Derleme (Review)

Pathogenesis and Risk Factors In Retinal Vein Occlusions

Retinal ven tıkanıklıklarında patogenez ve risk faktörleri

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Abstract
Retinal vein occlusions (RVO) are by far the most common cause of retinal vascular occlusive diseases especially in middle-aged and older individuals. Basically, there are two forms of RVO, namely, branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Even though mechanisms resulting in venous occlusion may differ, there are also similarities in the etiopathogenesis of these two types. Like other vascular occlusive diseases elsewhere in the body, it is very crucial to find out if there is an underlying cause and / or predisposing factor for RVO. Most researches show that the pathogenesis of RVO is multifactorial and the most common associated disease is arterial hypertension. Moreover, recent investigations have determined that numerous genetic and acquired disorders may predispose to RVO and thereby affect visual prognosis. In this review, it was aimed to consider the pathogenesis of RVO along with its local, systemic and haemostasis-related risk factors and to discuss well-known as well as new predisposing factors for thrombosis.
Key Words: **Pathogenesis; Retinal vein occlusion; Risk factors.**

Özet
Retinal ven tıkanıklıkları (RVT), özellikle ileri yaş grubundaki retinanın damarsal hastalıkları içerisinde en sık görülenlerinden birisidir. Temel olarak, retinal ven dal tıkanıklığı (RVDT) ve santral retinal ven tıkanıklığı (SRVT) olmak üzere iki bölümde incelenir. Her iki tip RVT olgularında venöz tıkanıklık yapan mekanizmalarda farklılıklar bulunsa da, etyopatogenezlerinde bazı benzer noktalar bulunmaktadır. Vücudun diğer her hangi bir bölümünde görülen tıkanıklıkta olduğu gibi, RVT için de altta yatan nedeni ve / veya predispozan faktörleri ortaya koyabilmek oldukça önemlidir. Birçok çalışma göstermektedir ki, RVT patogenezi çok faktörlüdür ve RVT hastalarında en sık görülen ortak hastalık da sistemik hipertansiyondur. Bununla birlikte, son yıllarda yapılan çalışmalar RVT oluşma riskini arttıran ve dolayısıyla görme prognozunu etkileyen çok sayıda genetik ve sonradan kazanılmış bozukluk tarif etmişlerdir. Bu derlemede, RVT patogenezini yerel, sistemik, hemostaz ilişkili risk faktörleri ile beraberce irdelemek ve yeni ve eski tüm predispozan faktörleri tartışmak amaçlanmıştır.
Anahtar Kelimeler:**Patogenez; Retinal ven tıkanması; Risk faktörleri.**

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Introduction

Retinal vein occlusion (RVO) is an important cause of severe visual loss affecting not only elderly individuals (1) but also young patients (2). In general, RVO can be divided into two anatomic categories such as branch retinal vein occlusion (BRVO), and central retinal vein occlusion (CRVO). Hemicentral retinal vein occlusion (HCRVO), which affects only half of the retina, is a pathologically variant of CRVO. The fundus photographs of CRVO and BRVO are shown in Figure 1 and 2.

Even though RVOs have attracted much attention in recent years, the pathogenesis of RVO is not clarified yet. As a result of numerous researches investigating the risk factors and the pathogenesis of RVO, authors have established a consensus view that RVO is a multifactorial disease and the underlying pathophysiologic factors seem to be complex and multiple. Several ocular and systemic risk factors such as hypertension, cardiovascular disease, diabetes mellitus, systemic vascular disease, systemic clotting disease, hyperlipidemia, hyperopia, pseudoexfoliation syndrome, and glaucoma have been shown to contribute to the pathogenesis of RVO (3 - 7).

Basically, thrombogenesis is associated with Virchow's triad including abnormalities of blood flow, abnormal blood constituents and vessel wall damage. Therefore, both acquired and genetic disorders may contribute to the pathogenesis of RVO through these factors.

