VASCULAR RETINAL VENOUS OBSTRUCTION AND NEOVASCULARISATION

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Abstract: *Central retinal vein occlusion (CRVO) represents a major cause of visual loss and the second-most common retinal vascular disorder. Branch retinal vein occlusion (BRVO) is a common, visually disabling disease and consists of two distinct clinical entities: major BRVO and macular BRVO. A variety of neovascular events can appear in eyes with CRVO and BRVO, these are iris neovascularisation, angle neovascularisation, disc neovascularisation, neovascular glaucoma (NVG) and vitreous hemorrhage. The vascular endothelial growth factor (VEGF) plays a major role in the development of neovascularisation in eyes with CRVO and BRVO. The aim of this study is to characterize neovascular events that can occur in eyes with CRVO or BRVO. We took in the study a total number of 110 eyes from patients hospitalized in the Clinical County Emergency Hospital of Sibiu for a period of 7 years (December 2010-December 2016), 75% eyes presented CRVO and 25% eyes with BRVO. From a total of 110 eyes with CRVO and BRVO, 15% presented at the time they were hospitalized poor vision, high intraocular pressure (IOP), optic disc neovascularisation and vitreous hemorrhage. The first attitude was to stop the neovascularization by administrating intravitreal anti-VEGF factor and later, photocoagulation of the retina. From hospitalized cases, 20% developed neovascular glaucoma and presented high IOP, so we used a treatment plan that can help us to keep the IOP to normal values and in cases that were refractory to treatment, we performed trabeculectomy. Clinical monitoring of vascular venous obstruction by ophthalmoscopy and OCT imaging brings into attention the neovascularisation appearance and NVG. Intravitreal administration of anti-VEGF agents is an option to stop the neovascularisation, much better in combination with photocoagulation.*

INTRODUCTION

Central retinal vein occlusion (CRVO) is an important cause of visual loss and the second-most common retinal vascular disorder.(1) Branch retinal vein occlusion (BRVO) is a common, visually disabling disease, and consists of two distinct clinical entities: major BRVO and macular BRVO.(2)

A variety of neovascular events can appear in eyes with CRVO and BRVO, these are iris neovascularization, angle neovascularization, disc neovascularization, macular edema, ischemic maculopathy, neovascular glaucoma (NVG) and vitreous haemorrhage.(3,4) Regarding these devastating complications associated with the severe form of CRVO, there are a number of classifications in the literature. They take into account the area of retinal capillary nonperfusion and the development of neovascular complications.(5) The frequency of ocular neovascularization (NVI) is indirectly proportional to the degree of retinal perfusion and is most likely to develop during the first 3 months after occlusion.(1,2,3)

Ischemic subtype CRVO accounts for about 20% of all CRVO cases, the majority of neovascular events occur in eyes with this subtype of the condition.

The vascular endothelial growth factor (VEGF) plays a major part in the development of neovascularization in eyes with CRVO and BRVO. Neovascular glaucoma is a very difficult complication of retinal ischemia that becomes very difficult to treat.(3)

AIM

The aim of this study is to characterize neovascular events that can occur in eyes with CRVO or BRVO, the treatment and follow up that can be applied.

MATERIALS AND METHODS

We took in the study a total number of 110 eyes from patients hospitalized in the Clinical County Emergency Hospital of Sibiu for a period of 7 years (December 2010-December 2016), 75% eyes presented CRVO and 25% eyes with BRVO.

All patients were evaluated by a complete medical history and an ophthalmologic examination that included measurements of BCVA using Snellen chart, slit-lamp examination, gonioscopy, IOP measurement with I-care tonometer or Aplanotonometer, binocular fundus examination, Spectral Domain Tomography (OCT) and fluorescein angiography(FA).

Patient data was retrospectively collected and included the type of vascular event (CRVO or BRVO), the course of vascular event - development of neovascularization, status of macular edema, course of vitreous hemorrhages and neovascular glaucoma with all complications, early administration of anti-VEGF treatment versus later treatment.

Macular edema was evaluated by correlating BVCA, fundus biomicroscopy and OCT, and the administration of anti-VEGF treatment was considered in cases with thickness over 250 μm.

