Original Article

Retinal arterial occlusions in the young: Systemic associations in Indian population

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Purpose: To determine the systemic associations in retinal arterial occlusions (RAO) in young Indian individuals less than 40 years of age. **Materials and Methods:** Case records of 32 patients (35 eyes) of less than 40 years, with non-traumatic RAO were analysed. All patients underwent detailed ophthalmic and systemic evaluation including hemogram, lipid profile, coagulation profile, vasculitis screening, carotid Doppler, echocardiogram. **Results:** In the study 21 were males and 11 were females. The age ranged from 11-39 years (Mean 27.6 ± 8.43). Nine (28%) patients were below 20 years of age. Among 35 eyes, 28 (80%) had central retinal artery occlusion (CRAO), three (8.6%) had branch retinal artery occlusion (BRAO), two (5.7%) each had cilio-retinal (CLAO) and hemi-retinal artery occlusion (HRAO). Vision ranged from no perception of light to 20/20. On systemic evaluation, in 21 (65.6%) patients a hypercoagulable state was responsible for the RAO. Conditions leading to a hypercoagulable state included hyperhomocysteinemia (21.9%), hyperlipidemia (15.6%), anticardiolipin antibody (6.2%), antiphospholipid antibody (6.2%), polycythemia, thrombocytosis, protein S deficiency, use of oral contraceptives and renal disorder (3.1% each). Six (18.7%) patients had cardiac valvular defects. Vasculitis screening was positive in three (9.4%) patients. Two (6.2%) had isolated systemic hypertension. In two (6.2%) patients no abnormality could be detected. **Conclusion:** The systemic associations of RAOs in the Indian population were distinctly different from those reported in the Western population. Hyperhomocysteinemia was the commonest association found. Whereas associations reported in the Western population such as cardiac abnormalities, coagulation disorders, hemoglobinopathies and oral contraceptive use were uncommon.

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.94049

Quick Response Code:

Key words: Hyperhomocysteinemia, retinal arterial occlusions, systemic associations, young age

Retinal artery occlusion (RAO) is mostly seen in the elderly with clinical findings suggestive of atheromatous emboli.[1] Among the numerous anecdotal reports of central retinal artery occlusion (CRAO) the earliest by von Graefe in 1859 described CRAO in a patient of endocarditis and multiple systemic emboli.[2] An estimated 0.85 per 10,000 patients over the age of 40 years are affected.[3] However, RAO is uncommon in the young population.[4,5] Information regarding risk factors in this age group is scanty. Various isolated case reports have reported a diverse and multifactorial etiology which includes cardiac valvular disorders and various vascular inflammatory disorders.[6] Only two major case series have been reported in patients younger than 40 years.[4,5] No reports are available regarding the risk factors in the Asian population. This retrospective study was done for the purpose of determining the clinical profile and etiological factors of RAO in young Indian individuals less than 40 years of age.

Materials and Methods

A retrospective record analysis of patients less than 40 years of age with RAO, presenting at a tertiary referral hospital between January 2004 and January 2009 was done. Patients with questionable diagnosis, history of trauma, age more than 40 years and incomplete investigative details were excluded.

Patients underwent a comprehensive medical and ophthalmic history and examination along with fundus fluorescein angiography (FFA) and thorough physical examination and cardiac evaluation. Investigations were done according to associated history and clinical findings. These included hemogram with erythrocyte sedimentation rate (ESR), lipid profile, renal function tests, vasculitis screening profile (Anti ds-DNA antibody, antihistone antibody, ANA, c-ANCA, p-ANCA), homocysteine levels, antiphospholipid antibody (Ab), anticardiolipin Ab, coagulation profile (Prothrombin time, APTT, bleeding time, clotting time, protein C and S levels), syphilis serology, ELISA for HIV, carotid Doppler, echocardiography, electrocardiogram and CT/MRI/MRA brain as and when needed.

