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Clinical characteristics of recurrent non-arteritic retinal artery occlusion

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ABSTRACT

Objectives To investigate the recurrent non-arteritic retinal artery occlusion (RAO) in the same or opposite eye.

Methods We searched the RAO registry at Seoul National University Bundang Hospital and included patients with recurrent RAO in the present study. Ophthalmic and systemic features were analysed to identify risk factors and visual outcomes.

Results Of the 850 patients in the non-arteritic RAO cohort, 11 (1.3%) experienced a second RAO recurrence, either in the same (5 patients; 0.6%) or opposite (6 patients; 0.7%) eye. The same eye group experienced an earlier recurrence (1–2 months, median 1 month) than the opposite eye group, where the time to recurrence was notably longer (8–66 months, median 22 months). Best corrected visual acuity (BCVA) in the same eye group decreased after the recurrence of RAO. In the same eye group, initial BCVA ranged from 20/200 to counting fingers (CF), while BCVA during RAO recurrence ranged from CF to hand motion. When RAO recurred in the opposite eye, the reduction in visual acuity was less severe than the reduction of the initial episode: initial episode ranged from 20/400 to light perception and recurrent episode ranged from 20/25 to 20/400. Patients exhibited varying degrees of carotid (81.8%) and cerebral (9.1%) artery occlusions. Additionally, one patient in each group (total 2 patients, 18.2%) experienced a stroke 6 months after RAO recurrence.

Conclusions Since the RAO recurrences could lead to devastating visual impairment, it is essential to emphasise the importance of risk factor screening to patients while collaborating with neurologists and cardiologists.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Retinal artery occlusion (RAO) is closely linked to systemic vascular conditions, and thromboembolic causes are well investigated. However, the recurrence of RAO has not been studied as extensively as stroke recurrence.

WHAT THIS STUDY ADDS

⇒ RAO recurrence in the same eye or the opposite eye has distinct characteristics and systemic vascular conditions affect the recurrence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians should be aware of the possibility of RAO recurrence after the first episode; therefore, adequate workups regarding vascular conditions should be assessed.

INTRODUCTION

Retinal artery occlusion (RAO) is a severe vascular disorder that results in irreversible damage to retinal tissue, as well as a sudden deterioration in visual acuity.[1] RAO is categorised, based on where the retinal artery is occluded, as either central RAO (CRAO) or branch RAO (BRAO). Patients with CRAO experience a marked reduction in visual acuity and defects of the visual field, whereas those with BRAO often maintain both.[2] The presence of an embolus or the formation of a blood clot in the narrowest part of the retinal artery are two causes of RAO, which can also be the result of hypercoagulability, vasospasm and vasculitis. Previous studies have found that thromboembolisms, which have causes similar to those of cerebral infarction, are linked to systemic vascular conditions, such as stroke and coronary artery disease.[3–5] When a patient presents to the emergency department with visual symptoms and is diagnosed with RAO by an ophthalmologist, it is recommended that rapid testing for stroke be performed.[4] At our hospital, patients diagnosed with CRAO undergo rapid brain imaging and/or transfemoral cerebral angiography with intra-arterial thrombolysis (IAT), and are hospitalised for monitoring and analysis of cardiovascular and cerebrovascular risks and complications.[6]

The present study evaluated the demographic and clinical characteristics of 11 patients who experienced a recurrent episode of non-arteritic RAO in the same or the opposite eye following the initial occurrence. Such cases are uncommon, and most reported cases of recurrent RAO are associated with specific vascular conditions, such as autoimmune diseases (Wegener granulomatosis, systemic lupus erythematosus, Churg-Strauss syndrome, antiphospholipid syndrome) or infectious diseases (mucormycosis, infective endocarditis, COVID-19).[7–13]

MATERIALS AND METHODS

Of the 850 patients diagnosed with any type of acute non-arteritic RAO who visited

Table 1 Demographics and clinical characteristics of recurred retinal artery occlusion (RAO) in the same eye

