

THE MAIN ASPECTS OF RETINAL VEIN OCCLUSION ETIOPATHOGENESIS IN YOUNG ADULTS. PART I. NEURORETINOVASCULITIS (PROTHROMBOTIC POTENTIAL, CLINICAL MANIFESTATIONS)

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For citation: Tultseva SN, Lisochkina AB, Titarenko AI, Turgel VA. The main aspects of retinal vein occlusion etiopathogenesis in young adults. Part I. Neuroretinovasculitis (prothrombotic potential, clinical manifestations). *Ophthalmology Journal*. 2018;11(2):57-67. doi: 10.17816/OV11257-67

Received: 02.04.2018

Accepted: 10.05.2018

✧ This review is dedicated to the neuroretinovasculitis, which is the leading cause of retinal vein occlusion in young adults. Presumed etiological factors, possible pathogenic mechanisms, and clinical manifestation are analyzed. Advisability of multidisciplinary approach in management and individual approach in treatment of patients with neuroretinovasculitis with secondary retinal vein occlusion are justified.

✧ **Keywords:** neuroretinovasculitis; retinal vein occlusion in young adults; thrombophilia; endothelial dysfunction.

ОСНОВНЫЕ АСПЕКТЫ ЭТИОПАТОГЕНЕЗА ОККЛЮЗИЙ ВЕН СЕТЧАТКИ У ЛИЦ МОЛОДОГО ВОЗРАСТА. ЧАСТЬ I. НЕЙРОРЕТИНОВАСКУЛИТЫ (ПРОТРОМБОТИЧЕСКИЙ ПОТЕНЦИАЛ, КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ)

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Для цитирования: Тульцева С.Н., Лисочкина А.Б., Титаренко А.И., Тургель В.А. Основные аспекты этиопатогенеза окклюзий вен сетчатки у лиц молодого возраста. Часть I. Нейроретиноваскулиты (протромботический потенциал, клинические проявления) // Офтальмологические ведомости. – 2018. – Т. 11. – № 2. – С. 57–67. doi: 10.17816/OV11257-67

Поступила в редакцию: 02.04.2018

Принята к печати: 10.05.2018

✧ Обзор литературы посвящён нейроретиноваскулиту, как ведущей причине окклюзии вен сетчатки у лиц молодого возраста. Рассмотрены предполагаемые этиологические факторы, возможные механизмы патогенеза и клиническая картина данного заболевания. Обоснованы целесообразность мультидисциплинарного подхода к ведению и индивидуальный подход в лечении пациентов с нейроретиноваскулитом со вторичной ОВС.

✧ **Ключевые слова:** нейроретиноваскулит; окклюзия вен сетчатки у лиц молодого возраста; тромбофилии; дисфункция эндотелия.

INTRODUCTION

Retinal vein occlusion (RVO) is one of the most widespread retinal vascular disorders, becoming

increasingly common among young and middle-aged people [4]. What is the cause of RVO in young, somatically healthy individuals? Despite

active research in this area, this question remains unanswered. It was found that thrombosis in RVO is caused by local impairments in the integrity and functional activity of the retinal vein endothelium, accompanied by secondary venous hypertension. This results in the breakdown of the internal hemato-retinal barrier and development of macular edema.

Local damage of retinal veins with subsequent endothelial dysfunction may be caused by inflammation of the vascular wall (phlebitis or vasculitis) [3, 5], vascular compression (in the arteriovenous junction and/or in the area of the lamina cribrosa), and the impact of venous blood as a contact media (increased viscosity, pressure, change in composition, etc.) [1, 4]. The predominant role of inflammation in RVO in young individuals is evidenced by multiple facts, including clinical manifestations typical of phlebitis, detection of concomitant specific and non-specific inflammation in the body, and the positive effect of anti-inflammatory therapy. The inflammatory process accompanies RVO in 18%–42% of young patients [3, 5] and 11.8% of patients of all ages [88]. Patients with RVO aged <41 years have a 3.6- and 8-fold higher chance of having inflammation compared with those aged 41–50 years and 51–60 years, respectively [3]. However, thus far, a causal relationship between inflammation and RVO has not been established. This problem remains unresolved, illustrated by the lack of universally adopted term for RVO with signs of pronounced neurovasculitis.