Results

Over a period of five years, 32 patients of non-traumatic RAO were identified and their case records were studied. The age ranged from 11 to 39 years (Mean 27.62 ± 8.43 years, Median 28 years). Most of the patients (n=14, 44%) were aged between 31-40 years while nine (28%) patients were between 21-30 years of age. Nine (28%) patients were less than 20 years of age. In our study there were 21 (65.6%) males and 11 (34.4%) females. Bilateral involvement was found in three (10%) patients, while the right eye was involved in 19 (59%) patients and left eye in 10 (31%) patients.

In 35 eyes with RAO, 28 (87.5%) had central retinal artery occlusion (CRAO), three (9.4%) had branch retinal artery

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Manuscript received: 17.12.10; Revision accepted: 24.10.11

occlusion (BRAO), two (6.2%) each had cilioretinal artery occlusion (CLAO) and hemiretinal artery occlusion (HRAO). The various associated systemic as well as ocular abnormalities are shown in Table 1.

The visual acuity ranged from normal to no light perception [Table 2]. Out of the 28 eyes with CRAO, four eyes (14.3%) had good vision due to sparing of the cilioretinal artery. However, two eyes (7.2%) had no perception of light (NPL). All the three patients with BRAO had good vision between 20/20-20/60. Among the patients with CLAO, one patient had 20/32 vision due to foveal sparing while the second patient had poor vision due to associated central retinal vein occlusion (CRVO). Both the patients with HRAO had poor vision, due to choroidal infarction in one eye and associated CRVO in the other.

Among the 32 patients with RAO, 94% patients complained of sudden, painless diminution of vision, 12.5% patients had severe headache while 9.4% had history of floaters. Only 3% patients reported transient diminution of vision. Relative afferent papillary defect (RAPD) was present in 65.6% of patients with RAO. One patient with CRAO also had 360º neovascularization of iris (NVI) with neovascular glaucoma (NVG).

All patients presented with common features of RAO which included retinal edema (80%), box-carring and retinal artery attenuation (77.1%), and cherry red spot (62.8%). Other features included disc pallor (31.4%), retinal hemorrhages (14.2%), disc edema (8.6%) and neovascularization (8.6%). Visible embolus was present only in one eye (2.8%). Table 3 lists the fundus findings.

Table 4 illustrates the various systemic disorders present among these 32 patients. Hypercoagulable state was the most common, seen in 21 (65.6%) of 32 patients. Among all the disorders leading to hypercoagulable state, the commonest disorder noted was hyperhomocysteinemia in seven (21.9%) patients. Among these seven patients, in four patients no other abnormality was found except the hyperhomocysteinemia, despite extensive investigations. However, among the remaining three patients, one patient had associated raised ESR level, one patient had mitral valve prolapse (MVP), mitral

Table 1: Demographic profile and systemic abnormality in patients with retinal arterial occlusions

Demographic Profile		Type	Eye	Vision		Systemic Abnormality
Age	Sex			OD	OS	
32	M	CRAO	OD	20/40	20/32	Raised plasma homocysteine
37	F	CRAO	OU	20/32	20/50	Quantiferon Tb Test +ve; ANA for Trep. Pallidum +ve
19	F	CRAO	OD	PL +	20/20	Anticardiolipin Ab present
30	F	BRAO	OD	20/32	20/20	Mitral Regurgitation, MVP Raised ESR Levels Raised plasma homocysteine
20	M	CRAO	OS	20/16	NPL	Raised Antiphospholipid Ab
11	F	CRAO	OD	PL +	20/20	None
18	M	CRAO	OD	20/32	20/20	MR, Trivial AR, Rheumatic Heart Disease
13	M	CRAO	OD	HMCF	20/20	None
30	M	CLAO with CRVO	OD	20/250	20/20	Raised plasma homocysteine
39	M	CRAO	OS	CFCF	PL +	Raised cholesterol levels Raised ESR
19	M	CRAO	OD	CFCF	20/16	SLE; Raised CRP, ANA, ACE levels and ESR
36	M	CRAO	OD	HMCF	20/20	Raised cholesterol levels Smoker and Alcoholic
28	F	CRAO	OS	20/20	HMCF	Oral contraceptive pills
35	M	CRAO	OD	HMCF	20/20	Hypertensive Raised cholesterol levels
39	M	CRAO	OD	20/200	20/20	Hypertensive Embolus visible
18	M	CRAO	OD	PL +	20/200	Raised ESR Raised plasma homocysteine
31	M	CRAO	OD	20/400	20/20	Raised plasma homocysteine
37	M	CRAO	OS	20/20	HMCF	CVA, HT Basal ganglia infarct
21	M	CRAO	OS	20/20	HMCF	Obstructive hydronephrosis, HT
38	F	CRAO	OU	20/200	20/120	Rheumatic heart disease SLE Renal disorder ANA raised; ESR raised