Case No	1	2	3	4	5
Age (years)	50–55	75–80	50–54	65–70	55–60
Sex	Female	Male	Female	Female	Male
Laterality	Right	Left	Left	Right	Right
Diabetes mellitus	No	No	Yes	No	Yes
Hypertension	Yes	Yes	No	Yes	Yes
Dyslipidaemia	No	No	No	Yes	No
Heart disease	No	No	No	No	No
Vasculitis lab	Non-specific	Non-specific	Non-specific	Non-specific	Non-specific
First event					
Symptom onset to arrival time (hours)	10	24	16	11	20
Initial BCVA	20/200	20/200	FC	FC	FC
Diagnosis	Incomplete CRAO (superior hemi-CRAO)	Incomplete CRAO	Complete CRAO	Incomplete CRAO (OAO)	Complete CRAO
Intra-arterial thrombolysis	No	No	Yes	Yes	No
Recurrence					
Duration from first occurrence (months)	*1*	*2*	*1*	*2*	*1*
Recurred BCVA	HM	FC	HM	FC	HM
Diagnosis	Complete CRAO	Complete CRAO	Complete CRAO	Complete CRAO (OAO)	Complete CRAO
Intra-arterial thrombolysis	No	No	No	Yes	No
Brain MRA TFCA	No steno-occlusive lesions	No steno-occlusive lesions	Left proximal ICA stenosis and occlusion (30%)	Right proximal ICA and ophthalmic artery stenosis (50%)	Right proximal ICA stenosis and occlusion (40%)
Final					
Follow-up period (months)	12	96	16	12	36
Final VA	HM	FC	LP	FC	HM
Further cerebrovascular-cardiovascular events	None	None	None	None	Stroke

BCVA, best corrected visual acuity ; CRAO, central retinal artery occlusion ; FC, finger count ; HM, hand motion ; ICA, internal carotid artery; LP, light perception; MRA, magnetic resonance angiography ; OAO, ophthalmic artery occlusion; TFCA, transfemoral cerebral angiography ; VA, visual acuity.

Seoul National University Bundang Hospital (SNUBH) between January 2007 and December 2021 (over a 15-year period) and enrolled in the SNUBH RAO cohort registry, the present study included 11 (1.3%) patients who experienced a recurrence of RAO, either in the same (5 patients; 0.6%) or opposite (6 patients; 0.7%) eye. Each of the patients underwent a complete ophthalmic evaluation, including best corrected visual acuity (BCVA), colour fundus photography, fluorescein angiography (FA) (VX-10; Kowa OptiMed, Tokyo, Japan) and spectral-domain optical coherence tomography (SD-OCT), as well as laboratory and cerebrocardiac assessments for vasculitis, including MRI and magnetic resonance angiography of the brain, transfemoral cerebral angiography, coronary angiography and echocardiography.

Among the 11 patients included in the present study, patients diagnosed as having acute non-arteritic CRAO received either the standard treatment or IAT, while those with BRAO received only the standard treatment. The standard treatment included observation, ocular massage and the use of intraocular pressure-lowering agents. In cases in which IAT was considered necessary, cerebral angiography was performed to test for cerebral vessel disease. The specific IAT techniques used have been discussed in our prior studies.[14 15] A 500 000-unit injection of urokinase (Green Cross, Yongin, South Korea) was administered to the proximal portion of the ophthalmic artery. Patient selection for IAT was based on the potential for visual improvement, considering the following factors: prolonged retinal artery perfusion, and symptom onset to a treatment time <24 hours for complete, or <1 week for incomplete, CRAO patients.

The five patients in the same eye recurrence group (all with CRAO) were categorised as having incomplete or complete CRAO, based on the results of colour fundus photography and FA. The six patients in the opposite eye recurrence group were categorised as having complete or incomplete CRAO, BRAO or

Table 2 Demographics and clinical characteristics of recurred retinal artery occlusion (RAO) in the opposite eye

