



## REVIEW ARTICLE

# Hyper-Homocysteinemia and other Inherited Thrombophilic Factors Inducing Retinal Vein Occlusion. The Employment of Novel Orals Anti-Coagulants is Possible?

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### Abstract

Retinal Vein Occlusion (RVO) is the second cause of unilateral visual loss, and can have ischemic or non-ischemic aetiology. The causes inducing RVO may be due to thrombophilia induced by acquired or inherited risk factors. We refer on inherited thrombophilic factors alone, such as Hyper-Homocysteinemia (HHcy) (due to Methylene-Tetra-Hydro-Folate Reductase (MTHFR) gene mutation), primary antiphospholipid syndrome, factor V Leiden mutation, protein C, protein S and antithrombin deficiencies, and prothrombin mutation. Medical treatment for RVO prevention, has been based on traditional anticoagulant drugs (heparins and oral vitamin K antagonists). But, New Oral Anticoagulants (NOACs), already employed with positive effects in other venous thromboses, such as deep venous thrombosis, pulmonary embolism a venous thromboembolism, could be considered in order to treat RVO both in acute phase and chronically, for prevent further events. But, the contemporary employment of antiplatelet agents and NOACs must be considered in RVO-HHcy induced.

### Keywords

Retinal Vein Occlusion (RVO), Thrombophilic risk factors, Low Molecular Weight Heparins (LMWHs)

## Introduction

Retinal Vein Occlusion (RVO) consists in the blockage of venous circulation that drains the retina. It is a rather frequent complication and represents the second most common cause of vision-threatening retinal disease in ageing patients [1]. Usually, RVO is directly caused by hypercoagulability and/or slowing down of vein retinal drainage [2]. In few cases, thrombotic accumulation in the adjacent

central retinal artery compresses the retinal vein causing a turbulent flow of vein retinal circulation, indirectly responsible for RVO. According to the different degree of occlusion, RVO is further divided in ischemic and non-ischemic, each having different indications for prognosis and treatment [3]. The difference is based on the area of capillary non-perfusion. In addition, in accordance with the site of occlusion, two types of RVO may be identified: Branch RVO (BRVO) and Central RVO (CRVO) [4]. BRVO is a blockage of the small veins of the retina. Inversely, CRVO consists in the occlusion of the central retinal vein. The visual prognosis is worse in those affected by CRVO than in patients with BRVO [5]. The risk of recurrence of RVO in the same eye or in the fellow eye is negligible and the cause of flow-restoration after RVO is unknown still now [6], even though it could be related to the balance of coagulation and anticoagulation [7,8].

As previously affirmed, thrombophilia is a cause of RVO, that may be acquired or inherited. Arterial hypertension, diabetes mellitus, atherosclerosis, increased plasma lipoprotein (a) Levels, advanced age and cigarette smoking, have been reported as acquired risk factors for RVO [9]. Other conditions, such as pregnancy, surgery, cancers, some myeloproliferative disorders, and the use of certain medications (i.e. contraceptive and menopausal hormone) may be also responsible of acquired thrombophilia [10]. On the contrary, Hyper-Homocysteinemia (H-Hcy) and Antiphospholipid Syndrome (APS) [11,12] can be causes of both acquired or congenital thrombophilia.



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In recent years, an increasing number of studies have been published searching for different genetic thrombophilic factors conferred by genes deriving from one or both parents. An inherited thrombophilic risk factor is: Congenital HHcy by Methylene-Tetrahydrofolate Reductase (MTHFR) gene mutation. Other inherited risk factors are: Primary APS; factor V Leiden mutation; prothrombin gene mutation; protein C and protein S and antithrombin deficiencies [13-15].

In this review, we will illustrate the risk factors of inherited thrombophilia alone and debate about their possible mechanisms of RVO.

