Review paper

Retinal artery occlusion and its association with stroke – literature review

Niedrożność naczyń tętniczych siatkówki i jej związek z udarem mózgu – przegląd piśmiennictwa

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Abstract

Retinal artery occlusion (RAO) leads to acute retinal ischemia. Despite the low incidence rate of RAO, the occurrence of this condition has very important clinical implications. It is an emergency condition that requires urgent diagnostic evaluation and treatment. RAO is the ocular equivalent of acute cerebral ischemia. Patients with RAO have similar etiology and risk factors to patients with ischemic stroke and also are at high risk of subsequent cardiovascular events. However, the impact of RAO on the risk of a further ischemic stroke is still a matter of debate. Herein, we present a literature review on the relationship between RAO and stroke.

Streszczenie

Niedrożność naczyń tętniczych siatkówki (RAO) prowadzi do ostrego niedokrwienia siatkówki. Mimo niskiej częstości występowania epizod RAO ma bardzo istotne implikacje kliniczne. Jest to nagły stan, który wymaga podjęcia pilnej diagnostyki i leczenia. Niedrożność naczyń tętniczych siatkówki jest odpowiednikiem ostrego niedokrwienia mózgu. Etiologia RAO oraz profil czynników ryzyka stwierdzanych u pacjentów z RAO porównywalny jest z tym, który występuje u pacjentów z udarem niedokrwiennym mózgu. Podobnie jak pacjenci z udarem mózgu pacjenci z RAO mają zwiększone ryzyko wystąpienia kolejnych incydentów sercowo-naczyniowych. Wpływ wystąpienia RAO na ryzyko udaru niedokrwiennego jest jednak nadal przedmiotem dyskusji. W niniejszym artykule przedstawiamy przegląd pismiennictwa na temat związku między RAO a udarem mózgu.

Introduction

Retinal artery occlusion (RAO) is one of the causes of acute retinal ischemia. Depending on the type of occluded vessel, RAO can be divided into central retinal artery occlusion (CRAO) and branch retinal artery occlusion (BRAO) (Figure 1) [1, 2].

Most cases of RAO have non-arteritic etiology, the main cause of which is embolism originating from the ipsilateral carotid artery, heart or aortic arch [1, 2]. Patients with RAO are burdened with numerous, often undiagnosed cardiovascular risk factors, including arterial hypertension, diabetes, obesity, hyperlipidemia, nicotinism, and chronic kidney disease [1–8]. The etiology of RAO and the profile of risk factors found in patients with RAO are comparable to those of patients with ischemic stroke. Similar to patients with stroke, patients with RAO have an increased risk of subsequent cardiovascular events, i.e. stroke, myocardial infarction, and death [1–24].

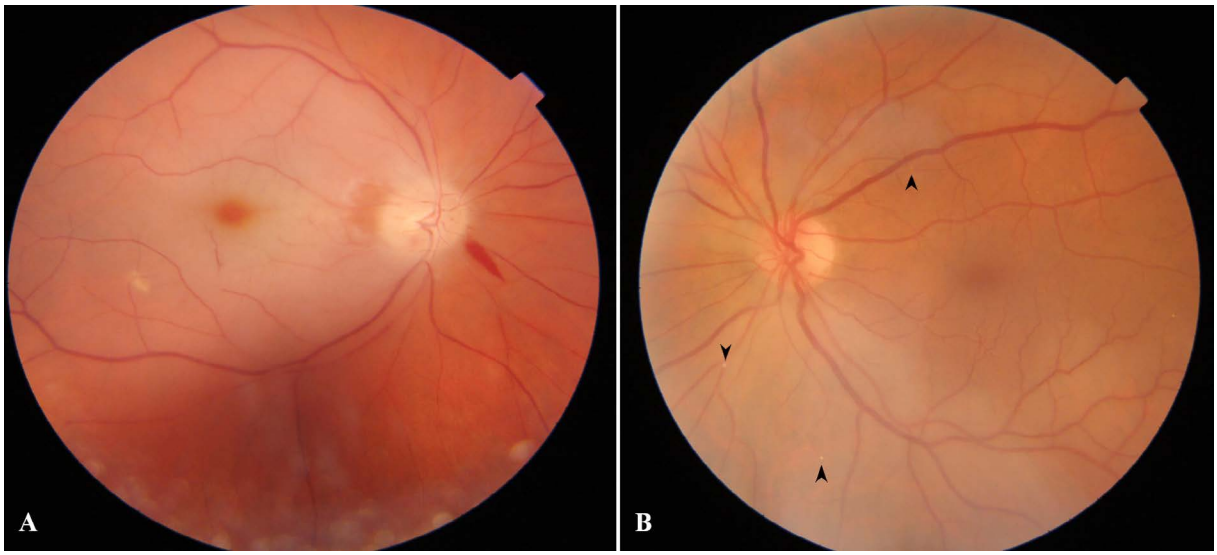

Figure 1. **A** – Fundus photography of a right eye with central retinal artery occlusion demonstrating retinal whitening surrounding the fovea, a cherry-red spot in the macula, peripapillary hemorrhage and generalized arteriolar narrowing. **B** – Fundus photography of a left eye with branch retinal artery occlusion with visible emboli in retinal arteries (arrowheads)

In 2013, the American Heart Association (AHA) and the American Stroke Association (ASA) recognized acute retinal ischemia as the equivalent of acute cerebral ischemia. AHA and ASA defined central nervous system infarction as brain, spinal cord, or retinal cell death attributable to ischemia [25].

