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Risk of Acute Stroke in Patients with Retinal Artery Occlusion

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Abstract

Neurologists and neuro-ophthalmologists promote aggressively themselves as the appropriate physicians to manage retinal artery occlusion (RAO) patients. They do this on the flawed premise that because both the retina and brain are neural tissues, they respond identically to acute ischemia, and thus their management is similar. This is an illogical conception because the two organs are very different in their morphology, physiology, and response to acute ischemia and reperfusion. Risk of development of ischemic stroke in retinal artery occlusion, differences in pathogeneses of RAO and acute cerebral ischemic stroke, and long-term management of patients with RAO are discussed.

Introduction

There are many reports of the development of ischemic stroke in patients with retinal artery occlusion (RAO), with controversial claims. To get a scientifically valid understanding of this association and RAO management, one needs to know the following:

1. What is the risk of the development of ischemic stroke in RAO?
2. How valid is it to consider RAO equivalent of acute cerebral ischemia?
3. How valid is the claim by neurologists that the long-term management of patients with RAO is like that of stroke?

Risk of Development of Ischemic Stroke in Retinal Artery Occlusion

In the literature, its reported incidence varies widely. For example, it was reported as 4% in 3778 central RAO (CRAO) within 1 year [1]; and 5.3% in 300 CRAO: 2.3% occurring 15 days before CRAO, 1.3% simultaneously with CRAO, and 1.7% occurring after CRAO [2]. In an RAO group of 19,809, none developed stroke in persons aged <20 years [3]. A systematic review and meta-analysis of acute cerebral ischemia, detected by MRI, within 7 days from diagnosis of acute CRAO, branch RAO (BRAO), and transient monocular vision loss showed 30% of patients with CRAO and 25% of patients with acute BRAO developed acute cerebral ischemia [4]. By contrast, a study, on a follow-up of RAO for 6 years, concluded that the number of strokes/transitory ischemic attacks within the first year is relatively low after RAO [5].

Levin P, et al. (2018) [6], based on a study of 103 CRAO patients concluded: "Patients with CRAO are at significant risk of future cardiovascular and cerebrovascular events." We investigated that claim in our prospective study of 439 consecutive RAO patients [7]. Among 234 CRAO patients, the incidence of stroke was 19%, while in age and period matched control population it was 4.3% ($p < 0.0001$); and the incidence of ischemic heart disease was in 26% and 10.7% ($p < 0.0001$) respectively. In 141 BRAO, stroke developed in 17% and ischemic heart disease in 26%, both were significantly higher ($p < 0.0001$) compared to an age and period matched population.

Embolism is by far the most common cause of the development of both RAO and ischemic stroke. RAO comprises CRAO, BRAO, and cilioretinal artery occlusion and, unlike a stroke, not all of them are always embolic. CRAO and BRAO are commonly embolic but not always. That is why the risk of development of stroke is similar in CRAO and BRAO. Cilioretinal artery occlusion is only rarely embolic. Emboli usually originate from atherosclerotic plaques in the carotid arteries, and much less commonly from the heart. Therefore, the incidence of the development of RAO and stroke is determined by the presence of the following risk factors: diabetes mellitus, arterial hypertension, and hypercholesterolemia, the main factors for the development of atherosclerosis. Variation in incidence of those factors in different reported studies may explain the variation of risk of development of stroke in RAO. That is why in an RAO group of 19,809 no persons aged <20 years developed stroke [3].

Differences in Pathogeneses of RAO and Acute Cerebral Ischemic Stroke

Neurologists and neuro-ophthalmologists aggressively promote the concept that RAO and acute cerebral ischemic stroke are equivalent clinical entities; because both the retina and brain are neural tissues, and they must, therefore respond identically to acute ischemia. They strongly claim that the long-term management of patients with RAO is like ischemic stroke, and so they are best suited to manage RAO. This is being perpetrated by them. However, RAO is a retinal vascular disorder and NOT a neurologic disorder. Therefore, RAO should fall in the domain of retina specialists, who have an in-depth knowledge of it, and NOT neurologists and neuro-ophthalmologists. Moreover, the latter ignores the basic fact that the retina and brain are very different in their morphology, physiology, and response to acute ischemia and reperfusion, as will be evident from the discussion below. Consequently, their equating RAO with ischemic stroke represents a fundamental flaw in their entire concept.