In the Russian medical literature, this condition is described as “inflammatory RVO,” whereas in the international literature it is usually referred to as “benign retinal vasculitis” [39], “optic disk (OD) vasculitis” [40], “enlarged blind spot syndrome” [42], “supposed OD phlebitis,” “central RVO (CRVO) in young patients” [27], “RVO due to retinal vasculitis” [80], and “RVO with inflammatory etiology” [88]. According to the pathophysiology of the process, in our opinion the most appropriate terms for these entities are “neuroretinovasculitis” or “neuroretinovasculitis with secondary RVO.”

The early detection of inflammation as the main etiologic factor in RVO dictates the diagnostic and treatment strategy, i. e., the need for identification

of an infectious agent, administration of active anti-inflammatory therapy, and involvement of other healthcare professionals.

This review aimed to analyze the currently available Russian and international medical literature focusing on RVO with signs of vasculitis in young adults and identify the main etiological aspects of the disease and diagnostic criteria allowing physicians correctly diagnose at the first visit to the clinic.

ETIOLOGY AND PATHOGENESIS OF NEURORETINOVASCULITIS WITH SECONDARY RVO IN YOUNG PATIENTS

The clinical manifestations of RVO in young healthy individuals and the potentially inflammatory nature of the disease have been discussed by ophthalmologists for more than 50 years. In 1961, T.K. Lyle and K. Wybar described seven patients aged 14–19 years with ophthalmoscopic picture similar to those observed in RVO, naming the condition retinal vasculitis. They concluded that it was associated with inflammation in the central retinal vein (CRV) and OD. In one case, the patient was also diagnosed with pulmonary tuberculosis; thus retinal vasculitis was considered as a manifestation of Eales disease [53]. Five years later, L.I. Lonn and W.F. Hoyt reported five cases with similar symptoms and used the term “papillophlebitis.” Consistent with the findings of Lyle and Wybar, Lonn and Hoyt suggested that RVO is primarily caused by inflammation in the veins and OD [42]. At that time, large-scale studies on RVO were not available, only several case reports in which the investigators described the disease as “mild retinal and papillary vasculitis” [17] or “benign retinal vasculitis” [39]. The main manifestation of this condition was rapid and unilateral painless vision loss in healthy individuals aged 20–35 years (more often observed in women). This was accompanied by cellular infiltration of the vitreous and typical ophthalmoscopic findings, including OD edema and hyperemia, pathologically dilated and tortuous retinal veins, and intraretinal hemorrhages along the retinal vessels. Of note, the investigators emphasized that the disease is relatively benign even in the absence of a

specific therapy and showed good response to treatment with glucocorticosteroids [27, 28]. Rarely, the disease may be complicated by complete RVO accompanied by impaired capillary perfusion and a significant decrease in vision [16, 36]. The majority of studies failed to demonstrate an inflammatory etiology of this process. However, several studies suggested an association with Eales disease [42], systemic lupus erythematosus, and systemic vasculitis [17]. Fact that inflammation of the retinal vein walls was preceded RVO is confirmed by typical clinical manifestations and the results of histological examination, which demonstrated mononuclear cell infiltration in the CRV and pronounced phlebitis of the OD vessels [12].

S.S. Hayreh has authored the most important publications focusing on this pathological condition. Using previously published case reports ($n = 32$) and personal observations ($n = 8$), he introduced the term “OD vasculitis” describing two types of the condition [40]. Type I OD vasculitis is characterized by unilateral OD edema and hyperemia with white exudates on and around the OD, peripapillary retinal edema, moderate dilated veins, intraretinal flame-shaped hemorrhages, and accompanying sheathing along the vessels. In one week the retinal edema resolved, and hard exudates were deposited. Fluorescein angiography (FA) demonstrated slow retinal vein filling without fluorescein staining of the venous wall. The perimetry shows an enlarged blind spot in the affected eye.