Case No	1	2	3	4	5	6
Age (years)	50–55	70–75	75–80	75–80	60–65	45–50
Sex	Male	Male	Female	Male	Female	Female
Diabetes mellitus	No	Yes	No	No	No	No
Hypertension	Yes	Yes	Yes	Yes	Yes	Yes
Dyslipidaemia	Yes	Yes	Yes	Yes	Yes	Yes
Heart disease	CAD	CAD	CAD	Atrial fibrillation	Atrioventricular mass	CAD
Vasculitis lab	No	No	No	No	No	No
Other systemic diseases	ESRD on PD	–	–	–	–	–
First RAO						
Laterality	Left	Left	Left	Right	Right	Left
Onset to arrival time (hours)	12	24	48	6	72	24
Initial BCVA	HM	20/50	HM	HM	20/100	FC
Diagnosis	Complete CRAO	BRAO	Complete CRAO	Complete CRAO	Cilioretinal artery occlusion	Complete CRAO
Intra-arterial thrombolysis	Yes	No	No	No	No	No
Opposite RAO						
Laterality	Right	Right	Right	Left	Left	Right
Duration from first RAO (months)	8	66	17	25	19	26
Initial BCVA	FC	20/25	20/400	20/25	20/25	20/200
Diagnosis	Complete CRAO	BRAO	Incomplete CRAO	BRAO	BRAO	Incomplete CRAO
Intra-arterial thrombolysis	Yes	No	Yes	No	No	No
Brain MRA TFCA	Both proximal ICA mild stenosis (30%) Right MCA near-complete occlusion (90%)	Both proximal, distal ICA severe stenosis (80%)	Both proximal, distal ICA severe stenosis (80%)	Both proximal ICA mild stenosis (20%)	Both distal ICA mild stenosis (30%)	Both proximal ICA mild stenosis (30%)
CAG Echocardiography	RCA total occlusion (100%)	Moderate stenosis (50%) Previous CABG, PCI history	Mild stenosis (20%) Hypertrophic cardiomyopathy	Moderate aortic regurgitation Mitral annular heavy calcification	Cardiac tumour (fibroelastoma)	RCA total occlusion (100%)
Final						
Follow-up period (months)	24	72	24	32	36	38
Final BCVA						
First	20/400	20/25	LP	HM	20/100	FC
Opposite	20/400	20/25	20/50	20/25	20/25	20/25
Further cerebrovascular-cardiovascular events	Stroke	None	None	None	None	None

BCVA, best corrected visual acuity; BRAO, branch retinal artery occlusion; CABG, coronary artery bypass graft; CAD, coronary artery disease; CAG, coronary angiography; CRAO, central retinal artery occlusion; ESRD on PD, end-stage retinal disease on peritoneal dialysis; FC, finger count; HM, hand motion; ICA, internal carotid artery; LP, light perception; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCI, percutaneous coronary intervention; RCA, right coronary artery; TFCA, transfemoral cerebral angiography.

cilioretinal artery occlusion. We documented demographic and clinical characteristics of the subjects, including age, sex, laterality, underlying systemic diseases, initial and final BCVA, symptom onset to arrival for the first event, duration from the initial occurrence to recurrence, final follow-up period,

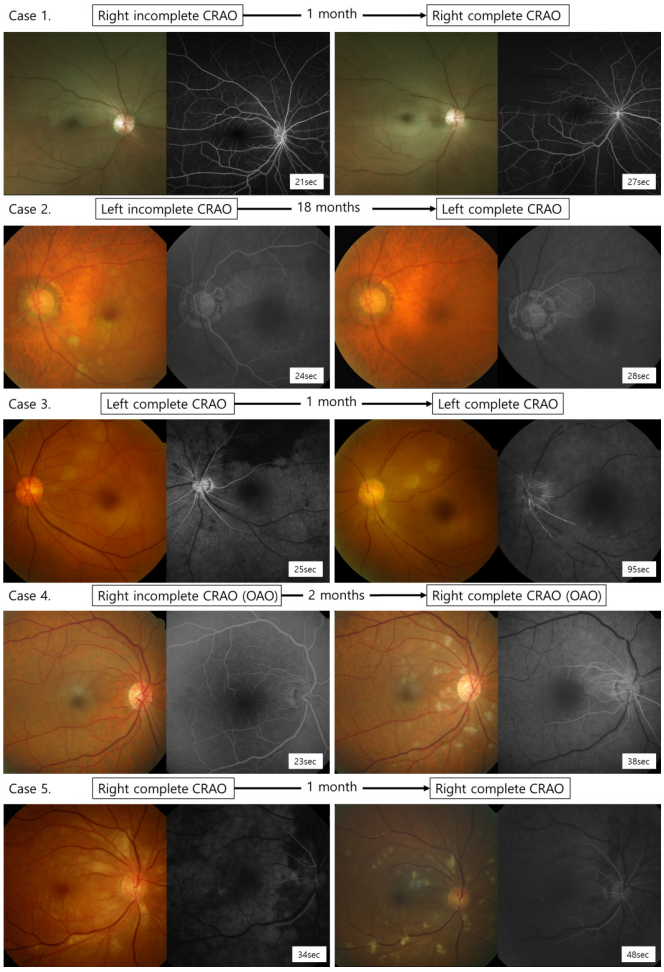

Figure 1 All five cases of retinal artery occlusion (RAO) recurrence in the same eye were documented using colour fundus photography and fluorescein angiography at both the initial episode (left) and the subsequent recurrence (right). Fluorescein angiography arm-to-retina time was emphasised. CRAO, central retinal artery occlusion; OAO, ophthalmic artery occlusion.

