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Risk factors in central retinal vein occlusion and activated protein C resistance

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ABSTRACT: Introduction. *Central retinal vein occlusion (CRVO) tends to be a disease of older individuals, with some known major risk factors, and activated protein C resistance seems to be one of the causes in younger patients. In this study, we reviewed risk factors including activated protein C resistance in a series of patients with CRVO.*
Methods. *Twenty-four patients with a diagnosis of CRVO presenting either acutely or for a follow-up visit during the study period, were enrolled. Ages ranged between 31 and 83 years (mean 59.7). The risk factors, presence of ischemia, the results of biochemical serological and hematological tests, especially activated protein C resistance (APC-R), were analysed.*
Results. *In 17 patients (71%) one or more of the following risk factors existed: hypertension, diabetes, oral contraceptive usage, family history of thrombosis, and previous operation. In 40% of the eyes, there were ischemic changes. Serum triglycerides were high in 4 of 21 patients (19%) and cholesterol and urea were high in 10 of 21 patients (19%). APC-R was found in 6 out of 24 patients (25%).*
Conclusions. *Besides known predisposing factors like hypertension, diabetes, glaucoma and hyperlipidemia, APC-R seems to be a risk factor for CRVO at all ages. (Eur J Ophthalmol 1999; 9: 43-9)*

KEYWORDS: Retinal vein occlusion, Activated protein C resistance, Coagulation factors

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INTRODUCTION

Central retinal vein occlusion (CRVO) is a common disease caused by a thrombus in the central retinal vein, in the area of the lamina cribrosa (1). High central retinal venous pressure, delayed perfusion time, retinal vascular tortuosity, hemorrhage and edema, cotton-wool spots, papiledema and macular edema are typically seen in CRVO.

Many systemic factors such as hypertension, diabetes mellitus and cardiovascular diseases are believed to affect vascular flow or cause vascular wall abnormalities, contributing to the development of CRVO especially in older patients (2), but associated systemic disease is much less frequent in patients under 50 years of age (3).

Systemic disease may influence thrombus formation in the central retinal vein through external compression, and primary thrombus formation through stasis or degenerative or inflammatory disorders of the vein itself (2). Anatomical factors such as shorter axial length can also be considered as a risk factor (4), perhaps causing physical blockage in the vein because of the smaller, narrower lamina cribrosa and scleral canal. CRVO has been described in cases with increased blood viscosity, hyperviscosity syndromes, increased platelet aggregability and other conditions that affect the clotting cascade and create a potentially hypercoagulable state, including protein S, C, antithrombin III deficiency and external hormonal supplementaton (5).

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A significant proportion of CRVO patients may have activated protein C resistance (APC-R) (6, 7). First described in 1993, this is a major hereditary risk factor for venous thromboembolism (8). In at least 90% of patients, APC-R is caused by a single point mutation in the Factor V gene (9, 10). This mutated Factor Va, also called Factor V Leiden, is resistant to APC-mediated inactivation, causing increased thrombin generation and a hypercoagulable state.

In this study, we reviewed 24 patients diagnosed with CRVO, considering risk factors and coagulation studies, especially APC-R.

PATIENTS AND METHODS

Twenty-four patients applying to the 3rd Eye Clinic of Ankara Numune Hospital during late 1996 and early 1997 were included in the study. The patients either presented acutely or had been diagnosed previously and were attending for a follow-up visit. The diagnostic criteria for CRVO were; scattered intraretinal hemorrhages, venous dilatation and tortuosity in all quadrants and papiledema. Hypertension, diabetes mellitus, immobilization, oral contraceptive usage, family history of thrombosis, previous operation and smoking were noted. The laterality of CRVO, presence of glaucoma, rubeosis iridis, retinal ischemia and any other eye disease were recorded. Cases with neovascularization of the anterior and posterior segment were classified as ischemic. In patients without any neovascularization, the ischemic state was determined by fundus flourescein angiography.