Contd...

Table 1: Contd...

Demographic Profile		Type	Eye	Vision		Systemic Abnormality
Age	Sex			OD	OS	
34	M	CRAO	OS	20/20	PL +	Smoker, Alcoholic Thrombocytosis HT
32	M	CRAO	OD	PL +	20/32	Polycystic kidney disease Raised plasma homocysteine Concentric LVH, HT
21	F	CRAO	OD	CFCF	20/20	Raised ESR Raised antiphospholipid Abs
15	F	BRAO	OS	20/20	20/20	Raised ESR MVP Grade I MR, AR Rheumatic heart disease
33	M	CRAO	OU	CFCF	20/200	Protein S Deficiency
27	F	CRAO With NVG	OS	20/40	CFCF	Rheumatic heart disease, severe MR
28	F	BRAO	OD	20/60	20/40	HT, raised cholesterol levels Rheumatic heart disease
36	M	HRAO	OS	20/20	PL +	Polycythemia Raised ESR
27	M	HRAO with CRVO	OD	20/600	20/20	Raised plasma homocysteine
28	M	CRAO	OD	HMCF	20/20	Rheumatic heart disease MR, MVP
16	F	CRAO	OD	NPL	20/20	Raised ESR Anticardiolipin Ab
36	M	CRAO	OS	20/20	20/32	Raised cholesterol levels HT

CRAO: Central retinal artery occlusion, BRAO: Branch retinal artery occlusion, CLAO: Cilioretinal artery occlusion, HRAO: Hemiretinal artery occlusion, PL: Perception of light, NPL: No perception of light, TB: Tubercular, ANA: Antinuclear antibody, Ab: Antibody, MVP: Mitral valve prolapse, MR: Mitral regurgitation, AR: Aortic regurgitation, SLE: Systemic lupus erythematosus, CRP: C-reactive protein, ACE: Angiotensin-converting enzyme, CVA: Cerebrovascular accident, HT: Hypertension, LVH: Left ventricular hypertrophy

Table 2: Visual status in patients with retinal arterial occlusion

RAO	Visual Acuity			
	20/20- 20/60	20/80-20/400	CFCF- PL+	NPL
CRAO n= 28	4 (14.3)	5 (17.8)	17 (60.7)	2 (7.1)
BRAO n= 3	3 (100)	-	-	-
CLAO n= 2	1 (50)	1 (50)	-	-
HRAO n= 2	-	-	2 (100)	-

RAO: Retinal arterial occlusion, CRAO: Central retinal artery occlusion, BRAO: Branch retinal artery occlusion, CLAO: Cilioretinal artery occlusion, HRAO: Hemi-retinal artery occlusion, Figures in parentheses are in percentage

