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Thrombophilic and cardiovascular risk factors for retinal vein occlusion

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ABSTRACT

Background: The role of thrombophilic and cardiovascular risk factors in different manifestations of retinal vein occlusion (RVO), i.e., central or branch RVO, and at different ages is still debated.
Aims: To evaluate the association between thrombophilic and cardiovascular risk factors and the risk of RVO (overall, separately for central and branch RVO, and at different ages).
Methods: Case-control study on 313 patients with a first objectively-confirmed RVO (216 central and 97 branch RVO) and 415 healthy individuals.
Results: Antithrombin, protein C or protein S deficiency (adjusted odds ratio [95%CI]: 15.60 [2.01–121]; $p = 0.009$), hyperhomocysteinemia (HHCy; 3.22 [1.38–7.49]; $p = 0.007$), high factor VIII (FVIII) levels (3.08 [1.20–7.89]; $p = 0.019$), factor V Leiden (2.93 [0.97–8.86]; $p = 0.058$) and the presence of at least one cardiovascular risk factor (1.79 [1.00–3.23]; $p = 0.050$) were associated with an increased risk of branch RVO. The association was weaker for central RVO, and limited to HHCy (2.15 [1.09–4.24]; $p = 0.027$) and high FVIII (1.99 [0.90–4.42]; $p = 0.091$). For HHCy, high FVIII and cardiovascular risk factors the association with the risk of RVO was stronger at an age > 50 years (3.41[1.29–8.99], $p = 0.013$; 2.57[1.00–6.68], $p = 0.050$; and 2.03[1.16–3.56], $p = 0.013$, respectively) than ≤50 years (1.93[0.85–4.36], $p = 0.114$; 1.67[0.54–5.12], $p = 0.371$; and 1.22[0.73–2.03], $p = 0.454$, respectively), whereas classic inherited thrombophilia (antithrombin, protein C or protein S deficiencies, factor V Leiden and prothrombin G20210A mutation) was slightly more prevalent at an age ≤ 50 years (1.62 [0.76–3.45], $p = 0.210$) than >50 years (1.11[0.44–2.79], $p = 0.833$).
Conclusions: Thrombophilic and cardiovascular risk factors are associated with RVO, particularly branch RVO. The risk of RVO associated with HHCy, high FVIII and cardiovascular risk factors is higher at an older age.

1. Introduction

Retinal vein occlusion (RVO) is an obstruction of the retinal venous system, and represents the second common cause of retinal vascular disease after diabetic rethinopathy, and the most common cause of vision loss [1,2]. RVO may involve the central vein or a branch vein (usually the superotemporal branch at the arterovenous crossing site) of the retina. A recent German population-based study reported a 0.4% prevalence of RVO, with a clear increasing trend by age (0.2% in individuals aged 35–54 years, 0.48% in those aged 55–64 years, and 0.92% in those aged 65–74 years) [3]. Cardiovascular risk factors (i.e., arterial hypertension, diabetes, hyperlipidemia, smoking) are the most common risk factors for RVO [3–8], while the role of inherited or acquired thrombophilia is controversial, particularly due to the small sample size of most of the studies on this topic [9,10]. Although some studies showed an association between RVO and deficiencies of the natural anticoagulant proteins antithrombin (AT), protein C (PC) or protein S (PS) [11–13], anticardiolipin antibodies [11,12,14], factor V Leiden (FVL) [11,12,15–18], G20210A prothrombin gene mutation (PT20210) [18,19] and hyperhomocysteinemia (HHcy) [11.12,20–22], a recent meta-analysis indicated that only HHcy and anticardiolipin antibodies were consistently associated with RVO [23]. Few studies have addressed the impact of cardiovascular and thrombophilic risk factors in young patients with RVO [12,18], and no study has concomitantly evaluated the different pattern of these risk factors according to the site of RVO (central or branch) and age categories.

With this as background, the objective of this case-control study was to evaluate in a large sample of patients with RVO the role of thrombophilic and cardiovascular risk factors, overall and separately for central and branch RVO and at different age categories (≤50 years. vs >50 years).

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2. Patients and methods

2.1. Study population

Patients with a first episode of RVO, consecutively referred to our Thrombosis Center for a thrombophilia work up between April 1997 and December 2010, were tested at least three months after RVO to avoid the possible interference of the acute phase on some coagulation tests. Diagnosis of RVO was made by an oculist on the basis of a retinal fundus examination, and objectively confirmed with a fundus fluorescein angiography. According to its presentation, RVO was divided into central RVO (extensive vascular signs in all quadrants) and branch RVO (vascular signs only in wedge-shaped area in the superotemporal quadrant) [1]. For the purpose of this study, we excluded patients with RVO secondary to glaucoma, one of the most common acquired risk factors for RVO, particularly of the central retinal vein [24]. No patient suffered from overt cancer nor was receiving (or had received) erythropoietin therapy at the moment of inclusion into the study.

Healthy individuals who were partners or friends of the whole population of patients referred to our Thrombosis Center, and agreed to be tested for thrombophilia, formed the control group. They were recruited during the same period of patients and had never had RVO or other thromboses [25].

