosed in one patient, who had complete loss of vision ipsilateral to an occluded ICA with associated neovascular glaucoma, clouding of the cornea, and neovascularization of the iris. Patients with clinically silent retinal emboli were not included in this study.

Patients with evidence of cardioembolic disease were excluded from the study. All patients were routinely evaluated for the presence of cardioembolic disease by history, physical examination, and admission electrocardiograms; results of transthoracic or transesophageal echocardiograms were available in 23 patients with retinal ischemia and in 94 patients with asymptomatic MCAs. Six MCAs were excluded in the group of patients with retinal ischemia and 57 in the group of asymptomatic MCAs. Reasons for exclusion were atrial fibrillation (n=29), prosthetic heart valves (n=13), akinetic segments (n=11) or aneurysms (n=6) of the left ventricle, cardiac thrombi (n=2), recent myocardial infarction (n=1), and right-left shunts (n=1). The presence of aortic arch atheroma with debris was not considered a criterion for exclusion.

After patients with cardioembolic disease were excluded, the study group consisted of 45 MCAs in 44 patients with ipsilateral retinal ischemia. All patients had unilateral symptoms except for one patient who had episodes of TMB affecting one eye or the

other at different times. Thirty MCAs were in patients with TMB alone, 7 in patients with TMB and transient ipsilateral hemispheric ischemia or infarction, 7 in patients with central or branch retinal artery occlusion, and 1 in a patient with ischemic oculopathy as described above. The 141 asymptomatic MCAs in 119 patients who had no symptoms of the ipsilateral retina or cerebral hemisphere and who had no cardioembolic lesions served as controls.

Antithrombotic medications prescribed during TCD testing were reviewed. In the group of symptomatic MCAs, 40 were in patients receiving antiplatelet agents or anticoagulants, 4 were in patients on no antithrombotic agents, and data were not available in 1 case. The corresponding figures for the asymptomatic group were 104, 34, and 3, respectively. An analysis of these data showed that the study sample was too small to determine the potential effects of these drugs on the prevalence of microembolic signals.

TCD Studies

Transcranial Doppler studies were performed on either a TC-2000 or a TC-2020 instrument (Nicolet/EME) equipped with software for microemboli detection. The Neurovascular Laboratory's methods and criteria for identification of microembolic signals have been described previously.[23, 28] The criteria for identification of microembolic signals are similar to the ones established by the Consensus Committee.[29]

Cerebrovascular Imaging Studies

The presence of ICA disease proximal to the corresponding MCA was determined by cerebral angiography, duplex ultrasound, or MR angiography (MRA). An Ultramark 9-HDI instrument (Advanced Technology Laboratories) was used for duplex imaging, and a 1.5-T Signa unit (General Electric Medical Systems) was used for MRI. The original films were reviewed to determine the degree of ICA stenosis. In patients with multiple imaging modalities, the cerebral angiogram was used whenever it was available, and the duplex ultrasound was preferred over the MRA. The degree of ICA stenosis was determined by contrast cerebral angiography in 63, duplex ultrasound in 101, and MRA in 18 arteries in the study. The distribution of these three imaging modalities was not different between the study and the control groups. Films were not available for review for seven arteries in the study group and 19 arteries in the control group, and the radiology reports were used instead. No imaging studies were obtained in four asymptomatic arteries. The methods of determining the degree of stenosis by contrast cerebral angiography and MRA have been described in an earlier report.[23] The severity of stenosis by duplex ultrasound was based on the criteria of Faught et al[30] and Hood et al.[31]

The degree of extracranial ICA was divided into one of four categories: mild stenosis (0% to 29%), moderate stenosis (30% to 69%), severe stenosis (70% to 99%), and occlusion.

Statistical Methods

All data were stored on a personal computer with the use of Microsoft Excel software (version 5.0). Group comparisons were made with the X^2 test, Fisher's exact test (two-tailed), or the Wilcoxon rank sum test. Adjusted group comparisons were made with the Mantel-Haenszel X^2 test. All statistical analyses were performed at the Data Coordinating Center of the Boston University School of Public Health with the use of the SAS System for Windows, Release 6.12.

Results

The mean ages of the study and control populations were 70.0 years (range, 51 to 91 years) and 67.1 years (range, 30 to 91 years), respectively. Age distribution was not significantly different between the two groups. All MCAs in the study group were from male patients, as were all but four MCAs in the control group.

Microembolic signals were detected in 40.0% of MCAs in the study group and in 9.2% of MCAs in the control group. The difference between the two groups was significant (**Table 1**). In the subgroup of patients with TMB (with or without associated cerebral ischemia), microembolic signals were detected in 16 of 37 MCAs (43.2%). Again, there was a significant difference with the asymptomatic group ($P<0.001$; OR, 7.5; 95% CI, 3.2 to 17.8).

The median time interval between onset of symptoms and TCD testing was 9 days (range, 0.16 to 250 days). Microembolic signals occurred in 13 of 21 study group MCAs (61.9%) that were tested within a week from symptom onset (**Table 1**) and in only 5 of 24 MCAs (20.8%) that were tested more than a week after the onset of

Table 1 Frequency of Microembolic Signals in MCAs of Patients with Ipsilateral Retinal Ischemia and in Asymptomatic MCAs

Subgroup	Frequency of Microembolic Signals	P	OR	95% CI
MCAs in patients with ipsilateral retinal ischemia	18/45 (40.0%)	<0.001	6.6	2.9–15.0
MCAs in patients with ipsilateral retinal ischemia tested within 7 days	13/21 (61.9%)	<0.001	16.0	5.6–45.7
Asymptomatic MCAs	13/141 (9.2%)	...	...	...

MCA = middle cerebral artery

symptoms. The difference between the two groups was significant (*P*=0.005; OR, 6.2; 95% CI, 1.6 to 23.1).

Twelve of the patients in the study group with microembolic signals underwent microembolic detection studies of both MCAs, one on the side of the symptomatic eye, and one on the asymptomatic side. Of these, 10 (83.3%) had microembolic signals only in the MCA ipsilateral to the symptomatic eye, 1 (8.3%) in both MCAs, and 1 (8.3%) in only the asymptomatic MCA. Thus, when present, microembolic signals usually occurred only on the side of the symptomatic eye.

The incidence of microembolic signals correlated with the degree of ICA stenosis proximal to the corresponding MCA. Microembolic signals occurred in 19 of 75 MCAs (25.3%) distal to ICAs with luminal stenosis of 70% or more and in only 12 of 107 MCAs (11.2%) distal to ICAs with luminal stenosis of 69% or less (*P*=0.013; OR, 2.7; 95% CI, 1.2 to 5.9). (Note that n=182 because there are no data available on the severity of ICA stenosis for four MCAs in the control group.)

Severe ICA stenosis occurred more frequently in the study group than in the control group (**Table 2**). Severe ICA stenosis or occlusion was present proximal to 33 of 45 MCAs (73.3%) in the study group and 42 of 137 MCAs (30.7%) in the control group (*P*<0.001; OR, 6.2; 95% CI, 2.9 to 13.2).

Table 2 Degree of ICA Stenosis Proximal to MCAs of Patients With Ipsilateral Retinal Ischemia and Asymptomatic MCAs

	Severity of ICA Stenosis			
Subgroup	**Mild (0–29%)**	**Moderate (30–69%)**	**Severe (70–99%)**	**Occluded (100%)**
ICAs in patients with ipsilateral retinal ischemia	5/45 (11.1%)	7/45 (15.6%)	27/45 (60.0%)	6/45 (13.3%)
ICAs proximal to asymptomatic MCAs	45/137 (32.8%)	50/137 (36.5%)	36/137 (26.3%)	6/137 (4.4%)

ICA = internal carotid artery; MCA = middle cerebral artery

ICA stenosis of less than 30% was observed in five study group patients, three without and two with microembolic signals in the MCA ipsilateral to the symptomatic retina. Transesophageal echocardiography showed moderate to severe aortic arch plaques exceeding 5-mm thickness in the latter two patients.

Because of the significant correlation between the frequency of microembolic signals and the degree of ICA stenosis and the higher frequency of severe ICA

stenosis in the study group, the interaction between these variables was analyzed further. After we controlled for the degree of ICA stenosis, the MCAs in the study group were still five times more likely to have microembolic signals than the MCAs in the control group ($P<0.001$; OR, 5.0; 95% CI, 2.2 to 11.4).

Discussion

In this study we determined the frequency of in vivo cerebral microembolism in patients with retinal ischemia. Microembolic signals were detected in 40% of MCAs in patients with ipsilateral symptoms of retinal ischemia and in 62% of those tested within a week from symptom onset. These rates are more than four and six times as high, respectively, as the rate of cerebral microembolism in the asymptomatic controls. In addition, microembolic signals were usually detected only on the side of the symptomatic eye, indicating that symptoms of retinal ischemia coincide with the presence of cerebral microembolism. Despite this high frequency of cerebral microembolism in the study group, it is likely that we underestimated the true frequency of cerebral microembolism. Half-hour microembolic signal detection studies may be too short to identify all patients with cerebral microembolism.[32] Furthermore, the frequency of microembolic signals peaks between 4 and 6 AM,[32] a test period that is outside the regular hours of our laboratory. In addition, although the microembolic signal criteria that we used were similar to those established by the Consensus Committee,[29] "small" particles less than 9 dB in intensity were excluded, possibly resulting in an underestimation of the true frequency of microembolism. Nevertheless, our findings support the notion of an embolic etiology[33] in the majority of cases with retinal ischemia. Embolism may either be the sole or one of several causal factors.

Retinal ischemia is associated with ICA disease.[5-7] In this study a high-grade ICA stenosis of 70% or more, or occlusion, was detected in 73% of cases with retinal ischemia. The frequency of cerebral microembolism correlated significantly with the severity of ICA stenosis, suggesting that the source of the microemboli was often the ipsilateral carotid artery. However, after we controlled for the degree of ICA stenosis, microembolism was still five times more likely to occur in the arteries of symptomatic patients, indicating that additional factors contributed to the association of cerebral microembolism with retinal ischemia. One of these factors might be the level of activity of the ongoing process in the vascular wall. It is of interest that embolism to the retina may arise from embolic sources other than the ICA. Two patients with cerebral microembolism and without ICA stenosis had severe atheromatous aortic arch plaques.

The majority of our patients with retinal ischemia and cerebral microembolism did not have symptoms of cerebral ischemia, nor did the cases with cerebral microembolism in the asymptomatic control group. These microemboli were "silent" in that they did not result in clinically detectable neurological deficits. Indirect evidence of clinically undetectable cerebral involvement in patients with retinal ischemia has been reported previously,[19] and pathological studies have shown incidental emboli in the lumen of cerebral arterioles without evidence of ischemic changes in the adjacent brain tissue.[34, 35] In addition, silent retinal embolism is frequently detected by routine funduscopic examination in patients without clinical evidence of retinal ischemia.[15, 36] Thus, asymptomatic retinal and cerebral emboli occur and do not always precede clinically or radiologically evidenced ischemia or infarction. Conversely, longitudinal follow-up studies suggest that retinal emboli as detected on funduscopic examination[2, 15] and cerebral microemboli[24] as detected by TCD are both associated with an increased risk for subsequent cerebral infarction. However, the magnitude of this risk is presently unknown.

This study has several limitations. First, the patient population consisted pre-dominantly of elderly white men, many with multiple risk factors for cerebrovascular disease referred to a tertiary care medical center. The relevance of our findings to an unselected population should be interpreted in this context. Other mechanisms of retinal ischemia may occur more frequently in different patient populations. Second, data were collected retrospectively and should be interpreted within the limits of such a study design. Third, the effects of antiplatelet agents and anticoagulant drugs on cerebral microembolism remain undetermined and may have affected the study's results. Lastly, various imaging modalities were used to determine the severity of ICA stenosis, thereby introducing a certain degree of inconsistency in the methods.

In summary, in patients without cardioembolic sources, cerebral microembolism is frequently present on the side of retinal ischemia, particularly during the week after onset of symptoms. It is often associated with severe stenosis or occlusion of the ipsilateral ICA.

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Chapter 4

Retinal Ischemia and Embolism. Etiologies and Outcomes Based on a Prospective Study

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Abstract

Objectives To identify the most likely mechanisms of retinal ischemia and embolism in a hospital referred population, and to determine the frequency of recurrent vascular events during the 3-month period following initial presentation.

Methods Consecutive patients presenting to 2 tertiary medical centers and their outpatient clinics were prospectively enrolled over a 22-month period. Eligible patients presented with histories of transient or permanent monocular visualloss, or had evidence of asymptomatic retinal embolism on routine ophthalmological examination. They underwent a rapid and standardized evaluation that included imaging studies as well as blood tests, and follow-up was obtained at 1 and 3 months.

Results Seventy-seven patients were enrolled. Enrollment diagnoses consisted of amaurosis fugax (n = 32), asymptomatic retinal embolism (n = 34), and central or branch retinal artery occlusion (n = 11). Eight different presumed etiologies of retinal artery distribution embolism or hypoperfusion were identified. Extracranial internal carotid artery occlusion or more than 50% stenosis was observed in 17/77 (22.1%) cases, making it the largest etiologic subgroup. Uncommon but treatable conditions were identified in 8/77 (10.4%) patients, and an etiologic diagnosis could not be made in 35/77 (45.5%) patients. Recurrent events occurred in, respectively, 14/77 (18.2%) and 6/73 (8.2%) patients at the 1- and 3-month follow-ups. They included 2 infarcts and 2 deaths; ischemic events of the retina were more common than those involving the brain.

Conclusions Severe stenosis of the extracranial internal carotid artery is the most common identified condition associated with retinal ischemia and embolism, but a variety of other, potentially treatable, conditions can be diagnosed if appropriate and specific evaluations are conducted. The frequency of recurrent vascular ischemic events is highest during the 1st month of follow-up and decreases during the 2nd and 3rd months. Recurrences range from relatively innocuous episodes of amaurosis fugax to vascular death.

Retinal ischemia and embolism have been associated with a multitude of etiologies including atherosclerotic plaques of the internal carotid artery and aortic arch[1, 2] cardiac lesions[3] and hematological or inflammatory disorders.[4, 5] The frequency of these conditions and their relationships with early retinal, cerebral and systemic vascular recurrences has not been assessed with currently available advanced diagnostic technologies except for a very limited number of studies.[6–8] This information is of special relevance in the clinical setting, when a patient presents with monocular visual loss of sudden onset or asymptomatic retinal embolism, and a decision has to be made regarding the pace and extent of the diagnostic workup and the corresponding, appropriate treatment.

The aim of this study was to identify the frequency of conditions associated with retinal ischemia and embolism in a population referred to two tertiary medical centers. A structured battery of diagnostic tests was used to detect these conditions. The second aim was to determine the frequency of recurrent vascular events during the 3 months following initial presentation.

Methods

Patients

Consecutive patients referred to the Neurology and Ophthalmology Departments of the Boston University Medical Center or the Boston Veterans Administration Medical Center and their outpatient clinics were prospectively enrolled in this study. Written consent was obtained from each patient, and institutional review board approval was granted by both hospitals.

In an effort to capture all eligible patients, Neurology and Ophthalmology Department staffs were repeatedly reminded of the study by means of posters, presentations, and one-on-one conversations throughout the duration of the study. The referral system was facilitated by daily interactions with fellows with dedicated beepers, and very active Stroke and Neuro-Ophthalmology Services that are traditionally the main care providers to patients with retinal and cerebral vascular disorders at both hospitals.

Patients were considered eligible for this study when they presented with a history of transient or permanent monocular loss of vision of sudden onset, or had an incidental finding of asymptomatic retinal embolism on routine ophthalmological examination. Based on the funduscopic findings, those with permanent loss of vision were classified as suffering from central or branch retinal artery occlusion. Patients with anterior ischemic optic neuropathy, retinal vein occlusion and giant-cell arteritis were excluded. Nonvascular causes of monocular loss of vision were ruled out, and subjects with histories of optic neuritis, classic

migraine, papilledema, and intrinsic eye disease such as uncontrolled glaucoma, bullous keratopathy, new vitreous hemorrhage, retinal detachment and macular degeneration were excluded.

By means of a standardized questionnaire, each patient was queried in detail about the nature of visual symptoms, previous medical history with a special attention to vascular, ophthalmological and neurological disorders and vascular risk factors. Each patient underwent detailed neurological and ophthalmological examinations, a duplex or magnetic resonance angiography (MRA) study of the carotid arteries, an echocardiogram, a transcranial Doppler study of the ophthalmic and intracranial arteries, and blood tests that included the erythrocyte sedimentation test. All evaluations were completed within 14 days from onset of symptoms, or from initial presentation for those who were asymptomatic. Patients were treated according to the discretion of their specialist physicians. Eight (10.4%) underwent carotid endarterectomy between enrollment and the 1-month follow-up mark.

Follow-up was obtained by means of a standardized telephone interview at 1 and 3 months post-enrollment. Again, a focused questionnaire was used and one of the study neurologists inquired about new symptoms of retinal or brain ischemia. Symptomatic patients were reevaluated in the outpatient clinic. In addition to the preceding investigations, other diagnostic studies were obtained as clinically needed.

