

ARTICLE



Aberrant filling of the retinal vein on fluorescein angiography in branch and hemi-central retinal artery occlusion

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OBJECTIVE: To study aberrant filling of the retinal vessels on fluorescein angiography (FA) images in patients with branch (BRAO) or hemi-central retinal artery occlusions (hemi-CRAO) and correlate with associated changes on optical coherence tomography (OCT).

METHODS: Cases of acute BRAO or hemi-CRAO having FA and OCT images at presentation between June 2017 to May 2022 were included. Comparisons were made between the cases with and without aberrant filling of the retinal vessel.

RESULTS: Thirty-nine eyes of 39 patients with acute retinal artery occlusions underwent FA and OCT imaging. Seven of the ten cases with either BRAO or hemi-CRAO showed aberrant filling of the retinal vein on FA. No case with CRAO showed aberrant filling on FA. The cases with aberrant filling showed a better presenting visual acuity and lesser severity of retinal ischemia on OCT. Shunts between the retinal artery in the unaffected region and the retinal vein in the affected segment was seen in two eyes. The remaining five eyes showed no arteriovenous anastomosis. Cases with aberrant filling had a better visual function even at the last visit.

CONCLUSION: Aberrant retinal vein filling across the horizontal median raphe in the affected region in BRAO or hemi-CRAO eyes had less severity of retinal ischemia and better presenting and final visual acuities. Reduced perfusion in retinal capillaries with altered retinal vascular anatomy or arteriovenous shunts could be probable reasons for the development of this FA finding. Presence of aberrant filling of the retinal vein could indicate better final visual prognosis.

Eye (2023) 37:2659–2663; <https://doi.org/10.1038/s41433-022-02379-7>

INTRODUCTION

Retinal artery occlusions, specially central retinal artery occlusion (CRAO) is a true ophthalmic emergency and has a poor prognosis unless intervention is initiated very early [1]. The visual prognosis in eyes with CRAO is generally poor compared to eyes with hemi-CRAO or BRAO which have a better visual prognosis [2]. The role of fundus fluorescein angiography (FA) in CRAO and hemi-CRAO has already been well-demonstrated [3, 4]. In a study by Gong et al., three types of CRAO were identified on FA, viz. poor perfusion, exudation and mixed patterns based on the arm-retina time and retina vascular leakage [4]. These findings have shown key benefits in predicting the visual prognosis in patients with CRAO. However, most clinicians prefer to avoid performing an invasive dye-based FA in patients with acute branch retinal artery occlusion (BRAO) due to less extensive area of retinal ischemia and better visual acuity at presentation. Schmidt D studied the FA images in patients with BRAO and described an extraordinary finding of retrograde filling of the dye in the retinal vessels in four cases with favorable visual outcomes [5]. However, the study failed to provide the possible explanations regarding the pathomechanism for this FA finding in BRAO patients.

In this retrospectively study, FA images in eyes with retinal artery occlusions (either total or hemi-CRAO or BRAO) were

analyzed and associated changes on optical coherence tomography (OCT) related to aberrant filling of retinal vessels were evaluated. Further, with this study we attempt to explain the possible pathomechanism related to the aberrant filling of the retinal vessels seen on FA in retinal artery occlusions.

METHODS

In this retrospective, descriptive study, we included cases of retinal artery occlusion diagnosed clinically as CRAO, hemi-CRAO or BRAO with acute presentation of symptoms (recent onset visual problems) and signs (presence of retinal opacification) and those who had undergone a dye-based standard-field FA and OCT at presentation between June 2017 to May 2022 at a tertiary eye hospital in South India. This study was approved by the Institutional Review Board (C-2022-05-003) and was in accordance with the tenets outlined in the Declaration of Helsinki. Informed consent for all retinal imaging, including for FA, had been obtained from all patients prior to the procedures.

