CLINICAL SCIENCE

Influence of factor V Leiden on the development of neovascularisation secondary to central retinal vein occlusion

C Hvarfner, A Hillarp, J Larsson

See end of article for authors' affiliations

Br J Ophthalmol 2003;**87**:305–306

Correspondence to:
Charlotte Hvarfner,
Department of
Ophthalmology, Lund
University Hospital,
211 85 Lund, Sweden;
charlotte.hvarfner@ofh.lu.se

Accepted for publication
4 September 2002

Aims: To investigate if the presence of factor V Leiden has an influence on the prognosis in central retinal vein occlusion (CRVO).

Methods: 166 patients with CRVO were studied retrospectively. They were tested for factor V Leiden using DNA analysis. The presence of the mutation was studied in correlation with the development of neovascular complications 1 year after the thrombotic event.

Results: 56 of 166 patients (34%) developed neovascular complications after 1 year. In the patients who had the studied mutation 11 of 20 (55%) had developed neovascular complications after 1 year, compared to 45 of 146 patients (31%) in the group without factor V Leiden ($p=0.04$).

Conclusion: The presence of factor V Leiden seems to enhance the risk of developing neovascular complications in CRVO.

Glaucoma, hypertension, arteriosclerosis, and diabetes are factors that are well known to be associated with central retinal vein occlusion (CRVO). These conditions affect vascular flow or cause vascular wall abnormalities, thereby contributing to the development of CRVO.^{1–5}

Hereditary alterations in the coagulation/anticoagulation pathways can result in thrombophilia, increasing the risk for thrombosis.^{6–7} It is, however, debatable whether hereditary alterations in the coagulation pathway are aetiological factors for CRVO.

Activated protein C resistance is the most common genetic cause of venous thrombosis.⁶ A point mutation in factor V (factor V Leiden) renders it resistant to the normal inactivation by activated protein C. This “activated protein C resistance” produces a mild thrombophilic state. There are studies in the literature pointing towards an association between CRVO and factor V Leiden,^{8–12} though most of the evidence today indicates that factor V Leiden does not have a major aetiological role in CRVO.^{13–22}

After thrombus formation, independent of cause, a restoration of the venous lumen can occur spontaneously.^{23–24} We do not know the exact mechanism of this recanalisation, but it could be related to the balance of coagulation/anticoagulation.²⁵ We stated the hypothesis that even though factor V Leiden has not been found to be an important risk factor for CRVO, it may have a more important role during the recanalisation phase after the thrombotic event. We wanted to investigate if the factor V Leiden influences the prognosis in CRVO, and so studied the prevalence of factor V Leiden in relation to the development of neovascular complications after CRVO.

PATIENTS AND METHODS

Patients

A total of 190 consecutive patients with CRVO examined in the eye clinic of Lund University Hospital from 1994 to 2000 were invited to take part in the study; of these, 166 patients agreed to participate. Venous blood samples were collected after informed consent was obtained. Of the 166 patients, 86 were men and 80 were women. The patients were aged between 22 and 91 years (mean age 64 (SD 15) years).

All patients were followed for at least 1 year. This time was chosen as we know that the majority of the patients who develop neovascular complications after CRVO have done so within this time period.^{26–29} The end point was the development of neovascular complications or not, 1 year after the thrombotic event. Neovascular complications were defined as any retinal, disc, iris, or chamber angle neovascularisations. Clinical information was derived from the patient records.

DNA analysis

Preparation of genomic DNA from EDTA blood and determination of the factor V Leiden mutation (G to A at nucleotide position 1691), which causes activated protein C resistance, was performed as described earlier.³⁰

RESULTS

After a year 56 of 166 patients (34%) had developed neovascular complications. Factor V Leiden was present in 20 of 166 patients (12%). The patients with factor V Leiden did not significantly differ in age or sex compared to the patients without the studied mutation. The patients with factor V Leiden, 10 men and 10 women, ranged in age between 22 and 86 years (mean 58 years; median 64 years). The patients without factor V Leiden, 76 men and 70 women, ranged in age between 28 and 91 years (mean 65 years; median 68 years).