A log of patients referred to the study team was kept throughout the duration of the study. From September 8, 1997 to June 30, 1999, 124 patients were entered into the log. Forty-seven were excluded for the following reasons: 14 could not be tested within the protocol's time limits, 19 did not satisfy the inclusionary criteria, 8 were excluded after enrollment because their diagnoses were changed after the results of their evaluations, and 6 refused to participate. The remaining 77 patients with 83 eyes of interest were enrolled. Information regarding recurrent vascular events during follow-up was available in all patients at 1 months, and 73/75 (97.3%) survivors at 3 months.

Etiologic diagnoses were made based on the clinical and laboratory data, and were always considered presumptive. The following vascular or cardiac lesions were considered potential sources of retinal embolism or hypoperfusion: extracranial internal carotid artery plaques causing occlusion or more than 50% stenosis, ophthalmic artery stenosis, aortic arch plaques 4 mm or more in thickness, atrial fibrillation, akinetic segments or aneurysms of the left ventricular wall, prosthetic cardiac valves, rheumatic valve disease with severe regurgitation or stenosis, patent foramen ovale, and left ventricular ejection fraction of less than 30%.

Six patients had both eyes involved. In 3 cases, asymptomatic embolism was present bilaterally. A review of the test results and follow-up data of these cases indicated that enrollment of either eye did not change the study's results. The other 3 patients presented with symptoms of retinal ischemia on one side and asymptomatic embolism on the other. Only the symptomatic side was enrolled in the study.

Imaging Studies

Duplex studies were performed on Ultramark 9-HDI (Advanced Technology Laboratories) instruments. MRA studies were obtained on 1.5-tesla Signa (General Electric Medical Systems), Gyroscan S15/ACS-II PT-1000 (Philips Medical Systems) or Gyroscan ACSNT (Philips Medical Systems) units. Echocardiograms were performed on Hewlett-Packard Sonos 1000, 1500 or 5500 instruments. TC-2000 or TC-2020 instruments (Nicolet) were utilized for trans-cranial Doppler testing.

The presence of extracranial internal carotid artery stenosis was tested in all patients by either duplex ultrasound alone (n = 43), MRA alone (n = 4), or both tests (n = 30). In addition, cerebral angiograms were obtained in 3 patients. Echocardiograms were available in 76/77 (98.7%) cases. One patient with retinal migraine did not undergo echocardiographic testing. Sixty-two patients received transthoracic echocardiograms, 7 had transesophageal studies, and another 7 had both. Transcranial Doppler studies were obtained in 76/77 (98.7%) patients and were considered technically suboptimal in 7. Official reports of imaging studies were used for this investigation.

Retinal photographs were obtained in 71 patients. In the remaining 6, the 2 participating ophthalmologists confirmed the diagnosis based on their personal examinations of the patients. Retinal photographs were obtained on a Topcon TRC.50X retinal camera, with fundus and disc pictures at, respectively, 50 and 35°.

Results

Patient Characteristics and Vascular Risk Factors

The mean age of the study population was 68.8 years (range 35–87). The gender distribution of 13 women and 64 men probably reflects the fact that more than half of the patients were recruited from a Veterans Administration Medical Center. The frequencies of associated vascular risk factors and histories of cerebrovascular disorders are presented in **Table 1**.

Table 1 Vascular Risk Factors in 77 Patients

Risk Factors	Patients	%
Hypertension	50/77	64.9
Diabetes mellitus	27/77	35.1
Hyperlipidemia	48/66[a]	72.7
Past or present history of smoking	63/75[b]	84.0
Coronary artery disease	34/76[c]	44.7
Cerebrovascular disease	20/77	26.0

[a] Risk factor unknown in 11 patients; [b] Risk factor unknown in 2 patients; [c] Risk factor unknown in 1 patient

Diagnoses and Presumed Etiologies

Enrollment diagnoses consisted of amaurosis fugax (n = 32), asymptomatic retinal embolism (n = 34) and central or branch retinal artery occlusion (n = 11).

The presumed etiologies of the retinal events are presented in **Table 2**. Extracranial internal carotid artery occlusion or greater than 50% stenosis was present in 17 (22.1%) patients. More than one potential source of retinal embolism was detected in 10 (13.0%) cases. This subgroup consisted of patients with internal carotid artery occlusion or severe stenosis and an additional potential source of emboli, such as atrial fibrillation or aortic arch plaque formation with more than 4 mm thickness. When these two subgroups are combined, 27 (35.1%) patients had evidence of severe internal carotid artery disease. An etiologic diagnosis could not be made in 35 (45.5%) cases, as none of the lesions presented in the Methods section were detected. Other potentially treatable causes included hematological disorders, thick aortic arch plaques without internal carotid artery lesions, ophthalmic artery stenosis, internal carotid artery dissection, and systemic lupus erythematosus. Together they constituted 10.4% of all cases.

The presumed etiology was also analyzed according to the 2 main enrollment diagnoses. A potential source of retinal embolism or hypoperfusion was detected in 21/32 (65.6%) patients with amaurosis fugax, and in 13/34 (38.2%) cases with asymptomatic retinal embolism ($p = 0.03$). The number of patients in other diagnostic subgroups was deemed to be too small for further analysis.

Table 2 Etiology of Retinal Ischemia or Embolism in 77 Patients

Diagnosis	Patients	%
Internal carotid artery stenosis >50%	17	22.1
More than 1 potential lesion	10	13.0
Cardiac lesions[a]	6	7.8
Aortic arch plaque >4mm	2	2.6
Ophthalmic artery stenosis	2	2.6
Hematological conditions	2	2.6
Internal carotid artery dissection	1	1.3
Retinal migraine	1	1.3
Systemic lupus erythematosus	1	1.3
No lesion identified	35	45.5

[a] Left ventricular akinesis or ejection fraction <30%, and Saint-Jude or rheumatic valves

Recurrent Retinal and Hemispheric Events

At the 1-Month Follow-Up. Data regarding clinically symptomatic, new vascular events are presented in **Table 3.** The cause of death was intracerebral hemorrhage in 1 patient and myocardial infarction in another. The number of recurrent amaurosis fugax attacks was quite variable in individual patients, ranging from 1 to more than 30.

Table 3 Number (%) of Patients with Recurrent Vascular Events During Follow-up

	1 st month	2nd and 3rd months
Amaurosis fugax	8 (10.4)	5 (6.9)
Transient ischemic attack	2 (2.6)	1 (1.4)
Death	2 (2.6)	0
Retinal infarct	1 (1.3)	0
Cerebral infarct	1 (1.3)	0
Total	14/77 (18.2)	6/73 (8.2)

When analyzed according to the 2 main enrollment diagnoses, recurrences occurred mostly in the group that presented with amaurosis fugax. Ten (31.3%) of 32 patients with that diagnosis had recurrences that included transient ischemic attacks and brain infarction, while only 2/34 (5.9%) patients with asymptomatic retinal emboli had recurrent events ($p = 0.01$).

Recurrences were also analyzed according to the presumed etiologic diagnosis. Five (29.4%) patients with recurrences belonged to the subgroup of 17 with extracranial internal carotid artery stenosis. With the exception of the patient who died from myocardial infarction, no patient had recurrent cerebral or retinal events after carotid endarterectomy. Recurrences were also reported in 2/10 (20.0%) patient with more than one potential source of embolism; both of these patients had severe stenoses of the internal carotid artery. In the subgroup of 35 patients in whom a causative lesion was not detected, 3 (8.6%) had recurrent events. The remaining recurrences were evenly distributed among the different diagnostic subgroups.

At the 3-Month Follow-Up. Two patients were lost to follow-up. Data regarding the remaining 73 survivors are presented in **Table 3**. Subgroup analyses were not performed because of the small number of patients with vascular events during this period.

Discussion

The findings of this study indicate that although extracranial internal carotid artery stenosis is the most common identifiable presumed cause of retinal ischemia and embolism, a plethora of etiologies are associated with this condition, and in more than 45% of patients a cause cannot be identified. Uncommon but treatable conditions can be detected when specific evaluations are undertaken. In addition, recurrent vascular events are common during the early follow-up period and range from relatively innocuous episodes of amaurosis fugax to death.

The age distribution of patients enrolled in our study and the high prevalence of the different vascular risk factors (**Table 1**) are similar to the findings of previous investigations.[7, 9, 10] They indicate that retinal ischemia and embolism often occur in elderly patients with extensive cerebral, coronary and systemic arterial disease.

Extracranial internal carotid plaque formation causing more than 50% stenosis or occlusion was the sole identified potential cause of ophthalmic artery distribution ischemia or embolism in 22.1% of patients (**Table 2**); in only 7.8% of patients was a cardiac lesion identified as the presumed etiology. This finding suggests that the cardiac chambers may be a less common source of embolism to the retina than to the brain, an observation supported by other studies as well.[7] The findings of this study also confirm that ophthalmic artery distribution ischemia and embolism can be the result of various pathological processes

requiring differing and specific treatments. Two patients had ophthalmic artery stenosis, and 3 had more than 4-mm-thick aortic arch plaques; both conditions[2, 11] can be difficult to diagnose clinically and require specific testing. Although each of the preceding conditions is uncommon when taken alone, together they constitute 10.4% of cases in this series, underscoring the need for structured evaluations.[12] Because the study was based on the real-life clinical setting of patients presenting with monocular loss of vision of sudden onset or asymptomatic retinal embolism, the preceding findings should be useful to clinicians making decisions regarding diagnostic testing.

The extensive standardized diagnostic evaluation that each patient underwent is considered a unique strength of this study. In spite of the testing, however, an etiologic diagnosis could not be made in 45.5% of our patients. This relatively high percentage is not different from the 45.3% of cerebral infarcts of unknown cause observed in the Stroke Data Bank project, [13] and it compares favorably with the findings of another study of retinal arterial occlusive disease.[7] Because detailed hematological evaluations were not obtained systematically in this study, it is possible that some patients in this subgroup suffered from hypercoagulable states.[14-16] Furthermore, transesophageal echocardiography was obtained in only 18.2% patients, so that some cardiac or aortic arch lesions may have been missed. Also, our protocol did not include serial retinal imaging or transcranial Doppler testing to identify patients with vasospastic amaurosis fugax.[17] The true prevalence of each of these etiologies remains unknown.

We were unable to identify a potential source for embolism in 61.8% of patients with observed retinal emboli. Similar findings have been reported by others.[18] Most emboli had features consistent with either cholesterol plaques or fibrin-platelet particles. This suggests that emboli may arise from arterial atheromatous plaques in the absence of substantial luminal encroachment.[19] The finding of hyperaggregable platelets in some patients with amaurosis fugax[20] raises the possibility that fibrin-platelet particles can form spontaneously at intravascular sites without stenotic lesions. Thus, retinal embolism may occur even when an embolic source cannot be identified,[21] and should be taken into consideration when therapeutic decisions are being made.

Symptomatic recurrent vascular events occurred in 18.2% of patients during the 1st month and 8.2% during the 2nd and 3rd months following presentation (**Table 3**). Most involved the ophthalmic artery circulation. Recurrences were not benign and occurred despite medical treatment: brain or retinal infarction occurred in 2.7% of patients and the mortality rate was 2.7% at the 3rd-month

follow-up. Thus, the diagnosis of retinal ischemia and asymptomatic embolism identifies patients with a non trivial risk for short-term vascular complications. The relatively high frequency of recurrences in patients with extracranial internal carotid artery stenosis greater than 50% is clinically relevant. In the North American Symptomatic Carotid Endarterectomy Trial, the 2-month period that followed an initial event was also a particularly high-risk period, since more than 50% of the first 2 years' events occurred during that period.[6] Given the proven efficacy of carotid endarterectomy, prompt testing to identify internal carotid artery stenosis seems appropriate for these patients.

Previous studies have assessed the rate of recurrent vascular events over relatively long periods of time extending from 3[22] to more than 6 years.[23] They have shown an increased rate of cerebral[24, 25] and myocardial[23, 25] infarction following retinal embolism as well as diminished survival.[23, 25–27] By and large these studies show an almost linearly additive effect of time, the decreased survivorship becoming significant only after 3 years.[25] These studies did not address the recurrence of transient retinal or cerebral events. Our findings differ from those of the preceding investigations in that we prospectively monitored the 3-month period following an event, allowing detection of relatively 'soft' symptoms that could have been missed in retrospective series.[25, 26]

A major limitation of this study consists of 'lumping' patients with related but differing diagnoses into one group. Data generated herein and published reports[22] suggest that subgroups, such as amaurosis fugax and asymptomatic retinal embolism, do exist. It is also recognized that these subgroups may differ with regard to their etiologies and natural courses, and that the lack of uniform treatment does not permit to assess the effect of therapy on outcome in this relatively small study group. In addition, transesophageal echocardiography testing and hematological evaluations were limited. Further studies of retinal vascular disease may choose to further assess the cardiac chambers and aortic arch, as well as hypercoagulable conditions. The aim of the present investigation, however, was to simulate the clinical setting, and the study design was prepared accordingly.

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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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Chapter 6

Retinal Ischemia in Atrial Fibrillation: Do Not Overlook the Carotid Artery

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Retinal ischemia is traditionally associated with internal carotid artery (ICA) stenosis and rarely results from cardiac emboli caused by atrial fibrillation.[1-3] In this report, we describe two patients who presented with retinal infarction and new onset atrial fibrillation. Both patients had evidence of an acute, probably cardio-embolic, occlusion of the extracranial carotid artery with secondary artery-to-artery embolism to the ophthalmic artery.

Case 1. A 57-year-old Chinese man experienced sudden loss of vision of his right eye. He had no vascular risk factors except for smoking. His general physical and neurological examination was unremarkable, except for an irregular pulse and complete loss of vision of the right eye with an amaurotic pupil. Ophthalmoscopy showed a white ground-glass appearance of the retina with a cherry red spot at the fovea consistent with central retinal artery occlusion. No retinal emboli were visualized. The electrocardiogram showed atrial fibrillation. Laboratory values including a sedimentation rate were unremarkable. He was started on an intravenous heparin infusion. A transthoracic echocardiogram showed atrial fibrillation, normal left ventricular function, and bi-atrial dilatation. The left atrial appendage was without thrombus, but was poorly visualized. A brain MRI showed no evidence of acute or chronic infarction. Time of flight MR angiography of the carotid arteries demonstrated an occluded right ICA just beyond the bifurcation; distal to the occlusion was a central intraluminal hypointensity suspect for thrombus; the left ICA was normal. A duplex ultrasound showed a very echodense large shadow in the proximal right ICA consistent with fresh thrombus, and highly resistant "to and fro" flow corresponding to a distal occlusion. Transcranial Doppler ultrasound (TCD) monitoring of the right middle cerebral artery (MCA) was positive for the presence of microembolic signals. He was discharged from the hospital on warfarin therapy.

Case 2. A 64 year-old man with a previous myocardial infarction presented with an acute left MCA infarction and new onset atrial fibrillation. He had an expressive aphasia, right-sided weakness, and loss of vision affecting part of the inferior visual field of the left eye. Opthalmoscopy revealed two acute retinal infarcts in the distribution of the superior temporal arteriole without retinal emboli. TCD examination of the left MCA demonstrated microembolic signals. He was treated with intravenous heparin therapy. A carotid ultrasound and MR angiogram showed near-occlusion of the common carotid artery and total occlusion of the external carotid artery on the left side. Subsequent digital subtraction angiography and a repeat carotid duplex study, 7 and 14 days after presentation, respectively, showed complete recanalization of the left common, external, and ICA with minimal residual stenosis. A transesophageal echocardiogram showed atrial fibrillation without a cardiac thrombus. He was treated with warfarin therapy.

We believe that both patients suffered an acute cardio-embolic occlusion of the carotid artery caused by atrial fibrillation with secondary embolization to the retina from the fresh carotid artery thrombus. The clinical presentation, the diagnosis of new onset atrial fibrillation in the absence of anticoagulation, the presence of microembolic signals in the MCA, the demonstration of fresh thrombus in the ICA in case 1, and the early resolution of carotid thrombus in case 2 strongly suggest this impression. Hemodynamic impairment may have been an additional contributory mechanism. To the best of our knowledge this large thrombus embolization to the ICA followed by microembolization to the ophthalmic artery has not been described before.

Retinal ischemia is uncommon in atrial fibrillation. In the Stroke Prevention in Atrial Fibrillation trials, the ratio of hemispheric versus retinal ischemic events among 2012 aspirin-treated patients was 25:1.[1] In a large hospital-based stroke registry with 2288 patients with cerebral and retinal ischemia, atrial fibrillation was more common in brain events than in retinal events, whereas severe ICA disease was less common.[2]

These data suggest that there are pathophysiological differences between retinal and brain ischemic syndromes. It has been proposed that embolic particles originating from a stenotic ICA lesion are more prone to be carried to the ophthalmic artery, whereas emboli from the left atrium are more likely to travel to the MCA.[2] Fibrin-platelet emboli from an ICA lesion are likely to be small and to be displaced by high flow velocities across a stenotic lesion in the periphery of the blood stream allowing entrance in the ophthalmic artery.[2] In contrast, emboli resulting from atrial fibrillation are large and more likely to remain mid-stream traveling to the cerebral branches of the ICA.[2] Support for this hypothesis is derived from models showing that particle size influences the position in a flowing liquid and the destination in the distal vasculature.[4-6] Furthermore, small particles entering the cerebral circulation are less likely to cause symptoms than the same size particles in the retinal circulation.[1,2,7]

Thus, our two patients demonstrate that in patients with atrial fibrillation, cardiac embolism with occlusion of the carotid artery and secondary embolization to the ophthalmic artery may be a potential mechanism of retina ischemia. Therefore, imaging of the ICA is indicated in these patients.

