CASE REPORTS

Multiple Heritable and Acquired Risk Factors in a Case of Recurrent Retinal Vein Occlusion

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Abstract

A 40 year old female presented with branch retinal vein occlusion in the right eye followed by a second episode, a year later, of central retinal vein occlusion in the left eye. The patient was found to be heterozygous for factor V Leiden and factor V HR2 haplotype G5380A. She had a history of use of oral contraceptives, had reduced levels of tissue plasminogen activator, positive for lupus anticoagulant and diagnosed with hypertension post second episode of RVO. Presence of both heritable and acquired thrombophilia along with hypofibrinolysis induced by reduced levels of tissue plasminogen activator might have led to the recurrence of retinal vein occlusion in this patient. This case illustrates the contribution of multiple hereditary and acquired risk factors in the clinical manifestation of recurrent retinal vein occlusion thereby warranting the application of a more thorough work-up in such cases. The case also briefly touches on the fact that treatment for every RVO cannot be the same and should be decided by taking into consideration the associated risk factors.

Introduction

Retinal vein occlusion (RVO) is a common ocular disease leading to acute visual loss with a prevalence of 8 per 1000 individuals reported in rural central India.[1] The pathogenesis is poorly understood. Being multifactorial, treatment is always a challenge and individualized or causal treatment for RVO is to be decided by clinician. Based on the site of vascular occlusion, RVO is divided into two types: (a) Central vein retinal occlusion (CRVO) and (b) Branch retinal vein occlusion (BRVO). BRVO is approximately seven times more common than CRVO [1].Hypertension, diabetes mellitus, arteriosclerosis and hyperlipidemia, glaucoma, advancing age are established risk factors for RVO however; the role of thrombophilia in RVO is still controversial.[2] Recurrent RVO is not frequently encountered in young adults. In RVO cases, extensive laboratory testing including thrombophilia is not indicated.[3] We report a case of recurrent RVO in a young female due to presence of multiple risk factors stressing on the warrant of a more thorough work-up in RVO cases with clinical features such as young age, recurrent presentations, or bilateral involvement.

Case Report

A 40 year old woman presented with a 11-day history of decreased vision in her right eye. Ophthalmoscopic examination showed retinal haemorrhages along with multiple cotton wool spots. A diagnosis of infero-temporal branch retinal vein occlusion (BRVO) with macular oedema was confirmed by fluorescein angiogram. Assessment of risk factors revealed her to be using oral contraceptives for the management of adenomyosis since two years. She received an intravitreal Avastin (Bevacizumab) injection for the right eye and her vision subsequently improved with conservative management. The use of oral contraceptives was discontinued. However, a year later she experienced blurred vision in her left eye. Ocular examination revealed non-ischemic central retinal vein occlusion (CRVO) with optic disc and macular oedema in the left eye.She received an intravitreal combination of Triamcinolone acetonide and Bevacizumab. Due to recurrence of RVO, warfarin therapy was initiated and continued for three months.

An extensive laboratory workup was done to find the cause of the occlusion (Table 1). Full blood count, blood glucose, erythrocyte sedimentation rate, lipid profile, bleeding and clotting time, prothrombin time, HLA B27 and serum homocysteine were all normal with slightly prolonged activated partial thromboplastin time (APTT). Clotting factors VIII, IX and XI were all normal. Inherited thrombophilia markers Protein C and S levels, antithrombin III levels were also normal. Moreover, genomic DNA was isolated from peripheral blood lymphocytes and genotyped for Factor V Leiden[R506Q] and other common polymorphisms implicated in thrombosis (Table 1). She was heterozygous for factor V Leiden and factor V HR2 haplotype G5380A. She was also heterozygous for methylenetetrahydrofolate reductase (MTHFR) C677T mutation. Acquired thrombophilia markers i.e. anticardiolipin antibodies, β2-glycoprotein 1 antibodies were absent however she was strongly positive for lupus anticoagulants (LA) (Siemens Healthcare Diagnostics, Marburg, Germany) which could have prolonged the APTT in the patient. All the fibrinolytic parameters including plasminogen, plasminogen activator inhibitor-1, thrombin activatable fibrinolysis inhibitor and alpha-2-antiplasmin were normal except for tissue plasminogen activator (tPA) levels which were reduced (Assay Pro, MO, USA).

Patient was diagnosed with

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Received: 10.10.2016; Revised: 10.08.2017; Accepted: 10.10.2017