Such a change in the approach to RAO indicates the need to undertake specific diagnostic and therapeutic management in patients with RAO, analogous to that dedicated to patients with ischemic stroke [26, 27] (Table 1). The American Academy of Ophthalmology (AAO) guidelines recommend that patients with acute RAO should be referred for urgent diagnosis to the nearest certified stroke center or hospital emergency department with access to such diagnosis within 24 h. For acute retinal ischemia, brain imaging is recommended, preferably with diffusion-weighted magnetic resonance imaging (DWI-MRI) [26, 27]. As the data show, compliance with AAO recommendations is still below the recommended standards [28].

The paradigm shift in the management of RAO patients that we are witnessing is still a subject of discussion [27, 29]. Submitting patients with RAO to urgent and detailed neurological diagnosis for ischemic stroke is controversial due to the fact that not all reports indicate a high risk of symptomatic stroke after RAO [15, 20, 29–31]. Studies on central nervous system (CNS) lesions found in patients with RAO in MRI have shown that the majority of new ischemic lesions found in patients with RAO are clinically silent [13, 14, 16, 23]. Nevertheless, the demonstrated association of RAO with cerebral small vessel disease sheds new light on the pathogenesis of these episodes, which also translates into planning the scope and time of proper diagnostics and secondary prevention in this group [32–35].

Below, we present a review of the literature on the relationship between RAO and stroke, with particular emphasis on the incidence of stroke after RAO, the nature of ischemic changes in the CNS found in patients with RAO, the risk of stroke depending on the etiology and type of RAO, and risk factors for stroke after an episode of RAO.

Discussion

There are only two meta-analyses of the relationship between RAO and stroke in the literature [22, 23]. Zhou *et al.* assessed the association of RAO and retinal vein occlusion (RVO) with cerebral incidents by searching the literature up to 2016 [22]. For the assessment of cerebral events in the group of patients with RAO, only three studies were included in the meta-analysis, indicating that the results should be interpreted with great caution due to the heterogeneity of the studies [10, 22, 36, 37]. The results of this analysis showed that RAO patients had an almost 2-fold higher risk of cerebrovascular disease (CVD) compared to controls (OR = 2.01, 95% CI: 1.21–3.34; $p = 0.005$) [22]. Additionally, it was shown that patients with CRAO (OR = 2.00, 95% CI: 1.12–3.56; $p = 0.02$) and BRAO (OR = 1.60, 95% CI: 1.03–1.48; $p = 0.04$) had a significantly increased risk of CVD compared to the control groups [22]. To date, the number of studies analyzing the relationship between RAO and stroke has increased significantly; however, due to methodological differences, direct comparison of these studies with each other is difficult, if not impossible [3–24, 30–33]. For the most part, due to the rarity of RAO, these are retrospective studies [5–14, 16–21, 24]; so far there have been only a few prospective studies

Table 1. Typical evaluation performed urgently in Certified Stroke Centers for patients with acute retinal ischemia based on the American Heart Association and National Stroke Association recommendations. Source: Biousse *et al*. [27], mod.

1	Assessment as soon as possible after acute vision loss occurs at a stroke center-related emergency center or a quick access clinic, subject to availability and local resources.
2	Blood tests* (complete blood count with platelets, biochemical panel, hemoglobin A1C, prothrombin time and partial thromboplastin time, lipid profile. Erythrocyte sedimentation rate and C-reactive protein are required for patients over 50 years of age – increased results of these parameters may suggest giant cell arteritis.
3	An electrocardiogram* should be performed as soon as possible after the event. Prolonged cardiac monitoring* (inpatient telemetry or Holter monitor) is useful in patients with an unclear etiology after initial brain/vascular imaging and electrocardiography.
4	Patients should be assessed for neuroimaging* within 24 h of onset of symptoms. MRI without contrast, including DWI, is the preferred method of diagnostic imaging of the brain. If MRI is not available, CT of the head should be performed.
5	Noninvasive imaging of the cervicocephalic vessels* should be performed routinely. MRA or CTA or carotid/transcranial Doppler ultrasound should be performed, depending on local availability.
6	Echocardiography* (at least transthoracic echocardiography). Transesophageal echocardiography is useful in identifying left atrial thrombus, patent foramen ovale, atherosclerotic aortic arch, and valve defect, and is warranted when identification of these conditions alters management. Outpatient echocardiography may be performed after discharge from hospital in patients with normal cardiac assessment.
7	It is prudent to hospitalize patients with RAO if they report within 72 h the event and if any of the following criteria are present: – Abnormal DWI-MRI image of the brain with evidence of acute cerebral infarction. – Large artery atherosclerosis found in non-invasive vascular imaging (e.g. stenosis of the internal carotid artery). – Abnormal cardiac evaluation. – Recurrent episodes (TIA crescendo) or inability to provide accelerated outpatient follow-up.

