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Do Patients with Retinal Artery Occlusion Need Urgent Neurological Evaluation?

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Whether patients with central (CRAO) or branch (BRAO) retinal artery occlusion should undergo urgently a detailed neurological workup for ischemic stroke is controversial. In a survey¹ of physicians in the United States, among those who responded, 35% of ophthalmologists but 73% to 86% of neurologists and neuro-ophthalmologists sent their patients with acute CRAO for immediate neurological workup. An anonymous survey of members of the American Academy of Neurology Stroke Section and vitreoretinal specialists of the American Academy of Ophthalmology showed that 75% neurologists pursue a hospital-based evaluation within 12 hours of retinal artery occlusion, whereas the 82% of retina specialists pursue an outpatient workup.²

In the literature, when considering the risk of developing ischemic stroke, patients with retinal artery occlusion, transient ischemic attack (TIA) and amaurosis fugax are usually lumped together; however, these three conditions are not synonymous. CRAO is of two types - arteritic and non-arteritic; my studies on CRAO have shown that it is only non-arteritic CRAO (NA-CRAO), which is usually embolic in nature, carries any risk of the patient developing ischemic stroke. TIA is not the same as amaurosis fugax, because TIA is due to transient cerebral ischemia, whereas amaurosis fugax is an ocular phenomenon, which can be caused by a large variety of conditions. For example, in my study³ of 2,725 eyes presenting with amaurosis fugax to my Ocular Vascular Clinic, its prevalence was 38% among eyes with central retinal vein occlusion with cilioretinal artery occlusion, 26.5% among giant cell arteritis due to optic nerve head ischemia, 15% among ocular ischemic syndrome, 14% among BRAO, 13% among hemi-central retinal vein occlusion patients, 12% among NA-CRAO, 5% among central retinal vein occlusion, 3% among nonarteritic anterior ischemic optic neuropathy, and 0.35% among branch retinal vein occlusion. Moreover, amaurosis fugax can occur due to ocular conditions other than ocular vascular disorders. Of all these disorders, those with NA-CRAO and BRAO carry the main risk of ischemic stroke. There are many retinal and ocular ischemic causes of amaurosis fugax and an evaluation by an ophthalmologist is required instead of assuming it is TIA.

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Based on misconceptions, the following are two examples for the preference for referring patients for immediate neurological workup.

1. Biousse⁴, a neuro-ophthalmologist, advocated that all patients with presumed transient or permanent retinal ischemia undergo urgent brain imaging and etiologic testing, like patients with cerebral ischemia. According to her, this is recommended by the guidelines by the National Stroke Association⁵, American Heart Association/American Stroke Association,⁶ and other international organizations⁷. Yet a review of those publications showed that the report of the National Stroke Association⁵ dealt with TIA only; the one by the American Heart Association/American Stroke Association⁶ made no mention of retinal artery occlusion; and Uehara and Minmatsu⁷ dealt with TIA and ischemic strokes. None of these publications actually dealt with permanent NA-CRAO, BRAO or amaurosis fugax, which ophthalmologists invariably deal with. American Heart Association/American Stroke Association⁶ in their definition (proposed by a group of cardiologists and neurologists), unfortunately, lumped TIA, stroke and retinal ischemia together. However, my basic and clinical studies on retinal ischemia showed that, pathogenetically and clinically, retinal ischemia is a very different clinical entity from TIA and stroke; therefore, it is not logical for the American Heart Association /American Stroke Association to lump it with TIA and stroke. For example, my experimental studies dealing with retinal tolerance time to acute ischemia showed that retinal tolerance time is very different from that of the brain.⁸