RESULTS

After we analysed the data that we collected, we observed that the event occurred more frequently in the left eye (59%) than the right eye (41%). In the gender-wise distribution, the incidence is more common in males (54%) than women

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(46%) but is not significant.

From a total of 110 eyes with CRVO and BRVO, 15% presented at the time they were hospitalized poor vision, high intraocular pressure (IOP), optic disc neovascularization and vitreous hemorrhage, and this group included the patients with neovascular glaucoma. The incidence of iris neovascularization in neovascular glaucoma in CRVO patients was significantly correlated with the extension of retinal capillary nonperfusion. Patients presented IOP between a minimum of 28 mmHg and maximum of 89 mmHg. To treat the patients with NVG we elaborated an algorithm of treatment.

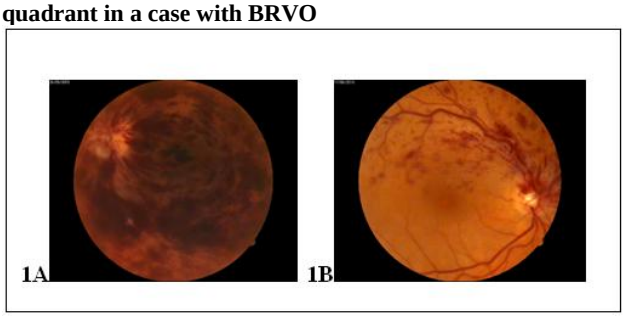
The first measure that we adopted was to assess the condition of the patient, by carrying out the blood exams and other examinations. To stop the neovascularization we administrated intravitreal anti-VEGF factor and later, photocoagulation of the retina. The general treatment of diabetes and hypertension was initiated after preliminary examination of the patient by a cardiologist and a diabetes specialist.

Type of vascular event (CRVO or BRVO)

The pathogenesis of CRVO is believed to follow the Virchow's triad with thrombogenesis, involving vessel damage, stasis and hypercoagulability. Risk factors that are more involved in the pathogenesis of CRVO and BRVO are: age over 50 years, and 25% of younger patients, hyperlipidemia, diabetes mellitus, and others (figure no. 1).

The difference between ischemic and nonischemic CRVO is difficult in early stages. Clinical finding as BCVA worse than 20/200, cotton-wool spots are suggestive of ischemic CRVO and can predict prognosis.(1) We correlated the clinical data with the presence of extensive nonperfused capillary areas in one or all four quadrants in the FA images and the OCT presence of cystoid macular edema. The OCT examination was useful for the measurement of central subfield mean thickness grading the macular edema. Some studies described the usage of OCT to find signs for ischemia in acute CRVO and the prognostic for later anterior segment neovascularization development, but no data was published.(4) This study found no correlation of any intervention for macular edema and retinal ischemia grade.(4)

Figure no.1 (A) Clinical presentation of patient with CRVO, the fundus shows retinal hemorrhages, dilated tortuous retinal veins, cotton-wool spots, macular edema, optic disc edema. (B), fundus retinal hemorrhages limited to superior quadrant in a case with BRVO



In this study, there were only 2 cases with BRVO in younger patients, the rest were over 50 years old. 45% were patients with diabetes and hypertension, and 25 % with hyperlipidemia.

Course of vascular event

Neovascularization of anterior and posterior segment of the eye is one of the most severe complications after venous vascular events of the retina. VEGF is strongly suspected to be a key mediator of angiogenesis and increased vascular permeability in human diseases, including ocular neovascular disorders.(6)

The identification of a close correlation between aqueous VEGF and the clinical course of NVI in CRVO is strong evidence of the role of VEGF in the pathogenesis of human ocular angiogenic diseases.(6) Clinically, VEGF inhibition delays the onset of neovascular events in eyes with CRVO as compared to the natural history of the disease. In the natural history subgroup of the landmark central vein occlusion study (CVOS), the vast majority of eyes that developed neovascularization did so within 6 months of study entry.(3)