CT – computed tomography, CTA – computed tomography angiography, DWI-MRI – magnetic resonance imaging with diffusion-weighted imaging sequences, MRA – magnetic resonance angiography, MRI – magnetic resonance imaging, RAO – retinal artery occlusion, TIA – transient ischemic attack.

**These tests are performed immediately in the emergency room during a 23-hour follow-up, during which the patient receives cardiac monitoring. These tests are part of the standard "stroke protocol" recommended by the American Heart Association/National Stroke Association. If there is no identified cause, the patient may be discharged home after 24 h with optimal secondary prevention of stroke. If an underlying cause is identified that requires immediate treatment (e.g. carotid stenosis of at least 50% or cardiac embolism), the patient should be admitted to a stroke unit. In all cases, the patient is discharged with appropriate secondary stroke prevention measures, including anticoagulants, statins for hyperlipidaemia, and blood pressure control. Outpatient neurological follow-up is recommended within 2 weeks after discharge from hospital to ensure optimal secondary prevention of stroke and other cardiovascular diseases. These recommendations are for patients in whom the diagnosis of giant cell arteritis is not considered.*

[3, 4, 15, 32]. The studies differ in the number of people included in the study. We have studies based on a small study group [3, 4, 6, 7, 15, 16, 20, 24, 31, 37] as well as studies based on large databases compiled on the basis of analyzing the International Classification of Diseases (ICD) codes [5, 9–12, 17, 18, 21, 36]. Recently, the results obtained from the analysis of large databases created with the use of ICD codes have been questioned [31]. Individual studies have a control group appropriately selected in terms of sex and age, or comorbidities [5, 7, 9, 10, 12]. Studies also differ in the duration of follow-up, ranging from a few days to several years [3–21, 24, 31]. Studies assessing the incidence of stroke after RAO assessed the combined risk of ischemic stroke, transient ischemic attack (TIA) and hemorrhagic stroke. In some studies, the risk of each of these episodes is estimated separately [3, 31, 24, 31]. There are also differences in the imaging diagnostics used; the latest studies are based on the detection of ischemic changes in the CNS in patients with RAO using DWI-MRI [13, 14, 16].

Studies assessing the incidence of acute cerebral ischemia detected by MRI within 7 days of the diagnosis of acute CRAO, BRAO and transient monocular vision loss, published up to January 2019, were included in the meta-analysis by Fallico *et al*. [23] The results showed that 30% of patients with acute CRAO and 25% of patients with acute BRAO had acute cerebral ischemia identified by MRI [23]. MRI studies in patients with RAO were a consequence of reports on the relationship between RAO and stroke [10, 11, 22].

One of the first large population studies to assess the risk of stroke related to the occurrence of RAO concerned the Asian population [5, 10, 11]. Due to the rarity of the RAO episode, these studies used the Korean and Taiwanese national registries' data and with the help of identifying ICD codes created larger groups of subjects [10, 11].

Chang *et al.* analyzed the Taiwanese national registry data to assess for stroke risk after RAO [10]. The study cohort consisted of patients diagnosed with RAO (n = 464). The control group consisted of randomly selected patients (n = 2748) matched to the study group in terms of age, sex, date of prescribed medical care and coexisting hypertension. 19.61% of RAO patients and 10.05% of the controls had a stroke ($p < 0.0001$) during the 3-year follow-up period. The incidence rates of stroke in patients with RAO were highest within the first month after RAO. The hazard ratio (HR) of having a stroke for RAO patients is increased by other factors such age, sex, and comorbid disorders; however, in this study, after adjusting for age, sex, and selected comorbid disorders, the HR of having a stroke for RAO patients was still 2.07 times higher than that of controls. In this study, the risk of stroke was assessed for ischemic stroke, hemorrhagic stroke, TIA, and unspecified stroke [10].