Blood samples were taken for analysis of serum triglycerides, cholesterol, fasting blood glucose, urea and liver function tests, and the results were considered elevated if they exceeded the normal values of the testing laboratory. Serological tests included anti-streptolysin-O (ASO), c-reactive protein (CRP), rheumatoid factor (RF) and antinuclear antibody. Hematological tests included erythrocyte sedimentation rate (ESR), hemoglobin (Hb), hematocrit (Htc), activated partial thromboplastin time (aPTT), fibrinogen, protein C, protein S and activated protein C resistance (APC-R) assays. Functional proteins C and S were measured by a clotting assay. Functional APC-R is expressed as the ratio of aPTT in the presence of APC to aPTT in its absence.

RESULTS

The patients' characteristics are summarized in Table I. Sixteen men and eight women, aged 31 to 83 years (mean 59.7 years) were studied. Eight were smokers, seven had hypertension, four diabetes, three immobilization, five had a history of previous operation (hernia, epidermal grafting, surgery on the vesicourethral system and orthopedic surgery) and one used oral contraceptives. Three patients suffered from asthma and one from arrythmia.

The mean time from onset of the occlusion to the study was 197.3 days (range 4-720 days). None of the patients were receiving any treatment affecting the coagulation system. Visual acuities at the time of the study ranged from lack of any perception to 0.5 (Snellen acuity). In one of the 24 patients (No. 7), CRVO was bilateral (4.16%). Otherwise the ratio of involvement of the right eye to the left was 9/10. Nine out of 25 eyes (41.6%) had ischemic changes. Four eyes developed neovascular glaucoma and two eyes were being treated for primary open-angle glaucoma. Four eyes developed rubeosis iridis and one developed neovascularization of the disc.

Serum triglyceride levels were increased in four patients (normal range 25-160 mg/dl), fasting blood glucose levels (normal range 70-110 mg/dl) were high in three (one had diabetes mellitus) and serum cholesterol was elevated in ten (normal range 130-200 mg/dl). Liver function results were within normal limits in all patients. Among serological tests, RF was positive in one patient, ASO and CRP were high in one patient each. Antinuclear antibody was positive in three patients.

The results of some of the hematological and coagulation tests are presented in Table II. Four patients had anemia (normal ranges; Hb 12-16 g/dl for females, 13.5-18 g/dl for males, Htc 37-51%). White blood cell count, platelet count, aPTT levels, prothrombin time and activity were within the normal ranges. Fibrinogen was high in one patient (normal range 2-4 g/l). Protein C and protein S activities were within normal limits (normal ranges: protein C 60-175%, protein S 73-210%, our findings: protein C 84.95 ± 27.38%, protein S 149.75 ± 56.50%).

APC-R was considered positive for results less than 1.80 and was found in six patients (25%). The average ratio for normals was 2.52 ± 0.63, compared to

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TABLE I - MAIN CHARACTERISTICS OF 24 CRVO PATIENTS

Patient	Sex/age	Risk factors	Smoking	Eye	Glaucoma	Rubeosis	Ischemia	Coexisting eye disease
1	52/M	HT	-	R	neovascular	+	+	-
2	41/F	-	-	R	-	-	-	-
3	60/F	-	-	-	-	-	-	
4	46/M	previous operation	-	R	-	-	-	-
5	74 M	previous operation	+	R	POAG	-	+	-
6	57/M	HT-family history of thrombosis	-	-	-	-	-	
7	55/F	DM	-	R L	- -	- -	- -	- -
8	75/M	arhythmia	-	L	-	-	-	-
9	64/M	HT-DM-immobilization previous operation	-	L	-	-	+	
10	65 M	HT-immobilization family history of thrombosis	+	L	-	-	-	-
11	76/F	DM-immobilization	-	L	-	-	-	POAG-cataract
12	63/M	-	-	L	neovascular	+	+	-
13	66/M	HT	-	R	phytisis bulbi (enucleation)			
14	34/M	-	+	L	-	-	+	-
15	31 /M	asthma-dermatomyositis	-	L	-	-	-	-
16	32/F	oral contraceptive use-family history of thrombosis	-	R	-	-	-	optic atrophy
17	68/M	-	+	R	-	-	-	branch arterial occlusion in the other eye
18	62/F	HT	-	R	-	-	-	-
19	83/M	-	-	L	-	-	+	pseudo-exfoliation
20	70/M	asthma	+	L	neovascular	+	+	pseudo-phakia
21	71 /M	-	+	L	-	-	+	pseudo-exfoliation
22	67/M	HT-DM-asthma-immobilization	+	R	neovascular	+	+	cataract
23	52/F	previous operation	-	R	-	-	-	-
24	69/F	previous operation	-	R	-	-	+	central retinal artery occlusion