Table 3: Fundus findings in patients with retinal arterial occlusions

Fundus Findings	CRAO n= 28	BRAO n= 3	CLAO n= 2	HRAO n= 2
Cherry red spot	20 (71.4)	-	1 (50)	1 (50)
Retinal edema	23 (82.1)	2 (66)	2 (100)	1 (50)
Box-carring/ Arterial attenuation	21 (75)	2 (66.6)	2 (100)	2 (100)
Disc pallor	10 (35.7)	-	-	1 (50)
Disc edema	2 (7.1)	-	1 (50)	-
Retinal/ Disc hemorrhages	3 (10.7)	-	1 (50)	1 (50)
NVD/NVE	3 (1.6)	-	-	-
RPE changes at macula	2 (7.1)	-	-	-
Visible embolus	1 (3.6)	-	-	-
Choroidal involvement	-	-	1 (50) *	1 (50)**

*: Patient 32 had old healed serpiginous choroiditis, **: Patient 28 had choroidal infarction, CRAO: Central retinal artery occlusion, BRAO: Branch retinal artery occlusion, CLAO: Cilioretinal artery occlusion, HRAO: Hemi-retinal artery occlusion, Figures in parentheses are in percentage, NVD: Neovascularization at disc, NVE: Neovascularization elsewhere, RPE: Retinal pigment epithelium

regurgitation (MR) and a raised ESR and the third patient had a polycystic kidney, hypertension and left ventricular hypertrophy.

Hyperlipidemia was responsible for the hypercoagulable state in five patients (15.6%). Except for one, all the patients with hyperlipidemia also had hypertension. Among other entities leading to a hypercoagulable state, anticardiolipin antibody (Ab) and antiphospholipid antibody was present in two patients (6.2%) each. One patient (3.1%) each had polycythemia with hypertension, thrombocytosis with hypertension, obstructive hydronephrosis with hypertension and protein S

Table 4: Systemic abnormalities in patients with retinal arterial occlusions*

Hypercoagulable state	21(65.6)
Hyperhomocysteinemia	7 (21.9)
Hyperlipidemia	5 (15.6)
Polycythemia	1 (3.1)
Thrombocytosis	1 (3.1)
Protein S Deficiency	1 (3.1)
Anti-cardiolipin Antibody	2 (6.2)
Anti-phospholipid Antibody	2 (6.2)
Oral Contraceptive Pills	1 (3.1)
Renal Disorder	1 (3.1)
Isolated Hypertension	2 (6.2)
Cardiac Abnormality	6 (18.7)
Rheumatic Heart Disease	6 (18.7)
Mitral Regurgitation	5 (15.6)
Aortic Regurgitation	2 (6.2)
Mitral Valve Prolapse	3 (9.4)
Vasculitis	3 (9.4)
Systemic Lupus Erythematosus	2 (6.2)
Tuberculosis / Syphilis	1 (3.1)
No abnormality found	2 (6.2)

*Multiple abnormalities were present in some patients, Figures in parentheses are in percentage

deficiency. In our study, only one patient (3.1%) had a history of oral contraceptive pills (OCP) intake.

Isolated hypertension was noted in two patients (6.2%). Among these two patients, patient no. 15 had a visible embolus in the infero-temporal branch of the central retinal artery. Patient no. 18 had a history of cerebrovascular attack with basal ganglia infarcts reported on MRI scan.

Six patients (18.7%) had cardiac abnormality due to the presence of rheumatic heart disease. Valvular disease was present in all these patients. None of the patients had atrial myxoma.

Vasculitis was seen in three patients (9.4%). Systemic lupus erythematosus (SLE) was the causative factor in two patients while one patient with vasculitis tested positive for both Quantiferon tubercular test and antinuclear antibody (ANA) for Treponema pallidum.

In two patients (6.2%) no abnormality could be detected despite extensive investigations.

Discussion

The most common cause of RAO is embolic obstruction, with carotid artery being the commonest source of endogenous emboli. Other mechanisms include exogenous emboli, thrombotic, vasospastic and vasculitic events. Usually, RAO occurs in the mean age group of 60-65 years and predominantly affects males.[7,8] A few studies also show that RAOs occur in young patients and the etiology is multifactorial.[4,5] Our study shows males to be more affected (65.6%) than females (34.4%). Brown *et al.*,[4] showed a nearly equal number of males and females involved while Greven *et al.*,[5] showed a female predominance.