In all, 39 eyes of 39 patients with good quality FA images were available in the setting of an acute retinal artery occlusion. From the early and middle phases of FA, the following details were noted; level of blockage of retinal artery (CRAO, hemi-CRAO or BRAO); arm-to-retina time; presence of cilioretinal artery, presence or absence of aberrant filling of retinal vessels in the affected segment and the time at which the aberrant filling of the retinal vessel was noted. Aberrant filling of the retinal vessel (artery or vein)

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Table 1. Patient characteristics and clinical findings of patients with acute retinal artery occlusion.

Case No	Eye	Age	Sex	Clinical diagnosis	Systemic illness	Duration of symptom (days)	Initial VA	FA		Aberrant filling	Filling vessel	Time at which Aberrant filling was noted (s)	Vessel of the affected segment crossing the horizontal median raphe	Optos®			Feeding vessel	Receiving vessel	OCT	Inner retinal layer hyperreflectivity	Inner retinal layer thickening	Loss of inner retinal layer structure organization	Severity of retinal ischemia	Follow-up duration (months)	Final VA
								CLA	ART (s)					Vessel anastomosis with the unaffected retinal segment	Anastomosis site										
1	LE	76	M	IT BRAO	Nil	4	6/36	No	16	No	NA	NA	No	No	NA	NA	NA	Yes	Yes	Yes	Severe	1	6/24		
2	LE	68	M	Inferior HCRAO	DM	4	6/12	No	17	Yes	Vein	24	No	No	NA	NA	NA	Yes	Yes	No	Moderate	1	6/12		
3	RE	50	F	IT BRAO	Heart disease	4	6/6	No	19	Yes	Vein	25	No	Yes	Temporal	Artery	Vein	Yes	No	No	Mild	1	6/6		
4	RE	75	M	ST BRAO	HTN	1	6/6	No	20	Yes	Vein	33	No	No	NA	NA	NA	Yes	Yes	No	Moderate	4	6/6		
5	LE	48	F	SN BRAO and inferior HCRAO	Thyroid	1	6/9	No	13	Yes	Vein	15	No	Yes	Temporal	Artery	Vein	Yes	No	No	Mild	1	6/6		
6	LE	69	M	ST BRAO	HTN, DM	5	6/18	No	22	Yes	Vein	28	No	No	NA	NA	NA	Yes	Yes	No	Moderate	4	6/12		
7	RE	51	M	SN and IT BRAO	Nil	2	6/60	No	22	No	NA	NA	No	No	NA	NA	NA	Yes	Yes	Yes	Severe	1	6/60		
8	RE	31	M	Inferior HCRAO	HTN, DM	1	6/6	No	23	Yes	Vein	37	No	No	NA	NA	NA	Yes	No	No	Mild	1	6/6		
9	LE	49	F	Superior HCRAO	Nil	1	6/24	No	12	No	NA	NA	No	No	NA	NA	NA	Yes	Yes	Yes	Severe	48	6/24		
10	LE	50	M	Inferior HCRAO	HTN	2	6/9	No	19	Yes	Vein	22	No	No	NA	NA	NA	Yes	No	No	Mild	1	6/9		

RE right eye, LE left eye, M male, F female, BRAO branch retinal artery occlusion, HCRAO hemi-central retinal artery occlusion, IT inferotemporal, SN superonasal, ST superotemporal, HTN hypertension, DM diabetes mellitus, VA visual acuity, CLA cilioretinal artery, ART arm-to-retina time, FA fluorescein angiography, OCT optical coherence tomography, NA not applicable.