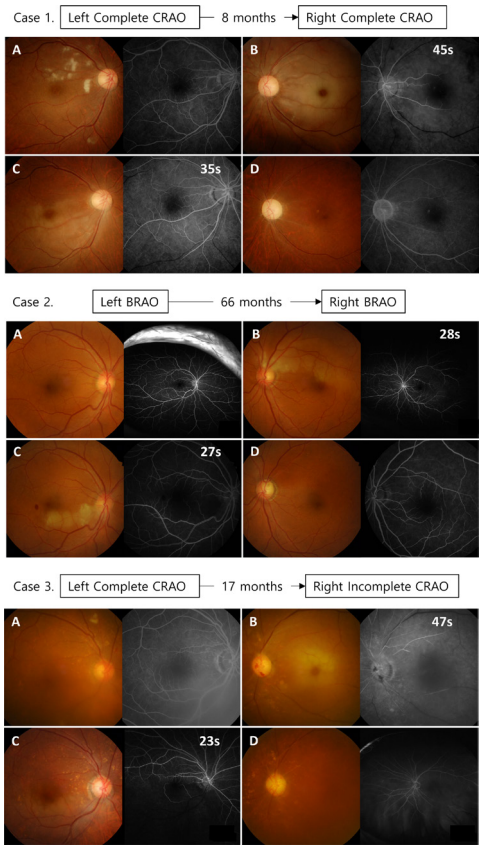

Figure 2 First three cases (cases 1–3) of retinal artery occlusion recurrence in the opposite eye were documented using colour fundus photography and fluorescein angiography at both the initial episode (A: right, B: left) and the subsequent recurrence (C: right, D: left). Fluorescein angiography arm-to-retina time was emphasised. BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion.

description of cerebrovascular evaluations and additional systemic vascular events. To accurately measure any clinical visual function changes, we allowed for an interval of at least 6 months between the recurrence and the final visit.

RESULTS

The present study included 11 individuals (1.3% of 850 patients with RAO) who experienced a recurrence of acute non-arteritic RAO in the same (5 patients; 0.6%) or opposite (6 patients; 0.7%) eye. The demographic and clinical characteristics of the participants are summarised in tables 1 and 2, respectively. Underlying systemic diseases, such as diabetes mellitus, hypertension, dyslipidaemia, heart disease and vasculitis, were evaluated. We also documented all 11 incidents of colour fundus photography and FA performed during the first occurrence and RAO recurrence (figures 1–3). In addition, representative cases of SD-OCT changes during the initial occurrence, recurrence of RAO and final follow-up were depicted in online supplemental figure 1.

The same eye recurrence group included two male and three female patients, with an average age of 60 (range, 50–75) years, the demographic and clinical characteristics for whom are outlined in table 1. Although the patients were diagnosed with a variety of underlying systemic diseases, none had any heart disease. Brain imaging results also varied among the included patients—cases 1 and 2 showed no steno-occlusive lesions on brain magnetic resonance angiography and transfemoral cerebral angiography, whereas cases 3–5 showed ipsilateral proximal internal carotid artery (ICA) stenosis and occlusion. Cases 1 and 2, who initially presented with incomplete CRAO and a BCVA of 20/200 during the first event, presented with complete CRAO with a BCVA of hand motion–finger count during the recurrent episode. Interestingly, however, there were no changes in the brain imaging findings in these two patients. All the patients in the same eye group experienced the RAO recurrence within 1–2 months of the first episode, and their visual acuity deteriorated to less than finger count