Ocular Risk Factors

Axial length and hyperopia:

In one of the studies by Green et al., it has been documented that a thrombus was shown histopathologically in the central retinal vein at or near the lamina cribrosa in eyes with CRVO (8). There are numerous systemic factors that may contribute to the formation of thrombus inside of central retinal vein. Besides these factors, the anatomic structure of the eye is also an important risk factor for thrombus. For instance, hyperopic eyes with a shorter axial length have a small lamina cribrosa and also narrow scleral canal, which may lead to a relative mechanical blockage in the vein. This blockage was thought to cause thrombus formation by leading to turbulence flow in the vein (9). Similarly, Brown et al. have speculated that eyes with a shorter axial length might be predisposed to crowding in the lamina cribrosa (10). Hyperopia is not only an important factor in CRVO but also in BRVOs. For example, Johnston et al. (11) and Appiah et al. (12) showed that hyperopia was significantly more prevalent in BRVO in their studies.

Pseudoexfoliation syndrome and glaucoma:

Glaucoma is an important risk factor for the development of RVO, especially CRVO (13). In a population-based study, persons with increased intraocular pressure and / or glaucoma were found to have a higher prevalence of RVO than persons with no history of elevated intraocular pressure (14). In another case-control study by Gumus et al., glaucoma was found to be a risk factor especially for CRVO (15). A popular theory how glaucoma increases the risk of RVO is that increased intraocular pressure causes external compression of the central retinal vein when it passes through the lamina cribrosa. This compression would probably result in turbulent blood flow and subsequent thrombus formation (16).

Pseudoexfoliation syndrome which is characterized by the intra- and extraocular deposition of abnormal extracellular matrix material is considered as a risk factor for numerous ocular complications, particularly chronic secondary open angle glaucoma, and has also been suggested to be associated with CRVO (17 - 19). It is thought that pseudoexfoliation had an indirect effect on the risk of RVO. Moreover, there is an interaction between pseudoexfoliation syndrome, glaucoma, systemic vascular disorders and retinal vein occlusion. In one study investigating the association of CRVO and pseudoexfoliation, it has been suggested that the high rise in intraocular pressure commonly seen in patients with pseudoexfoliation is probably the major cause of a high incidence of CRVO in these patients (20).

Inflammatory disorders:

The possible role of inflammation was first suggested in some types of CRVO especially in younger patients. In these patients, the presence of focal phlebitis, optic disc swelling, and vitreous cells make us think of underlying inflammatory process. Even though a definite inflammatory process has not been clarified yet, another point showing the role of inflammation in RVO indirectly is anecdotal cases that were treated with high-dose corticosteroids and intensive immunosuppressant agents and finally preserved their vision (21).

Systemic Risk Factors

RVO is not a disease that only the ophthalmologists must care about, but also it is often associated with the presence

of diseases related to internal medicine. Thus, a patient with RVO should be assessed meticulously with respect to below-mentioned systemic risk factors.

In fact, while talking about the risk factors for RVOs we should evaluate the risk factors separately according to the type or subtype of RVOs. Because, as Hayreh et al. supported this idea, it has been documented that prevalence of systemic diseases differed significantly not only among three main types of RVO (central retinal vein occlusion, hemi-central retinal vein occlusion and branch retinal vein occlusion), but also between their subgroups (22). For instance, in BRVO there was a significantly higher prevalence of arterial hypertension, peripheral vascular disease, venous disease, peptic ulcer, and other gastrointestinal disease than in central retinal vein occlusion (22). BRVO also had a significantly higher prevalence of arterial hypertension than that in hemi-central retinal vein occlusion (22). However, comparison of CRVO versus hemi-central retinal vein occlusion showed no significant difference in systemic diseases because of the pathogenical similarity (22). In literature, there are incompatible results of various studies. In the multicenter Eye Disease Case-Control Study (3, 23, 24) that evaluated the possible risk factors for CRVO, hemi-central retinal vein occlusion, and BRVO, they found increased risk with arterial hypertension and cardiovascular disease but not with diabetes mellitus in cases with BRVO (23). In CRVO, cardiovascular disease and diabetes mellitus were found to be associated with increased risk only for ischemic CRVO, whereas arterial hypertension was found to be associated with increased risk for both ischemic and nonischemic CRVO (3). In hemi-central retinal vein occlusion, it has been documented that there was an increased risk with arterial hypertension and diabetes mellitus (24). While evaluating the data of numerous researches on the subject of associated systemic diseases in RVOs, it is obvious that making any unifying comments about this issue is impossible except for arterial hypertension. Apparently in majority of reports, arterial hypertension has been considered as an important risk factor for most of the RVO cases.