was defined as identifying the filling of fluorescein dye in the retinal vessel in a direction from the retinal periphery toward the posterior pole and optic nerve head in the affected region of the arterial occlusion. The clinical features were documented on the ultra-widefield Optos Optomap Daytona Panoramic 200Tx (Daytona, Optos®, UK). Other data included demographic details, duration of symptoms, presence of associated systemic disease, presenting and final visual acuity and total follow-up duration. Furthermore, in eyes with aberrant dye filling, an attempt was made to determine whether any tributaries or branches of the major retinal vessels in the involved segment crossed the horizontal median raphe or anastomosed with the retinal vasculature in the uninvolved segment, either clinically or on FA. If such anastomosis was found, the location of the anastomosis on the clinical photograph was noted, as well as whether the feeding and receiving retinal vessel was an artery or a vein. The retinal changes at the posterior pole were documented using the spectral domain OCT on the Spectralis® device (Spectralis, Heidelberg Engineering, Heidelberg, Germany). On the OCT, three features were looked for viz., presence of inner retinal layer hyperreflectivity, inner retinal layer thickening and loss of organized inner retinal layer structure. Based on these three OCT features, the severity of retinal ischemia in the affected segment was categorized into three groups viz.; mild (presence of inner retinal layer hyperreflectivity alone), moderate (presence of inner retinal layer hyperreflectivity + presence of inner retinal layer thickening or loss of organized inner retinal layer structure) and severe (presence of all three OCT features) [6].

RESULTS

The study included 29 eyes clinically diagnosed with CRAO, 4 eyes with hemi-CRAO, 5 eyes with BRAO and 1 eye with a combination of inferior hemi-CRAO and superonasal BRAO having good quality FA images at presentation. Aberrant filling of the retinal vessel with the fluorescein dye in the occluded segment was noted in seven eyes. These included 3 eyes with BRAO, 3 eyes with hemi-CRAO and 1 eye with combined inferior hemi-CRAO and BRAO respectively. In none of the 29 eyes with acute CRAO, aberrant filling of the fluorescein dye was identified. With an objective to study the effects of aberrant filling of the fluorescein dye on the visual prognosis in eyes with arterial occlusion, the ten cases with subtotal retinal artery occlusion [hemi-CRAO (n=4), BRAO (n=5) and combined BRAO and hemi-CRAO (n=1)] were further analyzed. These included seven males and three females. Age of presentation of these patients ranged from 31 to 76 years. Clinical and imaging details of all these ten patients is mentioned in Table 1. Aberrant filling of the retinal vessels was noted in seven of the ten cases with subtotal retinal artery occlusions (Figs. 1 and 2). In all these cases, filling in to the retinal vein of the affected segment was identified. Furthermore, the tributaries of the affected segment’s major branch retinal vein did not cross the horizontal median raphe into the unaffected segment of the fundus. A patent cilioretinal artery was not identified in these eyes. Further comparisons were made between seven eyes which showed aberrant filling (Group 1) and three eyes which did not show aberrant filling (Group 2) on the FA. The age range in group 1 was 31–75 years and in group 2 was 49–76 years, respectively. The duration of symptoms in group 1 ranged from 1 to 5 days and in group 2 ranged from 1 to 4 days, respectively. The visual acuity in patients with retinal artery occlusions having aberrant filling on FA ranged from 6/6 to 6/12 while cases with retinal artery occlusions without aberrant filling on FA had presenting visual acuities ranging from 6/24 to 6/60. All the patients in group 1 had a history of systemic illness such as diabetes mellitus, heart disease, hypertension and thyroid disease. None of the patients in the study had an associated cilioretinal artery and the arm-retina time was ≤23 s. On the fundus image, a possible anastomosis was identified in two cases on the temporal aspect of the fundus between the retinal artery of the unaffected retinal quadrant and the retinal vein of the affected quadrant. In the remaining five eyes, no clearcut anastomosis was noted. The severity of the retinal ischemia ranged from mild-moderate in group 1 on OCT while all cases in group 2 showed severe grade of retinal ischemia. The patients belonging to group 2 had a lesser