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Chapter 7

Retinal Embolism: Risk Factors, Characteristics, Source and Prognosis

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Abstract

Background Retinal embolism is considered a marker for vascular disease. In this study the relationships between emboli characteristics, visual symptoms, potential embolic sources, and recurrent vascular events were analyzed.

Methods Funduscopic findings in consecutive patients with symptoms of retinal ischemia (n=43) or with asymptomatic retinal embolism (n=36) were analyzed. All patients underwent cardiac and carotid artery evaluations within 7 days of presentation, and were followed for 3 months.

Results Retinal emboli were detected in 28% of symptomatic patients, and in 48 patients overall. Two patients had too many emboli to count. In the remaining 46 patients, 68 retinal emboli were detected; of these, 85% were presumed to be composed of cholesterol. All but one patient had one or more vascular risk factors. A high risk cardio-embolic source or an ipsilateral severely stenotic vascular lesion was detected in 38% of patients overall; in 75% of symptomatic and in 25% of asymptomatic patients (OR 9.0, CI 1.0-60). During follow-up 33% of symptomatic patients had recurrent vascular events and 6% of asymptomatic patients (OR 8.5, CI 1.0 - 103).

Conclusions Patients with retinal emboli often harbor a high risk cardiovascular lesion. These patients are at risk for future vascular events. A detailed cardiovascular work-up should be considered both in symptomatic and in asymptomatic patients with retinal emboli.

Introduction

Retinal emboli are considered to be markers for vascular disease.[1-4] In two population based studies the prevalence of asymptomatic retinal emboli has been estimated to be 1.4-1.5%.[5, 6] Patients with asymptomatic retinal emboli, typically detected on routine ophthalmologic examination, carry an increased risk for future stroke and stroke-related death when compared to an age- and sex-matched population.[7-9] In patients with visual symptoms attributed to retinal ischemia the presence of emboli in the retina has been associated with an increased risk for future stroke and death when compared to those without retinal emboli.[10, 11]

Retinal emboli may be composed of atheromatous material containing cholesterol, so-called Hollenhorst plaques, platelet-fibrin material, or calcium. In rare instances air, fat, tumor cells, foreign material, or septic material can embolize to the retina.[12] Emboli composed of cholesterol and platelet-fibrin material usually originate from an atheromatous lesion in one of the major arteries, whereas calcific emboli are thought to typically originate from the heart valves.[10, 13]

In this prospective study, patients with retinal emboli underwent pre-planned, systematic and timely ophthalmologic, vascular and cardiac evaluations, and clinical follow-up. The study investigates the relationships among emboli characteristics, visual symptoms, potential sources of embolism, and the occurrence of recurrent vascular events during follow-up.

Methods

Consecutive patients with a history of sudden transient or permanent monocular loss of vision attributed to transient retinal ischemia or retinal infarction, or asymptomatic patients with emboli to the retina detected during a routine eye visit on dilated funduscopic examination, were evaluated. Patients had presented to the neurology or ophthalmology departments of Boston Medical Center or the Boston Veterans Administration Medical Center during a 22 months period and were prospectively enrolled. Transient monocular blindness was defined as reversible, painless, monocular loss of vision of sudden onset, usually lasting for minutes. Retinal infarction was diagnosed by a history of sudden, persisting loss of vision in (part of) the visual field of one eye in addition to the characteristic findings on funduscopic examination of central or branch retinal artery occlusion. Retinal embolism was diagnosed by evidence of embolic material in the retinal arterioles on funduscopic examination confirmed by fundus photographs. Patients with acutely elevated intraocular pressure, temporal arteritis, anterior

ischemic optic neuropathy, and those with a history of optic neuritis were excluded. Patients consented in writing for study participation, and institutional review board approval was obtained.

All patients underwent standardized non-invasive vascular and cardiac evaluations in search for a source for embolism. The evaluation included a structured interview regarding visual symptoms and medical history with special attention to vascular disease and vascular risk factors. Each patient underwent detailed neurologic and ophthalmologic examinations, fundus photographs, duplex ultrasound or magnetic resonance angiography (MRA) of the carotid arteries, echocardiography, and blood tests that included an erythrocyte sedimentation rate. All evaluations were completed within 7 days from symptom onset, or from presentation to the eye clinic for those who were asymptomatic, except for fundus photographs which were obtained within 14 days.

Retinal photographs were obtained on a Topcon TRC.50X retinal camera, with fundus and disc pictures at respectively 50 and 35 degrees. Fifty of the 53 retinas (94%) were photographed. For the remaining 3, results of the fundus examination were used for the purpose of this study. All retinal photographs were reviewed and scored by the two study ophthalmologists (BK, ICAM). The diameter of the emboli and their distance from the optic disc were measured from the retinal photographs and calculated relative to the diameter of the optic disc, which was presumed to be 1500 micra. The composition of the emboli was determined by their morphological characteristics, such as color and shape. It is recognized that both of these methods have limitations.[14, 15]

Follow-up was obtained by structured telephone interviews performed by a study neurologist at one and three months after study enrollment. During the interview patients were queried systematically about the occurrence of visual symptoms and symptoms consistent with cerebral ischemia. Patients with new visual or neurological symptoms were re-evaluated on an individual basis.

Group comparisons were made by means of odds ratios (OR) with corresponding exact 95% confidence intervals (CI), both in the cross-sectional and follow-up analyses.

Results

Ninety-nine patients met enrollment criteria during the 22-month study period. Twenty were excluded because they either could not be tested within the protocol's time limits (n=14), or they refused to participate (n=6). Of the

remaining 79 patients, 43 had experienced symptoms of retinal ischemia or infarction: transient monocular blindness in 32, central retinal artery occlusion in 6, and branch retinal artery infarction in 5 patients.[16] Forty-eight of the 79 patients had one or more retinal emboli and are the focus of this report. Twelve of the 48 (25%) had recently experienced visual symptoms: transient monocular blindness (n = 5), central retinal artery occlusion (n=4), and branch retinal artery occlusion (n = 3). Five patients (10%) had retinal emboli in both eyes. The mean age of the patient population was 72.6 (±9.5) years. Nine patients (19%) were female. One patient had no vascular risk factors, four patients had one vascular risk factor, 11 had two risk factors, and 32 patients had more than two vascular risk factors (**Table 1**).

Table 1 Risk Factors for Vascular Disease in 48 Patients with Retinal Embolism

Vascular Risk Factor	N (%) of Patients
Hypertension	35 (73)
Diabetes Mellitus	22 (46)
Hyperlipidemia	28 (68)[1]
Past or Present History of Smoking	35 (76)[2]
Coronary Artery Disease	21 (45)[3]
Cerebrovascular Disease	14 (29)

Risk factor unknown in 7 patients [(1)], in 2 patients [(2)], and in 1 patient [(3)]

Embolus characteristics

Emboli were found in 27 right and 26 left eyes. One asymptomatic patient had too many cholesterol emboli to count in both eyes. One patient with episodes of transient monocular blindness was observed to have mobile, probably fibrin-platelet, embolic material coursing through the retinal arterioles during her attacks.[17] In the remaining 46 patients (with 50 eyes) 68 distinct emboli were detected. In one eye 7 emboli were visualized, in 4 eyes 3 emboli, in 4 other eyes 2 emboli, and in the remaining 41 eyes 1 embolus. The presumed composition of the emboli was cholesterol in 85% (**Figure 1**), calcium in 9%, platelet-fibrin in 2%, and unknown in 4% of emboli. Embolus location, largest diameter, and its distance from the optic disc could be determined reliably for 60 (88%) of emboli. Median embolus size was 82 micra (range 30-290). Mean embolus-to-optic disc distance was 4.1 ± 2.7 mm. Two eyes had emboli in all four quadrants of the retina. In the remaining eyes 5% of emboli were located on the optic disc, 7% in the nasal, and 89% in the temporal vessels of the retina. Retinal infarction was detected in 9 (17%) eyes; 2 of these eyes were asymptomatic (**Figure 2**). No

Figure 1 Two cholesterol emboli in the retina found incidentally on routine funduscopic examination in an asymptomatic individual. (*For color full photograph see inside back cover*).

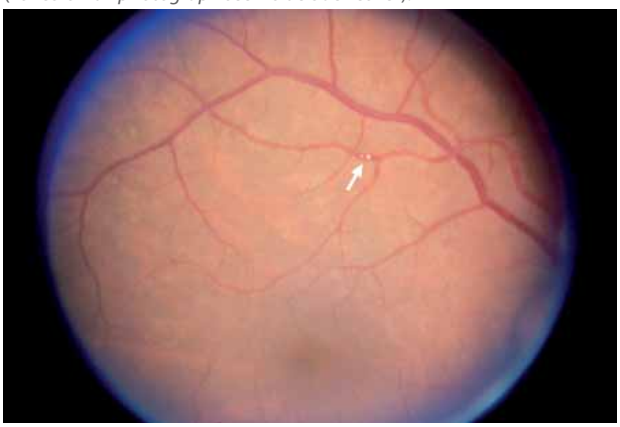
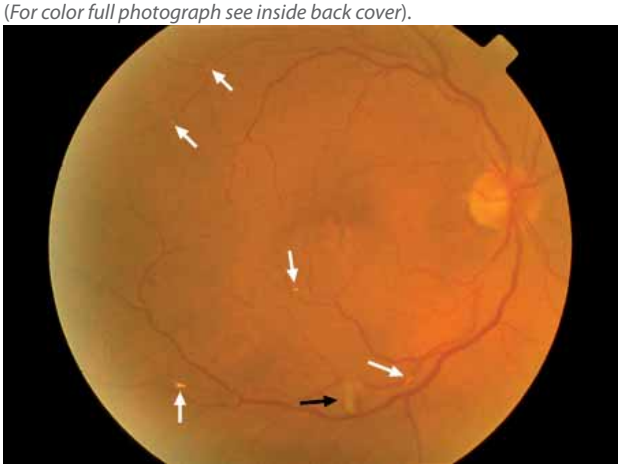


Figure 2 Several retinal emboli (white arrows) with an associated asymptomatic retinal infarct (black arrow) detected on routine funduscopic examination in a patient without visual symptoms. (*For color full photograph see inside back cover*).



relationship was found among the size, composition, number, and location of the emboli in the retina and the occurrence of visual symptoms, potential embolic source, and recurrent vascular events during 3 months of follow-up. Furthermore, the size of an embolus was not related to its distance from the optic disc.

Embolus source

The presence of extracranial internal carotid artery stenosis was evaluated by duplex ultrasound in 46 patients, and by MRA in two. Forty-four patients had

trans-thoracic echocardiograms. Five patients underwent trans-thoracic and trans-esophageal echocardiograms (TEE), and four underwent TEE alone.

Potential high risk arterial or cardiac sources for embolism were detected in 18 (38%) of patients (**Table 2**). Ipsilateral internal carotid artery stenosis of 70% or greater or severe ophthalmic artery stenosis was found in 10 (21%) patients. One or more high risk sources for cardioembolism were present in 11 (23%) of patients and included atrial fibrillation (N=4), mechanical heart valves (N=1), ruptured chordae (N=1), valvular mobile elements (n=1), akinetic left ventricular segments (N=8), and a low left ventricular ejection fraction of 15% (N=1). Both a high risk arterial and a cardiac source of embolism were detected in 3 (6%) patients. Echocardiographic evidence of calcifications of either the aortic or mitral valve was found in 30 (63%) patients. There was a greater likelihood of finding a high risk embolic source in symptomatic than in asymptomatic patients. Nine of the 12 (75%) symptomatic patients had a potential embolic source as compared to 9 of the 36 (25%) asymptomatic patients (OR 9.0, CI 1.0-60).

Table 2 High Risk Embolic Sources in 48 Patients with Retinal Embolism

	% ICA Stenosis 70-100%[2] N (%)	% ICA Stenosis < 70% N (%)	Total N (%)
High risk source for cardioembolism[1] N (%)	3 (6)	8 (17)	11 (23)
No source for cardioembolism N (%)	7 (15)	30 (63)	37 (77)
Total # (%)	10 (21)	38 (79)	48 (100)

ICA = Ipsilateral internal carotid artery
[1]This group does not include severe atheromatous plaque of the aorta (see text).
[2]One of these patients had a severe ophthalmic artery stenosis rather than severe internal carotid artery stenosis

Furthermore, in the nine patients who underwent TEE four had severe aortic arch plaque of 4 mm thickness or more. All four patients were asymptomatic, and two of them had retinal embolism affecting both eyes.

Vascular events during follow-up

During a 3-month follow-up period any vascular event (including vascular death) occurred in 6 (13%) patients: transient retinal or hemispheric ischemia in 3, retinal infarction in 1, a fatal myocardial infarction in 1, and a fatal hemorrhagic stroke in 1 (**Table 3**). Four of 12 (33%) symptomatic patients had recurrent vascular events as compared to 2/36 (6%) of asymptomatic patients (OR 8.5, CI 1.0-103).

Table 3 Vascular Events in 48 Patients with Retinal Embolism within 3 Months of Diagnosis.

Vascular Event	N (%) of Patients
Transient monocular blindness	2 (4)
Hemispheric transient ischemic attack	1 (2)
Retinal Infarction	1 (2)
Vascular death	2 (4)
Total	6 (13)

Discussion

In the original cohort of 43 patients with visual symptoms of retinal ischemia or infarction, the frequency of retinal embolism was 28% overall; 16% (5 of 32) in patients with transient monocular blindness, 67% (4 of 6) in those with central retinal artery occlusions, and 60% (3 of 5) in those with branch retinal artery occlusions. Previous studies have reported retinal emboli in only 3% of patients with transient monocular blindness, in 11-40% of patients with central retinal artery occlusion, and in 60-68% of patients with branch retinal artery occlusions.[11, 18-21] Although the relatively high frequency of retinal embolism in our study should be interpreted with caution given the small number of patients, we suspect that this high frequency may be due to the short time interval (of 7 days or less) between the onset of visual symptoms and ophthalmologic evaluation in all patients. Retinal emboli, in particular cholesterol emboli, are well known to change position in the retinal arterioles, moving peripherally, and many of them have been observed to disappear from the retina over time.[22] In fact, one of our patients with bilateral asymptomatic retinal emboli was observed to have cholesterol emboli traveling through the retinal vasculature in one of his eyes during a dilated funduscopic examination. We hypothesize that the longer the time interval between symptom onset and ophthalmologic evaluation, the greater the likelihood that retinal emboli have cleared from the retinal circulation. Thus, a dilated funduscopic examination soon after symptom onset can reveal important information in patients with symptoms suspect for retinal ischemia or infarction.

The predominance of cholesterol emboli, the size of the emboli, the preferential location in the temporal circulation of the retina, the high frequency of vascular risk factors, and the male predominance in this study correspond well with the findings of previous reports.[1, 3, 4, 6, 10, 13, 23-26] Emboli in the retina that are composed of cholesterol typically originate from atheromatous lesions of the aorta-carotid

system.[10, 13, 25, 27] In the present study, ipsilateral vascular lesions with 70% luminal stenosis or more were found in only 21% of patients. Thus, in contrast to patients with transient monocular blindness, carotid lesions with severe luminal stenosis are not common in patients with asymptomatic retinal emboli.[23, 25, 27, 28]

The results of this study indicate that retinal emboli as large as 290µ in size can course through the retinal circulation without causing visual symptoms. Most are presumably composed of cholesterol. Similar particles presumably course through brain arteries as has been demonstrated by pathological studies.[29, 30] We were unable to identify specific emboli characteristics that differentiated between symptomatic and asymptomatic patients: size did not seem to be an important determinant. Symptomatic and asymptomatic patients did differ, however, in that symptomatic patients had a higher prevalence of a high risk arterial or cardiac embolic source, and a higher chance of experiencing a future vascular event.

A potential high risk source for cardiac emboli was found in 23% of patients. However, since the large majority of retinal emboli are presumably composed of cholesterol, they probably did not actually originate from these cardiac lesions. Furthermore, it has been observed that transient monocular blindness is uncommon in patients with atrial fibrillation when compared to patients with carotid disease, suggesting that most retinal embolic events are due to artery-to-artery embolism, rather than a cardio-embolic mechanism.[31] Therefore, the relatively high frequency of high risk cardio-embolic sources in our study population probably reflects the high incidence of cardiovascular disease in patients with retinal embolism.[2, 3, 8, 26] In view of this high frequency of cardiovascular lesions a detailed cardiovascular evaluation appears warranted in these patients.

In 63% of patients in this study no apparent high risk source for embolism was identified. Since these patients all had proven retinal embolism, their emboli must have originated somewhere in the cardiovascular system. It is likely that any atheromatous lesion, including ones that don't cause substantial arterial stenosis, can serve as a source for cholesterol embolism. We suspect that the retinal emboli in some of our patients may have originated from carotid lesions causing less than 70% luminal stenosis. Furthermore, potential severe atheromatous lesions of the ophthalmic artery and the aorta and its major branches were probably missed, since these are difficult to detect by non-invasive imaging techniques. The aortic arch has previously been recognized as a potential source for cholesterol embolism including retinal embolism.[32] In our study severe atheromatous plaque of the aortic arch (≥ 4 mm thickness) was demonstrated in 4 of 9 (44%) patients

who underwent TEE, and in 2 of 5 (40%) patients with bilateral retinal emboli. We suspect that we would have found more patients with severe aortic arch disease had we routinely performed TEEs in all patients.