Apart from systemic arterial hypertension and diabetes mellitus, there are a number of anecdotal case reports and researches of RVOs with many systemic risk factors, including hyperlipidemia (25, 26), sex hormone use (27), malignancy (28), smoking (29), and myeloproliferative diseases (30). However, no consensus regarding these issues has been established till now. Further investigations should be performed with larger sample sizes of cases and controls to clarify the exact role of these factors and possibly to bring new important risk factors into light.

HAEMOSTASIS RELATED RISK FACTORS

The coagulation cascade is a complex system involving numerous reactions resulting with fibrin formation. However, there is also the anticoagulant system in which the protein C, protein S and antithrombin III are the most important factors. In normal circumstances, there is a sensitive balance between these two systems, which inhibits the formation of thrombosis (31). As a result of any acquired or genetic disturbances in these cascades, pathologic thrombotic attacks may occur elsewhere in the body.

Deficiencies of physiologic clotting inhibitors: As a result of coagulation cascade prothrombin is converted to thrombin. Thrombin has numerous roles in regulating thrombosis other than the production of fibrin from fibrinogen. Thrombin binds thrombomodulin and plays a critical role in the conversion of inactive protein C to an active form (activated protein C=APC) in the presence of protein S. Then APC binds to and inhibits the procoagulant action of activated factor V and factor VIII. Deficiencies of these naturally occurring anticoagulants such as protein C, S, and antithrombin III may be a contributing factor for RVOs (32).

Antithrombin (AT) III is the most important direct inhibitor of thrombin, factors IXa and Xa, and to a lesser extent, factors XIa and XIIa. The antithrombin gene is situated on chromosome 1 and numerous mutations have been identified that result in reduced antithrombin activity (33).

APC proteolytically inactivates factors Va and VIIIa in the presence of protein S. The protein C gene is situated on chromosome 2 and many mutations have been identified that result in reduced protein C activity (34). Protein C deficiency occurs in two types: type 1 with low antigen and activity levels and type 2 with normal antigen but low activity levels. Because multiple mutations may play a role in protein C deficiency, diagnosis should be based on documenting low levels of protein C activity.

Protein S is a cofactor for the inactivation of factors VA and VIIa by APC (34). It circulates both in a free form (40%) and as one-to-one complex with a binding protein

(60%) (34). However, solely the free form of protein S is active. The protein S gene is situated on chromosome 3, and like protein C and ATIII, many mutations have been identified that is responsible for reduced protein S activity (34).

In many researches investigating the risk factors of RVO, protein C, S, and ATIII were analyzed. In a study by Bertram et al., ATIII was pathologically reduced in one patient with BRVO, proteins C and S were severely altered in two patients with CRVO, in only one case with ischemic optic neuropathy, and in one case with branch arterial occlusion (35). In another study from Turkey that investigated these parameters in patients with CRVO and BRVO, it has been concluded that deficiency of anticoagulant proteins, especially protein C, might play a role in the etiology of RVO (36). However, in our previous research, there was no statistically significant difference with respect to protein C, S and ATIII among the groups (controls, CRVO and BRVO). All these data shows that superficially there may be an association between RVO and above-mentioned anticoagulants. To generalize these data based on the published researches will not be justifiable due to small sample sizes and lack of statistical power. Therefore, further investigations must be planned in order to show the exact role of deficiencies of natural anticoagulants in RVO.