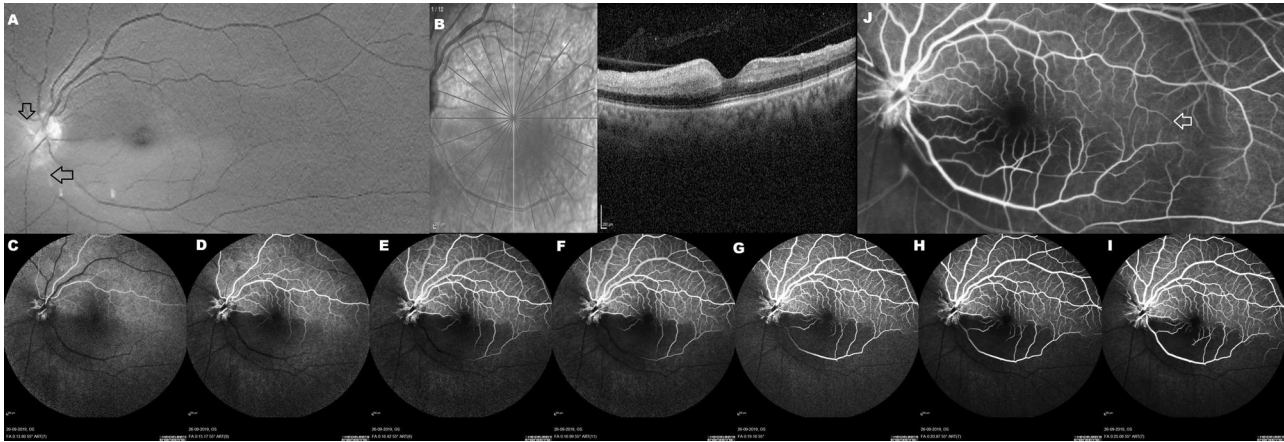


Fig. 1 Case details and retinal imaging showing the aberrant filling of the retinal vein in retinal artery occlusion (case 5). This is a case of a 48-year-old-female who complained of sudden onset blurring of vision and loss of superior field in the left eye for 1 day. Her presenting visual acuity was 6/9. **A** On dilated fundus examination, multiple emboli were noted blocking the superonasal branch of the central retinal artery (CRA) and inferior division of the CRA (black arrows). The superior branch of the CRA was not occluded. **B** Vertical line OCT scan passing through the fovea showed inner retinal hyperreflectivity with underlying outer retinal shadowing inferior to the fovea. No inner retinal layer thickening and loss of organized inner retinal structure was noted suggestive of a mild grade of retinal ischemia. The retinal layers superior to the fovea are normal. **C–I** Sequential early and mid-phase fluorescein angiography images depicting the aberrant flow of the dye into the retinal vein of the occluded segment. There is blocked choroidal fluorescence in the affected segment due to the presence of overlying retinal opacification. The tributaries of the retinal vein in the affected segment do not appear to cross the horizontal median raphe on the fluorescein angiogram. The tributaries in the affected segment show filling beginning in the region of the horizontal median raphe and progressing in a direction toward the optic disc. The filling of the retinal artery, capillaries and retinal vein in the unaffected segment appears normal. **J** Zoomed and cropped late phase FA image of the left eye showing the possible arteriovenous shunt between the retinal artery of the unaffected region and the retinal vein of the affected segment (white arrow).



Fig. 2 Case details and retinal imaging showing the aberrant filling of the retinal vein in acute hemi-central retinal artery occlusion (CRAO) (case 10). This is the case of a 50-year-old hypertensive man who presented to the retina clinic with complaints of sudden onset loss of the superior field in his left eye. His presenting visual acuity in the left eye was 6/9. **A** Clinical fundus exam documented on the Topcon® color fundus photograph was suggestive of inferior hemi-CRAO. **B** Vertical line OCT scan passing through the fovea showed inner retinal hyperreflectivity and no retinal thickening inferior to the fovea suggestive of a mild grade of retinal ischemia. **C, D** Images of early and mid-phase fluorescein angiography of the left eye showing abnormal dye filling into the retinal vein of the occluded segment. In this patient, there is no anastomosis of the retinal artery and vein between the unoccluded and occluded regions of the retina. On the fluorescein angiogram, the tributaries of the affected retinal vein appear to be filled in the region of the horizontal median raphe and then gradually filling the retinal vein in the occluded segment in a direction toward the optic disc. Because of the presence of overlying retinal opacification, choroidal fluorescence is blocked in the affected segment. The filling of the retinal artery, capillaries, and retinal vein, as well as the drainage of the retinal vein, appear normal in the unaffected segment.

