Activated Protein C Resistance, Factor V Leiden, and Central Retinal Vein Occlusion in Young Adults

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Objective: To confirm the relationship between resistance to activated protein C (APC), factor V Leiden, and central retinal vein occlusion in young adults as reported in a recent study of patients younger than 50 years.

Patients and Methods: Patients younger than 50 years with central retinal vein occlusion were identified from the medical records of the Wills Eye Hospital Retina and Retina Vascular Services. Blood samples were taken from each patient and analyzed for resistance to APC and identification of factor V Leiden.

Results: Only 1 (4.7%) of 21 patients evidenced resistance to APC and the presence of factor V Leiden. This patient was also the only one to report a family history of thrombotic disease.

Conclusions: We were unable to confirm the high percentage of resistance to APC among young adult patients with central retinal vein occlusion. The finding of resistance to APC in only 1 (4.7%) of 21 patients is similar to that found in the general population.
PATIENTS AND METHODS

RESULTS

Resistance to APC was seen in only 1 (4.7%) of the 21 patients studied (95% confidence interval = [0.572, 1.428], Poisson distribution.) The average APC ratio of the normal patients was 2.9 (range, 2.3 to >4.0). The APC ratio of the one patient who evidenced resistance to APC was 1.8. This patient also evidenced factor V Leiden. His father had a history of deep vein thrombosis and prolonged activated partial thromboplastin time. This family member had not had his condition evaluated for genetic abnormalities of coagulation. No patient evidenced presence of factor V Leiden with negative test findings for resistance to APC.

Of the 20 patients with no resistance to APC, 14 evidenced a nonischemic CRVO. The one patient with resistance to APC suffered an ischemic CRVO.

COMMENT

Among the 21 young adult patients with CRVO included in our study, only 1 (4.7%) showed resistance to APC and the presence of factor V Leiden mutation. This stands in contrast to the study of Larsson and colleagues16 in which 8 patients (26%) younger than 50 years and 11 patients (36%) younger than 45 years were resistant to APC. The prevalence of resistance to APC among the general population is approximately 5% in European population studies,19 and among white Americans the carrier frequency of factor V Leiden is 5.27%.20 From our study, it does not appear that there is a higher prevalence of resistance to APC among young patients with CRVO than there is in the general population. Similarly, in a study of 162 genetically affected family members in a study of 50 APC-resistant families, only 1 case of CRVO was found.21 Among those patients in our study evaluated for other inherited disorders of coagulation predisposing to thrombosis, no patient evidenced protein C, protein S, or antithrombin III deficiencies.

As in the study of Larsson and colleagues,16 the patients included in this study were chosen from the pa-
tient records of a university-associated ophthalmology hospital. Resistance to APC usually results from an inherited genetic abnormality. In our study, we were testing specifically for the inherited mutation, factor V Leiden. Therefore, the follow-up interval or timing of the testing relative to the occurrence of the CRVO is not important. The median age of 43.5 years (average age, 42 years) is similar to the median age of 40 years in the study of Larsson et al. One significant difference was the presence of 5 patients in their study with a family history of thrombosis. Interestingly, the only patient who related a family history of thrombosis in the present study also evidenced resistance to APC. This may reflect a selection bias affecting the differences in the results.

Other potential sources of bias include the means of selection of patients for this study. The patients recruited included both urban and suburban populations. The patients recruited retrospectively came from both the general clinic population of Wills Eye Hospital (the Retina Vascular Service) and the referral patients of the private practice of members of the Retina Service of Wills Eye Hospital. Six of 11 patients recruited retrospectively were from the general service and 5 from the private practice. Patients agreeing to participate generally represent the overall population of the greater Philadelphia metropolitan area. No attempt was made to specifically recruit patients with a family history of thrombophilia or recurrent thrombosis.

Resistance to APC that was not the result of factor V Leiden mutation has been reported in patients with acute strokes and in pregnancy. It is not clear that in these settings the APC resistance results in an increased thrombotic risk. The assay used by Larsson et al in their study of patients with CRVO would also detect these presumed acquired states of APC resistance. The assay method that we used is highly sensitive and specific for factor V Leiden mutation. It is possible that the difference between our results and those of Larsson et al is due to the use of different assays. However, we did use an assay similar to that used by Larsson et al in 6 patients and we obtained results identical to that obtained with the more specific assay.

Factor V Leiden mutation is highly prevalent in the general population. As an inherited genetic disorder, it causes a life-long increased risk of thrombosis and is inherited as an autosomal dominant trait. In extended family studies, approximately 25% of relatives with APC resistance had suffered a thrombotic event by the age of 50. The presence of APC resistance, when combined with other risk factors for venous thrombosis such as pregnancy, cigarette smoking, oral contraceptive use, surgery, or other genetic anticoagulant defects, afflicts the patient with a considerable risk for venous thrombosis. In the young patient who presents with a CRVO, especially if there is a family history of thrombotic disease or concomitant risk factors for thrombotic disease, screening for resistance to APC is indicated, and when results of such tests are positive, the patient should undergo genetic analysis to confirm the presence of factor V Leiden. Such patients may be counseled regarding the avoidance of risk factors that may increase their susceptibility to thrombotic disease, including the use of tobacco or oral contraceptives. These young patients may also benefit from prophylaxis against thrombosis if surgery or immobilization is required later in life. This present study, however, does not confirm that there is a 4 to 5 time greater risk for resistance to APC among young patients with CRVO than there is among the normal population. 

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