

Coagulation disorders and the risk of retinal vein occlusion

A subgroup analysis

Claudia Kuhli-Hattenbach¹; Inge Scharrer^{2,3}; Marc Luchtenberg¹; Lars-Olof Hattenbach^{1,4}

¹Klinik für Augenheilkunde, Klinikum der Johann-Wolfgang-Goethe-Universität Frankfurt am Main, Germany; ²Medizinische Klinik I, Klinikum der Johann-Wolfgang-Goethe-Universität Frankfurt am Main, Germany; ³III. Medizinische Klinik, Johannes-Gutenberg-Universität, Mainz, Germany; ⁴Augenklinik des Klinikums Ludwigshafen, Ludwigshafen, Germany

Summary

Over the past years, there has been a dramatic increase in the number of identifiable causes of thrombophilia. However, to date, there are no large, prospective studies to assess an optimal, cost-effective approach with regard to screening and case finding for thrombophilic risk factors in patients presenting with retinal vessel occlusion. Two hundred twenty-eight patients with retinal vein occlusion (RVO) and 130 age-matched healthy controls were prospectively screened for thrombophilic risk factors. Both cohorts were divided into three subgroups, depending on the patients' age at the time of the RVO or a previous thromboembolic event. Patient age ≤ 45 years was associated with a high prevalence of coagulation disorders ($p < 0.0001$). Among patients ≤ 45 years and > 45 to ≤ 60 years, a family history of thromboembolism was strongly associated with the presence of thrombophilic disorders. The absence of cardiovascular risk factors was found to be a strong pre-

dictor for the presence of coagulation disorders in all patient groups (≤ 45 years, $p = 0.003$; > 45 to ≤ 60 years, $p = 0.0008$; > 60 years, $p = 0.001$). Multivariate analysis revealed the presence of resistance to activated protein C ($p = 0.014$), antiphospholipid antibodies ($p = 0.022$), and deficiency of the anticoagulant proteins ($p = 0.05$) as independent risk factors for the development of RVO among patients ≤ 45 years. Our results indicate that thrombophilic disorders are associated with the development of retinal vein occlusion in patients ≤ 45 years by the time of the RVO or a previous thromboembolic event, in patients with a family history of thromboembolism, or in patients without cardiovascular risk factors.

Keywords

Retinal vein occlusion, APC resistance, thrombophilia, inherited coagulation disorders, risk factors

Correspondence to:

Claudia Kuhli-Hattenbach, MD
Department of Ophthalmology
Johann Wolfgang Goethe University Hospital
Theodor-Stern-Kai 7
60590 Frankfurt am Main, Germany
Tel.: +49 69 6301 5721, Fax: +49 69 6301 7795
E-mail: kuhli@med.uni-frankfurt.de

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Introduction

Inherited thrombophilic defects have been shown to be prevalent risk factors for venous thromboembolism (VTE) in the general population (1–3). However, the potential impact of coagulation abnormalities on retinal vascular occlusive diseases, individually and in combination with cardiovascular risk factors, remains unclear (4–15). Over the past years, several studies have strengthened the hypothesis that coagulation disorders are pathogenic for retinal vein occlusion (RVO). Examples include resistance to activated protein C (APC), heparin cofactor II deficiency, hyperhomocysteinaemia, and deficiencies in the anticoagulation system (protein C [PC], protein S [PS], or antithrombin [AT]) (4–15).

Because the average patient age by the time of a RVO is about 65 years (16), the majority of retinal vascular occlusions are primarily secondary to underlying cardiovascular diseases (17). As clinical thromboembolism is multicausal, resulting from the interaction of multiple genetic factors and environmental influences, it seems

plausible that screening for thrombophilic disorders in such patients should be selective, focusing on individuals with thromboembolic events at young age or a family history of thrombosis.

To date, there are no large, prospective studies to assess an optimal, cost-effective approach with regard to screening and case finding for thrombophilic risk factors in patients presenting with RVO. Moreover, the question of whether RVO patients with thrombophilic disorders should receive anticoagulant treatment remains unclear. The task of determining the appropriate therapeutic approach in RVO is complicated because severity of the disease and intervals between the patients' first symptoms and presentation differ widely and vision loss is related to the extent of macular damage from intraretinal edema, haemorrhage or capillary non-perfusion.

In the present study, we sought to investigate whether there is a relationship between various thrombophilic disorders and the development of RVO. Moreover, in light of the substantial expense of a comprehensive screening for thrombophilic defects (18), the

purpose of our study was to provide clinical guidelines for a selective thrombophilia screening of RVO patients.