CRVO: Central retinal vein occlusion; HT: Hypertension; DM: Diabetes; R: Right; L: Left; M: Male; F: Female; POAG: Primary open-angle glaucoma

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TABLE II - RESULTS OF SOME HEMATOLOGICAL TESTS

Patient	Hb(g/dl)	Htc (%)	Platelet count (x1000 / mm^3)	APC-R
1	14.1	42.4	303	1.95
2	8.8	29.0	470	1.83
3	14.6	43.5	336	1.24
4	15.3	43.8	263	3.71
5	13.7	40.1	212	1.63
6	15.4	46.6	277	2.25
7	9.57	28.6	319	1.40
8	15.6	45.5	204	3.18
9	12.4	37.4	423	2.37
10	13.9	39.2	204	2.29
11	8.5	25.1	260	2.09
12	16.4	48.7	288	1.73
13	14.6	42.8	381	1.97
14	15.9	48.3	335	3.95
15	15.2	45.1	275	2.22
16	12.6	39.0	233	2.05
17	14.9	45.2	162	3.04
18	14.4	41.1	256	2.02
19	14.4	39.5	201	2.21
20	14.9	44.3	257	3.0
21	15.3	47.2	225	3.07
22	14.7	43.1	126	2.22
23	14.2	42.8	258	1.63
24	12.8	40.3	296	1.67

Hb: Hemoglobin; Htc: Hematocrit; APC-R: Activated protein C resistance

1.55 ± 0.18 for abnormals. In patients with APC-R reanalysis after plasma dilution by a ratio of 1:5 showed the same results. The patients with APC-R were all over 50 years of age. One was a smoker, three had had previous surgery, one had diabetes mellitus and two had no known risk factors. The diabetic patient had bilateral involvement. Ischemic findings were present in two of the APC-R positive patients.

DISCUSSION

CRVO tends to be a disease of older individuals, 90% of the patients being over 50 (1). In our study group 70% of patients were over 50, the mean age of the group being 59.7. Mean ages ranged between 62 and 64 in similar studies (4, 11, 12) and in a case-control study group, 60% of the patients were 55-74 years old (13). Our patients were 66.6% men and a slight preponderance of males has been reported in other studies (2, 11, 12).

Recent reports emphasize the importance of systemic hypertension and history of diabetes as risk factors for CRVO and hemiretinal vein occlusion (14). In our study, the rates were 8.3% for diabetes, 20.8% for hypertension and 8.3% for both diabetes and hypertension, the percentages being lower than in other studies (4, 11, 12, 15). Oral contraceptives may be associated with the development of CRVO due to coagulation and vessel wall changes leading to secondary thrombosis (3). Only one of our patients had a history of birth control pill use, but the detection of an association with CRVO may be limited because of the infrequent use of birth control pills in Turkey. Smoking may induce intrinsic changes in vessel walls or alterations in blood constituents, and has been linked to CRVO. In our study 33.3% of the patients were smokers. Although CRVO is typically unilateral, it has been reported to be bilateral in 1-14% of the patients (1). In our group, one patient had bilateral involvement.

The association between increased intraocular pressure and CRVO may be attributed to mechanical and hemodynamic changes at the optic disc head, especially the lamina cribrosa (11). The incidence of chronic open angle glaucoma in patients with CRVO ranged from 2-82% (1, 4, 11, 12, 15). Two of our patients had POAG (8.3%).