final visual acuity (range: 6/24–6/60) compared to those in group 1 (range: 6/6–6/12). Repeat FA was not performed in any patient on the further follow-up visits.

DISCUSSION

This study described characteristics of abnormal filling of the retinal vessels in patients with hemi-CRAOs and BRAOs. The duration of acute symptoms did not have a bearing on the development of aberrant filling on FA. Patients demonstrating this

FA finding had less severity of retinal ischemia and better presenting and final visual acuities.

In the setting of an acute retinal artery occlusion, the final visual acuity depends upon the presenting visual acuity which in turn depends up on the severity of the occlusion and extent of retinal infarction (CRAO, hemi-CRAO or BRAO) and perfusion of the papillomacular bundle [2, 7, 8]. None of the CRAO patients in this study had aberrant retinal vessel filling. The cilioretinal artery was not patent in any of the cases. Only eyes with subtotal retinal involvement either due to occlusion of a branch of the main central

retinal artery (BRAO) or the superior or inferior division of the main trunk of the central retinal artery (hemi-CRAO) demonstrated the presence of aberrant filling on FA. Thus, this explains that the presence of a patent branch of a central retinal artery or a cilioretinal artery is mandatory for the development of aberrant filling. In CRAO, the further filling of the central retinal artery branches and retinal capillaries is affected, which explains the absence of the aberrant filling of the retinal vessels in such situations. However, in CRAO cases with a patent cilioretinal artery, aberrant filling of the dye into the retinal vessels could still be observed as was shown in a review article (Fig. 15 in the article) by Hayreh [8]. This also explains the poor visual prognosis in patients with CRAO (unless supported by a patent cilioretinal artery) compared to BRAO or hemi-CRAO.

The severity of retinal ischemia can be graded based on the OCT features such as inner retinal layer hyperreflectivity, retinal layer thickening and loss of retinal layer stratification [6, 9]. In the current case series, we noted that the eyes demonstrating aberrant filling of the retinal vein on FA showed mild to moderate severity of retinal ischemia and thus better presenting visual acuity.

It has been said that the retinal artery is an end artery (i.e., vessel which does not anastomose with its neighbor) [10]. However, in this series, we noticed that in two of the seven eyes, the retinal artery of the unaffected segment provided the aberrant filling into the affected segment's retinal vein. Therefore, the retinal artery might not actually be a true end artery in all practicality. Similar retinal arteriovenous shunts that supply blood from the artery to the vein without using the normal capillary bed have been previously described in literature [11]. Such shunts are seen in diseases affecting cerebral and coronary vasculatures [12–14]. On a routine fundus examination, these arteriovenous shunts are not visible because they could either be absent or still be collapsed. These shunts may develop newly or the collapsed shunts may reopen in the presence of retinal vascular diseases, allowing communication between a retinal artery and a retinal vein. Such arteriovenous shunts have been observed in a number of retinal vascular diseases, including diabetic retinopathy, central and branch retinal vein occlusion, CRAO, and miliary aneurysms, which could support this theory [15].