In the patients with factor V Leiden, 11 of 20 (55%) developed neovascular complications. In the patients without the mutation 45 of 146 patients (31%) developed neovascular complications ($p=0.04$; Fischer's exact test) (Fig 1). This gives an odds ratio of 2.7 (CI 95% 1.1 to 7.1).

DISCUSSION

In this study we have shown that the presence of factor V Leiden seems to increase the risk for neovascularisation secondary to CRVO.

The presence of factor V Leiden results in a mildly thrombophilic state. Although it has not been found to be an important risk factor for CRVO,^{13–22} it is possible that factor V Leiden may have a more important role in the recirculation phase after the thrombotic event. The mild predominance of coagulation over anticoagulation may contribute to a delayed

Figure 1 The presence of factor V Leiden correlated with the development of neovascular complication in CRVO. The result points towards an almost threefold risk of developing complications with the mutation present.

recirculation, and thereby possibly a more severe ischaemia resulting in a higher risk for neovascular complications. Our study points towards an almost threefold risk of developing neovascular complications after CRVO with factor V Leiden present. We have not seen other studies in the literature regarding factor V Leiden and the prognosis for CRVO.

As the presence of the studied mutation is independent of the time of the blood sample, this has enabled us to supplement the DNA tests independent of time for follow up. Since it is well established that the most important risk factor for the development of neovascular complications after CRVO is the extent of retinal ischaemia,^{2-29 31 32} it would have been of interest to see if the patients presenting with factor V Leiden mutation showed a more pronounced retinal ischaemia, as detected by fluorescein angiography, but a weakness of this study being retrospective is that this information is not complete. This would preferably be dealt with in another prospective study.

The incidence of neovascular complications in our patients during the first year after the thrombotic event is in accordance with earlier reports.^{26-29 31 32} The prevalence of factor V Leiden is also at the level expected in the normal population in the studied area,⁶ which confirms that factor V Leiden probably does not have an important aetiological role in CRVO, as pointed out earlier.¹³⁻²²

In conclusion, the presence of factor V Leiden seems to enhance the risk of developing neovascular complications in CRVO.

Authors' affiliations

C Hvarfner, J Larsson, Department of Ophthalmology, Lund University Hospital, Sweden

A Hillarp, Department of Clinical Chemistry, Malmö University Hospital, 211 85 Malmö, Sweden