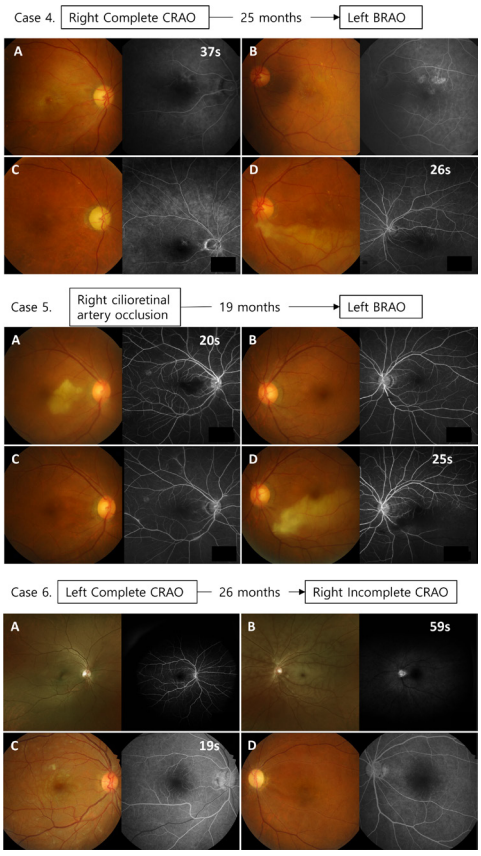

Figure 3 Other three cases (cases 4–6) of retinal artery occlusion recurrence in the opposite eye were documented using colour fundus photography and fluorescein angiography at both the initial episode (A: right, B: left) and the subsequent recurrence (C: right, D: left). Fluorescein angiography arm-to-retina time was emphasised. BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion.

in all cases. Of note, one patient (case 5) experienced a stroke 6 months after the recurrence of RAO.

The opposite eye recurrence group included three male and three female patients with an average age of 63.6 (range, 46–76) years, as detailed in table 2. In contrast to the same eye recurrence group, all of the patients in the opposite eye group had a history of hypertension, dyslipidaemia and a variety of heart conditions, including coronary artery disease, atrial fibrillation and an atrioventricular mass. Of note, case 1 had end-stage renal disease and was undergoing peritoneal dialysis. Brain imaging revealed varying degrees of bilateral ICA stenosis in all of the patients in the opposite eye recurrence group, ranging from mild to severe. Coronary angiography and echocardiography confirmed the presence of coronary artery occlusion, valve issues, cardiomyopathy and cardiac tumours of various severities among these patients. Case 2 experienced BRAO in both eyes, allowing the final visual acuity to remain at 20/25. Most of the patients in this group, however, had CRAO in both eyes, which led to a significant decline in vision. Case 1, with a total occlusion of the right coronary artery and a near-complete occlusion of the right middle cerebral artery, experienced a stroke 6 months after the recurrence of RAO. Case 5 had a cardiac tumour, and surgery was necessary to remove the mass due to the recurrence of RAO. A pathological examination confirmed the mass to be a fibroelastoma.

In summary, when comparing the clinical characteristics between the same eye and opposite eye groups, differences emerged in terms of duration from the initial to secondary occurrence (immediate 1–2 months vs gradual 8–66 months, respectively) and the severity of the cerebrovascular and cardiovascular conditions (varying degrees of unilateral ICA stenosis without heart disease vs bilateral ICA stenosis with severe heart disease).

DISCUSSION

Recurrence of non-arteritic RAO in the same or opposite eye is rare. Susac syndrome is a well-known, although rare, condition in which episodes of retinal vasculitis result in recurrent BRAO. The diagnosis of Susac syndrome involves the visualisation of hyperfluorescence of the arteriolar wall on FA, inner retinal atrophy on optical coherence tomography and lesions in the corpus callosum on brain MRI.[16] Herein, however, the recurrence of RAO was related to the recurrence of thromboembolism and/or stenosis, similar to the recurrence of cerebral ischaemia. Surprisingly, all six patients who experienced a recurrence of RAO in the opposite eye had bilateral ICA stenosis with pre-existing heart conditions, including coronary artery disease, atrial fibrillation and cardiac tumour, a significant difference from the same eye recurrence group, which presented with no definite underlying heart diseases. Brain imaging revealed varying degrees of stenosis in both the carotid and large cerebral arteries in most patients who experienced a recurrence of RAO; however, no steno-occlusive lesions were found in the two patients who experienced a recurrence in the same eye. Furthermore, the recurrence of RAO in the same eye predominantly occurred during the immediate period following the initial event, whereas the duration of RAO recurrence in the opposite eye was longer.