Briefly, our experimental study [8] in 38 rhesus monkeys showed that if CRAO lasts for an hour or less and the retinal circulation is then restored, the retina suffers no permanent ischemic damage. After that, the longer the CRAO, the greater the ischemic retinal damage, and if CRAO lasts 4 hours, it produces irreversible ischemic damage. The tolerance time of the brain to acute ischemia, by contrast, is much shorter. Briefly, the reasons for that are as follows:

(a) The brain has very scanty storage of intracellular glucose and depends entirely on the blood circulation to supply constantly not only oxygen but also glucose. In the retina, by contrast, (i) there is ample storage of glucose and glycogen in the Muller cells. (ii) The adjacent vitreous' glucose content is 3 times that of the retina. (iii) Probably the most important factor is that the choroidal vessels supply a major part of glucose and oxygen to the retina. This gives the retina self-sufficiency in glucose, and to some extent in oxygen, for much longer than the brain.

(b) It is well-established that acute ischemia of the neural tissues leads to the development of edema in them. When this occurs in the brain due to acute ischemia: (i) the rigid cranial cavity cannot accommodate the extra volume produced by brain edema; and (ii) since the brain is composed of dense, thickly packed, solid neural tissue, ischemic edema markedly compresses the brain tissues and obliterates the microvasculature in it. These two factors combine to produce obliteration of its microvasculature, and on the restoration of microcirculation, which results in a "no-reflow phenomenon", and instant infarction. That explains the irreversible brain damage seen after even transient brain ischemia (TIA). The retina, on the other hand, is a very thin membrane, set in surroundings that can accommodate the increased volume of the ischemic retina easily, so there is no "no-reflow phenomenon" in the ischemic retina, except in the macular region (Figure 1). In CRAO, classically there is a marked ischemic swelling in the macular retina (because this is the thickest part of the retina, with the largest number of ganglion cells); although the swelling is much less thick than in the brain, and yet, in transient CRAO, there is no "re-flow phenomenon" in the macular region. Therefore, these eyes develop a corresponding permanent, big central scotoma, with the rest of the visual field normal. Hence the striking difference in ischemic damage and tolerance times between the brain and retina. Thus, it is irrational to equate RAO and acute ischemic stroke.

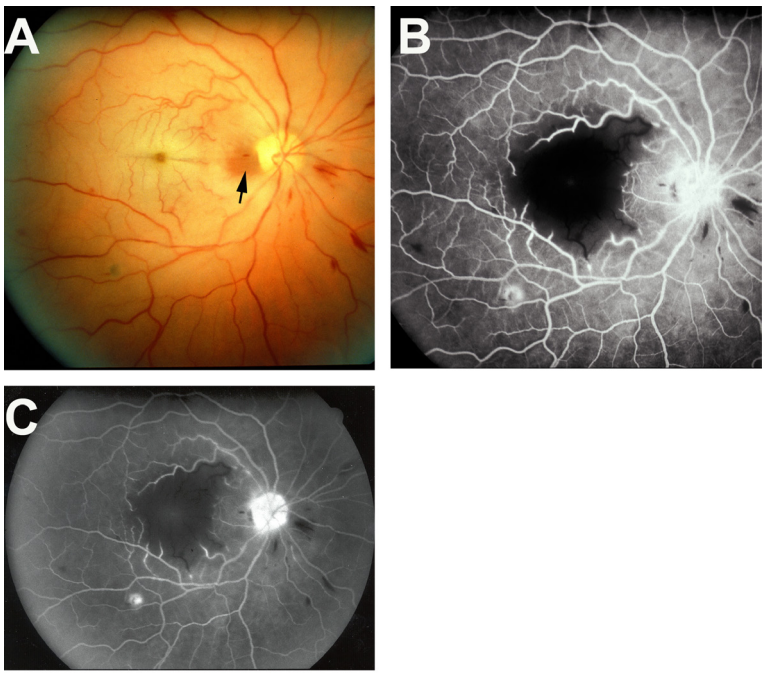

Figure 1: Fundus photograph (A) and fluorescein angiogram (B,C) of right eye at initial visit in an eye with transient non-arteritic CRAO 10 days earlier.

A. Fundus photograph shows cherry-red spot, retinal opacity of posterior fundus – most marked in the macular region, and a small area of normal retina temporal to the optic disc corresponding to a patent cilioretinal retinal artery (arrow).

B. Angiogram during the retinal arteriovenous phase shows normal filling of the retinal vascular bed with complete absence of filling in the macular region, corresponding to the area with most marked retinal swelling.

C. Angiogram during the late phase shows persistence of the complete absence of filling in the macular region.

Long-Term Management of Patients with RAO

There is a highly prevalent practice to refer RAO patients to neurologists for management, based on the widespread concept, aggressively promoted by neurologists and neuro-ophthalmologists, that RAO is equivalent to a stroke.