Table 5: Comparison with other studies

Features	Brown *et al.*[4]	Greven *et al.*[5]	Our study
No. of patients	27	21	32
M: F ratio	14:13	7:14	21:11
Age Range	9-29 (21.4)	23-38 (28 ± 2.9)	11-39 (27.6 ± 8.4)
Period of Study (years)	12	10	5
Pts with CRAO	33	23.8	87.5
Pts with BRAO	48.1	71.4	9.4
Pts with CLAO	18.9	4.8	6.2
Pts with HRAO	0	0	6.2
Systemic Associations			
Hypercoagulable State			
Hyperhomocysteinemia	0	0	21.9
Hyperlipidemia	0	0	15.6
Coagulation Disorders	29.6	9.5	9.4
Anticardiolipin/ Antiphospholipid Ab	0	9.5	12.5
Oral Contraceptive Pill use	11.1	19	3.1
Renal Disorder	0	4.8	3.1
Cardiac Abnormality	7.4	19	18.7
Isolated Hypertension	0	14.3	6.2
Vasculitis	7.4	9.5	9.4
Trauma	18.5	0	0
H/O Smoking/Alcoholism	0	23.8	6.2
Hemoglobinopathies	11.1	0	0
Normal Reports	14.8	9.5	6.2

Figures in parentheses are in percentage

In our study, hypercoagulable state was found to be a major cause responsible for 65.6% of retinal artery occlusions. Among all the conditions leading to a hypercoagulable state, hyperhomocysteinemia was the commonest cause found in 21.9% patients. Homocysteine is an amino acid derived from methionine, which can be converted into cysteine. The metabolic pathways involving homocysteine require vitamin $B_{12,}$ vitamin B_6 and folate for proper functioning. Various reports on hyperhomocysteinemia depict that arterial as well as venous vessels are involved in the disease.[9,10] The mechanism by which homocysteine causes vascular occlusion is presumed to be involving endothelial damage with increased endothelial tissue factor expression, activation of coagulation cascade, increased platelet adhesiveness and conversion of low-density lipoprotein cholesterol into smaller forms.[11] In most of the premature arteriosclerotic patients with hyperhomocysteinemia, methionine loading test shows a low cystathione synthase activity.[12] Elevated homocysteine and low methionine were found to be the risk factors for retinal venous occlusions in Indian population.[13] Unlike studies by Brown *et al.*,[4] and Greven *et al.*,[5] our study shows a larger number of patients with hyperhomocysteinemia. Table 5 shows the comparative data.

Hyperlipidemia was found in 15.6% patients in our study while there were none in either of the other two studies. High plasma lipoprotein concentration is an independent risk factor

for atherosclerosis and thrombosis.[14] Impaired fibrinolysis and atherogenesis induced by lipoprotein-A may play a role in the pathophysiology of CRAO.[15]

Coagulation disorders also play role in the pathogenesis of vascular occlusions. In their study Brown and associates[4] found 29.6% patients with coagulation disorder while in the study by Greven *et al.*,[5] 9% patients had coagulation disorders. In our study also 9% patients had coagulation disorders. Protein C and S are vitamin K-dependent plasma proteins that inhibit the clotting cascade at Factors V and VIII level. These can be inherited as autosomal dominant disorders or acquired due to liver disease.[16,17] Platelet coagulant activity has been related to RAO in the absence of other predisposing factors like HT and hyperlipoproteinemia.[18] The patients included in our study had protein S deficiency, thrombocytosis and polycythemia.

Antiphospholipid antibody syndrome occurs in people with either lupus anticoagulant or antibodies to phospholipids.[19] A study by Suvajach *et al.*,[20] showed that ocular arterial and venous occlusions were common in patients with antiphospholipid antibody syndrome and they suggest that all young patients with retinal artery occlusion should be investigated for the same. In our study 12.5% patients had antiphospholipid antibodies and anticardiolipin antibodies while Greven and associates[5] reported 9.5% patients with antiphospholipid antibodies.