Elevated levels of soluble endothelial protein C receptor (sEPCR):
The endothelial cell protein C receptor (EPCR) facilitates protein C activation by binding protein C and enhancing its activation by the thrombin-thrombomodulin complex. In 1997, a soluble form of EPCR (sEPCR) in human plasma was characterized for the first time, and it has been indicated that sEPCR inhibits both activated PC (aPC) activity and PC activation by competing for PC with membrane-associated EPCR (37-39). Therefore, it has been addressed that elevated levels of sEPCR might be a candidate risk factor for thrombosis (38). Whether elevated levels of sEPCR can be a risk factor for RVO was firstly investigated in our study, and it was concluded that elevated levels of sEPCR could be an important risk factor for CRVO (15). However, to clarify the association between RVO and sEPCR, further investigations should be performed.

Antiphospholipid antibodies:
Antiphospholipid antibodies, which have been recently attracted attention, are considered as important risk factors for multiple thromboembolic events. Strong associations have been documented between antiphospholipid antibodies and various vascular events (40-42). Antiphospholipid antibodies are circulating polyclonal immunoglobulins that bind anionic membrane phospholipids and coagulation plasmatic proteins (43). In some anecdotal cases with primary antiphospholipid syndrome, ocular disorders such as ischemic optic neuropathy, retinal artery and venous occlusion have been reported (41, 44-46). On the contrary, there are some studies in which no strong association was found in patients with RVO (15, 47). However, a general approach is that in cases without any conventional risk factors, antiphospholipid antibodies should be screened.

Activated protein C resistance and factor V Leiden:
In coagulation cascade, factor Va is inactivated by activated protein C (APC) and a single point mutation, which results in a Gln-for-ARG substitution at position 506 (factor V Leiden), renders factor Va resistant to inactivation by APC (48). Resistance to APC results in a thrombotic tendency. APC resistance does not occur only as a result of factor V Leiden mutation, but also it can be induced by pregnancy, estrogens, and elevated levels of factor VIII (49, 50). APC resistance and factor V Leiden mutation are two of the most investigated factors in retinal vein occlusions. However, there are incompatible results regarding the association of APC resistance / factor V Leiden mutation with RVO in the literature. While some of the studies have suggested that APC resistance / factor V Leiden mutation seem to be important factors especially for the young patients with CRVO (51, 52), the others have not shown the association in any types of RVO (53-55).

Prothrombin G20210A mutation:
A guanine to adenine transition (G20210A) in the 3'-untranslated region of the prothrombin gene results in elevated levels of prothrombin which have been found to increase the risk of deep venous thrombosis (56). When it was investigated in patients with RVO, most of the studies failed to find any association between prothrombin G20210A mutation and RVO (53, 57-59) except for few anecdotal cases (60, 61).

Hyperhomocysteinemia:
In recent years, hyperhomocysteinemia has gained much importance in various thrombotic conditions. Metabolic

or genetic disorders in the intermediary catabolism of homocysteine, resulting in mildly or severely elevated plasma levels of homocysteine is known to be an independent risk factor for retinal vascular occlusive diseases (62). Recently, it has become clear that apart from rare genetic defects in methylenetetrahydrofolate reductase (MTHFR) and cystathionine â-synthase which are known to be associated with elevated levels of homocysteine, certain nutritional deficiencies of folic acid, vitamin B6 and vitamin B12 are so important and should also be considered as common determinants of elevated homocysteine concentrations (63). Moreover, supplementation with these vitamins may lower elevated levels of homocysteine and may reduce the risk of vascular disease (64, 65).