Park *et al*. used the Korean national registry data [11]. The study enrolled 1,585 patients with a CRAO incident and found that 9.6% of patients with CRAO had a stroke within 1 year of CRAO, with the overwhelming majority being ischemic strokes, and with only 0.82% of patients with CRAO having hemorrhagic stroke [11]. Similar results were presented by Hong *et al.*, where ischemic stroke occurred in 8.6% of patients with RAO; none of the patients experienced a hemorrhagic stroke during the 1-year follow-up period [6]. In a study by Park *et al.* it was observed that the risk of ischemic stroke was increased as early as 180 days before CRAO with a higher risk 30 days before CRAO. In the 30 days after CRAO, the risk of stroke was even higher, peaking in the first week after CRAO. Although there were no statistically significant differences between patients with RAO ≥ 65 years of age and < 65 years of age, as well as between women and men, men and people under the age of 65 had a higher incidence rate of stroke [11].

In the study by Rim *et al.*, stroke occurred in 15.0% in the RAO group and 8.0% in the control group ($p < 0.001$). The occurrence of a RAO episode was statistically significantly associated with the occurrence of stroke after adjustment for comorbidities and sociodemographic factors [5]. In this study, the lower incidence rate of strokes diagnosed after RAO compared to the study by Chang *et al.* could be due to the fact that the analysis did not include TIA, as was the case in the study by Chang *et al.* [5, 10]. The risk of having a stroke was greater in younger adults aged < 65 years (HR = 3.11) than in older adults aged ≥ 65 years (HR = 1.26) [5].

Caution should be exercised when extrapolating the results of studies which assessed the risk of stroke after RAO in the Asian population for the white race. The results of a study by Shaikh *et al.* indicate that the black race, Asians, and Native Americans have a higher risk of stroke after RAO than the white race [17]. However, with regard to the incidence of stroke after RAO, studies including the Caucasian population have also shown an increased incidence of stroke after RAO compared to control groups [12, 21].

A study similar to the study by Park *et al.* on only the US population was conducted by French *et al.*, who determined the incidence of ischemic stroke in the 6-month periods preceding and following CRAO (CRAO – 3,338 people) among Medicare beneficiaries [11, 12]. The incidence of strokes in the CRAO group compared to the control group was significantly increased in the first and the second week after CRAO. Compared to the study by Park *et al.*, the peak incidence of stroke occurred in the second week after CRAO [11, 12]. Similar results were recently presented by Scoles *et al.* This study assessed the risk of stroke after both CRAO and BRAO and compared it, as in the study by French *et al.*, to the risk of stroke in patients with a hip fracture [12, 19]. The HR for having a stroke after RAO compared to a hip fracture was elevated for both CRAO and BRAO (CRAO HR = 3.24, 95% CI: 2.83–3.7; $p < 0.001$; BRAO HR = 2.76, 95% CI: 2.43–3.13; $p < 0.001$). The highest risk for stroke occurred in the days following a CRAO or BRAO [19].

Mir *et al.* assessed the incidence of acute ischemic events, including strokes, in patients hospitalized due to CRAO; the assessment concerned only the time of hospitalization [18]. This was a retrospective study involving 17,117 patients with CRAO. Information was obtained from the Nation-wide Inpatient Sample (NIS), which is the largest all-payer inpatient database in the United States. The incidence of in-hospital stroke was 12.9%; the vast majority of cases were ischemic. The incidence of developing TIA was much lower (2.5%). This study showed that the number of hospitalizations for CRAO tended to increase over the years, almost doubling in 2014 compared to 2003. The incidence of strokes also showed an increasing trend over the years, almost doubling in 2014 compared to 2003 (15.3% vs. 7.7%). The authors explain this increase in the percentage of strokes in patients with RAO by the aging of the US population and the increasing use, in recent years, of DW-MRI, which is more sensitive than computed tomography imaging, which results in higher rates of detection of ischemic lesions in the CNS [18].

A recently published study by Vestergaard *et al.*, which was based on an assessment of the Danish population diagnosed with RAO in the years 2000–2018, where the diagnosis was verified based on ICD codes, showed that among the European population of Danes, 5.9% of those surveyed experienced a stroke within 1 year after RAO [21]. The risk of stroke was highest between the 3rd and 14th day after RAO, i.e. immediately after the RAO episode, similar to the study by Chang *et al.* and Park *et al.* [10, 11, 21].

Another 12-year retrospective study on the European population showed that RAO patients who are younger than 75 years are significantly more likely to experience ischemic stroke after an occlusion event, as compared with individuals without RAO [7]. However, these associations were not demonstrated for patients aged 75 years or older [7]. These data are consistent with the results of previous studies and indicate that RAO may have a strong impact on the risk of stroke in younger age groups [7, 10, 11].

Four prospective studies assessing the relationship between RAO and stroke are currently available from Europe [3, 4, 15, 32]. The oldest study, from over thirty years ago, by Hankey *et al*., included 98 patients with RAO. In this study with a mean follow-up of 4.2 years, 10.2% of patients experienced a stroke [4].