Vascular events within 3 months of detection of retinal emboli were not uncommon and occurred in 13% of patients. Half of these were so-called 'hard' vascular endpoints including retinal infarction and vascular death. Symptomatic patients had a 9-fold increased odds of recurrent vascular events as compared to asymptomatic individuals.

A dilated funduscopic examination is not routinely pursued by the neurologist who evaluates a patient with symptoms suspect for transient retinal ischemia. Previous studies suggest that these patients are at an increased risk for stroke and death if they also have retinal emboli.[10, 11] Similarly, in patients with symptomatic carotid stenosis of 50% or more, the presence of microembolic signals detected by transcranial Doppler ultrasonography has been associated with an increased 90-day risk of stroke recurrence.[33] Thus, the presence of retinal emboli in patients with symptoms suspect for retinal ischemia may identify a subset of patients with an increased risk for future stroke. This issue requires further study.

The strengths of this study include its prospective character, the standardized cardiac and vascular work-up, and the documentation of retinal emboli with fundus photographs. Limitations include the relatively small number of patients, the short duration of the follow-up period, the non-invasive diagnostic work-up that did not routinely include TEE and MRA, and the historic assessment of vascular risk factors, rather than by established criteria. Nevertheless, some solid results can be derived from this study.

In summary, retinal emboli occur in patients with multiple risk factors for vascular disease. These emboli are common in patients with symptoms suspect for retinal ischemia or infarction, but can also occur in asymptomatic patients. More than one-third of patients with retinal emboli harbor either a high risk cardio-embolic source or an ipsilateral severely stenotic vascular lesion. Since these patients are at risk for future vascular events, a detailed cardiovascular work-up, including a TEE should be considered, even in those without symptoms.

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Chapter 8

Migrainous Visual Accompaniments Are Not Rare in Late Life. The Framingham Study

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Abstract

Background and Purpose Questionnaires to elicit symptoms of transient ischemic attacks (TIAs) may detect late-life transient visual symptoms similar to the visual aura of migraine, often without headache. We determined the frequency, characteristics, and stroke outcome of these symptoms in the Framingham Study.

Methods During 1971–1989, at biennial examinations, 2110 subjects of the Framingham cohort were systematically queried about the occurrence of sudden visual symptoms.

Results Visual migrainous symptoms were reported by 1.23% (26/2110) of subjects (1.33% of women and 1.08% of men). In 65% of subjects the episodes were stereotyped, and they began after age 50 years in 77%. Mean±SD age at onset of the episodes was 56.2±18.7 years. In 58% of subjects the episodes were never accompanied by headaches, and 42% had no headache history. The number of episodes ranged from 1 to 500 and was 10 or more in 69% of subjects. The episodes lasted 15 to 60 minutes in 50% of subjects. Sixty-five percent of the subjects were examined by a study neurologist, and only 19% of them met the criteria of the International Headache Society. Twelve percent of subjects sustained a stroke after the onset of migrainous visual symptoms: a subarachnoid hemorrhage 1 year later, an atherothrombotic brain stem infarct 3 years later, and a cardioembolic stroke 27 years later. In contrast, of 87 subjects with TIAs in the same cohort, 33% developed a stroke (P=0.030), two thirds within 6 months of TIA onset.

Conclusions Late-life-onset transient visual phenomena similar to the visual aura of migraine are not rare and often occur in the absence of headache. These symptoms appear not to be associated with an increased risk of stroke, and invasive diagnostic procedures or therapeutic measures are generally not indicated.

Introduction

Questionnaires used in epidemiological studies to identify symptoms of transient ischemic attacks (TIAs) may detect transient visual phenomena similar to the aura of migraine, often in the absence of headache. Fisher[1] emphasized the benign nature of these episodes and wrote in 1980: "It is an old observation that scintillating scotomas may appear for the first time in mid-life in the absence of a history of migraine or after a migraine-free period of many years." These episodes have been recognized as migrainous by several others and have been referred to as "migraine accompaniments," "acephalgic migraine," and "migraine equivalents.[2-11]" The International Headache Society (IHS) classified these episodes as "migraine aura without headache" and published diagnostic criteria in 1988.[12]

Our knowledge of migraine accompaniments is largely derived from clinical series.[1-3, 9, 11] Visual symptoms are the most frequent manifestation.[1, 3, 6] Typical migrainous visual symptoms include both positive (scintillations, fortification spectra, photopsia) and negative (scotoma, hemianopsia) visual features[6, 13, 14] and often present as a transient scintillating hemianopic visual disturbance.[6, 15] Isolated migraine accompaniments may occur with a prior, remote history of migraine headaches with or without aura. On the basis of his detailed clinical observations, Fisher[1] described a number of features of migraine accompaniments, including scintillations and other visual phenomena, buildup of scintillations and march of paresthesias, and progression of one neurological symptom to another. Other characteristics that he described were episodes lasting 15 to 25 minutes, two or more identical spells, a mid-life "flurry" of spells, and a benign course.

Diagnosis is not difficult when the spells are typically migrainous in character and two or more stereotypic spells have occurred. However, when the spells are atypical or when they occur for the first time in adult life in a person without a migraine history, other neurological diagnoses such as TIAs or seizures are a consideration. How frequently isolated migraine accompaniments occur is presently unknown. Since data on migraine accompaniments derived from population-based studies are sparse, this study was undertaken to further clarify the prevalence, characteristics, and outcome of visual migrainous symptoms in the Framingham Study population.

Subjects and Methods

The Framingham cohort of 5070 men and women between 30 and 62 years of age and free of cardiovascular disease, including TIA and stroke at entry, has been followed by means of routine examinations every 2 years from 1950 until the

present. Conduction of the study has been approved by the Institutional Review Board of Boston University, and all participants have given informed consent for their participation in the study. Details of the study design, implementation, and diagnosis criteria have been published previously.[16] At each biennial examination, subjects have been systematically queried about the occurrence of symptoms of TIA and stroke. Since 1968 all subjects were specifically asked about the following symptoms: unconsciousness, sudden difficulty with speech, sudden muscular weakness, numbness or tingling, double vision, loss of vision in one eye, and other sudden visual symptoms. The records of subjects responding affirmatively to any of these questions and with suspected symptoms of stroke or TIA were reviewed by a panel of investigators including a neurologist, and a diagnosis was established on the basis of detailed clinical, laboratory, and radiological data. Whenever symptoms were atypical or the available clinical information was insufficient to make a diagnosis with certainty, subjects were interviewed and examined by one of the study neurologists. In addition, stroke surveillance was maintained by daily monitoring of hospital admissions to the only general hospital in town, and since 1968, whenever possible, a study neurologist has examined subjects with TIA or stroke at the time of the hospitalization.

For the present study the nature of all first-ever episodes of sudden visual defect (SVD) reported at biennial examinations during 1971–1989 (examinations 12 through 20) was determined by a neurologist based on the available notes of the biennial examination, neurology clinic notes, records from hospitalizations and office visits, and previous reviews of study investigators (described above). Whenever the clinical features of the SVD corresponded to the characteristics of the visual aura of migraine headaches,[15] a number of variables were systematically recorded, including details on the character and number of episodes, their duration and mode of onset, accompanying headache, associated symptoms (neurological and nonneurological), and family history. In addition, it was determined whether the episodes fulfilled IHS criteria for migraine with aura or migraine aura without headache.[12]

Prevalence of visual migraine accompaniments was determined in all subjects who attended at least six of the nine biennial examinations during 1971–1989. Thus, each subject was queried on at least six different occasions about the occurrence of sudden visual symptoms over an 18-year period. Stroke incidence rates between groups with and without SVD were compared with the X^2 test. All testing was performed at a 5% significance level.

Results

Among the 2110 original cohort members who attended at least six biennial examinations during 1971–1989, 186 reported a first-ever SVD. Thus, the incidence of SVD in this population sample was 8.8%. With the use of all available information, a judgment was made about the cause of the SVDs in these 186 subjects (**Table 1**).

Table 1 Cause of First-Ever Sudden Visual Defect (SVD) Reported by 186 Subjects Who Attended at Least Six Framingham Study Biennial Examinations (1971–1989)

Cause of SVD	No. of Subjects	Percentage of Subjects
Ocular disease	32	17
Stroke	34	18
TIA	11	6
Transient monocular blindness	19	10
Unknown	41	22
Other causes	23	12
Migrainous visual symptoms	26	14
Total number of SVDs	186	99[1]

[1] Cumulative percentage is 99% because of rounding.

Ocular diseases resulted in SVD in 17% (32/186) of subjects, who typically presented with loss of vision, often persistent, affecting one eye. According to the report of the subject, subsequent ophthalmologic evaluation had identified an ocular cause such as retinal hemorrhage, retinal detachment, central retinal artery occlusion, and acute glaucoma. The largest single category of SVDs was due to stroke, TIA, or transient monocular blindness, which occurred in 34% (64/186) of subjects. SVD resulting from "other causes" included diagnoses such as presyncope, seizures, and temporal arteritis and occurred in 12% of subjects. Visual symptoms in this group varied widely and usually were associated with a number of other (nonvisual) symptoms or signs suggestive for the diagnosis. No definite cause for the reported SVD was found in 22% of subjects. These subjects frequently reported nonspecific visual symptoms such as blurring of vision affecting one or both eyes for which no cause was found.

Visual symptoms that corresponded to the visual aura of migraine were reported by 26 of 186 subjects (14%). The pattern of visual manifestations varied widely among subjects, and some of the more detailed descriptions are shown in **Table 2**. The prevalence of migrainous visual symptoms in this general population was

1.23% overall (1.33% in women and 1.08% in men). The prevalence of episodes of migrainous visual symptoms that were never accompanied with headache was 0.71% overall (0.70% in women and 0.72% in men).

Table 2 Some of the Patterns of Migrainous Visual Disturbances Described by Subjects in This Study

Heat rising off the ground and things jumping in front of both eyes followed by poor vision
Loss of vision on the right associated with zigzag lines, moving visual phenomena, and a halo around the area
Disco lights in front of both eyes and a bright silvery shape in the form of an eyebrow to the right of visual field
Vision like looking through a kaleidoscope
Bright lines in half of the visual field of both eyes interfering with ability to read
Geometric figures consisting of squares with circles in them
Bright wiggling lines in inferior left visual field advancing superiorly followed by left homonymous hemianopia
Wavy vision as on television when the picture is not focused
Vision is jumping like a film in an old film projector
Dancing spots off to one side followed by blurring of vision and hemianopia on the same side
Periphery of vision gets black and vision becomes as if looking through a pinhole followed by dancing black and white spots in front of both eyes
Sudden white sheet descending in front of both eyes

Details on the clinical features of the episodes, personal characteristics of the subjects, and their medical and family histories were recorded, whenever available (**Table 3**). In the majority of subjects the episodes were stereotyped (65%). The age of onset of the episodes ranged from 9 to 71 years and was greater than 50 years in 77% of subjects. Mean±SD age of onset was 56.2±18.7 years overall (58.1±16.3 years in women and 52.9±23.2 years in men). In 58% of subjects visual symptoms were never accompanied by headaches, and 12% experienced headaches with the spells occasionally. Forty-two percent of subjects had no history of recurrent headaches. In 8 of 11 subjects (73%) who had a documented family history, recurrent headaches occurred in siblings, parents, or children. The number of episodes ranged from 1 to

Table 3 Characteristics of 26 Subjects Who Reported Episodes Corresponding to Migrainous Visual Symptoms

Characteristic	No. (%) of Subjects (n=26)
Female	17 (65)
Age of onset >50 y	20 (77)[1]
Number of spells ≥10	18 (69)
Duration of spells is consistent	15 (58)[2]
Character of spells is stereotyped	17 (65)[1]
Spell is of sudden onset	9 (35)[3]
Both eyes are involved	19 (73)[2]
Positive visual phenomena are present	20 (77)[4]
Associated neurological symptoms	5 (19)[5]
Associated nonneurological symptoms	5 (19)[5]
Spells never occur with headache	15 (58)
History of recurrent headaches	14 (54)[1]
Family history of migraine headaches	8 (31)[6]
Subject evaluated by panel of investigators	21 (81)
Subject examined by a neurologist	17 (65)
Spells fulfill IHS criteria for migraine	5 (19)
Duration of spells[2]	
>1 and <15 min	7 (27)
15 to 60 min	13 (50)
Other	2 (8)
Visual field loss[7]	
Hemianopia	7 (27)
Scotoma	4 (15)
Other	5 (19)
Diffuse visual loss	5 (19)

[1]Characteristic unknown in 1 subject. [2]Characteristic unknown in 4 subjects. [3]Characteristic unknown in 12 subjects. [4]Characteristic unknown in 2 subjects. [5]Characteristic unknown in 3 subjects. [6]Characteristic unknown in 15 subjects. [7]Characteristic unknown in 5 subjects. IHS = International Headache Society.

500 and was 10 or more in 69% of subjects. In the majority (77%) the episodes lasted either several minutes or 15 to 60 minutes. The episodes lasted seconds in one case (4%), and their duration varied from seconds to hours in another (4%). Positive visual phenomena such as bright images ("bright lines," "flashes of light," "silver lightning," "sunburst," "disco lights"), colors ("zigzag rainbow colors,"

"colored lights"), and movement of images ("dancing," "jumping," "wavy or wiggling lines") were often reported (77%). Frequent descriptions of visual images included zigzag, wavy, or wiggling lines and wavy blurring of vision "as if heat is rising from the pavement" (38%). Exclusively negative visual phenomena were described in only one subject who experienced for more than 20 years "monthly episodes of marked decrease in peripheral vision either to the left or right lasting 5 minutes and not associated with any other symptoms." The most common pattern of visual loss was a hemianopia (27%). Neurological symptoms (other than migrainous visual symptoms) were associated with the episodes in 19% of subjects and included diplopia, dizziness, numbness, paresthesias, tinnitus, and aphasia. The migrainous nature of these symptoms was suggested by their occurrence in association with typical visual migrainous phenomena and the progression from one neurological symptom to the other in a stereotyped fashion in multiple episodes. Associated nonneurological symptoms included nausea in four subjects and eye pain in one.

Sixty-five percent of subjects were interviewed and examined by a study neurologist, and the clinical records of 81% were evaluated by a panel of investigators including a neurologist. The episodes of migrainous visual symptoms were always transient, and persistent visual deficits were not reported. Formal ophthalmologic examination was documented as normal in three subjects. All subjects that were examined by one of the study neurologists had full visual fields to confrontation and sharp discs on funduscopic examination. Neuroimaging studies were not routinely obtained in subjects in this study, largely because of the presumed diagnosis of migraine. Furthermore, CT imaging was not available in Framingham until 1978. Only in 19% of subjects did the migrainous visual episodes meet the criteria for migraine with aura or migraine aura without headache of the IHS, usually because one of the criteria ("at least one aura symptom develops gradually over more than 4 minutes") could not be reliably ascertained.

Three of 26 subjects (11.5%) sustained a stroke after the onset of episodes of migrainous visual phenomena: a subarachnoid hemorrhage 1 year after symptom onset (with negative carotid angiogram), an atherothrombotic brain stem infarct 3 years after symptom onset, and a cardioembolic stroke in the setting of atrial fibrillation 27 years after symptom onset. This stroke incidence rate of 11.5% was significantly lower than the stroke incidence rate of 33.3% in subjects with TIAs in the same cohort (P=0.030) and did not differ from the stroke incidence rate of 13.6% of those without migrainous phenomena or TIAs (**Table 4**). Among the cohort members with TIAs who developed a stroke, two thirds developed their stroke within 6 months of TIA onset.

Table 4 Stroke Rate in Subjects With Migrainous Visual Symptoms, Subjects With TIAs, and Subjects Without TIAs or Migrainous Visual Symptoms

Group of Subjects	No. of Subjects	Stroke Rate, No. (%)
Subjects with migrainous visual symptoms	26	3 (11.5)
Subjects with TIAs	87	29 (33.3)[1]
Subjects without TIA or migrainous visual symptoms	1997	272 (13.6)[2]
Total	2110	304 (14.4)

[1]Significantly different from subjects with migrainous visual symptoms (P=0.030).
[2]Not significantly different from subjects with migrainous visual symptoms.

Discussion

These data indicate that visual migrainous phenomena are not rare since they occur in 1.33% of women and in 1.08% of men in a general population sample. Previous studies have used various methodologies to estimate the prevalence of these phenomena. Rasmussen et al[17] conducted a general health survey with a focus on headache disorders in Denmark using the IHS criteria. Among 740 persons, lifetime prevalence of migraine was 16% (119/740), and that of migraine aura without headache was 0.95% (7/740). Details on the clinical features and personal characteristics of these subjects were not reported. Since subjects with visual migrainous phenomena may not seek medical attention, studies based on medical diagnosis are likely to underestimate their prevalence. In one such study, Stang et al[18] used a modification of the IHS criteria and identified 629 residents of Olmsted County, Minnesota, who met the criteria of migraine. Aura without headache was identified in 6.3% of the cohort (11% of men and 4.3% of women), and the mean age of presentation was 43.2 years (SD, 15.6). In clinical series, Alvarez[19] found in 618 cases of migraine with aura that 12% of men and 0.7% of women experienced episodes of migrainous visual symptoms without headache. Selby and Lance[20] reported migraine accompaniments in 6 (1.2%) of 500 subjects. Two of them had suffered typical migraine in earlier years.