Type II OD vasculitis is characterized by less pronounced OD edema with marked hyperemia, more dilated and tortuous veins, single cotton-wool spots, retinal hemorrhages of various sizes, spread to the middle periphery, exudation on the OD and along the arteries, macular edema, and opticiliary shunt vessels in the late stages. The hemorrhages are not as extensive as those observed in RVO. FA demonstrates significant delay of venous blood flow with vascular wall staining and fluorescein leakage from large veins. The perimetry shows scotomas corresponding to intraretinal hemorrhages and enlargement of the blind spot, less marked than those reported in type I OD vasculitis.

S.S. Hayreh suggested that type I OD vasculitis results from nonspecific vasculitis of the ciliary vessels in the prelaminar region, with subsequent increase in capillary permeability and accumulation of fluid in loose prelaminar tissue. The process is accompanied by OD swelling and vein compression in the prelaminar region, which increases OD edema. The OD edema may cause compression of the CRV in the OD area and secondary retinal venous stasis.

According to S.S. Hayreh, the primary cause of type II OD vasculitis is phlebitis of the CRV in the region of the optic nerve head or retrolaminar region. This leads to localized thrombosis in the CRV and specific clinical manifestations (without signs of arteriosclerosis typical of older patients with RVO). In such cases, the OD edema is most probably caused by coexisting vasculitis of the OD.

Thus, S.S. Hayreh considered OD vasculitis as nonspecific endogenous inflammation resulting from the sensibilization of vessels to intraocular (e. g., lens proteins) or extraocular (e. g., bacterial and viral) antigens, or the formation of complex auto-antibodies.

More recent studies (2012–2016) demonstrated an association between neuroretinovasculitis (accompanied by RVO) and seronegative rheumatoid arthritis, high titers of antinuclear antibodies, Crohn's disease [25, 29, 80], chorioretinitis, and infectious retinal vasculitis (bacterial, viral, and toxoplasmic). More than 50% of the patients demonstrated reactivation of herpesvirus, cytomegalovirus, and toxoplasmic infection at the onset of RVO [2]. The disease may also occur in patients with systemic, syndrome, and autoimmune disorders (Behcet's syndrome, Reiter's syndrome, and sarcoidosis), as well as in individuals with optic neuritis [3].

The most comprehensive Russian study in this field was conducted by T.E. Tankovskiy. He examined 611 patients and described a specific form of the disease: “inflammatory RVO.” His classification of RVO was based on etiological factors and contained information on the most common disorders associated with this process [3].

The detection of an infectious agent does not exclude other systemic risk factors, which prevalence varies between 30% and 70% [20, 41, 44, 67, 73, 75]. The role of hereditary thrombophilia in RVO is currently under debate [20]. A mutation of the factor V Leiden gene, observed in 8%–14% of cases, was shown to be significant [32, 47, 67]. Suthasinee et al. and KarskaBasta et al. demonstrated the important role of protein C and protein S deficiency, found in 3%–5% of patients with CRVO aged < 45 years [47, 75].

The most important vascular thrombophilias causing endothelial dysfunction in young individuals are hyperhomocysteinemia and arterial hypertension, observed in 44.5% and 30% of patients, respectively. Hypercholesterolemia, diabetes mellitus, and antiphospholipid syndrome, reported in 5.1%, 16.3%, and 2%–15% of cases, respectively, may also play an important role [6, 41, 44, 50, 73].