In the study by Callizo *et al*., the authors had a well-defined and homogeneous group of patients who were included in the prospective European Assessment Group for Lysis in the Eye (EAGLE) study. Seventy-seven patients with CRAO were sub-analyzed. Six percent had a stroke diagnosed by MRI during 4 weeks of follow-up. In 3 cases it was a recent stroke, in 2 it was the result of intra-arterial fibrinolysis. During the 4-week follow-up, 1 case of TIA was found [3].

The latest prospective study from Europe by Leisser *et al.* is based on a small study group of 30 RAO patients. Data on previous stroke/TIA in the year following the RAO episode were obtained based on a telephone conversation with the patient. Within 1 year of RAO, 1 patient had a second stroke, and one mentioned a history of TIA with amaurosis fugax in the patient interview. The authors note that RAO patients with a stroke episode, TIA, and/or amaurosis fugax in the medical history appear to have a higher risk of a cerebrovascular accident following RAO. This study noted a low number of strokes after RAO [15]. Hayreh and Zimmerman [30] and Chodnicki *et al.* [20] present a similar low percentage of strokes after RAO. In the study by Roskal-Wałek *et al.* [7], though the post-RAO stroke rate is comparable with the results of the study by Hankey *et al.* [4], it was not found to be statistically significantly higher than in the control group, as was the case in the study by Vestergaard *et al.* [21]. Moreover, in this study, no increase in symptomatic ischemic strokes was observed immediately after RAO, as was the case in other studies that were based on the analysis of large databases [5, 10–12, 21].

In the study by Laczynski *et al*., it was found that the risk of stroke after RAO was lower than the results of studies based on the analysis of large databases reported so far [31]. The authors noted that by selecting all patients diagnosed with RAO from the facility using ICD-9 codes, they obtained a group of 555 patients. In this group 22.5% had a stroke diagnosis according to ICD-9; a similar percentage is presented in studies based on large databases, which also verified patients with RAO and later episodes such as stroke with ICD-9 [5, 10–12]. Documentation review allowed for the verification of the diagnoses. There were 221 patients with a confirmed diagnosis of RAO. The authors finally found a stroke in 5 (2.3%) patients with confirmed RAO; four of the five strokes occurred during the RAO. The authors postulate that this difference undermines the results of studies analyzing large databases based on ICD-9 diagnoses and indicates that the risk of stroke after RAO may be much lower than previously reported [31].

The study by Lavin *et al.* assessed 103 patients hospitalized due to CRAO. MRI examinations of the brain were performed in 66% of patients and revealed a stroke in 37.3%; in many cases, importantly, the areas of ischemia in the CNS were small and were not accompanied by obvious clinical symptoms. Moreover, in most cases, the stroke was on the CRAO side and was associated with carotid ipsilateral disease; such a relationship was also observed in other studies [13]. Attention should also be paid to the fact that this study included a group of patients from the so-called "stroke belt" of the US, where there is a higher burden of stroke risk factors and a higher percentage of strokes is identified, which may have had a major impact on the results [13].

RAO and silent brain infarctions

The development of imaging technology as well as its availability provides the opportunity to better evaluate patients with RAO for the presence of ischemic lesions in the CNS (Figure 2). Studies evaluating the incidence of stroke in patients with RAO based on MRI show the presence of ischemic lesions, most of which are not accompanied by neurological symptoms [14, 16, 23].

In a study by Lee *et al*., stroke was found in 8 of 33 patients (24.2%) with RAO within 7 days of the RAO episode. In 37.5% of those with MRI-detected stroke, there were no neurological symptoms [14]. Here again, as in the Lavin *et al.* study, most lesions were numerous, small and diffuse [13]. In this study, however, there was exclusion of patients who did not have neuroimaging, which could also have had a significant impact on the results [14].

A recent meta-analysis by Fallico *et al.* looked at studies that analyzed the incidence of CNS ischemic lesions in patients after RAO, using DWI-MRI. This meta-analysis showed that 30% of patients with acute CRAO and 25% of patients with acute BRAO had acute cerebral ischemia on the MRI, both accompanied and not by neurological symptoms. Asymptomatic cerebral ischemia was found in 21% of patients with acute CRAO and 28% of patients with acute BRAO [23].