Demographic data, medical history, use of oral contraceptives, information on arterial hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg or use of anti-hypertensive drugs), hyperlipidemia (total cholesterol levels > 200 mg/dL and/or triglyceride levels > 150 mg/dL or use of statins), diabetes mellitus (fasting plasma glucose level of at least 126 mg/dL or use of anti-diabetic drugs), cigarette smoking (current vs non current smokers), were recorded. Neither patients nor controls were on anticoagulant or (for women) hormonal therapy at the time of blood sampling. The study was approved by the hospital institutional review board, and all patients and controls gave a written informed consent to participate to the study.

2.2. Laboratory tests

Patients and controls were tested for thrombophilia, that included measurements of AT, PC, PS, FVL, PT20210, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti β_2 glycoprotein 1 IgG and IgM antibodies), factor VIII and homocysteine. Tests were performed on citrated plasma, serum or DNA, as appropriate [26]. A positivity for antiphospholipid antibodies was diagnosed if at least one of the three classes of autoantibodies was positive (i.e., above the upper cut-off value of the normal laboratory reference range) and its positivity was confirmed in a separate measurement 12 weeks later, according to current guidelines [27]. Plasma homocysteine was measured both at fasting and after a methionine load of 3.8 g per square-meter of body surface area, using a high performance liquid chromatography and fluorometric detection as described [28]. HHcy was defined when levels exceeded the 95th percentile of the homocysteine distribution among controls (17 and 22 μmol/L fasting, 44 and 52 μmol/L post-methionine load for women and men, respectively). FVIII was measured with one-stage coagulation bioassay using factor VIII-deficient plasma as substrate and the activated partial thromboplastin time as reagent. Measurements were performed on multiple dilutions of standard and test plasmas and results were calculated with parallel-lines bioassays. Standard plasma was calibrated against the international standard for FVIII [29]. High plasma FVIII levels were defined when exceeding the 95th percentile of the distribution among controls (165 IU/dL). Cholesterol (total and HDL), triglycerides, glucose, serum cyanocobalamin and folic acid were also measured.

2.3. Statistical analysis

Assuming a 5% prevalence of HHcy, high FVIII, FVL or PT20210 (the most common thrombophilic abnormalities) among controls, with a case:control ratio of 1:1, a two-tailed α error of 0.05 and a 80% power, we calculated a minimal statistically significant relative risk of 2.35 with a sample size of 350 RVO patients and 350 controls. Continuous variables were expressed as median with interquartile range (IQR), and categorical variables as counts and percentages. To assess which predictor was associated with the risk of RVO, a multivariable logistic regression model containing thrombophilia abnormalities (AT, PC or PS deficiencies, FVL, PT G20210, antiphospholipid antibodies, high factor VIII, HHcy), cardiovascular risk factors (defined as the presence of at least one of the following: arterial hypertension, hyperlipidemia, diabetes or cigarette smoking), sex and age was fitted. Odds ratios (OR) and 95% confidence intervals (CI) were calculated as an estimate of the risk of RVO in carriers relative to non-carriers of the risk factor adjusting for the confounding effect of the other covariates. In sensitivity analyses, the contribution of all these risk factors was evaluated separately for central RVO and branch RVO, and in patients aged ≤50 years and >50 years. Finally, we tested the interaction between cardiovascular and thrombophilic risk factors on the risk of RVO. $P \leq 0.05$ was chosen as cut-off for statistical significance. All statistical analyses were performed with the statistical software R (release 3.0.1; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Three-hundred and thirteen patients with a first episode of RVO and 415 healthy controls were included in the study. The baseline characteristics of the study population are shown in Table 1. Women were more represented in controls, who were also younger than RVO patients. RVO

Table 1
Baseline characteristics of the study population.

	Patients	Controls
N.	313	415
Female sex, n (%)	166 (52)	295 (71)
Age at blood sampling (years), median (IQR)	55 (42–65)	41 (32–52)
Age at RVO (years), median (IQR)	54 (41–63)	NA
Creatinine clearance (mL/min), median (IQR)[a]	88.4 (65.7–110.3)	96.6 (73.2–118.4)
Localization of RVO, n (%)		NA
Central vein	216 (69)	
Branch vein	97 (31)	
Side, n (%)		NA
Left eye	172 (54)	
Right eye	141 (46)	
Thrombophilia abnormalities[b], n (%)		
None	225 (71)	348 (84)
AT, PC or PS deficiency	7 (2.2)	2 (0.5)
Factor V Leiden	17 (5.3)[c]	19 (4.6)
Prothrombin G20210A	11 (3.5)	19 (4.6)[c]
Antiphospholipid antibodies	12 (3.8)	6 (1.5)
Hyperhomocysteinemia[d]	41 (13)	25 (6)
Fasting homocysteine (μmol/L), median (IQR)	10.2 (8.0–13.1)	9.8 (7.9–12.0)
Factor VIII (IU/dl), median (IQR)	116 (97–140)	110 (93–129)
Risk factors, n (%)		
None	138 (43)	274 (66)
Oral contraceptives/HRT[e]	22 (13)	47 (16)
Hypertension	94 (30)	42 (10)
Hyperlipidemia	61 (19)	27 (7)
Diabetes	13 (4)	4 (1)
Cigarette smoking	47 (15)	91 (22)
Combined	52 (16)	18 (4)

IQR = interquartile range; AT = antithrombin; PC = protein C; PS = protein S; HRT = hormone replacement therapy; NA = not applicable.
[a] Calculated following the Cockroft-Gault formula.
[b] Some individuals carry more than one abnormality.
[c] One homozygous carrier.
[d] Fasting and/or post-methionine load.
[e] Percentage calculated on women only.

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