There are two possible mechanisms underlying the development of RVO in individuals with neuroretinovasculitis. The first mechanism is associated with vein narrowing caused by microbial agents and immune complexes. Soluble antigen–antibody complexes may be captured by arterial or venous elastic membranes or by basal membranes in veins resulting in activation of the complement cascade, mobilization of T lymphocytes, and direct cytotoxicity, which was confirmed for herpes simplex virus and cytomegalovirus [60, 61]. The second mechanism implies indirect damage to the endothelium caused by the viral/bacterial-induced expression of heat shock proteins and autoantibodies [23]. The following antigens may potentially damage retinal veins: myelin basic protein, myelin-associated glycoprotein, neurotrophic protein S100 beta, glial fibrillar acid protein, rhodopsin, and transducin. Of note, HLA-DR15 and B27 are homologous to uveogenic retinal S antigen; frequent detection of these antigens in patients with noninfectious retinovasculitis may be explained by cross-reactions [43]. Produced autoantibodies cause T-cell activation and increased production of TNF1, IL12, and IL-18 with subsequent endothelial damage.

The mechanism of vein compression by edematous OD tissue is described separately in the literature. Such compression may result in impaired venous outflow with the formation of turbulent blood flow, formation of lateral shear forces, and disintegration of the endothelial layer [40]. The mechanisms described above may be further aggravated by the narrowing of veins due to external compression caused by arteries affected by dyslipidemia and arterial hypertension (including masked hypertension) or because of increased arterial wall stiffness without its morphological changes in patients with vascular dysregulation. High levels of endothelin 1, erythropoietin, and hypoxia-inducible factor 1-alpha in the serum may also contribute to the pathological process in patients with vascular dysregulation [22, 26].

All mechanisms described above cause endothelial damage. Regardless of the mechanisms endothelial injury is associated with increased production of IL-1, IL-6, IL-8, ICAM, VCAM, MICA, heat shock proteins (HSP 60), and TNF-1 [19, 38, 55]. These cytokines increase the activity of the main tissue activator of the external hemocoagulation pathway and suppress the tissue plasminogen activator, which catalyzes the synthesis of the fibrinolytic enzyme plasmin. The local hemostatic system is thereby activated, leading to hypercoagulation, increased platelet and red blood cell aggregation, and formation of primary clots. This results in venous stasis and increased intravenous pressure, facilitating the accumulation of prothrombotic substances (normally removed with laminar blood flow) and hemoglobin denaturation. Destruction of hemoglobin stimulates the hypoxic response of leukocytes, platelets, and endothelial cells, exocytosis of Weibel–Palade bodies, production of the von Willebrand factor (vWF) and P-selectin, and their interaction with platelets, erythrocytes, and leukocytes. Hypoxia activates the production of the tissue factor from monocytes, which binds to factor VII and forms a reactive complex activated by Ca^{2+} and factor X [24, 52, 68, 74]. This condition may be aggravated by preexisting hereditary thrombophilia in young individuals or by increased blood viscosity associated with inflammation. Inflammation induces migration of leukocyte and ex-

pression of P-selectin, E-selectin, ICAM 1, VCAM 1, and proinflammatory cytokines. This results in increased production of procoagulants (TxA2, vWF, PAI 1, VCAM, ICAM, and TF) by endothelial cells, suppression of fibrinolysis, and decreased production of anticoagulants (EPCR, TM, PGI2, and tPA). The procoagulant effect of inflammation is also ensured by platelet activation and subsequent production of thrombin, endotoxin, adhesion molecules (fibrinogen, fibronectin, vWF, GPIIb/IIIa, and vitronectin),

coagulation factors (fibrinogen, F VIII, F XI, and F XII), PAI 1, and microparticles [74]. This cascade results in reduced blood flow and complete RVO (Fig. 1).

CLINICAL MANIFESTATIONS

The disease is characterized by acute onset with rapid and unilateral painless vision loss and metamorphopsia. This condition may be preceded by a prodromal period and herpetic rash [3, 5, 10]. Patients often have systemic or autoimmune disorders.