Methods

Patients and study design

We prospectively investigated a series of 228 patients who presented to our institution with RVO, and a control group of 130 healthy volunteers matched for age and gender. Performance of the study and data accumulation adhered to the requirements of our institutional review board. Research adhered to the tenets of the Declaration of Helsinki.

In all patients, complete bilateral ocular examinations including best-corrected visual acuity were conducted. Central retinal vein occlusion (CRVO) was defined as venous dilatation and tortuosity with scattered intraretinal haemorrhages in all four quadrants. The diagnosis of hemicentral retinal vein occlusion (HRVO) required venous dilatation and tortuosity with haemorrhages in two quadrants. Branch retinal vein occlusion (BRVO) was defined as venous dilatation and tortuosity with haemorrhages in the area of an occluded vein. Each subject's weight and height were recorded, and resting blood pressure was measured. Data on demographic and lifestyle variables, medical history including family and personal history of thromboembolic disease, history of diabetes mellitus, arterial hypertension, hyperlipidaemia, smoking habits, alcohol consumption, and use of medications including oral contraceptive and hormone replacement therapies were obtained by means of a standardised questionnaire. Subjects were classified as having a family history of thromboembolic disease if they had at least one parent or sibling with a history of thromboembolism before the age of 45. All patients underwent a fasting (≥ 8 hours) plasma glucose test. At repeated blood glucose levels >99 mg/dl, oral glucose tolerance testing (OGTT) was performed. The diagnosis of diabetes mellitus was made at blood glucose levels ≥ 200 mg/dl one hour after the intake of 75 g of oral glucose on more than one testing occasion. All patients underwent repeated resting blood pressure measurements. The diagnosis of previously unknown arterial hypertension required repeated blood pressure levels of $\geq 140/90$.

Patients were compared with a cohort of 130 healthy subjects. Both groups did not differ significantly with respect to age, sex, cigarette smoking, body mass index, and weekly alcohol intake. Both cohorts were subdivided into three subgroups (≤ 45 years, >45 to 60 years or >60 years), depending on the following criteria: Patients' age at the time of the RVO or a first thromboembolic event, or controls' age at the time of recruitment. In addition, presenting characteristics such as cardiovascular risk factors or history of familial thromboembolism were used to subdivide patients and to investigate their diagnostic value.

Laboratory analysis

After the diagnosis of CRVO, HRVO or BRVO was made, each patient was sent for a comprehensive thrombophilia screening, including protein C activity, free and total protein S, antithrombin activity and antigen, heparin cofactor II, histidin-rich glycoprotein, resistance to APC sensitivity ratio and genetic testing for factor V Leiden mutation if appropriate, antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies), factor VIII activity, lipoprotein (a), factor XII activity, prothrombin time (PT) and activated partial thromboplastin time (APTT). Laboratory tests for plasma homocysteine and prothrombin mutation were not available for all of the patients owing to commencing examination of these variables at a later stage in the study. Therefore, both coagulation disorders were excluded from subsequent statistical analysis. Blood samples were obtained three to six months after diagnosis of RVO. All study subjects rested for at least 20 minutes before blood sampling. Fasting venous blood was sampled from the antecubital vein for the laboratory evaluation and anticoagulated with sodium citrate. Plasma was separated from blood cells by centrifugation, snap-frozen in aliquots, and stored at -70°C until assay. Genomic DNA was isolated from leukocytes by standard methods.

We used enzyme-linked immunosorbent assays for the detection of immunoglobulin G (Ig) and IgM anticardiolipin antibodies (ACA) (Vareliisa Cardiolipin Antikörper Test[®], Pharmacia & Upjohn, Freiburg, Germany), and total and free protein S activity (Asserachrom[®] Protein S, Diagnostica Stago, Asnieres-Sur-Seine, France) in patients' serum. Protein C activity (Coamatic Protein C,

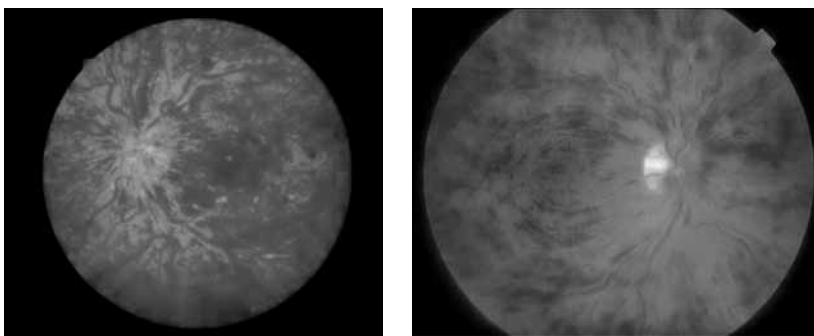


Figure 1 (left): Fundus photograph of a 47-year-old man demonstrating CRVO (OS) associated with homozygous resistance to APC. He had a remarkable medical history of deep-vein thrombosis at the age of 33 years. Based on the diagnosis of homozygous resistance to APC he was started on anticoagulation therapy with warfarin.