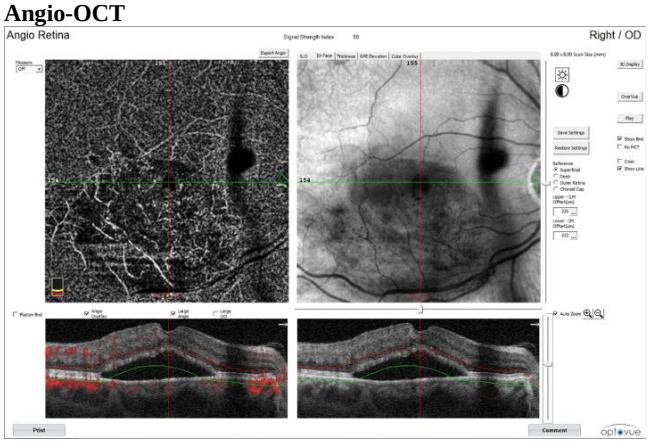
Follow-up included regular visits of the patients consisting of clinical examination, fundus examination and OCT. In 5 cases we succeeded to perform angio-OCT to visualize the chorio-capillary structure.

Early administration of anti-VEGF treatment versus later treatment

VEGF inhibition through intravitreal anti-VEGF injection is a frequent treatment modality for macular edema secondary to CRVO. The effect of this method of VEGF suppression on neovascularization is not well understood. Recent studies suggested therapeutic benefits of intravitreal steroids and anti-VEGF for treating macular edema. The Central Vein Occlusion Study (CVOS) recommended promptly the panretinal photocoagulation (PRP) over 2 h or more in the iris or any angle neovascularization.(1)

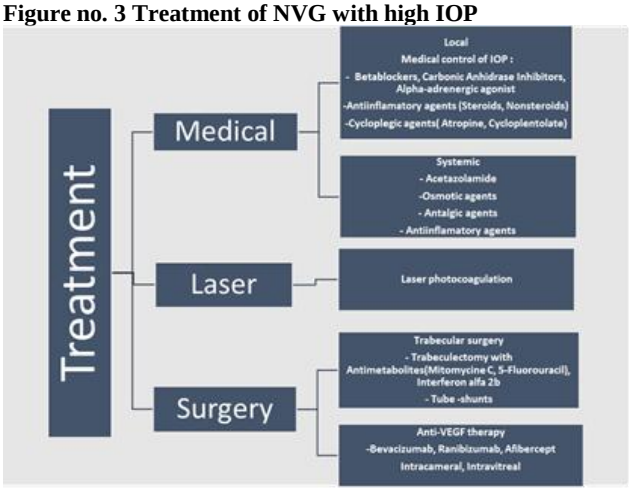
We used anti-VEGF agents in eyes with CRVO and BRVO to stop the neovascularization appearance and as treatment for macular edema. The first injection was made with Bevacizumab 1.25 mg/0.05 ml intravitreal and Triamcinolone acetonide 1 mg. We repeated anti-VEGF treatment between 4 and 6 weeks, after we checked the macular edema and neovascularization by BCVA, fundus examination and OCT (figure no. 2) Steroids reduce vascular permeability and stabilize the blood-retina barrier. The mechanism involves inhibition of inflammatory mediators and vascular permeability factors such as VEGF.(6)

Figure no. 2. Case of BRVO with acute macular edema after Angio-OCT



From hospitalized cases, 15% developed neovascular glaucoma and presented with high intraocular pressure so we used a treatment plan that could help us to keep the IOP to normal values and in cases that were refractory to treatment, we performed trabeculectomy. In complicated cases like NVG, the treatment was made following the algorithm. The algorithm was used to drop the high IOP with medical treatment applied locally and generally. After we succeeded to drop the IOP we made intravitreal injections with anti-VEGF agents and panphotocoagulation in cases where we had clear fundus examination. The surgery was done in 14 cases performing trabeculectomy with local application on the scleral spur of antimetabolites or Interferon alfa-2b (figure no. 3).

Figure no. 3 Treatment of NVG with high IOP



Case 1.

S.M., 35 years old, BRVO in 2014, Intravitreal Bevacizumab 3 injections repeated in 2014, 2016, 2017, after performing fundus examination, OCT, angio-OCT.