The prevalence of migraine equivalents in our study may well be an underestimate because our case ascertainment aimed at identifying subjects with visual symptoms. Although data from clinical series indicate that the vast majority of subjects with migraine accompaniments experience visual phenomena as part of the symptom complex, some subjects only experience nonvisual neurological disturbances during the attack.[1, 3] These subjects were not identified in our study. In addition, in a few subjects who reported an SVD, migraine accompaniments were suspected, but a reliable diagnosis could not be established

because of limited documentation of the details of the episode. Furthermore, a number of subjects with visual migraine accompaniments may have recognized these episodes as being similar to the visual aura that they experienced earlier in life in association with migraine headaches and may not have reported their symptoms as a SVD.

There are several clinical series of patients reporting symptoms of migraine aura in the absence of headache.[1-3, 9, 11] Fisher[1, 3] described a total of 205 cases of migrainous accompaniments in subjects older than 40 years in two reports. He excluded subjects with exclusively scintillating visual phenomena, stating that these episodes were well known to physicians.[1] Headache occurred in association with the spells in 40% to 50% of cases, and a history of recurrent headache was present in 50% to 65%.[1, 3] O'Conner and Tredici[9] described 61 cases, all men, seen during a 15-year period at the US Air Force School of Aerospace Medicine. These cases were derived from a selected group of highly trained young men whose profession requires outstanding visual abilities. Age of onset of spells was 12 to 44 years. Family history was present in 15 (24.6%) of the cases, and a history of migraine was present only in 2 (3.3%). Eighteen subjects (29.5%) experienced neurological deficits other than visual phenomena during the episodes. Permanent neurological deficit occurred in 1 patient. Cohen et al[2] reported 31 cases of transient visual phenomena attributed to migraine. Headache was present in 20 patients (64.5%). Sixty-one percent of cases had a positive family history, and 57% had a personal history of migraine. During a mean follow-up of 2.2 years, 1 patient had died of cardiac disease, none suffered a stroke, 1 developed amaurosis fugax, and 1 developed transient global amnesia. Whitty[11] described 16 cases, 7 women and 9 men. Headaches occurred with some of the spells in 9 cases (56%). None of them developed a persistent neurological deficit. Wiley[21] reported 10 patients, 7 women and 3 men, with scintillating scotomas without headache. Eight of the 10 had no family history of migraine, and none developed persistent neurological sequelae after an average follow-up of 1.5 years.

The findings of our study are comparable to those described in these clinical series. Mean age of onset of spells was 56.2 years in our study. Headache was present with all spells in 30% and with some spells in 12% of cases. Fifty-four percent of cases had a history of recurrent headaches. A family history of migraine headaches was present in 72% of subjects with a documented family history.

One of the characteristic features that distinguish migraine accompaniments from TIAs is a benign course in the former[1]. In one study,[22] vascular events occurred in 1 of 50 cases (2%) of "migraine aura without headache" compared with 5 of 50

(10%) in age-matched controls with TIA. However, there are occasional reports of ischemic[4, 23] and hemorrhagic[24] cerebral infarction associated with migraine accompaniments. In addition, migraine has been identified as an independent risk factor for ischemic stroke in men older than 40 years[25] and in women younger than 45 years.[26-30] However, the absolute risk of stroke associated with migraine is small.[31] In this study we did not find an increased stroke risk in association with migrainous visual symptoms, confirming the experience derived from previous clinical series.

Study Strengths and Limitations

This study was based on a general population sample and thus minimized the bias of case selection encountered in clinical series. Cohort members were systematically queried every 2 years on the occurrence of visual symptoms during an 18-year period, ensuring that as many index cases as possible were identified. Because of the prospective study design, stroke risk in subjects with migraine accompaniments could be directly compared with cases with TIA and cases without migraine accompaniments within the same cohort. Because of the nature of the study we had to rely on documentation of symptoms in the medical record, which were obtained before the publication of the IHS criteria.[12] Therefore, fulfillment of the criteria of migraine with aura or migraine aura without headache could not be verified in the majority of subjects. Nevertheless, we believe that the migrainous character of the visual episodes was convincing and consistent with the diagnosis of migraine. Finally, the Framingham population is predominantly white, and it would be difficult to justify generalizing the results of this study to other racial groups.

Conclusions and Clinical Implications

Episodes of migrainous visual symptoms in mid or late life are not rare and occur in 1.33% of women and 1.08% of men. These episodes may occur for the first time after age 50 years, in the absence of headache, and a history of recurrent headaches may not be present. Diagnosis is largely based on the clinical features of the episodes; however, noninvasive tests (carotid duplex, transcranial Doppler, MR angiography) may occasionally be indicated to exclude vascular disease in cases with an atypical presentation. Migrainous visual symptoms appear not to be associated with an increased risk of stroke, and invasive diagnostic procedures or risky therapeutic measures are generally not indicated.

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Chapter 9

Incidence and Prognosis of Transient Monocular Blindness in Systemic Lupus Erythematosus

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Abstract

Background and Purpose: Patients with systemic lupus erythematosus (SLE) are at an increased risk for recurrent arterial and venous thrombotic events. Transient monocular blindness (TMB) is common in SLE patients and has been associated with an increased risk of stroke. In a previous cross-sectional study we found a high prevalence of TMB in an unselected hospital-based cohort of 175 SLE patients. In the current study, we report on the follow-up of this cohort with an emphasis on the occurrence of arterial vascular events in patients with and without transient monocular blindness (TMB).

Methods: 175 unselected SLE patients, who fulfilled at least 4 criteria of the American College of Rheumatology for classification of SLE were interviewed by a neurologist about the occurrence of any monocular visual disturbances, and of any major vascular events, at baseline and during follow-up by means of a standardized questionnaire. Visual symptoms were classified as TMB, migraine, primary ocular disease or non-specific symptoms. Major vascular events included vascular death, retinal infarction, stroke, and myocardial infarction.

Results: At baseline 10/175 (5.7%) of patients had experienced TMB at any time in the past. During a mean follow-up of 5.7 years, 4/165 (2.4%) additional patients developed TMB, corresponding with an incidence of 425 per 100,000 person-years (95% CI 94-1088 per 100,000 person-years). During follow-up, major vascular events occurred in 5.7% of patients, corresponding to an incidence rate of 1103 per 100,000 person-years (95% CI 481-1845 per 100,000 person-years). Ten percent (1/10) of patients with TMB at baseline experienced a major vascular event, against 5.5% (9/165) of patients without TMB (OR 1.9, CI 0.2-16.9).

Conclusions: The incidence of TMB in patients with SLE is relatively high. We could not demonstrate a significant different risk of major arterial vascular events in patients with SLE with and without TMB.

Patients with systemic lupus erythematosus (SLE) are at increased risk for arterial and venous thrombotic events at young age, particularly in the presence of antiphospholipid antibodies (aPL).[1-6] Visual symptoms, including transient monocular blindness (TMB), are common in patients with SLE and in patients with aPL (but without SLE).[7-11] TMB is typically considered a transient ischemic attack in the supply territory of the internal carotid artery and has been associated with an increased risk of future arterial vascular events, in particular cerebral infarction.[12, 13] Recurrent TMB in young people often remains unexplained and has a more benign prognosis than TMB in elderly people.[14, 15]

In a previous cross-sectional study of an unselected cohort of 175 SLE patients we estimated the prevalence of TMB at 158 cases per 100,000 per year.[16] In the same cohort, we found no relation between symptoms of TMB and the presence of risk factors for atherosclerosis, antiphospholipid antibodies (aPL), or livedo reticularis. However, we did find an association between the occurrence of cerebral ischemia (defined as a history of cerebral infarction and/or cerebral transient ischemic attacks) and the presence of elevated levels of aPL.[16] Because of the high frequency of TMB in patients with SLE and the lack of an association between TMB and the presence of aPL we hypothesized that TMB in patients with SLE may not herald the same risks for future cardiovascular complications of arterial origin as TMB from atherosclerotic vascular disease. In the current follow-up study we compared the event rates in SLE patients with and without TMB.

Methods

A cohort of 175 non-selected patients with SLE who were followed up at the University Medical Center Utrecht, The Netherlands, participated in this study.[16] Patients fulfilled at least 4 criteria of the American College of Rheumatology for classification of SLE.[17] At baseline patients were interviewed in person by a neurologist by means of a standardized questionnaire about the occurrence of any visual symptoms. Monocular visual disturbances were independently classified as TMB, migraine, primary ocular disease, or non-specific symptoms by two investigators; any disagreements were resolved by discussion. In addition, patients underwent a physical examination and blood samples were obtained for the detection of aPL. Data on the presence or absence of livedo reticularis were also collected. Further details of the cross-sectional part of this study have been described in an earlier report.[16]

At follow-up patients were interviewed by means of a standardized telephone interview by one of two neurologists (CACW, RCJMD) about the occurrence of any sudden visual symptoms and of any major cardiovascular events including

transient ischemic attacks, stroke, retinal infarction, or myocardial infarction. Patients were also asked about the use of antithrombotic therapy and treatment for SLE (prednisone, azathioprine, cyclophosphamide, and hydroxychloroquine) in the preceding period. The neurologists who performed the interviews were not aware of visual symptoms, vascular events, or any other characteristics at baseline. In addition to the telephone interviews a comprehensive review of the medical records was performed covering the period of follow-up by a third investigator (MDOP) to detect any new symptoms suggesting TMB or the occurrence of any major cardiovascular events. The study was approved by the institutional review board of the University Medical Center Utrecht. Informed consent was obtained at the time of the baseline interview and verbally confirmed during the follow-up telephone interview. The follow-up period started on the day of the baseline visit and ended on the day of the follow-up interview.

Any reported visual symptoms during follow-up were classified according to predefined criteria as: TMB, migrainous visual phenomena, primary ocular disease, or non-specific visual phenomena. TMB was diagnosed if at least four of the following criteria were met: transient loss of vision in one eye affecting the entire or part of the visual field, loss of vision consisting of negative symptoms (blackening, greying or blurring of the visual field), alternate covering of eyes to prove involvement of one eye only, sudden symptom onset or a "curtain" that suddenly moved into the visual field, and duration between minutes and hours. Ocular symptoms were attributed to migraine when four of the following criteria were met: attacks of transient monocular blindness or scotoma, the presence of "positive" symptoms (enlarging star-shaped figures with scintillations, colors or flashing lights), unilateral headache, gradual development of symptoms; and duration of symptoms less than one hour.[18]

Major arterial vascular events were defined as vascular death, retinal infarction, stroke and myocardial infarction. Venous thrombotic events were not included in the primary endpoint. Each vascular event was reviewed and classified by a panel of 4 physicians after review of all available medical records and imaging studies. Similarly, for patients who died during follow-up, the cause of death was determined by a panel of four physicians after review of all available information. The cause and date of death were retrieved through the general practitioner and the local hospital records. Death was considered vascular in nature if it resulted from a documented myocardial infarction, stroke, or heart failure or if it occurred suddenly, within one hour of symptom onset. All other causes of death were considered nonvascular. The panel was unaware of baseline visual symptoms or vascular events.

Data analyses

In the primary analysis we related the presence of visual symptoms caused by TMB and the presence of stroke, transient cerebral ischemia, aPL and livedo reticularis, all at baseline, to the occurrence of major cardiovascular events of arterial origin during follow-up using odds ratios (OR) with the corresponding 95% confidence intervals (CI).

Results

Baseline characteristics

Mean age of the cohort at baseline was 36 ± 10 years. Most patients (91%) were female. Age, sex, disease duration and disease activity did not differ between patients with and without TMB. Mean follow-up was 5.7 years (998 patient years). Only 3 (1.7%) patients were lost to follow-up and another 3 (1.7%) declined participation in the follow-up telephone interview. Fifteen patients (8.6%) died during follow-up; 5 (2.9%) as a result of a presumed vascular event. Thus, 154 (88%) of the original 175 patients were interviewed during follow-up. Of these 154, 30 (19%) patients were on antiplatelet therapy and 35 (23%) received anti-coagulant therapy. Sixty-three percent of patients reported that they had received prednisone at any point during the follow-up period, 54% hydroxychloroquine, 38% azathioprine, and 10% cyclophosphamide.

At baseline 10 of the 175 patients (5.7%) had visual symptoms that were consistent with the diagnosis of TMB.[16] Six patients had experienced more than 10 episodes of TMB and five had experienced distinct episodes that affected different eyes. Eight of the 10 patients experienced sudden onset of symptoms. The duration of the attacks typically was anywhere between 1 and 30 minutes, but in 2 patients attacks lasted for hours. One patient with TMB at baseline had a history of cerebral infarction. Seven of the 10 patients with TMB at baseline had undergone duplex ultrasonography of the carotid arteries; none of them had evidence of significant carotid disease. There was no association between the diagnosis of TMB and SLE disease activity or the presence of aPL at the time of the baseline evaluation.[16] Six of the 10 patients with TMB at baseline were positive for aPL. Three received aspirin therapy during the follow-up period and 7 received no antithrombotic therapy. Four patients continued to experience episodes of TMB during follow-up. Of these, three patients were positive for aPL at baseline and two received aspirin therapy during the follow-up period. The distribution of vascular risk factors was not different between patients with or without TMB at baseline (**Table 1**).[16]

Table 1 Risk Factors for Atherosclerosis and Previous Arterial Vascular Events in 175 SLE Patients With and Without TMB

RISK FACTOR OR ARTERIAL VASCULAR EVENT	TMB N=10 N (%)	No TMB N=165 N (%)
ARTERIOSCLEROTIC RISK FACTOR		
Smoking	4 (40)	66 (40)
Diabetes mellitus	1 (10)	1 (1)
Intermittent claudication	1 (10)	2 (1)
Hypercholesterolemia	3 (30)	35 (21)
Angina pectoris	1 (10)	4 (2)
Hypertension	5 (50)	67 (41)
PREVIOUS ARTERIAL VASCULAR EVENT		
Previous Myocardial infarction	. . .	5 (3)
Previous cerebral infarct	1 (10)	14 (8)
Previous transient ischemic attack	. . .	7 (4)
Antiphospholipid antibodies*	6 (60)	74 (45)
Raynaud phenomenon	6 (60)	85 (51)

* Lupus anticoagulant or anticardiolipin antibodies, or both

Events during follow-up

During follow-up of 941 patient years in total four (2.4%) patients developed new-onset TMB, which corresponds to an incidence of 425 per 100,000 person-years (95% CI 94-1088). Of these four, three patients were positive for aPL. Two patients received anticoagulation and none received antiplatelet therapy during follow-up.

During follow-up, 11 major arterial vascular events occurred in 10 patients, corresponding to an incidence rate of 1103 per 100,000 person-years (95% CI 481-1845) (**Table 2**). One of these patients had had TMB at baseline corresponding to an event rate of 1.8% per year in patients with TMB at baseline (95% confidence interval 0.04-9.8). This patient was a 36-year-old woman who had a positive anticardiolipin antibody and who was treated with aspirin. She suffered a retinal and a cerebral infarct, 7 days apart, during follow-up and eventually died as a result of progressive renal failure. Patients with and without TMB did not differ with respect to cardiovascular vascular events during follow up (OR 1.9, CI 0.2-16.9) (**Table 3**). None of the 4 patients who experienced new onset TMB during follow-up experienced a major vascular event.

Table 2 Major Arterial Vascular Events (N=11) in 10 of 175 SLE Patients During 5.7 Years of Follow-up

Major arterial vascular event	N (%)
Vascular Death	5 (2.86)
Retinal Infarct	1 (0.57)*
Cerebral Infarct	4 (2.29)*
Myocardial Infarction	1 (0.57)
Total	11 (6.3)

* One patient experienced both a retinal and a cerebral infarct, only 7 days apart

We found no significant correlation between the occurrence of major vascular events during follow up and the presence of TMB, aPL, previous cerebral ischemic events, or livedo reticularis at baseline (**Table 3**). Also the use of antithrombotic medication during follow-up did not correlate with the occurrence of vascular events during follow up. Only five of the fourteen patients with TMB at any time received antiplatelet or anticoagulant therapy during the follow-up period.

Table 3 Frequency of Major Arterial Vascular Events in Association With TMB, the Presence of aPL, Previous Cerebral Ischemia, and Previous Livedo Reticularis in 175 Patients With SLE During 5.7 Years of Follow-up

	Patients with major arterial vascular events (N=10)	OR (95% CI)
Previous TMB (n=10)	1 (10.0)	1.9 (0.2-16.9)
No previous TMB (n=165)	9 (5.4)	
aPL (n=103)	6 (5.8)	1.1 (0.3-3.9)
No aPL (n=72)	4 (5.6)	
Previous cerebral infarct (n=15)	2 (13.3)	2.9 (0.6-15.2)
No previous cerebral infarct (n=160)	8 (5.0)	
Previous transient ischemic attack (n=7)	0 (0)	. . .
Previous livedo reticularis (n=39)	3 (7.8)	1.5 (0.4-6.2)
No previous livedo reticularis (n=136)	7 (5.1)	

TMB = Transient monocular blindness; aPL = antiphospholipid antibodies

Discussion

In this cohort of SLE patients we found a high incidence of TMB, of 425 per 100,000 person-years (95% CI 94-1088 per 100,000 person-years). This rate may be an underestimate, because 12% of patients did not participate in the follow-up telephone interview. In the general population the mean incidence of TMB is estimated at 14 per 100,000/year, and in the age-group 25-44 years 3 per 100,000/year.[19] Thus the incidence of TMB in patients with SLE is approximately 100 times higher than that in an age-matched normal population.