Figure 2 (right): Fundus photograph of the same patient two years later revealing CRVO in his contralateral eye (OD). By this time, anticoagulation therapy had been discontinued for one year.

Chromogenix, Mölndal, Sweden) and functional antithrombin activity (IL-Test-Antithrombin; Instrumentation Laboratories, Milano, Italy) was determined with a chromogenic substrate. Immunologic AT assays for the quantitative determination of antithrombin in human citrated plasma, using the Laurell technique (19), were performed as previously described (Immune serum Assera AT; Diagnostica Stago). APC sensitivity ratios in patients and controls were determined with the Coatest APC Resistance-C kit (Chromogenix) on an ACL research coagulometer (Instrumentation Laboratory, Warrington, UK). The phenotype of functional APC resistance was confirmed by genetic testing for the factor V Leiden mutation, defined as a single base transition (G to A) at position 1691 of the factor V gene, resulting in the amino acid sequence of the mature protein from Arg to Gln at position 506, by polymerase chain reaction (PCR). APTT, factor VIII activity, and factor XII activity were measured in an ACL 300 research coagulometer (Instrumentation Laboratories) using a one-stage clotting assay with a cephalin-kaolin reagent (Industry Laboratories) and a specific factor VIII or factor XII deficient plasma (Instrumentation Laboratories). Histidine-rich glycoprotein (HRG) and heparin cofactor II were determined using the Laurell technique. If laboratory results were abnormal, testing was repeated at follow-up at three months, six months, and 12 months.

Statistical analysis

Testing for any relationship between age or risk factors and the presence of thrombophilic disorders was performed using Fisher's exact test. All tests were two-tailed, and acceptable significance was recorded when p -values were <0.05 . Analyses were performed with the SAS statistical software package (SAS Institute, Inc., Cary, NC, USA). Moreover, we performed a multivariate logistic regression analysis using a backward stepwise model to compare the prevalences of thrombophilic risk factors among patients and controls.

Multivariate logistic regression analysis was used to estimate the association of independent risk factors and the presence of thrombophilic disorders among patients. We used two separate regression models. The first included thrombophilic risk factors (resistance to APC, factor XII, aPL, deficiencies of the anticoagulant proteins PC, PS, AT, heparin cofactor II, hyperfibrinogenaemia, increased plasma levels of Lp(a) and factor VIII) among the young patients and age-matched controls. The second analysis included the following possible risk factors among all patients: absence of cardiovascular risk factors, personal or family history of thromboembolism, gender, and age. Acceptable significance for the elimination of variables was recorded when p -values were <0.1 . All logistic models were estimated with use of the BIAS statistical software package (version 8.0.5, epsilon, Hochheim Darmstadt, Germany).

Results

Of the 228 patients enrolled in the current study, 80 (35.1%) subjects aged 45 years or less by the time of the RVO or a previous thromboembolic event. A total of 90 (39.5%) patients aged >45 years to 60 years and 58 (25.4%) subjects aged >60 years. Baseline characteristics of patients and controls are outlined in ► Table 1.

The diagnosis of CRVO was made in 168 patients, whereas HRVO was found in one patient and BRVO was observed in 59 patients. We observed a high prevalence of thrombophilic risk factors among patients with RVO or a first thromboembolic event prior to the age of 45 years: Of the 80 patients ≤ 45 years, 40 (50%) had thrombophilic defects compared with 11 of 84 controls (13.1%) in the same age group. This difference was statistically significant ($p < 0.0001$). Moreover, patients in the group ≤ 45 years were more likely to have coagulation defects than patients in the older age groups (50% vs. 25.5%; $p = 0.0014$; 50% vs. 25.9%; $p = 0.0089$). Twenty-three of 90 (25.5%) patients >45 to 60 years and 16 of 58 (27.6%)

Table 1: Patients and controls characteristics.