REFERENCES

- McGrath MA, Wechsler F, Hunyor AB, et al. Systemic factors contributory to retinal vein occlusion. *Arch Intern Med* 1978;**138**:216-20.
- Ring CP, Pearson TC, Sanders MD, et al. Viscosity and retinal vein thrombosis. *Br J Ophthalmol* 1976;**60**:397-410.
- Elman MJ. Systemic associations of retinal vein occlusion. *Int Ophthalmol Clin* 1991;**31**:15-22.
- Hirota A, Mishima HK, Kiuchi Y. Incidence of retinal vein occlusion at the glaucoma clinic of Hiroshima University. *Ophthalmologica* 1997;**211**:288-91.
- The Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion. *Arch Ophthalmol* 1996;**114**:545-54.
- Dahlback B. Blood coagulation. *Lancet* 2000;**355**:1627-32.
- Spek CA, Reitsma PH. Genetic risk factors for venous thrombosis. *Mol Genet Metab* 2000;**71**:51-61.
- Greiner K, Hafner G, Dick B, et al. Retinal vascular occlusion and deficiencies in the protein C pathway. *Am J Ophthalmol* 1999;**128**:69-74.
- Albisinni R, Coppola A, Loffredo M, et al. Retinal vein occlusion and inherited conditions predisposing to thrombophilia. *Thromb Haemost* 1998;**80**:702-3.
- Glueck CJ, Bell H, Vadlamani L, et al. Heritable thrombophilia and hypofibrinolysis. Possible causes of retinal vein occlusion. *Arch Ophthalmol* 1999;**117**:43-9.
- Greiner K, Peetz D, Winkgen A, et al. Genetic thrombophilia in patients with retinal vascular occlusion. *Int Ophthalmol* 1999;**23**:155-60.
- Marcucci R, Bertini L, Liotta AA, et al. Activated protein C resistance is a risk factor for central retinal vein occlusion. *Ann Ital Med Int* 2000;**15**:195-8.
- Ciardella AP, Yannuzzi LA, Freund KB, et al. Factor V Leiden, activated protein C resistance, and retinal vein occlusion. *Retina* 1998;**18**:308-15.
- Larsson J, Sellman A, Bauer B. Activated protein C resistance in patients with central retinal vein occlusion. *Br J Ophthalmol* 1997;**81**:832-4.
- Gottlieb JL, Blice JP, Mestichelli B, et al. Activated protein C resistance, factor V Leiden, and central retinal vein occlusion in young adults. *Arch Ophthalmol* 1998;**116**:577-9.
- Graham SL, Goldberg I, Murray B, et al. Activated protein C resistance—low incidence in glaucomatous optic disc haemorrhage and central retinal vein occlusion. *Aust NZ J Ophthalmol* 1996;**24**:199-205.
- Hodgkins PR, Perry DJ, Sawcer SJ, et al. Factor V and antithrombin gene mutations in patients with idiopathic central retinal vein occlusion. *Eye* 1995;**9**:760-2.
- Linna T, Ylikorkala A, Kontula K, et al. Prevalence of factor V Leiden in young adults with retinal vein occlusion. *Thromb Haemost* 1997;**77**:214-6.
- Raguene O, Mercier B, Escoffre M, et al. [1691 G to A mutation of the factor V gene: no association with thrombosis of the central retinal vein] *Presse Med* 1996;**25**:460.
- Salomon O, Moisseiev J, Rosenberg N, et al. Analysis of genetic polymorphisms related to thrombosis and other risk factors in patients with retinal vein occlusion. *Blood Coagul Fibrinolysis* 1998;**9**:617-22.
- Johnson TM, El Defrawy S, Hodge WG, et al. Prevalence of factor V Leiden and activated protein C resistance in central retinal vein occlusion. *Retina* 2001;**21**:161-6.
- Scott JA, Arnold JJ, Currie JM, et al. No excess of factor V:Q506 genotype but high prevalence of anticardiolipin antibodies without antithrombotic cell antibodies in retinal vein occlusion in young patients. *Ophthalmologica* 2001;**215**:217-21.
- Chan CC, Green WR, Rice TA. Experimental occlusion of the retinal vein. *Graefes Arch Clin Exp Ophthalmol* 1986;**24**:507-12.
- Green WR, Chan CC, Hutchins GM, et al. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Trans Am Ophthalmol Soc* 1981;**79**:371-422.
- Meissner MH, Zierler BK, Bergelin RO, et al. Coagulation, fibrinolysis, and recanalization after acute deep venous thrombosis. *J Vasc Surg* 2002;**35**:278-85.
- The Central Vein Occlusion Study Group N report. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. *Ophthalmology* 1995;**102**:1434-44.
- Magargal LE, Brown GC, Augsburger JJ, et al. Neovascular glaucoma following central retinal vein obstruction. *Ophthalmology* 1981;**88**:1095-101.
- Magargal LE, Donoso LA, Sanborn GE. Retinal ischemia and risk of neovascularization following central retinal vein obstruction. *Ophthalmology* 1982;**89**:1241-5.
- Sinclair SH, Gragoudas ES. Prognosis for rubeosis iridis following central retinal vein occlusion. *Br J Ophthalmol* 1979;**63**:735-43.
- Zoller B, Svensson PJ, He X, Dahlback B. Identification of the same factor V gene mutation in 47 out of 50 thrombosis-prone families with inherited resistance to activated protein C. *J Clin Invest* 1994;**94**:2521-4.
- Hayreh SS, Rojas P, Podhajsky P, et al. Ocular neovascularization with retinal vascular occlusion—III. Incidence of ocular neovascularization with retinal vein occlusion. *Ophthalmology* 1983;**90**:488-506.
- Quinlan PM, Elman MJ, Bhatt AK, et al. The natural course of central retinal vein occlusion. *Am J Ophthalmol* 1990;**110**:118-23.