An association between hyperlipidemia and CRVO was found in a series of young adults with CRVO (1). Out of five young patients in our study three had hyperlipidemia and, as a whole, 13 of the 24 patients showed increased levels of either triglycerides or cholesterol or both. Blood cholesterol may be increased in patients with retinal vein occlusion, although not higher than controls (16).

The anatomical conditions predisposing the central retinal vein to thrombus formation result in blood flow turbulence and slowing within the vein, also activating the clotting cascade. CRVO has also been associated with central retinal artery occlusion (5). One of our patients had this combination.

When CRVO was compared with branch retinal vein occlusion (BRVO), increased ESR were significantly more prevalent in the former (17). In 13 of the 24 patients (54%) ESR levels were higher than normal (normal range 2-15 mm/s, mean 28.3 mm/s, range 2-77

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mm/s). The association between ESR and CRVO may possibly be due to changes in shear forces and plasma viscosity (11).

APC-R, a newly recognized condition, is present in approximately half of the thrombosis-prone families and has an autosomal-dominant inheritance pattern with variable penetrance (18). One study reported a higher percentage of patients with CRVO (12%) and APC-R than controls (5%) (7) and in another study considering young CRVO patients, 26% of all the cases and 36% of the patients younger than 45 years were resistant to APC (6). Considering patients older than 50 years of age with CRVO, APC-R was similar to the normal incidence in the same geographic area (10-11%) and no mutation was found (19). APC-R was found in 6 of the 24 patients in our study (25%) but factor V mutation was not analyzed because it was not available when the study was in progress. The mean APC ratio was 2.29 ± 0.71; in the abnormal group it was 1.55 and in the normal group 2.52. The cut-off for the diagnosis of APC-R depends on the laboratory or the method used (16, 17, 20).

APC-R, associated with a mutation in the FV gene, is a common, strong risk factor for thrombosis (21). A modified test is recommended, with dilution of the patient's plasma in factor V-deficient plasma because of its effectiveness for screening for factor V Leiden (22). In our CRVO group, although no genetic study could be done, six patients were APC-R positive (also with the modified method), and four of these presented associated underlying pathologies.

It is proposed that especially in young CRVO patients if initial screening for APC-R is negative, then screening should be done for lupus anticoagulant, anticardiolipin antibody, protein C, protein S and antithrombin III and a DNA-based assay for genetic defects is necessary for APC-R positive patients (23). In patients with this mutation the risk of developing venous thromboembolism is 2.7-10 fold for heterozygotes, 50-100 fold for homozygotes (24, 25); the increased risk of thrombosis is life-long and and increases with age. The coexistence of other genetic defects and certain environmental risk factors increase the risk of thrombosis (26). In patients with APC-R who suffer multiple thrombotic episodes, life-long anticoagulation may be required (16, 18), but the decision to provide indefinite anticoagulation for patients with APC-R and a single thrombotic event must be made on a case-by-case basis (27).

Hypertension, diabetes, atherosclerotic conditions, hyperviscosity states, rheological factors, smoking, oral contraceptive usage, immobilisation, operations and glaucoma are all factors contributing to thrombus formation in CRVO cases. APC-R should also be investigated since a large proportion of patients have positive results and prophylaxis can be planned.