Characteristics	Patients				Controls			
	Total group	P ₁ (≤ 45 years ¹)	P ₂ ($>45 \leq 60$ years ¹)	P ₃ (>60 years ¹)	Total group	C ₁ (≤ 45 years ²)	C ₂ ($45 \leq 60$ years ²)	C ₃ (>60 years ¹)
Number of patients [n*]	228	80	90	58	130	84	24	22
Mean age [years]	51.2	36.4	52.8	69.3	42.7	32.6	53.4	69.8
Age range [years]	16 – 85	16 – 45	46 – 60	61 – 85	20 – 88	20 – 45	46 – 60	61 – 88
Male [n]	94	37	33	24	60	39	11	10
Female [n]	134	43	57	34	70	45	13	12
CRVO [n]	168	69	63	36	-	-	-	-
HRVO [n]	1	1	0	0	-	-	-	-
BRVO [n]	59	10	27	22	-	-	-	-

*Number of patients and controls. ¹age at time of RVO or first thromboembolic event. ²age at time of examination. CRVO, central retinal vein occlusion; HRVO, hemi-retinal vein occlusion; BRVO, branch retinal vein occlusion.

Type of cardiovascular risk factor	Patients		
	P ₁ (≤45 years) n = 80	P ₂ (>45≤60 years) n = 90	P ₃ (>60 years) n = 58
Total number of CVRF	46 = 57.5 %	66 = 73.3 %	38 = 65.5 %
Arterial hypertension	10 = 12.5 %	46 = 51.1 %	27 = 46.6 %
Diabetes mellitus	3 = 3.8 %	6 = 6.7 %	4 = 6.9 %
Cigarette consumption	19 = 23.8 %	8 = 8.9 %	4 = 6.9 %
Obesity	10 = 12.5 %	13 = 14.4 %	5 = 8.6 %
Hyperlipidemia	4 = 5 %	10 = 11.1 %	9 = 15.5 %
Oral contraceptive use	16 = 37.2 % ¹	2 = 3.5 % ²	0
Hormone replacement therapy	1 = 2.3 % ¹	10 = 17.5 % ²	3 = 8.9 % ³

CVRF, cardiovascular risk factor. ¹Number of women among patient group P₁ = 43. ²Number of women among patient group P₂ = 57. ³Number of women among patient group P₃ = 34.

Table 2: Prevalence of cardiovascular risk factors (CVRF).

patients >60 years were tested positive for thrombophilic disorders compared to 25% and 22.7%, respectively, of age-matched controls. These differences were not statistically significant.

Seven (8.75%) of the 80 patients ≤45 years had a previous major thromboembolic event. Among these, three developed RVO at an age ≤45 years. Subgroup analysis of patients who aged ≤45 years at the time of RVO revealed a high prevalence of thrombophilic disorders compared with age-matched controls ($p < 0.0001$).

The prevalence of cardiovascular risk factors including hypertension, diabetes mellitus, cigarette consumption, obesity, oral contraceptive use, hormone replacement therapy, or hyperlipidemia was 65.8% among all patients (► Table 2). In all patient groups, individuals without cardiovascular risk factors had a statistically significant higher frequency of coagulation disorders than patients with these risk factors (patients ≤45 years, $p = 0.003$; 45 to 60 years, $p = 0.0008$; >60 years, $p = 0.001$). Furthermore, there was a strong association between the presence of thrombophilic disorders and a family history of thromboembolism among patients ≤45 years ($p < 0.0001$) and >45 to ≤60 years ($p = 0.0008$). Among patients ≤45 years, the combination of these criteria, i.e. absence of cardiovascular risk factors and family history of thromboembol-

ism, yielded a chance probability of 100% of identifying individuals with thrombophilic defects. Multivariate logistic regression analysis revealed that a family or personal history of thromboembolism ($p = 0.002$, odds ratio [OR]: 2.86), the absence of cardiovascular risk factors ($p < 0.0001$, OR: 12.32), and a young age at the time of RVO or a previous thromboembolic event ($p = 0.022$, OR: 1.03) were independent risk factors for the presence of thrombophilic disorders (► Table 3).