### Inherited HHcy

Hcy is a sulfhydryl-containing amino-acid and represents an intermediate metabolite of the methionine cycle. The product can be further remethylated to methionine or trans-sulphurated to cysteine. Its reduced serum concentration happens for remethylation, through the enzyme Methylene-Tetrahydro-Folate Reductase (MTHFR). On the contrary, the genetic defect of this enzyme is a cause of inherited HHcy. MTHFR contains two cytosine nucleotides at position 677 (677CC).

One cytosine nucleotide might be replaced by thymine (C677T) in a single helix of DNA (heterozygotes) or in both helices (homozygotes). Homozygotes have approximately 70% reduction of normal MTHFR activity, whereas heterozygotes have almost 40% reduction of normal enzyme activity. C677T gene mutation of MTHFR enzyme is a most frequent cause of congenital H-Hcy, responsible for inherited thrombophilia [16,17]. But, although a correlation between C677T mutation and RVO was hypothesized, the role of this mutation in RVO pathogenesis remains unclear. In this connection, a recent meta-analysis of Li, et al. confirmed no significant association between MTHFR C677T genotype and RVO [18].

It is known that HHcy is a risk factor for both arterial and venous disease. Specifically, moderate HHcy is a frequent and independent risk factor for premature coronary, cerebral and peripheral diseases. But, the association of HHcy with venous thrombosis was also shown. That generally occurs in heterozygotes with mild HHcy and Factor V Leiden mutation and involves a 10-fold increase in the risk of venous thromboembolism. Among the modalities hypothesized by thrombophilia depending on HHcy in the RVO pathogenesis there are: The toxic action of Hcy on endothelial cells, the impairment of thrombomodulin expression, the activation of factor V, the low-density lipoproteins oxidation, and the inhibition of activated of protein C [19].

### Antiphospholipid syndrome

APS can be both primary and secondary to another pathology, such as lupus erythematosus, infection or pregnancy [20]. Although the precise mechanism whereby APS can induce a hypercoagulable state remains unclear, some

theories have been advanced. Among these, inhibition of C protein pathway, inhibition of its activation, or inhibitions of antithrombin activity are included. The most common venous thrombosis associated to anticardiolipin antibodies is Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), but sometimes these antibodies may also cause RVO [21].

### Factor V Leiden mutation

Factor V Leiden (FVL) mutation is found as a common cause of inherited thrombophilia [22,23]. It involves a G (guanine) to A (adenine) substitution at nucleotide 1691. This mutation is characterized by a poor anticoagulant response to Activated Protein C (APC) that favors an increased risk for venous thromboembolism [24]. Therefore, the terms FVL mutation and APC resistance should be considered synonymous. Heterozygous mutation of FLV increases the risk of venous thrombus 3-to 7 fold, while homozygous mutation increases the risk to approximately 80 fold. Some authors reported the prevalence of FVL mutation both in CRVO [25] and BRVO [26]. Recurrent BRVO induced by Factor V Leiden mutation was also described by Banik and coll [26]. Salim, et al. reported a case of young woman with CRVO due to a hypercoagulable state secondary to FLV mutation, despite systemic anticoagulation therapy [27]. Other authors refer on CRVO occurrence by FLV despite the use of warfarin [28].

### Prothrombin mutation

A point mutation of prothrombin was identified at position 20210 (change G-A). Specifically, prothrombin mutation causes elevated plasma prothrombin levels, increasing thrombin formation. In turn, high prothrombin serum levels induce activated protein C resistance and promote formation of abnormal fibrin networks. Prothrombin mutation is associated with venous thromboembolism and previous literature clearly illustrated its role in mediating RVO [29].

### Natural anticoagulant deficiencies

Deficiencies of natural anticoagulants are rare and, combined are found in less than 15% of all individuals. Specifically, Protein C (PC) deficiency occurs 1 every 200/500 people, whereas Protein S (PS) deficiency is expected 1 every 500 individuals, and antithrombin III (AT III) deficiency is present 1 every 2000/5000 persons.