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REFERENCES

1. Gutmann FA. Central retinal vein occlusion. Supplement to Chibret International Journal of Ophthalmology. Philadelphia: JB Lippincott Company, 1989; 91: 101.
2. Elman MJ, Bhatt AK, Quinlan PM, Enger C. The risk for systemic vascular diseases and mortality in patients with central retinal vein occlusion. Ophthalmology 1990; 97: 1543-8.
3. Fong ACO, Schatz H. Central retinal vein occlusion in young adults. Surv Ophthalmol 1993; 37: 393-417.
4. Arltürk N, Oge I, Erkan D, Süllü Y, Mohajery F. Relation between retinal vein occlusions and axial length. Br J Ophthalmol 1996; 80: 633-6.
5. Elman MJ. Systemic associations of retinal vein occlusion. Int Ophthalmol Clin 1991; 31 (3): 15-22.
6. Larsson J, Olafsdottir E, Bauer B. Activated protein C resistance in young adults with central retinal vein oc-

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clusion. Br J Ophthalmol 1996; 80: 200-02.
7. Williamson TH, Rumley A, Lowe GDO. Blood viscosity, coagulation, and activated protein C resistance in central retinal vein occlusion: a population controlled study. Br J Ophthalmol 1996; 80: 203-8.
8. Dahlback B, Carlsson M, Svensson PJ. Familial thrombophilia due to previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: Prediction of a cofactor to activated protein C. Proc Natl Acad Sci USA 1993; 90: 1004-8.
9. Bertina RM, Koeleman BPC, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994; 369: 64-7.
10. Voorberg J, Roelse J, Koopman R, et al. Association of idiopathic venous thromboembolism, with a single point mutation at ARG 506 of factor V. Lancet 1994; 343: 1535-6.
11. Appiah AP, Trempe CL. Differences in contributory factors among hemicentral, central, and branch retinal vein occlusion. Ophthalmology 1989; 96: 364-6.
12. Arend O, Remky A, Jung F, Kiesewetter H, Reim M, Wolf S. Role of rheological factors in patients with acute central retinal vein occlusion. Ophthalmology 1996; 103: 80-6.
13. The Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion. Arch Ophthalmol 1996; 114: 545-4.
14. Sperduto RD, Hiller R, Chew E, et al. Risk factors for hemiretinal vein occlusion: comparison with risk factors for central and branch retinal vein occlusion: the eye disease case-control study. Ophthalmology 1998; 105: 765-71.
15. Lang GE, Spraul CW. Risk factors for retinal occlusive diseases. Klin Monatsbl Augenheilkd 1997; 211: 217-26.
16. Williamson TH. Central retinal vein occlusion: What's the story? Br J Ophthalmol 1997; 81: 698-704.
17. Appiah AP, Trempe CL. Risk factors associated with branch vs central retinal vein occlusion. Ann Ophthalmol 1989; 21: 153-5, 157.
18. Brey RL, Coull. Cerebral venous thrombosis, role of activated protein C resistance and factor V gene mutation. Stroke 1996; 27: 1719-20.
19. Larsson J, Sellman A, Bauer B. Activated protein C resistance in patients with central retinal vein occlusion. Br J Ophthalmol 1997; 81: 832-4.
20. Trope GE, Lowe GDO, McArdle BM, et al. Abnormal blood viscosity and haemostasis in long-standing retinal vein occlusion. Br J Ophthalmol 1983; 67: 137-42.
21. Koeleman BP, Reitsma PH, Allaart CF, Bertina RM. Activated protein C resistance as an additional risk factor for thrombosis in protein C deficient families. Blood 1994; 84: 1031-5.
22. Vine AK, Samama MM. Editorial: Screening for resistance to activated protein C and the mutant gene for factor V:Q506 in patients with central retinal vein occlusion. Am J Ophthalmol 1997; 124: 673-6.
23. Hunt BJ. Activated protein C and retinal vein occlusion. Br J Ophthalmol 1996; 80: 194.
24. Rosendaal FR, Koster T, Vanderbrouke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 1995; 85: 1504-8.
25. Ridker PM, Hennekes CH, Lindpaintner K, et al. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke and venous thromboembolism in apparently healthy men. N Engl J Med 1995; 332: 912-7.
26. Hellgren M, Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thromboembolism associated with pregnancy and oral contraceptives. Am J Obstet Gynecol 1995; 173: 210-3.
27. Dulli DA, Christopher CL, Williams EC, Schutta HS. Cerebral venous thrombosis and activated protein C resistance. Stroke 1996; 27: 1731-3.