It is critical to put this highly prevalent misleading practice in a proper scientific perspective. As discussed above, it is scientifically inaccurate to equate RAO and acute ischemic stroke. I recently discussed the management of RAO in my article entitled "Do patients with retinal artery occlusion need an urgent neurological evaluation?" [9] This was based on my comprehensive, prospective studies in over 500 RAO patients for more than half a century. Based on that knowledge, the following is a brief discussion.

In a survey [10] of physicians in the United States, among those who responded, 35% of ophthalmologists, but 73–86% of neurologists and neuro-ophthalmologists, sent their patients with acute CRAO immediately for extensive neurological and radiological evaluation. 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% of neurologists pursue a hospital-based evaluation within 12 hours of RAO, whereas 82% of retina specialists pursue an outpatient evaluation, with no difference in the outcome. Needless to say, inpatient hospital evaluation is far more expensive than the outpatient evaluation, as well as more disruptive, and worrying to the patient's life.

In the literature, patients with RAO, TIA, and amaurosis fugax are usually lumped together when considering the risk of developing ischemic stroke. However, these 3 conditions are not synonymous. As mentioned above, RAO is usually embolic; however, our study [11] of 209 patients with amaurosis fugax showed that it is not always embolic but can be due to many other reasons, and it is illogical to include amaurosis fugax with stroke. Biousse [12], a neuro-ophthalmologist, has forcefully 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 following guidelines by the National Stroke Association, [13] American Heart Association/American Stroke Association, [14] and other international organizations [9]. But one must put the recommendations of these associations in proper perspective. Most importantly, the retinal ischemia does not fall in the domain of expert knowledge of any of these associations; that raises an important issue about the validity of their recommendations about RAO management. Moreover, a review of those publications showed that the report of the National Stroke Association [13] dealt with TIA only; the one by the American Heart Association/American Stroke Association [14] made no mention of RAO; and Uehara T, et al. (2014) [15]. dealt with TIA and ischemic strokes but not with RAO. Thus, none of these publications dealt with CRAO and BRAO, with which ophthalmologists and retina specialists invariably deal. The views expressed by these publications are based on those of neurologists and cardiologists, who, as discussed above, primarily do not see RAO patients. Therefore, the argument by Biousse [12] that RAO patients should undergo urgent brain imaging and etiologic testing recommended by these associations is invalid.

My comprehensive basic and clinical studies on RAO over the past half-century have shown that, pathogenetically and clinically, RAO is a very different clinical entity from TIA, stroke, and amaurosis fugax; therefore, it is a fundamental mistake for the American Heart Association/American Stroke Association to equate RAO with TIA, amaurosis fugax and stroke.

In our study of 234 CRAO and 141 BRAO patients [7], plaques in the carotid arteries were found to be the most common cause of embolism, and these were seen in 71% of CRAO and 66% in BRAO patients. The ipsilateral internal carotid artery had >50% stenosis in 31% of 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 the development of RAO than the degree of carotid stenosis. On echocardiography, an embolic source was found in 52% of CRAO and 42% of BRAO cases. In another study [16] of consecutive patients with amaurosis fugax (in 57 RAO eyes), >50% carotid artery stenosis was seen in 72%; carotid artery stenosis was worse in them than in BRAO or CRAO patients, indicating that poor perfusion pressure played an important role in the development of amaurosis fugax.

Therefore, there is an urgent need to determine as soon as possible the source of the embolism that caused the RAO, as well as stroke/TIA in some of them, and then try to eradicate that source of embolism, if possible. Given that, what is needed immediately is to find the source of embolism and deal with that, rather than detailed, highly expensive neurologic and radiologic evaluations (unless, of course, neurologic symptoms are present).

In conclusion, for proper management of CRAO, BRAO, and amaurosis fugax, urgent evaluations of the carotid artery, heart, fasting lipid levels, and complete blood count constitute the most important investigations, rather than extensive neurologic

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evaluations — unless, of course, there are neurologic 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. I have discussed elsewhere the reasons for that misconception [17].

Thrombolytic Therapy

This therapy has been found beneficial in ischemic stroke and heart attack, if the treatment is started within the first few hours of the onset of symptoms - the sooner the treatment begins, the better the results. Neurologists, who equate CRAO with stroke, advocate this thrombolytic therapy in CRAO patients. Recombinant tissue plasminogen activator and urokinase are commonly used, thrombolytic agents. Stroke trials have included intravenous studies, intra-arterial studies, and combinations of both. One of the most important predictors of clinical success is the time from onset to treatment, with early treatment of <3 hours for intravenous tissue plasminogen activator and <6 hours for intra-arterial thrombolysis demonstrating significant improvement in terms of 90-day clinical outcome and reduced cerebral hemorrhage.