Use of oral contraceptive pills (OCP) and hormonal therapy are associated with numerous ocular disorders, retinal vascular occlusion among them.[21,22] The use of OCP is more frequent in the Western population, therefore studies by Brown *et al.*,[4] and Greven *et al.*,[5] show a larger number of female patients with RAO and a history of OCP use (11.1% and 19% respectively) as compared to our study (3.1%).

A case report on idiopathic renal infarction causing CRAO has been published even though much data to support the role of kidney disorders causing retinal vascular occlusion is unavailable.[23] A comparable number of patients in our study (3.1%) and in that by Greven *et al.*,[5] (4.8%) were found to have renal disorder leading to RAO.

Cardiac causes for the occurrence of RAO have been documented. Cardiac abnormalities were found in six (18.7%) patients in our study. Among them mitral regurgitation was found in five (15.6%) and mitral valve prolapse in three (9.4%) patients. These have been implicated as etiological factors for vascular occlusions.[24] The vascular occlusion follows a calcific, platelet or fibrinous embolus. But none of our patients with cardiac abnormality had any visible embolus. Rheumatic heart disease (RHD) has also been considered as an etiological factor predisposing to retinal vascular occlusions.[25,26] In our study 18.7% patients had RHD.

RAO secondary to vasculitis has been encountered in many conditions. A study by Au and O'day has shown presence of retinal artery occlusion in 4.5% patients of systemic lupus erythematosus (SLE).[27] They further suggest that the incidence of retinal arterial occlusion was greater than venous occlusion (P=0.0338). Vasculitis was diagnosed to be the etiological factor in 9.4% patients in our study as compared to 7.4% and 9.5% in the other two studies.[4,5]

Smoking and alcoholism are considered as risk factors in the development of emboli causing retinal arterial occlusions. In a study by Hayreh and associates,[28] in patients who smoked, a high prevalence of RAO was seen. In this subgroup of patients, CRAO was common in males while BRAO was common in females.

Sickle cell disease is a major cause of thromoboembolic events in young patients.[29] It is imperative to do a hemoglobin electrophoresis in all young patients with RAO. Though sickle cell trait is a benign condition numerous case reports and studies show that under stress, hypoxia due to trauma or concomitant systemic disease it becomes a pathological factor.[30] Though none of the patients in our study had hemoglobinopathies 11% patients in the study by Brown and associates[4] had sickle cell disease.

Studies have shown that isolated hypertension is a major risk factor leading to vascular occlusions.[31,32] It is more pronounced in the elderly age group but the younger generation too is being affected with increased incidence of retinal vascular occlusions.[33] Our study had 6.2% patients with isolated hypertension as compared to 14.6% patients in the study by Greven and associates.[5]

Despite extensive investigations, in two patients (2.6%) there was no evidence of any systemic or ocular abnormality which could be accounted for the presence of retinal artery occlusion.

Conclusion

We found major differences in the causative factors responsible for retinal arterial occlusions in young Indian patients as compared to those seen in the Western population. The commonest cause of retinal arterial occlusion in young adults of Indian origin was found to be hyperhomocysteinemia. This was conspicuously absent in the two reported series from the Western population. The highly prevalent nutritional deficiency in the Indian subcontinent is likely responsible for the hyperhomocysteinemia. Ethnic variations may also be responsible. In contrast, coagulation disorders, cardiac abnormalities, hemoglobinopathies and oral contraceptive use were cited as the major causes of retinal arterial occlusions in the Western population. Further studies are warranted to analyze these ethnic differences in detail. It would be interesting to see whether any genetic predisposition to hyperhomocysteinemia and retinal arterial occlusions exists in the Indian population.

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Cite this article as: Ratra D, Dhupper M. Retinal arterial occlusions in the young: Systemic associations in Indian population. Indian J Ophthalmol 2012;60:95-100.

Source of Support: Nil. **Conflict of Interest:** None declared.