These results contradict Hayreh's assumptions according to which a patient with RAO lacking neurological symptoms is unlikely to have MRI changes. Hayreh recommend performing such imaging in RAO

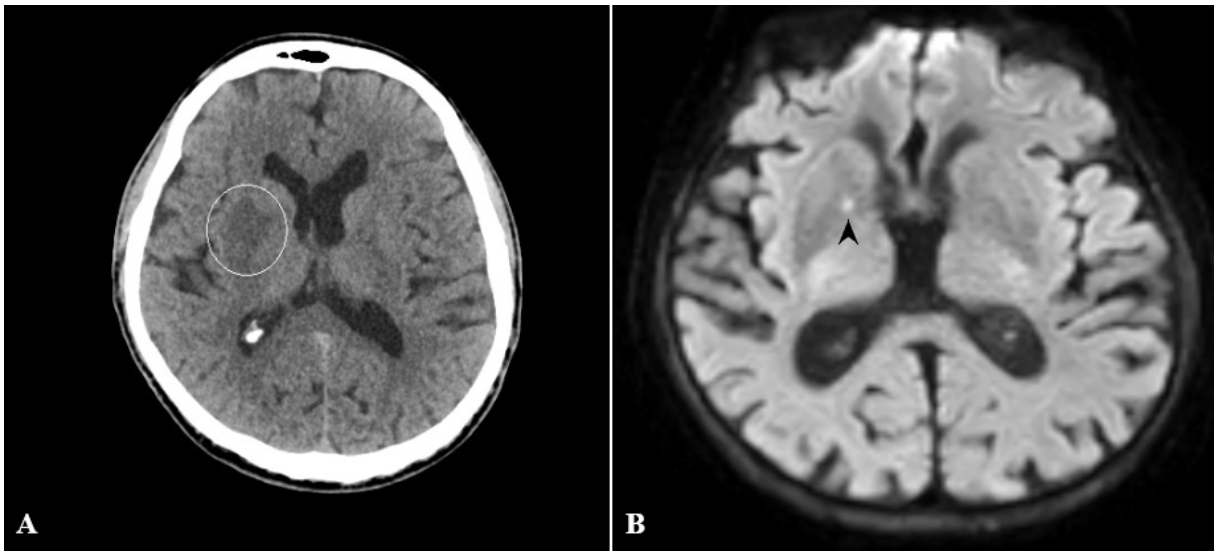

Figure 2. **A** – Head computed tomography of a patient with central retinal artery occlusion showing hypodense area on the right (marked by a circle) which corresponds to the ischemic change during evolution. **B** – Brain magnetic resonance image (diffusion-weighted image) of another patient with central retinal artery occlusion obtained within 5 days after a central retinal artery occlusion, showing small hyperintense lesion (black arrowhead) consistent with acute cerebral ischemia

patients only if neurological symptoms are present [29]. In contrast to Hayreh, most authors advocate a different approach, one that is consistent with recent AHA/ASA, AAO guidelines which recommend that all patients with suspected cerebral or retinal ischemia should undergo immediate brain imaging and etiologic evaluation of these incidents [13, 14, 16, 23, 27]. It is noted that doing so may reduce the risk of stroke recurrence and would obviously be more beneficial to both the patient and the healthcare system, since the economic and social costs of disability outweigh the economic burden of urgently referring these patients to an emergency department or stroke center [23].

It should be noted that a significant percentage of observed silent brain infarctions (SBI) in patients with RAO has significant clinical implications and provides valuable information. First, the presence of SBI is associated with subtle neurological deficits, cognitive impairment, and psychiatric disorders. SBI is associated with the risk of another stroke and early mortality [23, 34]. Secondly, as demonstrated in several studies, the presence of SBI in a patient with RAO correlates with the establishment of the etiology of the RAO episode, which is most often carotid atherosclerosis [14, 16, 23]. This is an important relationship for determining the etiology of the SBI themselves. Data from the literature provide contradictory conclusions as to whether the presence of SBI in patients with carotid stenosis results from an increased generalized cardiovascular risk in these patients, or whether carotid stenosis is a direct source of SBI embolism [35]. It was assumed that if the carotid artery stenosis was causally related to SBI, one would expect a higher incidence of SBI in the cerebral hemisphere on the side of the diseased carotid artery compared to the opposite hemisphere [35]. In studies evaluating the presence of CNS ischemic lesions in RAO patients using MRI, the SBI found were more likely to occur ipsilaterally to the involved eye and carotid artery disease, which indirectly provides evidence for the association of SBI with carotid artery disease [13, 14, 16, 23]. Recently, a meta-analysis by Finn *et al.* found that two distinct manifestations of carotid atherosclerosis, increased carotid intima-media thickness and carotid artery stenosis, were associated with the presence of SBI. This relationship was maintained whether or not patients had additional known stroke risk factors [35].

RAO etiology and the risk of stroke

Correctly determining the etiology of the stroke is crucial to the treatment modality, timing of diagnostic tests, and the implementation of prophylaxis. The most important predictor of early stroke recurrence is probably the etiologic subtype of the initial ischemic stroke. The highest risk of early stroke recurrence applies to patients with stroke of thrombotic or embolic etiology in the course of large vessel atherosclerosis, especially with stenosis of the carotid arteries or other peripheral arteries of more than 50% of the vessel lumen. Of these patients, 18% suffer a repeat stroke within 30 days [38].