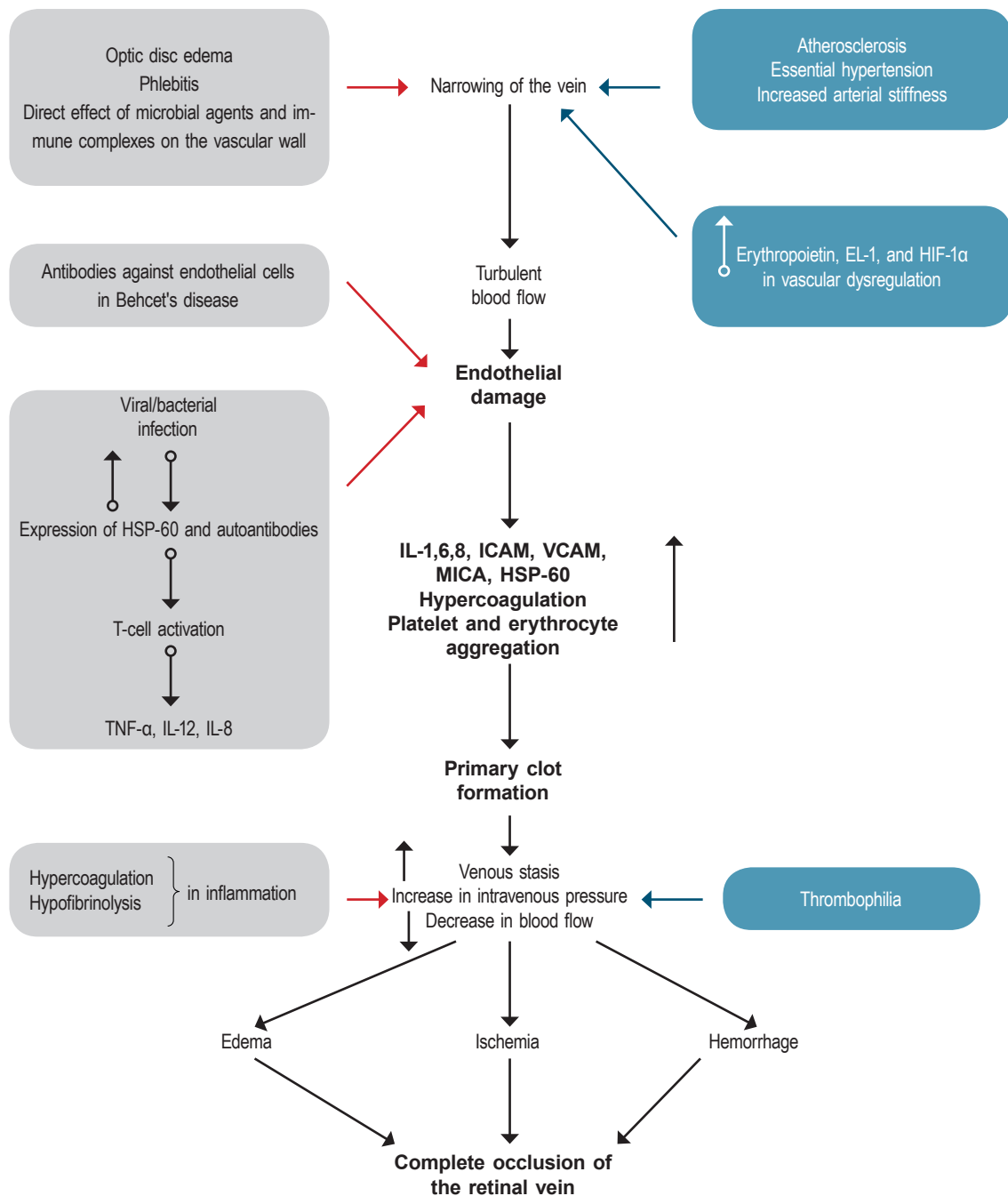


Fig. 1. Pathogenesis of retinal vein occlusion against the background of neuroretinovasculitis

Рис. 1. Патогенез окклюзии вен сетчатки на фоне нейроретинovasкулита

They usually present with cellular and protein infiltration of the vitreous, edema and hyperemia of the OD with exudates, dilated and tortuous retinal veins with exudates along the retinal vessels (segmental or confluent; perivenous lymphocytic or lymphoplasmacytic), intraretinal hemorrhages of various sizes, and occasionally cotton-wool spots [16, 21, 36]. Many patients develop macular edema with detachment of the neuroepithelium and subsequent macular star pattern through resorption.