In the patient group ≤45 years, the prevalence of resistance to APC ($p = 0.025$), antiphospholipid antibodies ($p = 0.025$), and factor XII deficiency ($p = 0.006$) was significantly different compared with age-matched controls. Moreover, we observed a significantly higher frequency of deficiencies of the anticoagulant proteins antithrombin, PS, PC and heparin cofactor II in the young patient group (8.75 %) as compared to age-matched controls (1.2%); ($p = 0.03$). In contrast, we found a similar prevalence of elevated plasma factor VIII levels ($p = 0.7$), increased plasma levels of lipoprotein (a) ($p = 0.2$), and hyperfibrinogenemia ($p = 1.0$) among young patients and young controls. Multivariate analysis using a stepwise logistic regression model revealed the presence of resistance to APC (OR: 5.33, $p = 0.014$), antiphospholipid antibodies (OR: 4.84, $p = 0.022$), and deficiency of the anticoagulant proteins antithrombin, PS, PC and heparin cofactor II (OR: 8.7, $p = 0.05$) as independent risk factors for the development of RVO among patients ≤45 years.

Interestingly, one patient in the younger age group suffered bilateral RVO within four weeks. This patient was a 43-year-old man with a remarkable personal and family history of deep-vein thrombosis (DVT). Screening for thrombophilic risk factors revealed homozygous resistance to APC.

Discussion

Several previous studies have suggested an association between thrombophilic defects and the development of RVO (4–7, 10–13,

Table 3: Association between various risk factors and the presence of thrombophilic disorders.

Type of risk factor	Wald's p	Odds ratio	95%-CI
Absence of arterial hypertension	0.0007	3.30	1.65 – 6.59
Absence of diabetes mellitus	0.034	5.95	1.15 – 8.59
Absence of nicotine abusus	0.018	3.25	1.23 – 8.59
Young age ¹	0.02	1.03	1.01 – 1.05
Presence of a personal or family history of TE ²	0.0014	3.09	1.54 – 6.18

¹Young age at the time of the first thromboembolic event. ²TE, thromboembolism.

20–22), whereas others failed to demonstrate a relationship (9, 14, 23–25). Unfortunately, available data often derive from case series that have serious methodologic limitations, such as the retrospective assembly of cohorts, small sample size, or the lack of appropriate controls (4, 9, 12, 23). Here, we prospectively performed a comprehensive thrombophilia screening in a large series of patients with RVO and matched controls.

A striking feature of the present study was that patients ≤ 45 years by the time of their RVO or a first thromboembolic event exhibited a significantly higher prevalence of coagulation defects as compared to controls. This is consistent with the observation that patients with inherited thrombophilia typically develop the first thrombotic event at a young age (26). Moreover, our finding that patient age is associated with the prevalence of thrombophilic disorders in RVO patients compares favorably with the results of several previous studies on the role of coagulation disorders in retinal vascular occlusive diseases (6, 12, 20–22, 27–29). Just recently, Arsene et al. (27) reported on a higher frequency of hereditary thrombophilic defects among RVO patients less than 60 years of age. Lahey et al. (28) found a prevalence of 27% among 55 CRVO patients less than 56 years and Abu el-Asra et al. (29) observed a statistically significant higher prevalence among 17 RVO patients < 45 years. However, due to relatively small sample sizes or a lack of appropriate controls, these studies have been inconclusive with regard to a causal relationship.

Other investigators failed to demonstrate a high prevalence of thrombophilic disorders in young patients with RVO. In a series of 21 patients, Gottlieb et al. (23) found resistance to APC in one RVO patient (4.7%) younger than 50 years. Interestingly, this patient had a family history of thromboembolism. Graham et al. (14) found no correlation between resistance to APC and CRVO in a group of 23 patients. However, of these, only 11 subjects were assigned to a younger patient group.

A methodological factor that may have affected the reported prevalences of thrombophilic disorders in previous ophthalmologic studies is the exclusion of patients who had an episode of VTE prior to the RVO or a family history of VTE (30). Numerous studies on major thromboembolism have demonstrated that thrombophilia should be suspected in patients who develop idiopathic thromboembolic events at a young age, recurrent thrombosis, thrombosis at unusual sites, or if there is a family history of VTE (26). In our study, we observed a strong association between the presence of thrombophilic disorders and a family history of thromboembolism among patients with RVO.

Another interesting finding of the current study is that the absence of cardiovascular risk factors in RVO patients appears to be a strong clinical predictor of harboring a thrombophilic disorder. Over the past years, a number of risk factors for CRVO and BRVO have been identified including hypertension, diabetes, or an increased body mass index (17). In our study, patients without cardiovascular risk factors were more likely to have thrombophilic disorders than patients with cardiovascular diseases in all three subgroups. This compares favorably with the observation that thrombophilia should be suspected in idiopathic major thromboembolism without environmental influences. Subgroup analy-

sis of patients ≤ 45 years by the time of the first thromboembolic event who had a family history of thromboembolism but no cardiovascular risk factors revealed a 100% chance of identifying a thrombophilic disorder.