The most common etiology in studies of RAO episodes is carotid atherosclerosis. In a study by Callizo *et al.*, carotid artery disease was found to be the most important risk factor for RAO; carotid artery steno-

sis above 70% affected 40% of subjects [3]. In a study by Hayreh and Podhajsky, carotid artery stenosis equal to and above 50% was found in 34% of patients with CRAO and 30% of patients with BRAO. A much higher percentage of patients presented the presence of hemodynamically insignificant atherosclerotic plaques, found in 71% of CRAO patients and 66% of BRAO patients [1]. Also, in a study by Hong *et al.*, large artery atherosclerosis (LAA) was the most common etiology of RAO, and patients with RAO and LAA had a four times greater risk of developing ischemic incidents than those with RAO without LAA [6]. Similarly, a study by Golsari *et al.* showed that LAA with carotid artery stenosis plays a major role in the pathogenesis of acute retinal ischemia [32]. The frequent occurrence of internal carotid artery stenosis in patients with acute retinal ischemia increases the risk of early strokes in this group. This is particularly important given the updated AHA and American Society for Vascular Surgery guidelines, which recommend carotid endarterectomy within 14 days of an episode of ischemia. The efficacy of carotid endarterectomy is highly dependent on the timing of the procedure [27].

It is worth noting that in studies evaluating the risk of stroke in RAO patients using DWI-MRI, the etiology of RAO/ischemic events was determined according to the ischemic stroke etiologic classification TOAST (Trial of ORG10172 in Acute Stroke Treatment). However, it is noted that the TOAST-based etiologic classification of stroke has its limitations with regard to causality. It is also still unclear whether the onset of RAO is not influenced by other mechanisms regardless of the presence of large vessel atherosclerosis [6, 14, 16, 33].

A study by Kim *et al.* analyzed the incidence of cerebral small vessel disease in patients with RAO [33]. The spectrum of the issue of cerebral small vessel disease includes the mentioned SBI, microhemorrhages and leukoaraiosis. It has been suggested that damage and inflammation of cerebral vessels and cells in the course of cerebral small vessel disease may cause fragility of these vessels and endothelial instability, resulting in hemorrhagic or ischemic changes [33]. A study by Kim *et al.* also estimated the prevalence of cerebral small vessel disease according to the etiology of RAO. As in other studies, small vessel disease was most often found in patients with RAO and large vessel atherosclerosis; however, of note in this study is the high percentage of small vessel disease found in patients without an established embolic etiology of RAO, indicating that the need for more careful diagnosis and follow-up of patients without an established cause of RAO who are found to have cerebral small vessel disease should be considered, especially since its presence indicates an increased risk of recurrent stroke [33].

Golsari *et al.* conducted the RETIS (Frequency of Acute Silent Brain Infarction and Systematic Evaluation of Stroke Risk in Retinal Ischemia) study, a single-center, prospective, observational study that included ophthalmologic examination, brain MRI and diagnosis of vascular risk factors and cause of stroke [32]. The study evaluated the percentage of patients with RAO and associated MRI lesions, i.e., SBI and leukoaraiosis. SBI was found in 15.1% of patients, severe leukoaraiosis in 26% of patients. Stenosis of the internal carotid artery was the only significant predictor of SBI in the multivariate analysis. However, the authors note an important association. They identified severe leukoaraiosis in 26% of patients with retinal ischemia. This indicates a significant overlap between LAA and small vessel disease in the pathogenesis of RAO and this translates into an assessment of overall cerebrovascular risk, in which both macroangiopathic and microangiopathic changes should be considered [32]. The Rotterdam study showed that the increased risk of stroke in patients with SBI and white matter lesions persisted after cardiovascular risk factors were taken into account. This suggests that SBI and white matter lesions may be markers of other, as yet unknown, factors leading to symptomatic stroke [34].

In the study by Lauda *et al.*, the percentage of identified RAO etiology was higher in patients with concomitant acute cerebral ischemic lesions than in patients without such lesions (59.2 vs. 36.6%); however, this study notes the high percentage – 40.8% – of undetermined RAO etiology in patients with positive DWI, which is quite high compared to previous studies. The authors point out that this may be due to undetected atrial fibrillation (AF) [16].