MTFHR is a pivotal enzyme that is important for the remethylation pathway of homocysteine. A point mutation, 677C-T, which substitutes alanin for valine results in a less active thermolabile form of the MTHFR enzyme and also elevated levels of homocysteine (62). While heterozygotes have a reduced enzyme activity to 65% of normal, homozygotes has solely 30% of normal activity (66). Many investigations have been performed to identify whether this mutant MTHFR causes an increased risk for RVO. On the other hand, while some studies found a significant number of patients carried this mutation and suggested widespread screening (58, 67); the others did not support a relation between the MTHFR mutation and RVO (68, 69).

Elevated levels of lipoprotein (a):

Lipoprotein (a) is one of the novel independent risk factors for most of the thrombotic disorders. Recently, it has been documented that elevated levels of lipoprotein (a) might be associated with thrombogenesis and atherosclerosis (70). Even though several meta-analyses have provided support for an association between lipoprotein (a) and coronary artery disease, the exact physiological role of lipoprotein (a) is not clarified yet. However, lipoprotein (a)' s association with thrombotic process can be linked to its striking homology with plasminogen, such that it competes with plasminogen for fibrin binding thus inhibiting fibrin degradation (71, 72).

Nowadays, the attention in the issue regarding whether lipoprotein (a) might be correlated with increased risk of RVOs has gradually increased. For instance, in one study by Stojakovic et al., markedly elevated concentrations of lipoprotein (a) was found both in cases with RVO and retinal artery occlusion (73). Similarly, according to our previous study investigating the numerous thrombophilic risk factors in RVO, elevated levels of lipoprotein (a) were found to be a risk factor for CRVO (15). In another study, it has been suggested that while lipoprotein (a) might also be involved in RVO, it does not seem to be a prognostic factor for RVO (71). In line with these results, Muller et al. have also stressed that there was a significant association between RVO and lipoprotein (a) (74).

Elevated levels of PAI-1 and polymorphism of PAI-1 gene:

It is well known that after the fibrin clot is formed it is lysed through the action of plasmin (fibrinolysis), which arises from plasminogen. Tissue plasminogen activator plays a critical role during the conversion of plasminogen to plasmin and it is inhibited by plasminogen activator inhibitor-1 (PAI-1). At this point, the relationship between PAI-1 and lipoprotein (a) is very interesting. For instance, Glueck et al. has stressed that patients with RVO and with the 4G/4G and 4G/5G genotypes were more likely to have high lipoprotein (a) levels than normal controls with the same genotypes (57). There is also limited evidence about the association of PAI-1 and its genetic polymorphisms with RVO. In one of these studies, elevated levels of PAI-1 in CRVO were documented by Marcucci et al (75). However, further investigations are needed to clarify the exact role of hypofibrinolysis in RVO.

Plasminogen deficiency:

There are few studies regarding plasminogen deficiency and its association with RVO in literature. In one case report with unilateral CRVO and ipsilateral cilioretinal artery occlusion, it was concluded that the combination of decreased plasminogen activity and elevated lipoprotein (a) levels should be considered as a possible cause of both retinal vein and artery occlusions (76). In another case report, a case of central retinal vein and branch artery occlusion associated with inherited type I plasminogen deficiency (68%) and permanent elevation of lipoprotein (a) (460 mg/l, S2 phenotype) in a 45 year old white woman with no associated local or systemic risk factors was presented by Tavola et al (77).

Factor XII deficiency:

Factor XII deficiency is also among the coagulation disorders that have been implicated in major thromboembolic events. However, there is limited data

about an association of this coagulation disorder and RVOs. In one study that investigated the prevalence of factor XII deficiency in patients with RVO, while factor XII deficiency is found to be highly prevalent in RVO patients under 45 years of age, the prevalence of factor XII deficiency in RVO patients older than 45 years appears to be similar to that seen in healthy individuals (78).