No association was found between a history of TMB at baseline and the presence of vascular risk factors, aPL, and previous or subsequent vascular events.[16] The 10.0% arterial vascular event rate over 5.7 years in SLE patients with TMB corresponds to 1.8% per year (95% confidence interval 0.04-9.8). This relative high rate of arterial vascular events is in agreement with previous reports of patients with SLE.[1-5, 20-22] In earlier studies the major vascular event rate following TMB caused by atherosclerotic vascular disease was 3-5% per year.[12, 23-25] Although no significant correlation was found between TMB and major cardiovascular events of arterial origin during follow-up in our cohort, the number of patients with TMB was relatively small, resulting in limited power to detect such relationships.

Many patients with TMB had frequent attacks and half of them had attacks affecting a different eye at different points in time. No evidence of atherosclerotic changes in the internal carotid artery was found in seven of the ten TMB patients who underwent carotid ultrasonography and no atherosclerotic changes were found on funduscopic examination.[16] Thus, TMB in SLE patients probably is not a thrombo-embolic event in the distribution of the ophthalmic artery. In the absence of retinal findings detected by funduscopic examination and in the absence of an association between episodes of TMB and SLE disease activity, it seems unlikely that the visual symptoms are caused by vasculitis. A cardiac source of embolism also seems unlikely given the high number of retinal events in the absence of cerebral ischemic events. Furthermore, no arrhythmia's or other cardiac abnormalities were found among patients with TMB at the baseline assessment. TMB caused by vasospasm of the retinal vasculature is a possibility since it may explain the high frequency of the attacks, often affecting each eye separately, and the lack of an association of TMB with vascular risk factors and with future vascular events.[15, 26, 27] Alternatively, the symptoms of TMB may be mediated through immunological mechanisms related to the SLE itself.

The majority of SLE patients with TMB has no evidence of atherosclerotic disease and has a favorable prognosis. However, from a clinical point of view these patients may be indistinguishable from the occasional SLE patient with TMB caused by atherosclerotic disease. Therefore, a comprehensive diagnostic work-up for a cardiac or vascular lesion, including an ophthalmologic evaluation, as well as blood tests for the presence of aPL seems appropriate in patients with SLE who present with TMB.[28] In addition, transcranial Doppler ultrasonography to measure the frequency of microembolic signals in the intracranial vasculature may point to the presence of an underlying embolic lesion and guide treatment.[29] If all diagnostic tests, including blood tests for the presence of aPL, are negative, we believe that these patients do not routinely require long-term antithrombotic therapy. In patients with aPL and TMB, there are occasional reports of a decrease in the number of TMB attacks with the institution of antithrombotic therapy.[10]

To our surprise, we did not find a correlation between the presence at baseline of previous cerebral ischemia, aPL or livedo reticularis and the occurrence of major vascular events during follow-up, whereas we did find these relationships at baseline.[16] Typically, SLE patients with aPL are at a higher risk for thromboembolic events than those without aPL. [2-5] The absence of this relationship during the follow-up period may be caused by the small number of events overall or, less likely, may be a result of medical therapy.

Strengths of this study include its prospective character, the small number of patients lost to follow-up, and the detailed assessment of the cohort at the baseline assessment. Weaknesses include the small number of arterial vascular events during follow-up, resulting in limited power, and the absence of vascular imaging studies of 3 patients who had reported TMB at the baseline assessment. Further, our data do not allow the assessment of the effect of antithrombotic or immune-modulating therapy on the rate of TMB or arterial vascular events during follow-up.

In conclusion, TMB is common in patients with SLE, but is not associated with a significantly increased risk of subsequent major arterial vascular events. Its cause remains elusive. Since SLE patients with TMB may also have atherosclerotic vascular disease a complete diagnostic work-up including an ophthalmologic evaluation, vascular imaging of the carotid-ophthalmic system, a cardiac assessment, and blood tests for the presence of aPL seems appropriate in the individual SLE patient who presents with TMB.

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Chapter 10

Discussion

Blood flow to the retina is predominantly supplied by the central retinal artery, which is the first intra-orbital branch of the ophthalmic artery. The ophthalmic artery is the first branch of the internal carotid artery (ICA) and provides most of the blood flow to the cerebral hemisphere. The ocular fundus is the only place in the human body that allows direct visualization of blood vessels without invasive techniques. As such, the retina functions as a "window" for the intracerebral vasculature. Elucidating the mechanisms and causes of retinal ischemia and embolism may thus provide further insight in the pathophysiology of cerebral ischemia.

Mechanisms and Causes of Retinal Ischemia and Embolism

Retinal ischemia

Sudden painless loss of vision in one eye with complete recovery, known as transient monocular blindness (TMB) or amaurosis fugax, is considered a transient ischemic attack in the territory of the ICA, because it is commonly associated with atheromatous disease of the ipsilateral ICA.[1-4] In our retrospective study we found severe ipsilateral ICA stenosis in 73% of patients who presented with symptoms and/or signs of retinal ischemia (chapter 3). However, there are many causes of transient visual symptoms that mimic retinal ischemia. These include transient ischemia of the anterior optic nerve, other diseases of the optic nerve, retinal or intraocular hemorrhage, raised cerebrospinal fluid pressure, migraine (chapter 8), diseases affecting the vitreous body or the lens, systemic lupus erythematosus (chapter 9), or other miscellaneous conditions.[4-7] Several characteristics of the attack of TMB may increase the likelihood of finding an ipsilateral ICA stenosis as the underlying cause.[8, 9] However, given the considerable overlap in clinical presentation among the various causes of TMB, it is difficult to establish a firm etiologic diagnosis on clinical grounds alone.

As in cerebral ischemia, symptoms are transient if blood flow to the retina is interrupted temporarily, but if retinal blood flow is decreased below a critical threshold for a prolonged period of time, retinal infarction is likely to occur. The principal mechanisms of retinal ischemia are embolic obstruction, occlusion in situ (thrombosis, hemorrhage into a plaque), inflammatory arteritis (e.g. giant cell arteritis), vasospasm (retinal migraine), and arterial occlusion that occurs hydrostatically (glaucoma, occlusive disease of the feeding vessels, severe hypotension, central retinal vein occlusion, ocular compression). [5, 8, 10, 11] The most common cause of retinal ischemia is arteriosclerotic vascular disease as confirmed by several studies in this thesis (chapters 3 through 7). However, there are many non-arteriosclerotic disease processes that may result in retinal ischemia. The most

important of these are non-arteriosclerotic vasculopathies (e.g. Moya-moya disease, ICA dissection, giant cell arteritis, fibromuscular hyperplasia, vascular malformations), retinal artery spasm, and states of altered coagulability (sickle cell disease, polycythemia vera, antiphospholipid antibody syndrome).

Atheromatous vascular lesions may cause retinal ischemia by compromising retinal blood flow due to severe stenosis of the feeding blood vessels or by causing embolism to branches of the ophthalmic artery. In our retrospective study 62% of patients who were tested within a week of symptom onset had evidence of microembolism in the middle cerebral artery ipsilateral to the symptomatic eye, supporting the notion that embolism rather than hypoperfusion is the predominant mechanism of retinal ischemia associated with ICA stenosis (chapter 3).[12] This finding corresponds well with previous clinical observations[13-17] and with studies suggesting that hemodynamic compromise is not the predominant mechanism in the pathogenesis of retinal ischemia.[18, 19]

Retinal embolism

Retinal emboli can be found in a subset of patients with symptoms of retinal ischemia.[15, 20] In our prospective cohort we found retinal emboli in 28% of patients with symptoms consisted with transient retinal ischemia or retinal infarction (chapter 7). However, most commonly retinal emboli are observed in asymptomatic individuals during routine ophthalmologic examination.[21] Retinal emboli observed by direct ophthalmoscopy vary in size and composition (chapter 7). Most retinal emboli are composed of atheromatous material containing cholesterol (chapter 7). Less commonly, retinal emboli consist of platelet-fibrin material (chapter 1), or calcium. Cholesterol and platelet-fibrin emboli usually originate from an atherosclerotic lesion of one of the major arteries, whereas calcific emboli are thought to find their origin more commonly in calcified heart valves.[8, 22]

Not all emboli that cause visual symptoms are visible by direct inspection of the retina. In our prospective study we found that only a quarter of patients with visual symptoms suggesting retinal ischemia have retinal emboli (chapter 7). Whether or not an embolus in the supply area of the ophthalmic artery causes visual symptoms is probably associated with its size. Large emboli are more likely to lodge in blood vessels proximal to the retina, compromising retinal blood flow in the ophthalmic artery or central retinal artery, whereas small emboli may course through the retinal arterioles in asymptomatic individuals. In our prospective cohort we found that emboli up to 290μ can course through the retinal vasculature (chapter 7). The notion that embolus size and composition determine the

association with retinal ischemia is highlighted by our observations in two patients with symptoms of retinal ischemia and atrial fibrillation (chapter 6). Both patients had a source of embolism in the heart (atrial fibrillation), a thrombus having lodged in the ipsilateral carotid artery and secondary microembolization from the fresh blood clot to the ophthalmic artery (chapter 6).

Symptomatic versus asymptomatic retinal emboli

Although there are many potential sources of retinal emboli, there are probably pathophysiologic differences between patients with symptomatic and asymptomatic retinal embolism (chapter 5). We were able to identify a potential source of embolism in three quarters of patients with symptoms of retinal ischemia in our prospective study cohort, which was three times higher than in patients with asymptomatic retinal embolism (chapter 7). Furthermore, patients with symptoms of retinal ischemia were more likely to have an ipsilateral severely stenotic ICA lesion than patients with asymptomatic retinal emboli (chapters 5 and 7). However, the observation of recurrent platelet-fibrin emboli in one of our symptomatic patients suggests that not all symptomatic emboli occur in the presence of severely stenotic vascular lesions (chapter 1). [23, 24]

Since asymptomatic retinal emboli are less common associated with severely stenotic ICA lesions, they may originate from non-stenotic ICA lesions or from a more proximal atherosclerotic large-vessel or cardiac lesion, in particular the aortic arch.[25] We found severely atheromatous aortic arch plaques of at least 4 mm thickness in four of nine patients with asymptomatic retinal emboli who underwent transesophageal echocardiography (chapter 7). Moreover, ten percent of these patients in our prospective study cohort had (asymptomatic) retinal emboli in both eyes, which provides further support for the notion of a proximal source of retinal embolism in these patients (chapter 7). Although we identified cardioembolic lesions in approximately 20% of patients with retinal emboli of our prospective cohort (chapter 7), this association most likely reflects the generally high rate of cardiovascular disease in these patients rather than a true source of retinal emboli.[26, 27] Cardiac embolism as the cause of retinal ischemia is probably rare (chapter 6)

Cerebral microemboli

We found that emboli that travel to the retina are often accompanied by silent microemboli that travel to the brain (chapters 2 and 5). Microembolic signals detected in the cerebral vasculature by transcranial Doppler ultrasonography usually do not cause symptoms of cerebral ischemia, but they are associated with vascular lesions and an increased risk of recurrent cerebral or retinal ischemic

events as observed by us (chapter 2) and confirmed by others.[28-31] In patients with acute ischemic stroke microembolic signals have been associated with small cortical and subcortical lesions on diffusion-weighted imaging MRI.[32, 33] Furthermore, in patients with symptomatic ICA stenosis anti-platelet therapy reduces the frequency of asymptomatic cerebral microembolization.[34] Thus, the presence of cerebral microemboli in patients with visual symptoms suspect for retinal ischemia increases the likelihood of finding an underlying atheromatous vascular lesion.

Prognosis of Retinal Ischemia and Embolism

TMB or amaurosis fugax is associated with an increased risk of cerebral or retinal infarction, in particular in patients with a high-grade stenosis of the ipsilateral ICA.[4, 35-37] Data derived from a pooled analysis including 654 patients with TMB showed a cumulative 5-year incidence of ischemic or retinal infarction of 7.7% (95% CI 5.2% to 10.2%).[38] Characteristics associated with an increased risk for subsequent stroke or retinal infarction were age ≥65 years, a history of stroke, a history of intermittent claudication, diabetes mellitus, Rankin score ≥3, more than three attacks of retinal ischemia and any degree of ipsilateral ICA stenosis. Also asymptomatic retinal embolism, detected on routine ophthalmological examination, has been identified as an important risk factor for future vascular events including stroke, myocardial infarction, and vascular death.[15, 20, 39, 40]

In our prospective cohort with symptoms of retinal ischemia or asymptomatic retinal embolism recurrent vascular events occurred in 18% of patients during the 1st month of follow-up and in 8% in the second and third months despite appropriate medical (or surgical) management (chapter 4). Most recurrent vascular events were symptoms of transient retinal or cerebral ischemia. However, 5% of patients experienced retinal or cerebral infarction or a vascular death during the 1st month following presentation. Recurrent vascular events were more common in patients with symptoms of retinal ischemia (31%) than in patients with asymptomatic retinal embolism (6%) (chapters 4 and 7). Recurrences were also more common in patients with a potential source of embolism than in patients without an identifiable causative lesion (chapters 4 and 7).

Since TMB is a clinical syndrome, defined only by the history, and since there are many non-vascular causes of TMB, not all patients who experience visual symptoms consistent with TMB are at an increased risk of future vascular events. This observation may explain why patients with TMB carry a more favorable prognosis than patients with cerebral transient ischemic attacks.[4] In the Framingham cohort we found that visual migrainous phenomena, reminiscent of symptoms caused by

transient ischemic attacks, are common in the general population, but that these are not associated with an increased risk of future stroke (chapter 8). Thus, transient neurological symptoms that are clinically difficult to distinguish from symptoms caused by transient brain or retinal ischemia "dilute" the risk of future vascular events in patient series. In other words, a subset of patients may experience visual symptoms that are clinically indistinguishable from episodes of retinal ischemia caused by atheromatous vascular lesions. Examples of this are patients with systemic lupus erythematosus. TMB is more common in these patients than in the general population (chapter 9). However, we found that the majority of SLE patients with TMB have a favorable prognosis with respect to future cardiovascular complications (chapter 9).

Limitations of the Studies in This Thesis

The studies described in this thesis have substantial limitations. First of all, lumping TMB, central retinal artery occlusion, branch retinal artery occlusion and asymptomatic retinal embolism under the umbrella term of "retinal ischemia and embolism" is an oversimplification. Each of these clinical syndromes is different in terms of the most likely cause. However, given the considerable overlap in the disease conditions underlying each of these syndromes we felt it was justified to study them together in our patient series (chapters 3 through 7). Secondly, data presented in chapters 2 and 3 were collected retrospectively and should be interpreted with the provisos inherent to such a study design. Furthermore, our retrospective and prospective cohorts consisted entirely (chapter 2 and 3) or in part (chapters 4, 5, 6, and 7) of a patient population of predominantly elderly white males with multiple vascular risk factors, derived from a Veterans Administration hospital. Our findings may therefore not be applicable to an unselected population. Lastly, the numbers in some of the studies are rather small and there are slight differences in methods between each of the studies. For example, the cut-off values for severe ICA stenosis and the decibel cut-off for microembolic signals differ between chapters.

Conclusions and Clinical Implications

The retinal vasculature should be considered an informative 'window' for obtaining insight in the pathogenesis of ischemic cerebral diseases. Symptoms of retinal ischemia and asymptomatic retinal emboli are most commonly caused by atheromatous vascular disease and associated with an increased risk of future vascular events. The predominant pathophysiologic mechanism of retinal ischemia is embolism to the ophthalmic artery, but many other causes exist and need to be considered in the differential diagnosis. Some mechanisms that underlie retinal

ischemia may also play a role in cerebral ischemia. Examples are in situ formation of emboli (chapter 1), vasospasm (chapter 9), and secondary microembolization from a cardiac embolus lodged in a more proximal blood vessel (chapter 6).

Patients who present with symptoms of retinal ischemia or who are diagnosed with retinal embolism require a timely and meticulous cardiovascular work-up in search for a source of embolism, because these patients are at risk for recurrent vascular events. A transesophageal echocardiogram and a dilated funduscopic examination should be strongly considered, in particular when no vascular lesion is identified in the carotid-ophthalmic system and when vascular risk factors are present. Transcranial Doppler ultrasonography may help identify patients with symptoms of retinal ischemia caused by atherothromboembolic vascular disease. Strict management of vascular risk factors seems appropriate in these patients.

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Summary

The ocular fundus allows direct visualization of the retinal vasculature, blood vessels that are part of the cerebral circulation. Unraveling the mechanisms and causes of retinal ischemia may provide further insight in the pathophysiological processes that underlie cerebral ischemia. The primary aim of the studies described in this thesis was to elucidate the causes, pathophysiology, and prognostic implications of retinal ischemia and asymptomatic retinal emboli in several patient populations.