Table 1: Laboratory investigations done in this patient

Parameters	Result
Activated partial thrombo-plastin time (APTT) (secs)	31.2 (26.7)
APTT with low phospholipids (secs)	40.2 (31.7)
Prothrombin time (PT) (secs)	13.1 (12.8)
Plasma fibrinogen levels (mg/dl)	213 (200-400)
FVIII: C (%)	90 (50-150)
FIX: C (%)	100 (50-150)
FXI: C (%)	68 (50-150)
Protein C antigen (%)	100 (70-140)
Protein C activity (%)	119 (55-123)
Protein S antigen (%)	100 (70-140)
Protein S activity(%)	81 (70-130)
Antithrombin III activity (%)	114 (70-140)
Plasminogen (µg/ml)	500 (380-600)
Tissue Plasminogen activator (tPA) (ng/ml)	0. 60 (0.9-2.0)
Plasminogen activator inhibitor -1 (PAI-1) (ng/ml)	14.5 (< 60)
Thrombin activatable fibrinolysis inhibitor (ng/ml)	300 (100-350)
Alpha-2-antiplasmin (ng/ml)	51.63 (50-175)
Fibrinogen (mg/dL)	213 (200-400)
Homocysteine (µmol/L)	11.36 (3.7-17.9)
Lupus anticoagulant (LA)‡	Positive (LA1/LA2 = 1.89)
Factor V Leiden G1691A (rs6025)	G/A (G/G)
Factor V HR2 haplotype A4070G (rs1800595)	A/A (A/A)
Factor V HR2 haplotype G5380A (rs6030)	G/A (G/G)
Prothrombin G20210A (rs1799963)	G/G (G/G)
MTHFR C677T (rs1801133)	C/T (C/C)
MTHFR A1298C (rs1801131)	A/A (A/A)
Factor XIII Val34Leu (rs5985)	G/G (G/G)
PAI-1 4G/5G (rs1799768)	5G/5G (5G/5G)
PAI-1 -844 G/A (rs2227631)	G/G (G/G)
tPA -7351 C/T (rs2020918)	C/C (C/C)

Normal range/ Reference value/ Genotype in parenthesis; ‡Normal: Negative (LA1/LA2 < 1.3)

hypertension after the second incidence of RVO and put on antihypertensive drugs. She is presently asymptomatic and there has been no recurrence during six months of follow-up.

Discussion

A combination of inherited and acquired thrombophilia and presence of vascular risk factors could have led to the recurrent RVO in this patient. She was heterozygous for both Factor V Leiden mutation and for Factor V HR2 haplotype G5380A. This co-existence imparts increased risk of venous thromboembolism by contributing to the activated Protein C resistance.[4] Though pathogenesis and risk factors of RVO are different from those of deep vein thrombosis and other systemic diseases,[5] Factor V Leiden has been implicated in increasing the risk of RVO including recurrence.[6-10] Patient also carried MTHFR C677T mutation with normal homocysteine levels.

The patient tested positive for LA. LA are immunoglobulins, which bind to complexes of various proteins with phospholipids, associated with the cell membrane. It is a well established acquired risk factor for venous as well as arterial thrombosis. Though not commonly found, LA may constitute a contributory factor in RVO.[11]

Patient has a history of adenomyosis which is a heterogenous gynaecological condition and women with adenomyosis may experience heavy menstrual bleeding, dysmenorrhoea, and longer menstrual cycles than normal or may even remain asymptomatic.[12] She was on oral contraceptive pills for the management of adenomyosis for two years before the first episode of RVO. Oral contraceptive is known to be a strong risk factor for development of RVO.[13] She was also diagnosed with hypertension after second RVO. It is also plausible that hypertension may have been a side effect of the use of oral contraceptives as a result of alteration of the renin angiotensin system.[14] Hypertension, an established strong risk factor for RVO,[2] was either overlooked or delayed[15] and could have resulted or increased recurrence risk.

Fibrinolytic parameters are rarely studied in RVO. Abnormal fibrinolysis due to deficiency of tPA has been associated with retinal vein occlusion.[16] The patient was found to have reduced tPA level. However, we could not detect any sequence variations in tPA gene associated with decreased tPA levels. LA has already been associated with increased plasminogen activator inhibitor levels (PAI) in stroke patients[17] and reduced tPA and increased PAI activities in patients with SLE[18] leading to depressed fibrinolytic activity. In this case, it is plausible that presence of LA could have altered the levels of tPA.

There is no standard proven treatment for RVO and therapy is rather aimed to prevent any further vision loss from complications such as macular oedema. Sector laser photocoagulation may be used for severe or diffuse macular oedema to improve vision. Other options widely used include injecting the eye with steroids and anti-vascular endothelial growth factor (anti-VEGF). After second RVO in this patient, an intravitreal combination of steroids and anti VEGF was given along with initiation of warfarin therapy maintaining recommended therapeutic INR level. Her vision improved over time with the reducing oedema and retinal haemorrhages.Warfarin therapy initiation however does not exclude the possibility of recurrence[19] indicating that same treatment for every RVO patient may not be fruitful. As this patient was found to have reduced tPA levels, whether intravitreal tPA administration could have normalized patient's hypofibrinolytic state and prevented the recurrence is not clear.[16] A follow up sample still tested positive for LA with reduced tPA levels.

Conclusion

This case illustrates the contribution of multiple thrombophilic and vascular risk factors in clinical manifestation of recurrent retinal vein occlusion suggesting that RVO development is more likely multigenic and heterogenous than being caused by a single risk factor. This case also stresses on the warrant of a more thorough work-up in RVO cases with clinical features such as young age, recurrent presentations, or bilateral involvement. This case also raises a question as whether causal or individualized treatment should be taken up by the clinicians for better outcome in such cases. Effective prophylaxis can be achieved by identifying the risk factors in RVO cases and help decreasing its incidence.

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