Another possible and most likely mechanism for this FA finding could be explained based on the poor filling in the retinal capillaries of the affected segment due to the arterial occlusion. In normal retinal circulation, the blood from the retinal arteries and arterioles travels through the capillaries to the retinal venules and eventually emptying from the eye by the central retinal vein [10, 16]. The retinal artery fills from the optic disc to the retinal periphery. The proximal-most part of the retinal artery fills first as blood enters a major branch of the central retinal artery. This segment of the retinal artery supplies the retinal arterioles, which in turn supply the retinal capillary plexuses in the superficial and deeper layers of the inner retina in that region. Finally, blood from the retinal capillaries enters post-capillary venules and then the major branch of the accompanying retinal vein before draining into the central retinal vein. As the retinal artery fills up further, another segment of retinal capillaries fills up, eventually filling up that segment's retinal vein. Hence, in a normal circulation, the blood fills the retinal veins from the optic disc to the retinal periphery, while the blood drains from the retinal vein toward the optic disc into the central retinal vein (Fig. 3). In an acute BRAO or in a hemi-CRAO, the filling of the retinal capillaries in the involved segment gets reduced and as a result, the accompanying retinal vein of the involved segment fails to fill up as well [17]. Hence, the retinal vein does not show the normal filling pattern i.e., from the optic disc to the retinal periphery. In addition, in all eyes with abnormal retinal vein filling, the tributaries draining into the affected branch of the retinal vein began filling from the region of horizontal median raphe without crossing it. This could imply that the capillaries in the unaffected segment were crossing the horizontal median raphe and filling the tributaries of the affected segment's retinal vein. This filling occurred near the horizontal median raphe from the temporal aspect