Given an increased risk of recurrent thromboembolism in RVO patients with underlying thrombophilic disorders raises the question of whether these patients should receive anticoagulants. It has been demonstrated that patients who had an unprovoked episode of major VTE associated with coagulation defects are at increased risk of recurrence (2, 3). Moreover, randomised trials have shown unequivocal benefit of continuing anticoagulant therapy in such patients (31). The occurrence of two or more spontaneous thromboembolic episodes generally prompts the continuation of oral anticoagulant therapy for life (32). However, thus far, previous VTE has been used as a collective term for DVT and pulmonary embolism (PE). The strong association between thrombophilic disorders and a personal or family history of VTE observed in our study would support the consideration of RVO as a major risk factor for recurrent thrombosis when deciding upon the initiation or continuation of anticoagulant therapy in such patients. It is a well established observation that patients with a first episode of idiopathic VTE have a high rate of recurrence if anticoagulant therapy is discontinued after three months (30). Several studies found that continuation of anticoagulant therapy for more than three months appears to be particularly useful in patients with persistent antiphospholipid antibodies (1), and there is mounting evidence that heterozygosity for factor V Leiden or prothrombin G20210A is associated with an increased risk of recurrence (33, 34). Patients with a first spontaneous VTE carrying multiple or homozygous defects are considered to have a particularly high risk of recurrence and are potential candidates for life-long secondary prophylaxis (2, 3, 35). In our study, eight young patients had multiple or homozygous thrombophilic defects compared with none of age-matched controls. This difference was statistically significant ($p = 0.0013$). In contrast, there is no evidence as yet to support the use of anticoagulation in the treatment and prevention of recurrence of RVO. Because visual function in RVO primarily is a result of ischaemia and retinal changes such as oedema, haemorrhage or capillary non-perfusion, long-term anticoagulation is unlikely to improve visual outcomes. Moreover, in the acute phase of RVO, the decision whether anticoagulant treatment should be initiated will depend on ocular findings rather than on the presence of thrombophilic defects.

Preventing VTE in patients at risk is clearly preferable to treating the condition after it has appeared, a view that is supported by cost-effectiveness analysis (36). The identification of thrombophilic disorders among RVO patients may enable prevention to be assured by adopting antithrombotic measures during risk situations and avoiding hormonal treatments (36, 37). Moreover, it may enable appropriate lifestyle advice and consideration of drugs that lower cardiovascular risk. The knowledge of underlying thrombophilia can lead to signs and symptoms of VTE not being underestimated, allowing early recognition of unprovoked events.

On the basis of our findings, it is clear that to use medical resources appropriately and improve the level of interdisciplinary

What is known about this topic?

- Inherited coagulation disorders are established risk factors for major thromboembolism.
- The potential impact of thrombophilic risk factors on retinal vascular occlusive diseases remains unclear.
- To date, there are no large, prospective studies to assess an optimal, cost-effective approach with regard to screening for thrombophilic risk factors in retinal vein occlusion (RVO) patients.

What does this paper add?

- We found a high prevalence of coagulation disorders among patients ≤ 45 years by the time of the RVO or a previous thromboembolic event.
- We found a strong association between a family history of thromboembolism and the presence of coagulation disorders among RVO patients ≤ 60 years by the time of the RVO or a previous thromboembolic event.
- The absence of cardiovascular risk factors is a strong predictor for the presence of thrombophilic risk factors among RVO patients.

patient care in RVO, subgroup analysis is required. Since RVO has a strong pathogenic correlation with the presence of hypertension or arteriosclerosis, and the average age of affected patients is usually within the sixth or seventh decade of life, thrombophilia screening of RVO patients poses a particularly difficult diagnostic challenge. Overall, the present study demonstrates the significant role of coagulation disorders in specific subgroups of RVO patients and provides recommendations for clinical practice. Our results indicate that thrombophilic risk factors are significantly more prevalent among patients ≤ 45 years of age at the time of the RVO or a previous thromboembolic event, among patients with a remarkable family history of thromboembolism prior to the age of 45 years, or among patients without cardiovascular risk factors. According to our data, screening for resistance to APC, aPL, factor XII deficiency, and deficiencies of the anticoagulant proteins should be considered first. A more comprehensive thrombophilia screening may be warranted in selected cases.

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