The risk of development of TIA/stroke in patients with retinal artery occlusion is well-known, but its incidence is highly controversial, as is evident from the following very brief review. Golsari et al.⁹ in 112 patients (77 retinal artery occlusion and 35 with amaurosis fugax) reported silent brain infarctions in 15%, with internal carotid artery stenosis as the only significant predictor of silent brain infarctions, in multivariate analysis. Lauda et al.¹⁰ in a retrospective MRI study, within 24 hours after onset of CRAO (100 patients), BRAO (45 patients), and amaurosis fugax (68 patients), found brain infarctions in 23%, 90% of whom had no neurological symptoms. Chang et al.¹¹, in a retrospective Taiwan nationwide population-based study of retinal artery occlusion, reported a stroke in 20% compared to 10% in their control group during a 3-year follow-up period. Rim et al.¹², based on National Registry data of the Korean National Health Insurance Service, found that stroke occurred in 15.0% of the retinal artery group and in 8.0% of the comparison group; however, they stated that these findings were limited by uncontrolled confounding factors. Callizo et al.¹³ found stroke in 11 of 77 (14%) CRAO patients - 5 of those within 4 weeks after the CRAO occurred. Helenius et al.¹⁴ in a retrospective study, based on 129 patients with monocular ischemic visual loss and diffusion-weighted imaging, reported acute brain infarctions in 24%. Lee et al.¹⁵, in a retrospective MRI study of 18 patients with CRAO and 15 with BRAO, within 7 days of the onset of visual symptoms, reported evidence of acute ischemic stroke in 24.2%. Lee's group, in a study¹⁶ based on a review of database of the "National Health Insurance Review and Assessment Service of Korea", found reports of 1,585 patients with CRAO; their stroke incidence one year before and one year after onset of CRAO was 9.18%. By sharp contrast, in my comprehensive study¹⁷, of 196 consecutive CRAO and 119 BRAO patients, the incidence of symptomatic TIA/stroke before or after onset was 7% in CRAO patients (52% of them seen within a week and 82% within 2 weeks¹⁸) and 3% in BRAO patients with a median followup of 1.8 (IQR 0.2–4.7) years; the Kaplan-Meier

estimate of the incidence of TIA/stroke developing within 3 months after onset was 1% (95% CI, 0.3%–4.1%) for CRAO, whereas among BRAO patients only 2 had a stroke/TIA >5 years after the onset. This difference between the study by Lee et al.¹⁵ and my study¹⁷ seems to be due to problems with the study by Lee et al.¹⁵; they had 53 subjects with retinal artery occlusion but they gave data about 33; their retrospective study was done jointly with a neurology department, which further biased the study towards a very high incidence of stroke/TIA. Study design, after all, determines outcome. The study designs of Lee's group¹⁶ and that of mine¹⁷ differ markedly; therefore, the findings of the two studies cannot be compared. My study¹⁷ reports the absolute incidence of stroke/TIA among these ocular conditions, based on data carefully collected by a single investigator. Their data were based on the "National Health Insurance Review and Assessment Service", and they compared relative risks of stroke at time intervals from onset of the CRAO; but that does not provide the absolute risk. From their data, the risk of ischemic stroke was 3% within 90 days after the onset of CRAO in patients who were followed, while in my study¹⁷ it was 1%. Thus, my study and others contradict the conclusions of Lee's group^{15,16}. Also, Brown and Vasudevan¹⁹ pointed out a flaw in the study by Lee et al.¹⁵: in their retrospective study, there is no mention of how many patients first presented with new neurological deficits and vision loss. Moreover, patients who have no neurological symptoms are unlikely to have an abnormal brain MRI, so it serves no useful purpose to subject them to MRI evaluation.

Trobe²⁰ reported that the risk of future stroke in untreated patients with amaurosis fugax, retinal plaques, and infarcts is less than 3% per year, far lower than that expected for cerebral (hemispheric) TIAs. Hankey et al.²¹, in a study of 99 patients with retinal artery occlusion, over the following five years found the actuarial average absolute risk of stroke 2.5% per year. Dunlap et al.²² in 130 consecutive patients with a diagnosis of Hollenhorst plaques, CRAO or BRAO, found that they are associated with a low prevalence of extracranial cerebrovascular disease to require intervention. The European carotid surgery trial²³ showed that the odds of stroke were decreased in patients with ocular ischemia alone (amaurosis fugax or retinal artery occlusion) compared with those with cerebral TIA or stroke. De Potter and Zografos²⁴, in a study of 151 patients with retinal arterial obstruction, reported that the survival rate of the entire group with retinal artery occlusion was not significantly different from that of the age- and sexmatched group ($p = 0.29$).