The primary causes of CRAO are cardioembolisms and artery-to-artery embolisms of the carotid artery; however, approximately half of all CRAO cases are due to an unknown aetiology, which is much higher than the proportion of stroke cases with unknown causes.[17] Differences in cerebrovascular and cardiovascular factors between patients with recurrence in the same eye and those with recurrence in the opposite eye may suggest variations in the thromboembolic risk associated with recurrent RAO.[18 19] This implies that although the patients did not have any obvious cerebrovascular abnormalities, and had a low likelihood of systemic vascular disease, there was still a possibility of RAO recurrence. Individuals with a history of diabetes, hypertension, dyslipidaemia and/or cerebrovascular atherosclerosis, however, are more likely to experience a recurrence of

RAO, primarily due to retinal emboli composed mainly of cholesterol and platelet-fibrin emboli. These emboli are typically observed in conjunction with mural thrombus formation in the carotid artery or the cardiac valvular structures.[20 21]

Several studies have examined the occurrence of subsequent strokes following the initial stroke, and most suggest that the risk of recurrent stroke is the highest immediately after the first stroke.[22 23] One study found that the 3-year cumulative risk of stroke recurrence was 14%, and that diabetes mellitus and atrial fibrillation were associated with stroke recurrence.[24] Other studies have reported 3-year cumulative risks ranging from 6% to 25%.[25 26] Although recurrent stroke is common, the recurrence of non-arteritic RAO has rarely been reported. A previous study focusing on emboli and blood flow in the ophthalmic artery analysed using a computational fluid dynamics model proposed that emboli must be of a specific size and location to result in RAO, while other emboli usually flow into the cerebral artery without entering the ophthalmic artery.[27] These findings may explain the very low incidence of recurrent RAO compared with stroke recurrence. Given that RAO is associated with a very high risk of cerebrovascular and cardiovascular complications, the recurrence of RAO may be viewed as a subsequent stroke event that increases the likelihood of morbidity and mortality.[22–26]

Considering the association between RAO and embolic sources from the heart,[17] it is crucial to perform cardiac evaluations, such as coronary angiography and transthoracic echocardiography, in addition to brain imaging, especially in high-risk patients. Previous studies have shown that approximately 50% of patients with non-arteritic CRAO have abnormal echocardiographic findings, indicating an embolic source.[4 5] Another recent study highlighted that patients with RAO were more likely to have valvular diseases and be readmitted for atrial fibrillation/dysrhythmias than patients with acute ischaemic stroke.[25 26]

In the present study, all cases of recurrent RAO in the same eye were diagnosed as CRAO. Interestingly, although the initial occurrence was mild in three patients, who presented with incomplete CRAO, the subsequent recurrences were uniformly severe, resulting in complete CRAO and significant vision loss. Conversely, the recurrence of RAO in the contralateral eye presented with both BRAO and CRAO. Although the first occurrence was severe and led to visual deterioration, the second recurrence was relatively mild. In our cohort of six patients with recurrence in the opposite eye, vision was maintained in the opposite eye, ranging from 20/400 to 20/25. Individuals who experience vision loss following the initial RAO incident may struggle with depression and anxiety regarding the potential loss of vision in their remaining eye like patients who lost unilateral vision from age-related macular degeneration (AMD).[28 29] Therefore, it is essential to provide psychological and emotional support to these patients.

The present study had several limitations. First, despite our efforts to gather as many cases of recurrent RAO as possible, the incidence of this condition was exceedingly low, resulting in only 11 cases available for presentation. The analysis of such a limited number of patients could potentially impact the results, especially concerning subsequent cerebrovascular and cardiovascular complications. Second, we were unable to analyze data differentiating between CRAO and BRAO, owing to the scarcity of recurrent cases. Third, it may be necessary to extend the follow-up period to >3–5 years for a more comprehensive analysis of the effects of recurrent RAO. Nevertheless, it is a strength of our study that we analysed quite a large number of 850 patients with non-arteritic RAO and thus, we could reveal the approximate incidence of recurrence.

In conclusion, the recurrence of non-arteritic RAO can occur in the same or opposite eye via different mechanisms. Because recurrent RAO can result in severe vision loss, it is crucial to stress the significance of screening for risk factors to patients and to work closely with neurologists and cardiologists.

Contributors Both authors (HMK and SJW) were involved in the planning, conduct, reporting, conception and design, acquisition of data or analysis and interpretation of data.The corresponding author, SJW, accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The protocol for the present retrospective study was approved by the institutional review board of Seoul National University Bundang Hospital (SNUBH) (B-2109-709-102 and B-2306-837-103) and was performed in accordance with the principles of the Declaration of Helsinki. Informed written consent was obtained from all participants. It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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