In particular, deficiencies of activated PC and PS are responsible for inhibition of some anticoagulant cofactors (factor Va and factor VIIIa), while AT III deficiency acts by inhibiting the serine proteases (factor III, X, XI, XII). Inherited deficiencies of these anticoagulants represent important risk factors for RVO, particularly in young individuals [30]. Therefore, although the prevalence of these deficiencies is low, they should be screened for all thrombophilic patients affected by RVO [31-33].

## Treatment

Thrombophilia is a condition predisposing to thrombosis occurring both in arterial vessels and in veins. Obviously, different anti-thrombotic treatments are requested for these two conditions. Arterial thrombi must be treated with antiplatelet drugs, while venous thrombosis requires anticoagulant compounds [34].

RVO is consequent to retinal vein thrombosis happening directly, via slowing down, hypercoagulability, and turbulence of retinal vein flow or (less frequently) indirectly, via compression of blood venous flow and subsequent its slowing down, performed by adjacent arterial retinal thrombus previously organized. Therefore, both in acute phase and to prevent recurrent events, RVO-patients may benefit from anticoagulant drugs. Current guidelines recommend an initial treatment with Low Molecular Weight Heparins (LMWHs) [35]. These are useful for their additional properties, such as anti-angiogenic effect [36], anti-inflammatory and immunomodulatory properties [37-39]. Practically, if diagnosed within 15 days, LWMH must be administered for two first weeks. Afterwards, LWMH treatment must be followed by oral Vitamin K Antagonists (VKAs), for long-term anticoagulation. Regular coagulation-time monitoring and dose adjustment of VKAs, to maintain the Index of Normalization Ratio (INR) in the therapeutic range are required for whole duration of therapy. My experience performed in few cases only of RVO-HHcy dependent, confirms these therapeutic modalities. In fact, a partial improvement of visual acuity was obtained when LWMH was used in the early phase for 1-3 months in comparison with those received antiplatelet drugs. Successively, aspirin was administered again, to prevent possible cardiovascular events induced by inherited HHcy. The Guidelines of the Royal College of Ophthalmologists also recommend against the use of antiplatelets for primary prevention of RVO [40]. But referring to RVO-HHcy induced, recently Ageno, et al. on purpose of the treatment of venous thrombosis in unusual sites, affirmed that RVO-HHcy related appears to be a different disease entity caused by either local or systemic cardiovascular risk factors. For this reason, the need for anticoagulant therapy is extremely uncertain and antiplatelet agents are frequently prescribed [41].

In recent years, Novel Oral Anticoagulant Drugs (NOACs) have developed [42]. These offer a number of advantages over VKAs, such as predictable dose response, fewer drug and interactions, and no need for laboratory monitoring of the INR or other coagulation tests. These drugs were already successfully employed to prevent DVT, PE, Venous Thrombo-Embolic (VTE) and recurrent events [43]. Nevertheless, several uncertainties still persist about the use of NOACs instead of antithrombotic drugs in RVO-dependent by inherited thrombophilia, as HHcy, because of concomitant pro-thrombotic effects of that, favouring atheroscle-

rotic lesions. With reference to the venous thromboses induced by inherited thrombophilia in unusual sites. Undas and Goralczyk in a serie of 33 patients with severe thrombophilia provided the first-life experience with Non-Vitamin K Antagonists Oral Anticoagulants (NOACs), given instead of VKAs (warfarin or acenocumarol) [44]. In this study, thrombophilia was dependent on anti-thrombin deficiency, Protein C, or Protein S deficiencies, Factor V Leiden or pro-thrombin G20210A mutations, but not on HHcy, and AA did not discussed this occurrence. In my opinion, in the presence of RVO-HHcy induced, at antiplatelet drugs (previously administered to prevent athero-thrombotic events), should be added NOACs. These will be given at the same time, both in acute phase and during the following 3-6 months, even through this behaviour increases the bleeding risk. Subsequently, antiplatelet drugs alone should be indefinitely continued.

## Disclosure Statement

The Author declares to have no conflict of interests.

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