Elevated levels of factor VIII Factor VIII is a cofactor for factor X activation by factor IXa. In plasma it is bound to von Willebrand Factor (vWF), which protects factor VIII from APC inactivation (32). Among a few clotting factors in coagulation cascade, factor VIII attracts the most attention. The most important cause of its importance is the fact that the morbidity for cardiovascular diseases is less among hemophiliacs than those in the general population. Because of this, factor VIII levels were investigated in various types of thrombotic events. On the light of these investigations, it has been reported that high levels of factor VIII might be associated with increased thrombotic risk (79, 80). In another study, it has been documented that high levels of factor VIII and thrombin activatable fibrinolysis inhibitor (TAFI) were found as mild risk factors for venous thromboembolism especially in factor V Leiden carriers (81). However, when the literature data about factors VIII and thrombosis is evaluated, it may be speculated that elevated factor VIII levels play a role in combination with other inherited deficiencies in the development of thrombosis. Factor VIII was also investigated in our previous study and it was concluded that the patients with CRVO had significantly higher levels of factor VIII when compared to those of controls (15). However, in another study, factor VIII and vWF were not found to be important risk factors for CRVO and the authors did not recommend the routine evaluation of these factors in CRVO patients (82). Finally, further larger case-control studies should be carried out to give more information about the exact role of factor VIII in cases with RVO.

In addition to all these factors, many others such as TAFI (83) and 807C/T polymorphism in platelet glycoprotein Ia gene (84) have been recently investigated to lighten the pathogenesis of RVO. However, further clinical and laboratory-based investigations are needed to understand the exact mechanisms as to how RVO occurs and which factors play direct role in the formation of thrombosis.

Consequently, retinal venous thrombosis seems to be multifactorial except in rare cases and generally more than one above-mentioned abnormality needs to be present for the formation of thrombosis. Furthermore, if a hereditary defect and / or acquired metabolic abnormalities related to thrombosis are found, the patient with RVOs must be referred to a hematologist and an internist in order to discuss treatment modalities and thereby to prevent further severe thrombotic attacks in the following years.

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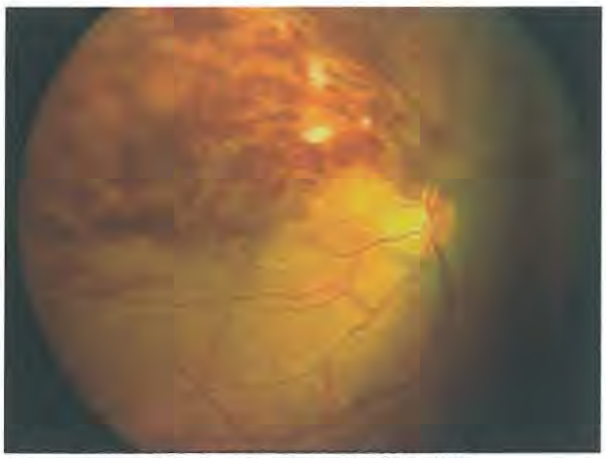

Figure 1. Fundus photograph of BRVO

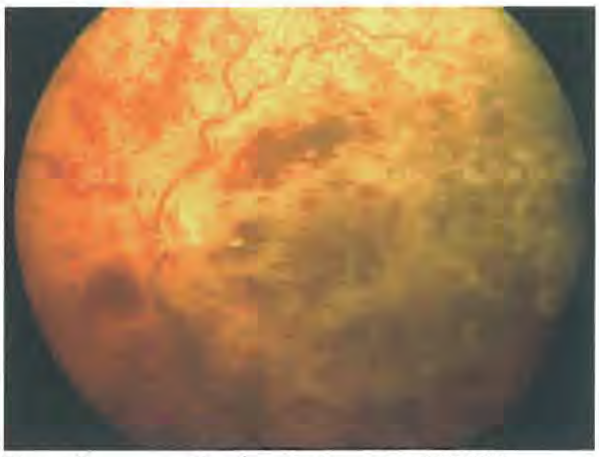

Figure 2. Fundus photograph of CRVO

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