Chapter 1 is a general introduction to the subject that includes an illustrative case-report. Transient monocular blindness (TMB) or amaurosis fugax (fleeting blindness) denotes an episode of sudden, painless, monocular loss of vision lasting for minutes to hours. TMB is often attributed to transient retinal ischemia and has been associated with ipsilateral internal carotid artery (ICA) disease and an increased risk of future stroke. TMB is thus regarded a transient ischemic attack in the supply territory of the ICA. It may be caused by emboli to the ophthalmic artery distribution, retinal hypoperfusion (due to vasospasm or severe narrowing or occlusion of feeding blood vessels), states of altered coaguability, and inflammatory disorders; however, there are many non-vascular causes of transient visual symptoms that are clinically indistinguishable from TMB caused by retinal ischemia. Transcranial Doppler ultrasonography (TCD) allows for *in vivo* monitoring of microemboli in the cerebral vasculature. Such cerebral microemboli have been found in patients with ICA stenosis, aortic arch plaque, and cardioembolic lesions.

In a retrospective cohort study (**chapter 2)** we tested the hypothesis that the presence of cerebral microemboli detected by TCD in patients with symptoms of cerebral or retinal ischemia identifies patients who are at an increased risk for early recurrent (cerebral or retinal) ischemic events. Of 229 patients who pre-sented with symptoms of cerebral or retinal ischemia, ten patients experienced an early recurrent ischemic event in the territory of the initial symptomatic artery. Nine of 10 events occurred in the supply territory of arteries with microemboli ($P<0.001$). Microemboli were more than twice as common in symptomatic (29%) than asymptomatic (12%) arteries ($P<0.001$). Furthermore, microemboli were more frequent in arteries with severe (≥70%) luminal stenoses as compared to without ($P=0.016$). No association between cerebral microemboli and recurrent vascular events was detected in the subgroup of patients with cardiac lesions. This study shows that in patients without a cardioembolic source, cerebral microemboli in the territory of a symptomatic cerebral artery can be precursors of recurrent cerebral or retinal ischemic events in the distribution of that artery. In addition, the findings show that cerebral microemboli are relatively common in the vascular distribution of arteries with severely stenotic lesions.

In **chapter 3** we investigated the frequency of cerebral microemboli and of ipsilateral ICA stenosis in 44 patients who presented with TMB or retinal infarction and who did not have a potential source of emboli in the heart. Control patients did not have symptoms of retinal or cerebral ischemia. Cerebral microemboli were detected in 62% of arteries of patients with retinal ischemia who were examined within a week of symptom onset as compared to in 9% of control arteries ($P<0.001$). Severe (≥70%) ICA stenosis or occlusion ipsilateral to the symptomatic eye was present in 73% of patients. Cerebral microemboli were detected more commonly distal to ICAs with severe (≥70%) stenoses than distal to ICAs without severe stenoses ($P=0.013$). The results of this retrospective study confirm the previously observed association between retinal ischemia (TMB or retinal infarction) and severe stenosis or occlusion of the ipsilateral ICA; however, more importantly, this study supports the notion of an embolic cause in the majority of patients who present with symptoms of retinal ischemia or infarction.

In **chapters 4, 5, 6, and 7** we report our findings in a prospective unselected hospital-based cohort of 77 patients with TMB, retinal infarction, or asymptomatic retinal emboli. All patients underwent a timely and standardized non-invasive diagnostic evaluation, including TCD, and were followed up for 3 months.

In **chapter 4** we report the most common causes of retinal ischemia and asymptomatic retinal emboli in this cohort. Enrollment diagnoses consisted of TMB ($n = 32$), asymptomatic retinal embolism ($n = 34$), and central or branch retinal artery occlusion ($n = 11$). All patients underwent vascular imaging studies of the ICA, echocardiograms, ophthalmologic examinations, retinal photographs, and blood tests. In addition, the frequency of recurrent arterial vascular events during 3 months of follow-up was determined by means of a structured telephone interview. We found eight different (presumed) etiologies of retinal artery distribution ischemia or embolism in this cohort. Ipsilateral ICA stenosis of more than 50% (or occlusion) was present in 35% of patients and various uncommon but potential treatable conditions (systemic lupus erythematosus, hematological disorders, ICA dissection, aortic arch disease, ophthalmic artery stenosis) were diagnosed in another 10% of patients. An etiologic diagnosis could not be made in 46% of patients overall, and in 62% of those with asymptomatic retinal emboli. Recurrent vascular events occurred in, respectively, 14/77 (18%) and 6/73 (8%) patients at 1- and 3-month of follow-up and included a retinal infarct, a cerebral infarct and two vascular deaths. This study shows that ipsilateral ICA stenosis is the most common identifiable presumed cause of retinal ischemia and embolism, but a variety of other etiologies are associated with this condition, and can be identified when specific diagnostic evaluations are undertaken.

In addition, this study shows that early recurrent vascular events are common in patients who present with retinal ischemia or asymptomatic retinal emboli and range from relatively innocuous episodes of TMB to vascular death.

Chapter 5 compares the frequency and source of cerebral microemboli in 37 patients with retinal ischemia (TMB or retinal infarction) with those in 27 patients with asymptomatic retinal emboli (in 29 eyes); all underwent TCD monitoring of the middle cerebral artery ipsilateral to the symptomatic eye. TCD examinations were performed within 7 days of symptom onset and within 14 days of the detection of retinal emboli in asymptomatic patients. Microemboli in the cerebral vasculature were significantly more prevalent in patients with symptoms of retinal ischemia (11 of 37) than in patients with asymptomatic retinal emboli (3 of 29) when compared to asymptomatic controls (0 of 15) (P=0.02). Furthermore, nine of 11 symptomatic patients with cerebral microemboli had an ipsi-lateral ICA stenosis of 50% or more, as compared with 0 of 3 in the asymp-tomatic group with cerebral microemboli (P=0.03). Both microemboli and ICA stenosis of 50% or more were present in 9/37 (24%) cases in the symp-tomatic and in 0/29 (0%) cases of the asymptomatic group(P=0.0036). Hence, in contrast to patients with asymptomatic retinal emboli, cerebral microemboli are common in patients with symptoms of retinal ischemia and are associated with severe ipsilateral ICA stenosis. This suggests that symptomatic and asymptomatic retinal emboli have different pathophysiologic mechanisms. The clinical correlate may be the increased risk of retinal or brain infarction after an episode of TMB as compared with asymptomatic retinal embolism.

Retinal ischemia rarely results from cardiac emboli caused by atrial fibrillation. The clinical presentation and diagnostic work-up of the two patients described in **chapter 6** suggest that in patients with atrial fibrillation cardio-embolic occlusion of the extracranial carotid artery, with secondary artery-to-artery embolism to the ophthalmic artery, is a potential mechanism of retinal infarction. To the best of our knowledge this mechanism of retinal ischemia has not been described previously.

In **chapter 7** we studied 48 patients with retinal emboli detected by ophthalmological examination and confirmed by retinal photographs. We investigated the relationships between emboli characteristics (based on the funduscopic examination), the presence of visual symptoms, (potential) embolic source, and recurrent vascular events. Twelve patients had symptoms of retinal ischemia and 36 had asymptomatic retinal emboli that were detected on routine ophthalmologic examination. Most retinal emboli (85%) were composed of

cholesterol and localized in the temporal arterioles of the retina (89%). Two patients had additional asymptomatic retinal infarcts. We did not find an association between embolus size, composition, number, and location, and the presence of visual symptoms, embolic source, and recurrent vascular events. A cardio-embolic source or an ipsilateral severely stenotic vascular lesion was detected in 38% of patients overall; in 75% of symptomatic and in 25% of asymptomatic patients (OR 9.0, CI 1.0-60). During 3 months of follow-up 4 of 12 symptomatic patients had recurrent vascular events as compared to 2 of 36 of asymptomatic patients (OR 8.5, CI 1.0 - 103). This study shows that patients with retinal emboli detected on funduscopic examination, with or without visual symptoms, may harbor a high risk vascular or cardio-embolic lesion. Therefore, a detailed cardiovascular work-up, including a transesophageal echocardiogram, should be considered, even in those without symptoms. This is of particular relevance given a substantial short term risk for future recurrent vascular events.

In the last two chapters of this thesis (**chapters 8 and 9**) we assessed the incidence of transient visual symptoms and the associated risk of future arterial vascular events in two different cohorts. Chapter 8 focuses on migrainous visual accompaniments in the Framingham cohort and chapter 9 on symptoms of transient retinal ischemia (TMB) in an unselected, hospital-based, cohort of patients with systemic lupus erythematosus.

Chapter 8 investigates the frequency, characteristics, and stroke outcome of mid- and late-life transient visual symptoms similar to the visual aura of migraine in 2110 subjects of the Framingham cohort. Between 1971 and 1989, at biennial examinations, 2110 subjects of the Framingham cohort were systematically queried about the occurrence of sudden visual symptoms. For the purpose of this study, the nature of all first-ever episodes of sudden visual loss was determined by a neurologist after review of the available notes of the biennial examination, neurology clinic notes, records from hospitalization and office visits, and the previous review of the visual symptoms by Framingham investigators. Between 1971 and 1989, 186 subjects (8.8%) reported sudden visual symptoms. TMB occurred in 19 (10%) and migrainous visual symptoms in 26 (14%). Thus, the prevalence of visual migrainous phenomena in this general population sample was 1.23% overall, 1.33% in women and in 1.08% in men. In three-quarters of subjects symptoms started after age 50 and in 60% of them they occurred in the absence of headache. A history of recurrent headache was present only in half of the subjects. When compared to subjects who experienced transient ischemic attacks, migrainous visual accompaniments were not associated with an increased risk of future stroke. Thus, transient visual symptoms similar to the

visual aura of migraine are common in mid- and late-life and often occur in the absence of headache or a history of recurrent headaches. Invasive diagnostic procedures or risky therapeutic measures are generally not indicated in people with migrainous visual phenomena.

Patients with systemic lupus erythematosus (SLE) are at an increased risk for stroke, in particular in the presence of antiphospholipid antibodies. Visual symptoms, including TMB, are common in patients with SLE. In **chapter 9** we investigated the incidence and prognosis of TMB in an unselected cohort of 175 patients with SLE during a mean follow-up of 5.7 years. At the baseline assessment, 10 patients (5.7%) had experienced one or more episodes of TMB at any time in the past. During follow-up, the incidence of TMB was 425 per 100,000 person-years (95% CI 94-1088 per 100,000 person-years). This incidence is approximately a hundred times greater than the incidence of TMB in the general population. During follow-up, the incidence rate of arterial vascular events in the entire cohort was 1103 per 100,000 person-years (95% CI 481 - 1845 per 100,000 person-years). Patients with SLE who suffered from TMB did not have a significantly greater risk of arterial vascular events than patients with SLE without TMB (OR 1.9, CI 0.2-16.9). Thus, TMB in SLE patients may not always represent a thrombo-embolic event in the distribution of the ophthalmic artery; its pathophysiology remains elusive. One proposed mechanism of TMB in these patients is retinal vasospasm, which would account for the high frequency of the attacks, often affecting each eye separately, the absence of vascular risk factors, and its benign prognosis.

Chapter 10 discusses the implications of the studies described in this thesis. The most important cause of retinal ischemia is arteriosclerotic vascular disease and the predominant pathophysiologic mechanism is embolism from a proximal vascular lesion, rather than hypoperfusion. However, there are many other causes and mechanisms of retinal ischemia that need to be considered in the differential diagnosis of an individual patient. The presence of cerebral microemboli in a patient with symptoms of retinal ischemia increases the likelihood of finding an underlying atheroembolic lesion. We hypothesize that some of the pathophysiological vascular processes that may play a role in retinal ischemia may also be important in cerebral ischemia. Examples are: in situ formation of emboli, vasospasm, and secondary microembolization from a cardiac embolus.

Retinal emboli, visualized on funduscopic examination, can be found in patients with symptoms of retinal ischemia, but more often occur in asymptomatic individuals during routine ophthalmologic examination. Whether an embolus to the ophthalmic artery distribution is visible in the retinal arterioles and whether it causes visual symptoms is probably related to its size. Larger emboli are more

likely to cause symptoms and to lodge in blood vessels proximal to the retina, whereas smaller emboli may course through the retinal arterioles in asymptomatic individuals.

In patients with symptomatic retinal embolism (TMB and retinal infarction), ipsilateral ICA stenosis, cerebral microemboli, and early recurrent vascular events are more common than in patients with asymptomatic retinal emboli, suggesting that there are pathophysiological differences. Patients with asymptomatic retinal emboli are more likely to have a more proximal atherosclerotic vascular lesion that serves as a potential source of emboli, such as the aortic arch or one of its major branches.

Patients who present with retinal infarction, symptoms suspect for retinal ischemia, or asymptomatic retinal emboli are at an increased risk for recurrent vascular events. Therefore, a timely and meticulous diagnostic work-up for an underlying cardio-vascular source of embolism is indicated in these patients. In addition, modifiable vascular risk factors should be carefully monitored and treated.

Samenvatting

De fundus van het oog maakt directe inspectie mogelijk van de retinale bloedvaten die deel uitmaken van de hersencirculatie. Het ontrafelen van de pathofysiologische mechanismen en oorzaken die ten grondslag liggen aan ischemie van het netvlies vergroot wellicht het inzicht in de pathofysiologie van hersenischemie. Het doel van het onderzoek dat beschreven wordt in dit proefschrift is meer inzicht te verkrijgen in de oorzaken, ontstaanswijze en prognose van retinale ischemie en van asymptomatische retinale embolieën, in verschillende groepen patiënten.

In de inleiding (**hoofdstuk 1)** wordt de probleemstelling uiteengezet en toegelicht aan de hand van een patiënt. Een aanval van plotseling, tijdelijk en pijnloos verlies van het gezichtsvermogen aan één oog staat ook bekend onder de naam "amaurosis fugax". Amaurosis fugax wordt meestal veroorzaakt door een tijdelijk verminderde bloedtoevoer naar de retina en is eerder al in verband gebracht met aandoeningen van de arteria carotis en een verhoogd risico op beroertes. Amaurosis fugax wordt dus beschouwd als een 'transient ischemic attack' in het stroomgebied van de arteria carotis interna (ACI). Het kan veroorzaakt worden door embolieën naar de arteria ophthalmica, door verminderde bloedtoevoer naar de retina (vanwege vaatspasme of een ernstige vernauwing of occlusie van één van de bloedtoevoerende vaten), door aandoeningen die de kans verhogen op trombose en door aandoeningen die gepaard gaan met ontsteking van de vaatwand. Er zijn echter ook vele niet-vasculaire oorzaken van tijdelijke uitval van het gezichtsvermogen aan één oog, die klinisch niet te onderscheiden zijn van visuele stoornissen op basis van verminderde bloedtoevoer naar de retina. Transcranieel Doppler onderzoek (TCD) kan in vivo embolieën detecteren in de hersenarteriën, met name in de arteria cerebri media (ACM). Dergelijke cerebrale microembolieën zijn eerder beschreven bij patiënten met vernauwingen van de ACI of atherosclerotische afwijkingen van de aorta, en bij patiënten met een cardiale emboliebron.

In een retrospectief cohort onderzoek (**hoofdstuk 2)** bestudeerden wij of de aanwezigheid van microembolieën in de ACM, vastgesteld met TCD, het risico verhoogt op een vroeg recidief van ischemie (in hersenen of retina) bij patiënten die zich presenteerden met symptomen van cerebrale (of retinale) ischemie. Tien van 229 patiënten hadden opnieuw cerebrale of retinale ischemie en negen van deze episodes vonden plaats in het stroomgebied van arteriën met microembolieën ($P<0.001$). Vergeleken met asymptomatische arterieën (12%) kwamen microembolieën meer dan twee keer zo vaak voor in het stroomgebied van symptomatische (29%) arterieën ($P<0.001$). Microembolieën werden ook vaker gezien in het stroomgebied van arterieën met ernstige (≥70%) stenoses

dan in arterieën zonder ernstige stenoses (P=0.016). Wij vonden geen verband tussen microembolieën en nieuwe cerebrale of retinale ischemie in de subgroep van patiënten met een emboliebron in het hart. Dit onderzoek laat zien dat bij patiënten die geen emboliebron in het hart hebben, microembolieën in de hersenvaten voorlopers kunnen zijn van recidiverende cerebrale of retinale ischemie in het stroomgebied van de desbetreffende arterie. Verder laat dit onderzoek zien dat microembolieën vaker vóórkomen in het stroomgebied van bloedvaten met een ernstige stenose dan in bloedvaten zonder ernstige stenose.

In **hoofdstuk 3** onderzochten we de prevalentie van cerebrale microembolieën in de ipsilaterale ACM en de prevalentie van een ipsilaterale ernstige stenose van de ACI bij 44 patiënten met retinale ischemie (amaurosis fugax of retina infarct) die geen emboliebron in het hart hadden. De controle groep bestond uit ACMs van asymptomatische patiënten. Wij vonden cerebrale microembolieën in 62% van de ipsilaterale ACMs van patiënten met retinale ischemie die binnen een week na aanvang van hun symptomen werden onderzocht, en slechts bij 9% van de controle groep (P<0.001). Een ernstige stenose (≥70%) of occlusie van de ACI ipsilateraal aan het symptomatische oog werd vastgesteld bij 73% van de patiënten. Cerebrale microembolieën werden vaker gezien in het stroomgebied van ACIs met een ernstige (≥70%) stenose dan in het stroomgebied van ACIs zonder een ernstige stenose (P=0.013). De resultaten van dit retrospectieve onderzoek bevestigen het al eerder beschreven verband tussen retinale ischemie (amaurosis fugax of retina infarct) en een ernstige stenose of occlusie van de ipsilaterale ACI. Tevens ondersteunt dit onderzoek het concept van embolieën als één van de belangrijkste oorzaken van retinale ischemie.