It could be argued that my study and several others were based on symptomatic stroke/TIA, while a few other studies were based on discovery of silent cerebral infarcts on MRI, which showed a much higher incidence of stroke compared to those without MRI evaluation. I did have patients in my study with negative findings on neurological evaluation.

From the point of view of immediate, logical management of retinal artery occlusion patients and the associated complications of both symptomatic stroke/TIA and silent infarcts, the crucial action that matters is to determine the cause of retinal artery occlusion and treat that to prevent further episodes. Both retinal artery occlusion and associated cerebral ischemia are almost invariably due to a common denominator, i.e. embolism. Therefore, from the practical point of view of management, the most important consideration is the need to immediately find the source of the embolism which causes the retinal artery occlusion, as well as, stroke/TIA in some cases, and then try to eradicate that

source of embolism, if possible. In view of that, what is needed immediately is to find the source of embolism and deal with that, rather than a detailed, expensive neurological evaluation (unless neurological symptoms are present).

In my Ocular Vascular Clinic, I did comprehensive studies on the etiologies of 234 consecutive NA-CRAO and 141 BRAO patients.²⁵ Since embolism is the most common factor causing retinal artery occlusion, amaurosis fugax, stroke, and TIA, and the emboli originate from the carotid artery or the heart, these patient were immediately evaluated for carotid artery disease (by Doppler/angiography) and heart lesions (by echocardiography). Plaques in the carotid arteries were found to be the most common cause of embolism and these were seen in 71% in NA-CRAO and 66% in BRAO patients. The ipsilateral internal carotid artery had $\geq 50\%$ stenosis in 31% of NA-CRAO patients and 30% of BRAO; my study showed that the presence of plaques in the carotid artery was generally of much greater importance for development of retinal artery occlusion than the degree of stenosis in the artery. On echocardiography, an embolic source was found in 52% of NA-CRAO and 42% of BRAO. In another study¹⁷, carotid artery plaques were seen on the involved side in 86% of 52 patients with amaurosis fugax, and carotid artery stenosis of $> 50\%$ in 72%; carotid artery stenosis was worse in them than in BRAO or NA-CRAO patients, indicating that poor perfusion pressure, apart from embolism, played an important role in amaurosis fugax. Our study²⁶ has also shown that Serotonin, in the presence of atherosclerotic lesions in the carotid artery, can cause transient or complete occlusion of the central retinal artery. I have seen amaurosis fugax caused by platelet emboli due to platelet aggregation abnormality.

As far as the ethnic make-up of the population of my cited comprehensive studies dealing with retinal artery occlusion, majority of the patients were Caucasian, reflecting the racial make-up of our Midwest population base. One concern raised could be that the results of my cited studies may not be generalizable to other different ethnic groups; however, I am not aware of any valid scientific published study that has shown that ethnicity is a significant determining factor in the causes of retinal artery occlusion or its outcome or complications. Similarly, the population in these studies was primarily a referral population to a large academic center, similar to other published large studies. This is because the incidence of retinal artery occlusion is sufficiently low, requiring its comprehensive study to be conducted in a large academic referral population in order to have enough patients to make the results meaningful.

In conclusion, for proper management of NA-CRAO, BRAO and amaurosis fugax, urgent evaluations of carotid artery, heart, fasting lipid levels and complete blood count constitute the most important investigations, rather than neurological evaluations - unless, of course, there are neurological symptoms. This has been my policy of management of these disorders for about half a century. I have found that, unfortunately, there is a misconception that the absence of any abnormality on carotid artery evaluation or echocardiography of the heart always rules out those sites as the source of embolism. I have seen patients with CRAO, BRAO or emboli in the retinal arteries, without either of these tests showing any abnormality at all. I have discussed elsewhere the reasons for that misconception.²⁷

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