FA of the retina is considered the most sensitive method for the diagnosis and management of patients with neuroretinovasculitis [8–10, 57, 78]. The main angiographic signs of neuroretinovasculitis are fluorescein leakage and staining of the venous wall caused by breakdown of the internal hemato-retinal barrier. Capillary leakage in various parts of the retina in combination with leakage from the OD (known as “hot” OD) is also considered to be diagnostically important. This leakage from dilated capillaries is caused by primary OD infiltration or by secondary vascular changes in response to inflammation. Patients with occlusive neuroretinovasculitis may have increased arteriovenous transit time, increased venous perfusion time, pulsating blood flow, and areas without capillary perfusion at the retinal periphery [71].

Laser photometry is recommended for the differential diagnosis of retinovasculitis, allowing quantitative and objective evaluation of cell infiltration and opalescence in the anterior chamber and vitreous [81]. Studies using laser photometry to assess the damage to the hemato-retinal barrier in RVO found a slightly increased flare with a maximum of 9.9 ± 2.4 photons/ms [64]. In contrast, patients with neuroretinovasculitis demonstrated a significantly increased flare (2.9 – 3.9 photons/ms) that correlated with inflammation activity and the etiological factor. In patients with sarcoidosis-associated posterior uveitis, the amount of protein was 26.9 ± 4.6 photons/ms; in herpetic uveitis 25.8 ± 6.1 photons/ms; and in Behcet's disease 22.1 photons/ms (5.4 – 623 photons/ms) [37, 86].

Sarcoidosis neuroretinovasculitis, observed in 20% of cases, is usually bilateral. The symptoms

of inflammation include periphlebitis with nodular or segmental perivenous epithelioid cell infiltration (candle wax exudates) [30].

One of the ocular manifestations of Behcet's disease is periphlebitis observed in 1%–22% of cases and accompanied by cystoid macular edema [60, 63, 83]. Also, inflammatory occlusion of CRV and its branches may be associated with Behcet's disease [79]. The diagnosis of ocular lesions in Behcet's disease is based on the criteria developed in 1990 by the International Study Group for Behcet's Disease [18]. These criteria include recurrent (at least three times per year) aphthous stomatitis in combination with at least two of the four following criteria: recurrent genital aphthae, symptoms of intraocular inflammation, skin vasculitis, and a positive test for skin hypersensitivity.

One of the typical manifestations of multiple sclerosis (MS) is retinal periphlebitis, similar to that observed in sarcoidosis and reported in 11%–25% of patients with an established diagnosis. Lymphoplasmacytic infiltrates, typical for retinal periphlebitis, are used as a biomarker reflecting the activity of MS [56]. Moreover, perivasculitis in MS is characterized by recurrent intraretinal and preretinal hemorrhages. The progression of periphlebitis results in occlusive peripheral vasculitis that may be complicated by peripheral retinal neovascularization with subsequent traction retinal detachment [65, 82].

Neuroretinovasculitis with secondary RVO is found in 1% of patients with Crohn's disease [25, 29, 76]. Hypofibrinolysis and hypercoagulability are considered as a predisposing factor [25, 29, 76].

One of the noninfectious vasculitides is idiopathic frosted branch angiitis, an immune-mediated response to provoking antigens [66]. The nature of these antigens remains elusive. They include antigens of the herpes virus, adenovirus, cytomegalovirus, Epstein–Barr virus, varicella zoster virus, Coxsackie virus, rubella virus, measles virus, tuberculo-protein, and antistreptolysin [59, 66, 76, 89]. Clinical manifestations of diffuse periphlebitis include perivenous infiltration, intraretinal hemorrhages, deposition of hard exudates, and serous exudative retinal detachment in the macular region

and periphery without signs of venous stasis or occlusion using FA. However, eight cases describing idiopathic retinovasculitis complicated by RVO have been reported [7, 35, 51].