In **hoofdstuk 4 tot en met 7** beschrijven wij onderzoekingen die gebaseerd zijn op een prospectief cohort van 77 patiënten met retinale ischemie (amaurosis fugax of retina-infarcten) of met asymptomatische retinale embolieën (vastgesteld middels een routinematig oogheelkundig onderzoek). Alle patiënten ondergingen een gestandaardiseerd diagnostisch onderzoek, inclusief TCD, en werden gedurende 3 maanden prospectief gevolgd.

In **hoofdstuk 4** beschrijven wij de meest voorkomende oorzaken van retinale ischemie of retinale embolieën in dit cohort. Patiënten werden in het onderzoek opgenomen met één van de volgende diagnosen: amaurosis fugax (n=32), asymptomatische retinale embolieën (n=34), en een infarct in het stroomgebied van de arteria centralis retinae of een aftakking daarvan (n=11). Alle patiënten ondergingen beeldvormend onderzoek van de ACI, echocardiografie van het

hart, oogheelkundig onderzoek, fundus foto's en laboratoriumonderzoek. Tevens werd het vóórkomen van vasculaire complicaties bepaald gedurende een observatieperiode van 3 maanden door middel van een gestructureerd vraaggesprek over de telefoon. Wij vonden acht verschillende (mogelijke) oorzaken van ischemie of embolieën in het stroomgbied van de arteria centralis retinae in dit patiëntencohort. Een ipsilaterale stenose van de ACI van 50% of meer (of occlusie) werd vastgesteld bij 35% van de patiënten, en een aantal zeldzame, maar mogelijk behandelbare aandoeningen (systemische lupus erythematosus, hematologische aandoeningen, dissectie van de ACI, ernstige atherosclerose van de aortaboog, stenose van de arteria ophthalmica) werd gediagnostiseerd bij 10% van de patiënten. Er werd geen duidelijke oorzaak vastgesteld bij 46% van alle patiënten en bij 62% van de patiënten met asymptomatische retinale embolieën. Vasculaire complicaties traden binnen één maand op bij 14/77 (18%) en tussen één en drie maanden bij 6/73 (8%) van de patiënten. Deze complicaties betroffen onder andere een retina-infarct, een herseninfarct en twee keer overlijden door een vasculaire oorzaak. Dit onderzoek laat zien dat ipsilaterale stenose van de ACI de meest voorkomende (waarschijnlijke) oorzaak van retinale ischemie of embolieën is, maar dat er ook verschillende andere mogelijke oorzaken bestaan, die kunnen worden vastgesteld wanneer specifieke diagnostiek wordt uitgevoerd. Dit onderzoek laat ook zien dat patiënten met retinale ischemie of embolieën risico lopen op vroege vasculaire complicaties, die kunnen variëren van relatief onschuldige aanvallen van amaurosis fugax tot overlijden.

Hoofdstuk 5 vergelijkt de prevalentie en bron van ipsilaterale cerebrale microembolieën in de ACM bij 37 patiënten met retinale ischemie (amaurosis-fugax of retina-infarct) met 27 patiënten met asymptomatische retinale embolieën (in 29 ogen) en met 15 controle personen zonder retinale embolieën. TCD onderzoek werd uitgevoerd binnen 7 dagen van het onstaan van symptomen en binnen 14 dagen na het vaststellen van retinale embolieën bij asymptomatische patiënten. Cerebrale microembolieën waren vaker aanwezig bij patiënten met symptomen van retinale ischemie (11 van de 37) dan bij patiënten met asymptomatische retinale embolieën (3 van de 29), of bij een controlegroep (0 van de 15). Negen van de 11 symptomatische patiënten die tevens microembolieën hadden, bleken ook een ipsilaterale ACI stenose van minstens 50 % te hebben. Daarentegen had geen van de drie asymptomatische patiënten met microembolieën een ACI stenose (P=0.03). Zowel micro-embolieën als een ACI stenose van minstens 50% werden vastgesteld bij 9/37 (24%) patiënten in de symptomatische groep en bij 0/29 (0%) van de patiënten in de asymptomatische groep (P=0.0036). Dus, anders dan bij patiënten met asymptomatische retinale embolieën, komen cerebrale microembolieën en

een ernstige ipsilaterale ACI stenose vaak voor bij patiënten met klachten die veroorzaakt worden door retinale ischemie. Deze bevinding impliceert dat symptomatische en asymptomatische retinale embolieën een verschillende ontstaanswijze hebben. Het klinische belang is mogelijk gelegen in een hoger risico op een retina- of cerebraal infarct na een aanval van amaurosis fugax dan na het vastellen van een retinale embolus bij een asymptomatische patiënt.

Retinale ischemie wordt zelden veroorzaakt door embolieën uit het hart als gevolg van boezemfibrilleren. De klinische presentatie en de resultaten van het diagnostisch onderzoek van de twee patiënten die beschreven worden in **hoofdstuk 6** suggereren dat een mogelijke oorzaak van een retina-infarct bij patiënten met boezemfibrilleren bestaat uit een occlusie van de arteria carotis door een embolus uit het hart, met secundair microembolieën naar het stroomgebied van de arteria ophthalmica. Voor zover wij weten is deze oorzaak van retinale ischemie niet eerder beschreven.

In **hoofdstuk 7** bestudeerden wij 48 patiënten met retinale embolieën, waargenomen tijdens een routinematig oogheelkundig onderzoek en bevestigd met foto's van de retina. Wij stelden als doel de verbanden te onderzoeken tussen enerzijds karakteristieken van de embolieën (op basis van het oogheelkundig onderzoek), en anderzijds de aanwezigheid van visuele symptomen, een mogelijke emboliebron in het hart, en het optreden van vasculaire complicaties gedurende een observatieperiode van 3 maanden. Twaalf patiënten bemerkten tijdelijke of blijvende uitval van het gezichtsvermogen en 36 andere patiënten hadden geen verschijnselen van de retinale embolieën (die waren ontdekt ten tijde van het routinematig oogheelkundig onderzoek). De meeste embolieën (85%) bevatten cholesterol en bevonden zich aan de temporale zijde van de retinale circulatie (89%). Twee patiënten hadden tevens asymptomatische retinale infarcten. We konden geen verband vinden tussen de grootte van de embolus, de samenstelling van de embolus, het aantal embolieën, en de plaats van de embolus in de retina aan de ene kant, en de aanwezigheid van visuele symptomen, de bron van de embolus, en het optreden van vasculaire complicaties aan de andere kant. Wij vonden een cardiale emboliebron of een ernstige ipsilaterale stenose van de ACI bij 38% van alle patiënten, en vaker (75%) bij patiënten met visuele verschijnselen dan bij asymptomatische patiënten (25%;'odds ratio' 9.0, BI 1.0-60). Gedurende een observatieperiode van 3 maanden kregen 4 van de 12 symptomatische patiënten een vasculaire complicatie en slechts 2 van de 36 asymptomatische patiënten ('odds ratio' 8.5, BI 1.0 - 103). Dit onderzoek laat zien dat patiënten met retinale embolieën vastgesteld door middel van een oogheelkundig onderzoek, met of zonder klachten daarvan, mogelijk een onderliggende vasculaire of cardiale emboliebron hebben. Het is

daarom belangrijk om gedetailleerde cardio-vasculaire diagnostiek uit te voeren bij deze patiëntën, inclusief een trans-oesophageale echo van het hart, zelfs bij patiënten zonder visuele verschijnselen. Dit is vooral van belang vanwege het verhoogde korte-termijn risico op vasculaire complicaties.

In de laatste twee hoofdstukken van dit proefschrift (**hoofdstukken 8 en 9**) onderzochten wij de incidentie en prognose van tijdelijke uitval van het gezichtsvermogen in twee verschillende cohorten. Hoofdstuk 8 gaat in op visuele klachten veroorzaakt door migraine bij het Framingham cohort en hoofdstuk 9 gaat in op amaurosis fugax bij een ongeselecteerde ziekenhuispopulatie van patiënten met systemische lupus erythematosus.

In **hoofdstuk 8** onderzochten wij de frequentie, karakteristieken en prognostische betekenis van tijdelijke visuele symptomen gelijkend op een visueel aura van migraine bij 2110 personen van het Framingham cohort. Tussen 1971 en 1989 werden 2110 personen van het Framingham cohort om het jaar systematisch ondervraagd over het optreden van plotselinge visuele symptomen. De aard van alle voor het eerst vermelde aanvallen van plotselinge uitval van het gezichtvermogen werd geclassificeerd door een neurologe, na het doornemen van alle beschikbare aantekeningen over het tweejaarlijkse onderzoek, eventuele gegevens van de polikliniek neurologie, ziekenhuisopnames, andere bezoeken aan een arts, en eerdere verslagen van de Framingham onderzoekers met betrekking tot de visuele verschijnselen. Tussen 1971 en 1989 vermeldden 186 personen (8.8%) voor het eerst een aanval van plotseling verlies van het gezichtsvermogen. Amaurosis fugax werd gediagnosticeerd bij 19 (10%) van hen en migraineuze visuele symptomen bij 26 (14%). De prevalentie van visuele migraineuze klachten in deze steekproef van de algemene populatie was derhalve 1.23% (1.33% bij vrouwen en 1.08% bij mannen) in 17 jaar. Bij driekwart van de personen begonnen de klachten na het 50ste levensjaar en bij 60% traden ze op zonder hoofdpijn. Een voorgeschiedenis van terugkerende hoofdpijn werd gemeld in slechts de helft van deze gevallen. Wanneer deze personen vergeleken werden met personen van het Framingham cohort met de diagnose 'transient ischemic attacks', vonden wij geen verband tussen migraineuze visuele klachten en een verhoogd risico op een beroerte. De conclusie is dat tijdelijke visuele symptomen lijkend op de visuele aura van migraine regelmatig vóórkomen bij mensen van middelbare en oudere leeftijd, ook zonder begeleidende hoofdpijn of een voorgeschiedenis van hoofdpijn, en dat deze verschijnselen géén voorbode vormen van een beroerte. Invasieve diagnostiek of risicovolle behandelingen zijn daarom bij deze mensen in de regel niet aangewezen.

Patiënten met systemische lupus erythematosus (SLE) hebben een verhoogd risico op een beroerte, vooral bij de aanwezigheid van antifosfolipiden antistoffen. Visuele klachten, inclusief amaurosis fugax, komen regelmatig voor bij patiënten met SLE. In **hoofdstuk 9** onderzochten wij de incidentie en prognose van amaurosis fugax bij een ziekenhuiscohort van 175 patiënten met SLE, gedurende een observatieperiode van gemiddeld 5.7 jaar. Aan het begin van de observatieperiode vermeldden 10 patiënten (5.7%) ooit klachten van amaurosis fugax te hebben gehad. Gedurende de observatieperiode kregen 4 andere patiënten amaurosis fugax, overeenkomend met een incidentie van 425 per 100,000 persoon-jaren (95% BI 94-1088 per 100,000 persoon-jaren). Deze incidentie is ongeveer honderd keer zo hoog als in de algemene bevolking. Arteriële vasculaire complicaties deden zich gedurende de observatieperiode voor bij 10 patiënten, overeenkomend met een incidentie van 1103 per 100,000 persoon-jaren (95% BI 481 - 1845 per 100,000 persoon-jaren). Patiënten met SLE en amaurosis fugax hadden geen significant hoger risico op arteriële vasculaire complicaties dan patiënten met SLE zonder amaurosis fugax ('odds ratio',1.9, BI 0.2-16.9). Dit betekent dat amaurosis fugax bij patiënten met SLE waarschijnlijk niet altijd veroorzaakt wordt door een trombo-embolie in het stroomgebied van de arteria ophthalmica. De onderliggende pathofysiologie blijft onduidelijk. Een mogelijke oorzaak van amaurosis fugax bij deze groep patiënten is spasme van de retinale vaten, hetgeen een verklaring kan vormen voor de hoge frequentie van de aanvallen, vaak van één van beide ogen afzonderlijk, alsmede voor de afwezigheid van risicofactoren voor atherosclerose, en het (in de regel) ongecompliceerde beloop.

Hoofdstuk 10 is gewijd aan de implicaties van de studies die beschreven zijn in dit proefschrift. De belangrijkste oorzaak van retinale ischemie is atherosclerose en het meest voorkomende pathofysiologische mechanisme is embolisatie vanuit een stroomopwaarts gelegen atherosclerotische plaque. Er zijn echter vele andere mogelijke oorzaken en ontstaanswijzen van retinale ischemie, die betrokken moeten worden in de differentiële diagnose van de individuele patiënt. De aanwezigheid van cerebrale microembolieën bij een patiënt met klachten die mogelijk veroorzaakt worden door retinale ischemie verhoogt de kans op een trombo-embolie uit een onderliggende atherosclerotische laesie. Wij veronderstellen dat sommige pathofysiologische processen die een rol spelen bij retinale ischemie eveneens van belang zijn bij het onstaan van hersenischemie. Voorbeelden hiervan zijn: lokale vorming van embolieën, vaatspasme, en secundaire embolisatie uit een in de hals vastgelopen cardiale embolus.

Retinale embolieën vastgesteld gedurende een oogheelkundig onderzoek kunnen vóórkomen bij patiënten met tegelijkertijd klachten passend bij retinale ischemie, maar zij komen vaker voor bij patiënten zonder visuele klachten. Waarschijnlijk is het de grootte van de embolus die bepaalt of een embolus in het stroomgebied van de arteria ophthalmica al dan niet tot uitval van een deel van het gezichtsveld leidt, en of deze zichtbaar is tijdens een oogheelkundig onderzoek. Grotere embolieën veroorzaken waarschijnlijk vaker klachten en komen vaker vast te zitten in bloedvaten proximaal van de retina, terwijl kleinere embolieën onmerkbaar hun weg door de retinale vaten kunnen vinden.

De waarneming dat bij patiënten met symptomatische retinale embolieën (amaurosis fugax en retina-infarcten) vaker een ipsilaterale ACI stenose, microembolieën in de hersenen en vasculaire complicaties in het ziektebeloop vóórkomen dan bij patiënten met asymptomatische retinale embolieën, leidt tot de veronderstelling dat er pathofysiologische verschillen zijn tussen symptomatische en asymptomatische embolieën in het netvlies. Patiënten zonder verschijnselen hebben mogelijk vaker een proximale atherosclerotische emboliebron, zoals de aortaboog of één van de grote aftakkingen van de aorta.

Patiënten met retina-infarcten, patiënten met symptomen die verdacht zijn voor retinale ischemie, en patiënten met asymptomatische retinale embolieën hebben allen een verhoogd risico op vasculaire complicaties, zij het in verschillende mate. Tijdige en uitgebreide diagnostiek naar een mogelijke emboliebron in het hart of de grote vaten is aangewezen bij deze patiënten; daarbij behoren risicofactoren voor vaatziekten nauwkeurig te worden nagekeken en behandeld.

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Curriculum Vitae

Cristanne Wijman, M.D., was born in 1965 in Amsterdam to Cunie and Jan Wijman. Jan was a gynecologist and Cunie was a nurse. Cristanne attended high school at the European School in Mol, Belgium, and the Gemeentelijk Gymnasium in Hilversum, the Netherlands. She graduated from the University of Leiden Medical School in 1992. While in medical school, Cristanne developed her interest in neurology and in clinical research. She received a scholarship from 'Stichting de Drie Lichten' to study hand function in quadriplegic patients at Case Western Reserve University in Cleveland, OH, under the supervision of Hunter Peckham, Ph.D., Professor of Biomedical Engineering.

Cristanne completed an internship in internal medicine at MetroHealth Medical Center in Cleveland, OH, and residency in neurology at Boston University Medical Center. During her chief year, she met David Reitman, a medical student, whom she married 3 years later. Cristanne pursued subspecialty training in Stroke at Boston University Medical Center and Neurocritical Care at John Hopkins University Medical Center while David completed his residency in internal medicine in Boston. Most of the research described in this thesis was done during Cristanne's two-year stroke fellowship in Boston with Viken Babikian, M.D., Professor of Neurology. In 1999, Cristanne and David moved to Utrecht, the Netherlands, where Cristanne served for two years as a junior faculty member in the department of neurology at Utrecht University. Their children, Fred and Anna, now 8 and 6 years old, were born during that time.

In 2001, the family moved to California. Since that time, Cristanne has served on the neurology faculty at Stanford University and joined the Stanford Stroke Center. She currently is Associate Professor in Neurology and Director of the Stanford Neurocritical Care Program. In addition to building a very busy clinical service, Cristanne has developed a successful clinical research program that receives grant funding from the American Heart Association and the National Institutes of Health. Her current research focuses on the diagnostic and prognostic utility of state-of-the art magnetic resonance imaging techniques and biomarkers in hypoxic-ischemic brain injury and spontaneous intracerebral hemorrhage.

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