Thrombophilic Risk Factors in Different Types of Retinal Vein Occlusion in Tunisian Patients

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Background: Retinal vein occlusion (RVO) is the second most common cause of vision loss because of retinal vascular disease. There are 2 types of RVO: branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). The pathogenesis of RVO is multifactorial. The role of factor V Leiden (FVL) and prothrombin mutations was examined in patients with CRVO and BRVO. *Methods:* FVL and prothrombin were investigated by extracting DNA of 88 patients with RVO. Sixteen of the patients were diagnosed with CRVO, 4 with hemispheric retinal vein occlusion, and 68 with BRVO. The genotyping was performed by polymerase chain reaction–*restriction fragment length polymorphism*. *Results:* Significant differences were found in the frequencies of the genotypes for both the FVL (G1691A) ($P < 10^{-3}$, odds ratio [OR] = 17.4, confidence interval [CI] = 6.20-59) and prothrombin (G20210A) ($P = .007$, OR = 5.11, CI = 1.30-29) polymorphisms between RVO patients and healthy controls. Additionally, the frequency of the GA genotype for the G1691A polymorphism was significantly higher among the patients in a subset of BRVO compared with controls ($P < 10^{-3}$, OR = 21.4, CI = 7.34-74.2). However, no statistically significant differences were found in the frequencies of the prothrombin G20210A polymorphism between the BRVO group and healthy controls ($P = .09$, OR = 3.13, CI = 64-19.9). The frequency of both G1691A and G20210A genotypes among the patients of a CRVO subgroup was significantly higher compared with controls ($P < 10^{-3}$, OR = 11.4, CI = 2.94-44.2; $P = .007$, OR = 10.8, CI = 2.15-54.1, respectively), suggesting an association between these polymorphisms and CRVO. *Conclusions:* Large study would be required to understand completely the contribution of these markers in the risk of all types of RVO. **Key Words:** Retinal vein occlusion—branch retinal vein occlusion—central retinal vein occlusion—G1691A—G20210A—polymerase chain reaction–restriction fragment length polymorphism.

Introduction

Retinal vein occlusion (RVO), a potentially blinding eye disease, is a significant cause of visual loss of variable degree and affects not only the elderly but also the young.[1-3] Typically, however, it occurs in people aged more than 50 years and affects men and women equally.[4] RVO is the second most common retinal vascular abnormality after diabetic retinopathy.[5,6] RVO is an obstruction of the retinal venous system.[7] The pathogenesis of RVO is

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related to compression of the vessel wall and damage to the endothelium, leading to thrombus formation.[8] Depending on the location of occlusion, it can be classified into occlusions of the central vein, hemicentral vein, major branch vein, and the macular branch vein. Branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) are the 2 basic types of venous occlusions.[9] BRVO is approximately 3-4 times more common than CRVO.[8]

BRVO is a common retinal vascular disease and it may cause immediate vision loss.[10] The pathogenesis is multifactorial and may be because of a combination of the compression of the vein at the arteriovenous intersection, degenerative changes in the vessel wall, and abnormal hematologic factors.[11] CRVO, another retinal vascular disorder, is the most common visually disabling disease affecting the retina and remains a significant cause of visual loss. Patients generally present with painless visual loss in the affected eye.[12,13] The pathogenesis of CRVO is multifactorial with both local factors and systemic diseases being etiologically important.[13] Hemi-CRVO is a variant of CRVO and also consists of 2 distinct entities: nonischemic and ischemic hemi-CRVO. Pathogenetically, CRVO and hemi-CRVO are identical in nature.[14]

The causes of RVOs are multifactorial and include thrombophilia, abnormalities of the venous wall, and blood flow pathologies.[15] The thrombophilic aspects have been investigated intensively and etiologic significance has been attributed to factor V Leiden (FVL) and abnormal prothrombin 20210.[15] Moreover, many systemic disorders that contribute to thrombus formation can predispose to the development of RVO, such as hypertension, diabetes mellitus (DM), arteriosclerosis, and cardiovascular diseases.[16]

Patients and Methods

Subjects

We prospectively investigated 88 subjects with RVO. The age of these patients ranged from 12-82 years with a mean age of 54.17 ± 17.22 (standard deviation [SD]) years at the time of study. The average age of the patients at the time of diagnosis was 49.79 ± 17.32 (SD) years (range 11-82 years). Patients were selected consecutively from the Department of Ophthalmology. Each patient underwent a complete ophthalmologic examination. The diagnosis of RVO was confirmed by fluorescein angiography and was further classified as CRVO, hemispheric retinal vein occlusion (HRVO), or BRVO according to the site of occlusion.

Additionally, the control group consisted of 100 age- and gender-matched healthy subjects recruited from the Military Hospital of Tunis and originating from different regions of Tunisia.

Baseline medical and ocular data were recorded for each patient. Particular attention was given to risk factors for vascular disease (eg, smoking, diabetes, and hypertension). Baseline ocular history and visual examination findings were recorded from each patient's initial evaluation.

A review of fundus photographs, fluorescein angiograms, and written records of RVO patients were provided by the participating institutions where the subjects were registered, examined, and initially diagnosed. This study was approved by the Ethics Committee of the Military Hospital of Tunis.

Methods

After a diagnosis of CRVO, HRVO, or BRVO, each patient was sent for a comprehensive thrombophilia screening. Peripheral blood was obtained from patients after receiving informed consent.

Genomic DNA recovered from the peripheral blood leukocytes of patients with DNA extraction kit (QIAmp blood kit; Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocol was amplified by polymerase chain reaction. The fragment was cleaved by *Mnl*I and *Hin*dIII endonuclease restriction for FVL (G1691A) and prothrombin (G20210A) mutations, respectively. The bands that were formed by agarose gel electrophoresis were evaluated.

Statistical Analysis

All analyses related to the case–control study were performed using the Statistical Package for the Social Sciences v. 17 (IBM, Armonk, NY). Differences between cases and controls were evaluated by using the chi-square test for qualitative variables. In addition, the odds ratio (OR) and 95% confidence intervals (CIs) were calculated. Probability values $P < .05$ were considered to be statistically significant.

Results

Epidemiologic characteristics of the patients are presented in Table 1. Subjects and controls were well matched for age and sex. There were 26 females and 62 males (female/male ratio = .42). The diagnosis of RVO was made in 88 patients of whom HRVO was found in 4 patients, CRVO in 16 patients, and BRVO was observed in 68 patients. The mean ages at disease onset for the 2 case groups (BRVO and CRVO patients) were 49.48 ± 17.69 (SD) years and 51.5 ± 18.48 (SD) years, respectively.

RVO occurred in the right eye in 40 patients (45.45%), in the left eye in 42 patients (47.72%), and in both eyes in 6 patients (6.81%). The associated systemic and ocular pathologies of the patients are shown in Table 1. The patient group had statistically significant risk factors of hypertension ($P < 10^{-3}$, OR = 14.4, CI = 5.35-39.0) and diabetes ($P < 10^{-3}$, OR = 24.6, CI = 7.23-83.6) (see Table 2).