The herpes viruses and cytomegalovirus may cause necrotizing herpetic retinopathy in young individuals. Although this disease affects primarily immunocompromised patients, it may also be observed in individuals with normal immunity [58, 69, 77].

There are very few publications available discussing herpes virus-associated necrotizing retinovasculitis [15, 48, 49, 85]. The disease manifests with peripheral occlusive retinovasculitis without signs of necrosis but with areas of ischemia at the retinal periphery and subsequent neovascularization [45]. In most cases, retinovasculitis is accompanied by cystoid macular edema.

Increased levels of immunoglobulins M to herpes viruses in the serum and their avidity indicate the infectious etiology of the disease. Detection of pathogenic DNA in the anterior chamber and/or vitreous using polymerase chain reaction is the most reliable, highly sensitive, and specific diagnostic method [84]. The positive clinical and immunological response to antiviral therapy confirms the herpetic etiology of this disease. However, in routine clinical practice, the diagnosis of herpes-associated non-necrotizing retinitis is based only on clinical data [45].

Ocular tuberculosis manifests with choroiditis complicated by occlusive peripheral periphlebitis and neovascularization in approximately 35% and 29% of cases, respectively [11]. Eye lesions in tuberculosis may be caused by direct infection or develop due to hypersensitivity to mycobacterial antigens [70, 72]. This hypersensitivity may also be involved in the development of Eales disease. This is an idiopathic, usually bilateral peripheral retinovasculitis primarily affecting young males (age of onset: 30–40 years) with the highest prevalence reported in India, Pakistan, and Afghanistan [13]. Biswas et al. suggested that retinal vasculitis in patients with Eales disease results from cell-mediated tissue damage caused by inactive mycobacterial antigens in a phenotypically predisposed popula-

tion [13, 14, 54]. The inflammation manifests with occlusive periphlebitis [14] emerging in multiple quadrants of the retina anterior to the equator. Early disease is asymptomatic; the main complaints usually appear only in the late stages of the disease following the development of complications, such as retinal neovascularization accompanied by recurrent hemorrhages in the vitreous and traction retinal detachment.

One of the rare causes of neuroretinovasculitis is benign lymphoreticulosis (cat scratch disease) induced by *Bartonella henselae*. Several cases of neuroretinovasculitis complicated by occlusion of the retinal vein and artery have been reported in patients with cat scratch disease [31, 33].

CONCLUSION

RVO is a complex disorder with multiple factors involved in its pathogenesis. The main and additional risk factors for RVO are well established today; however, their combination may be distinct in each patient. In middle-aged and elderly individuals, the main risk factors are atherosclerosis and arterial hypertension, whereas the most common additional risk factors include dyslipidemia, hyperglycemia, hyperhomocysteinemia, and primary glaucoma. In young patients, this combination is more specific. The main cause of the disease is inflammation manifesting with neuroretinovasculitis, whereas additional risk factors include various acquired thrombophilic disorders, local hemodynamic disorders, and several other pathological processes.

Therefore, in cases of young patients diagnosed with an RVO-like condition, initially is necessary to exclude the presence of infectious inflammatory diseases and subsequently search for rarer risk factors. In case if family history of thrombosis or taking oral contraceptives it is recommended to test prothrombotic genetic risk factors, plasma coagulation, platelet aggregation, and parameters of local and general hemodynamics.

Detailed immunological examination and the involvement of other healthcare professionals (i. e., virologists, rheumatologists, infectiologists) may assist in identifying the causes of neuroretinovascul-

litis. Specific manifestations of a particular type of retinovasculitis may be identified through additional ophthalmological examinations, including wide-field FA, laser photometry, and detection of microbial DNA and proinflammatory cytokines in the anterior chamber and vitreous.

Multiple factors are involved in the development of RVO in young individuals. Therefore, it is recommended to use a multidisciplinary approach and personalized therapy in the management of these patients.

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