From the practical point of view of the management of RAO, the most important consideration is also the time since onset of RAO to therapy. Acute retinal ischemia by CRAO lasting for more than one hour produces progressive ischemic damage so that by 4 hours the retina has suffered irreversible damage [8]. The beneficial effect occurs only if the therapy is given before the development of irreversible infarction. So, there is a very narrow window of opportunity for any treatment to cause visual improvement.

I have discussed intra-arterial thrombolysis in CRAO in detail elsewhere [18]. It is claimed that thrombolytic therapy when administered anywhere from within 6 hours to 50 hours has a beneficial effect. Almost all these studies claim that it helps to improve visual outcomes, and some have even claimed that in some eyes the visual acuity returned to normal. By contrast, other studies have shown that it has no beneficial effect.

Almost all the published literature germane to local intra-arterial fibrinolysis in cases of CRAO is retrospective and non-randomized, except for one prospective, randomized, multicenter clinical trial [19]. In that study, there were 84 CRAO patients, of whom 40 received conventional standard treatment and 44 received local intra-arterial fibrinolysis. The mean best-corrected visual acuity improved significantly in both groups (both $P < 0.0001$) and did not differ between groups ($P=0.69$). Clinically significant visual improvement (> or = 0.3 logMAR) was noted in 60.0% with the conventional standard treatment and in 57.1% with the local intra-arterial fibrinolysis. Two patients in the conventional standard treatment group (4.3%) and 13 patients in the local intra-arterial fibrinolysis group (37.1%) had adverse reactions. Adverse reactions, such as hemorrhage, hemiplegia, hypertensive crisis, and even death following this therapy have been reported by other studies also. The randomized study [19] concluded that considering these 2 therapies' similar outcomes and the higher rate of adverse reactions associated with local intra-arterial fibrinolysis, they could not recommend local intra-arterial fibrinolysis for the management of acute CRAO. I feel that should settle the issue of the role of thrombolytic therapy in CRAO. Thus, thrombolytic therapy is much less successful in CRAO than in stroke and heart attack.

A meta-analysis article of 7 CRAO studies (including 121 patients), reported 62 patients showed improvement in visual acuity (52.0%; 95% CI, 34.0-70.0%) following rt-PA intravenous thrombolytic therapy. The observed improvement rate in the intravenous rt-PA treatment group was significantly higher than the conservative treatment group (40.4% vs. 13.0%; OR=5.16; 95% CI, 1.90-14.05%). Eleven out of the 121 patients developed complications: hemorrhage (9/11) was the major complication [20].

Conclusion on Thrombolytic Therapy

The claimed beneficial effect of thrombolytic therapy in ischemic stroke cannot be applied to CRAO, for the following important reason. Very few CRAO patients are seen in a hospital with available thrombolytic therapy, within 3 hours or so of the loss of vision – they are mostly seen much later - even days after the onset, because the visual loss in one eye, with normal vision in the fellow eye, even may not be noticed immediately, and that may not worry the CRAO patient immediately to the extent stroke and heart attack do.

Moreover, a critical review of the published thrombolytic therapy studies in CRAO showed several fundamental problems. These include the following:

(1) Almost all studies are retrospective except for one discussed above [19].

(2) The fundamental flaw in most studies claiming visual improvement is that they contain no angiographic evidence to document improved blood flow immediately after the thrombolytic therapy compared to beforehand. For thrombolytic therapy to be effective, it must immediately restore the retinal circulation to normal or improved significantly.

(3) Practically all the studies lack comparison with a satisfactory natural history control. Unfortunately, improved visual acuity, which may simply reflect improved natural history [14], has often been erroneously attributed to treatment,

(4) Almost all studies have lumped all types of CRAO together, and not classified it into its 4 distinct types (nonarteritic CRAO, arteritic CRAO, CRAO with cilioretinal artery sparing, and transient CRAO) [21] to determine the visual outcome. My study [21] has shown that visual outcome varies greatly among the four different types.

(5) Thrombolytic therapy lacks a scientific rationale in most cases because only 15% of emboli are platelet-fibrin in nature [22], and amenable to fibrinolytic therapy –the remaining 85% of the emboli are made of cholesterol or calcified material, which the fibrinolytic agents cannot dissolve.

(6) Thrombolytic therapy in these studies has invariably been administered 6 to 18 hours or even longer after the onset of CRAO, by which time the retina already has suffered irreversible ischemic damage [8]. A dead retina does not improve!

(7) A systematic review of all available randomized trials of thrombolysis in acute ischemic stroke concluded that "Thrombolysis requires further testing in large, randomized trials because the risks seem substantial, and the benefit uncertain" [23].

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