Cardiogenic embolism in the course of asymptomatic arrhythmias or unrecognized cardiac defects is thought to be responsible for most cryptogenic strokes. The probability of diagnosing paroxysmal AF in a patient with a stroke of unclear etiology increases when multiple cerebral vascular lesions or an ischemic focus involving the cortex or cerebellum is seen in imaging studies [39]. It should be noted that about 1/3 of all strokes are caused by AF. Often, stroke is the first clinical manifestation of AF [40–42]. Recently, increasing attention has also been paid to the involvement of cardiac arrhythmias in the etiology of RAO [36, 40]. Available data indicate that patients with AF who develop RAO have a nearly 40% higher risk of thromboembolic complications than patients with AF without an episode of RAO [36]. It should be noted that the percentage of detected arrhythmias in patients with RAO increases with longer monitoring time. The effect of RAO on increasing the risk of stroke in patients with AF is of particular importance also because of the stratification of the risk of thromboembolic episodes, which is the basis for decision-making regarding anticoagulant treatment in patients with AF. It is recommended that a patient with AF should receive 2 points for having an episode

of RAO, which is equivalent to a stroke, in the risk stratification of subsequent thromboembolic episodes according to the CHA2DS2-VASc score [40].

Risk factors for stroke following RAO

Knowledge of the prognostic factors of recurrent stroke is important because it allows us to identify patients at high risk of recurrence and possibly change the secondary prevention routinely used [38].

Several studies have evaluated risk factors for stroke in patients with RAO [5, 6, 10, 16–18, 24, 32].

In the study by Chang *et al*., risk factors for stroke included being over 50 years of age, the presence of hypertension, diabetes and atherosclerosis [10]. In the Mir study, the risk factors were being female, and also hypertension, carotid artery stenosis, aortic valve disease, smoking, alcohol dependence or alcohol consumption [18]. In the study by Hong *et al*., LAA was an independent risk factor for a vascular incident [6]. In the study by Lauda *et al*., old age, hypertension, AF and RAO type were associated with the risk of symptomatic stroke and SBI. In multivariate analysis, only age and type of occlusion, BRAO to be precise, remained positive predictors of SBI [16]. In the study by Golsari *et al*., internal carotid artery stenosis was the only significant predictor of silent cerebral infarction in multivariate analysis [32]. In a study by Rim *et al*., comorbidities such as hypertension, ischemic heart disease and AF were significantly associated with a subsequent stroke [5].

In a study by Avery *et al*., logistic regressions suggested that in CRAO and BRAO patients, the degree of ipsilateral carotid stenosis may not be useful in stratifying the risk of stroke [24]. Similarly, the study by Lauda *et al*. found no correlation between the LAA as the etiology of monocular vision loss including RAO and coexisting cerebral infarctions [16].

In the study by Shaikh *et al*., surprisingly, carotid artery stenosis, coronary artery disease, and TIA were independently associated with a reduced risk of stroke in patients with RAO [17]. The authors believe that it is possible that earlier diagnosis and treatment of these conditions, as well as lifestyle changes in these patients, ultimately may have led to a reduction in subsequent stroke risk. The study also found that cardiovascular catheterization had a significant independent association with reduced stroke risk in RAO patients. The authors hypothesize that these patients may be receiving therapy that also reduces stroke risk. Variables associated with a significantly increased risk of stroke in this analysis included valvular heart disease, hypertension, hyperlipidemia and smoking [17].

CRAO and BRAO vs. stroke risk

In the available literature, a comparison of the incidence of stroke after CRAO and BRAO is available in only a few papers, which present divergent results [5, 8, 10, 14–16, 24, 33, 43]. The results of Chang *et al.* [10], Schoor *et al.* [8] and also Avery *et al*. [24] show a higher rate of stroke after CRAO than after BRAO. In a study by Lauda *et al*., the type of occlusion – BRAO – was associated with a higher risk of finding ischemic lesions in the CNS [16]. In contrast, studies by Rim *et al.* [5], Lee *et al.* [14], Leisser and Findl [15] and Roskal-Wałek *et al.* [43] found no statistically significant differences between stroke rates after CRAO and BRAO. Also, a meta-analysis by Fallico *et al*. found no statistically significant differences between patients with CRAO and BRAO in the rate of both symptomatic and asymptomatic fresh CNS ischemic lesions [23]. In the study by Kim *et al*., where the presence of stroke and small vessel cerebrovascular disease was assessed, the authors found no statistically significant difference between patients with CRAO and BRAO [33].

Reports of the same risk of stroke after CRAO as BRAO have important implications, especially given the need for specific diagnostic and therapeutic interventions for patients with BRAO as well [43].

Conclusions

The association between RAO and subsequent CNS ischemic episodes that was demonstrated in several studies necessitates prompt referral to the emergency department or stroke unit for neurological evaluation, brain imaging and urgent expanded diagnostics to search for the cause of the ischemic incident, as well as evaluation of these patients for concomitant cardiovascular risk factors. Since the coverage and accessibility of health care systems vary from country to country, the strategy for immediate assessment and intervention in patients with RAO should be optimized based on local public health systems. Taking appropriate preventive measures as well as administering appropriate treatment provides an opportunity for the medical team to achieve its goal of reducing the risk of another thromboembolic incident and improving the prognosis in terms of the survival of these patients.

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Conflict of interest

The authors declare no conflict of interest.

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