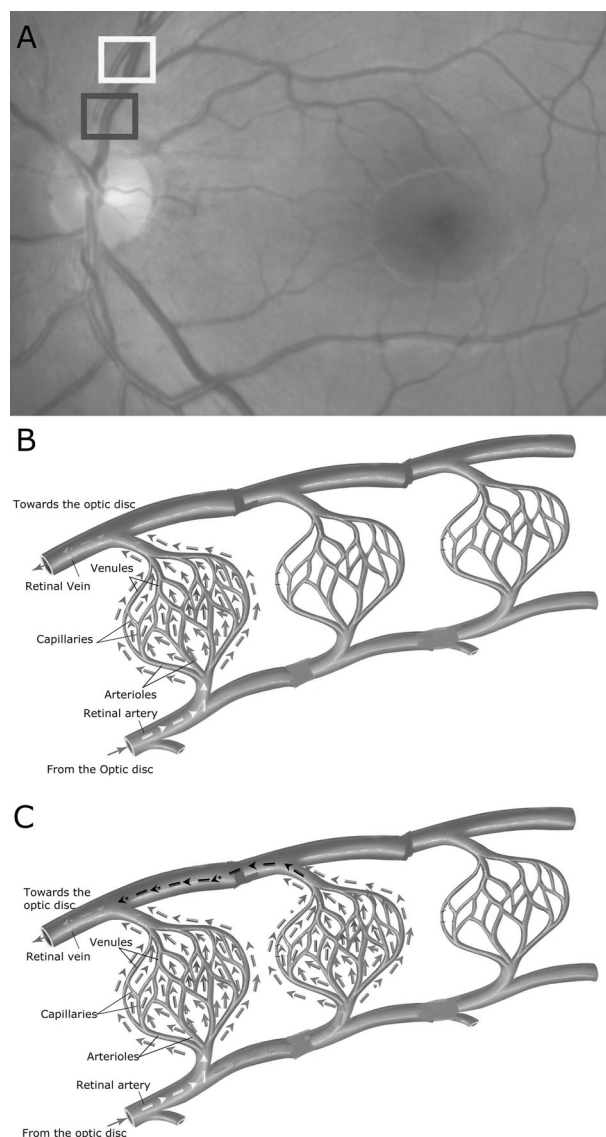


Fig. 3 Normal retinal circulation. **A** Color fundus image of a normal eye. Two regions are marked along the superotemporal arcade; one closer to the superior margin of the optic disc (empty box with blue margin) and another away from the optic disc margin (empty box with yellow margin). **B, C** Diagrammatic representation of the filling of the retinal artery, capillaries and vein and direction of the drainage of the branch retinal vein into the central retinal vein toward the optic disc in the region of blue box. The retinal artery fills from the optic disc to the retinal periphery (yellow arrows). This segment of the retinal artery supplies the retinal arterioles (red arrows), which in turn supply the retinal capillary plexuses in the superficial and deeper layers of the inner retina in that region (red–blue arrows). Finally, blood from the retinal capillaries enters post-capillary venules (blue arrows) and then the major branch of the accompanying retinal vein (orange arrows) before draining into the central retinal vein. As the retinal artery fills up further (green arrows), as noted in the region of the yellow box, another segment of retinal capillaries fills up, eventually filling up that segment's retinal vein (black arrows). Thus, in an eye with normal retinal circulation, the blood fills the retinal veins from the optic disc to the retinal periphery, while the blood drains from the retinal vein toward the optic disc into the central retinal vein.

of the macula in the distal portions of the affected retinal vein (i.e., away from the optic disc) before draining into the central retinal vein. As a result, this hypothesis most likely explains the theory of abnormal filling of the retinal vein in the involved segment in a BRAO

or hemi-CRAO, followed by normal blood drainage direction toward the optic disc. The better visual outcomes could be explained by the filling of the retina vein in the affected area, which may reduce the severity of retinal ischemia.

Another interesting observation encountered in this study was the aberrant filling occurring only in the temporal retinal vessels. We do not have a clear explanation for the temporal predilection for the aberrant filling of the retinal vessels. This could plausibly be explained by the fact that the temporal retinal vessels supply a larger area of the retina compared to its nasal counterparts [18]. Thus, a BRAO or a hemi-CRAO could trigger a spontaneous compensatory healing by the aberrant filling of the retinal vein to supply the retina in the affected segment so as to reduce the level of retinal ischemia.

In comparison to the paper published by Schmidt, this study established that the retrograde filling of the dye in the affected quadrant retinal vein from the unaffected quadrant retinal artery [5]. The study also supports the theory of spontaneous healing in retinal artery occlusions with retrograde filling and better visual prognosis as suggested by Schmidt [5].

A larger sample size and a longitudinal analysis of FA images in these patients were lacking from the study, which would have allowed for the detection of aberrant filling. This knowledge would have been helpful in determining the proper pathogenesis for the occurrence of aberrant filling in BRAO and hemi-CRAO patients. This study adds to the body of literature by describing the value of performing an FA in patients with BRAO or hemi-CRAO to detect the presence of aberrant filling of the dye and provide the patient with better presenting visual acuity.

In conclusion, aberrant dye filling in BRAO or hemi-CRAO appears to be nature's instinctive response to lessen the retina's negative effects from retinal infarction and ischemia and improve the patient's visual outcome. All patients with acute BRAO or hemi-CRAO are advised to have an FA done in order to determine how the arterial occlusion will likely progress. In addition to FA, patients with retinal artery occlusions should undergo a thorough medical and neurological examination that includes cardiac echography and carotid doppler ultrasound.

SUMMARY

What was known before

- Abnormal filling of the retinal vessels in retinal artery occlusions on fluorescein angiography is not a frequently described finding.
- The exact pathogenesis for the aberrant filling in BRAO or in hemi-CRAO is not clear.

What this study adds

- Aberrant filling of the retinal vein in the affected region in eyes with BRAO or hemi-CRAO showed less severity of retinal ischemia and better presenting and final visual acuities.
- Arteriovenous shunts or low perfusion in retinal capillaries with altered retinal vascular anatomy could be the probable reasons of the development of this FA finding.
- Presence of abnormal filling of the retinal vein could indicate better final visual outcome.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

RV, JC, and NGR: conceptualizing the study, data acquisition, analyzing the data, interpreting the findings, writing and reviewing the manuscript. SS, RM, YP, and AA: data acquisition, analyzing the data and reviewing the manuscript. NKY: analyzing the data, interpreting the findings, reviewing the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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