Photocoagulation was made after intravitreal injection to avoid edema, and was repeated until we managed to photocoagulate all areas adjacent to the obstructed vessel (figures no. 4,5).

Figure no. 4. (A,B,C,D) Fundus examination between 2014 and 2017 after we performed the treatment

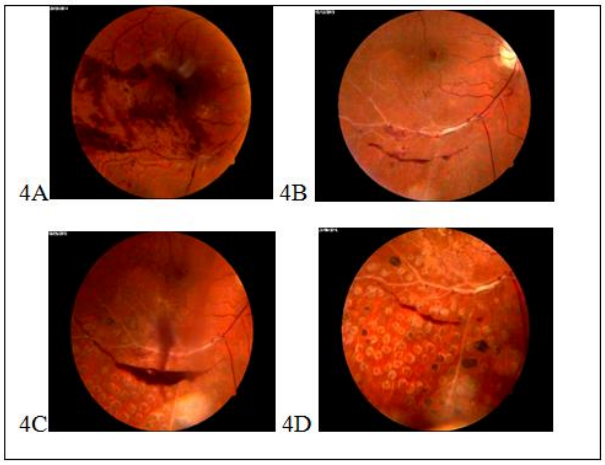
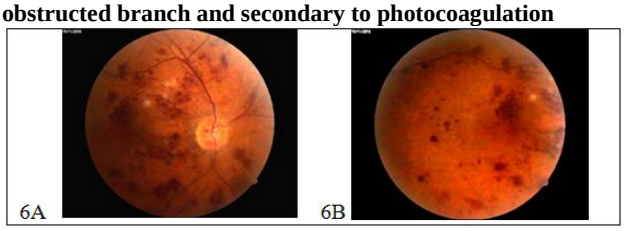


Figure no. 5. Angio-OCT examniation to the same patient in 2017 showing retinal non-perfusion area adjacent to obstructed branch and secondary to photocoagulation

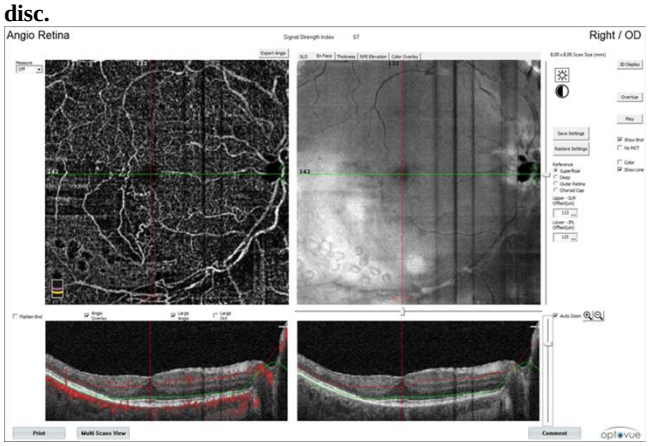


Case 2

J.S,man, 62 years old, with Hypertension, and CRVO, the first attitude was to make 1 injection with Bevacizumab.

3 months later, the patient prezented with high IOP, headache, iris and angle neovascularization, neovascularization on the optic disc. After we made one injection with Bevacizumab, we tried to drop the IOP with medical therapy.(7,8) The IOP was still high so we conducted trabeculectomy with Interferon alfa-2b.

Figure no. 6. (A,B) fundus examination, CRVO with multiple hemohrrages and neovascularization of the optic disc.



Follow-up included regular check of the neovascularization appearance, changes in IOP, or visual acuity.

OCT was done 4 weeks later, after the 3rd injection with Bevacizumab for macular edema assessment and as response to treatment.(9,10,11)

Angioflorography(AFG) is useful to check the type of vascular event, the ischemic form that can lead to neovascularization apperance.

Nowadays Angio-OCT can sometimes replace the AFG.

CONCLUSIONS

Clinical monitoring of vascular venos obstruction by ophthalmoscopy and OCT imaging brings into attention the neovascularization appearance and neovascular glaucoma.

Intravitreal administration of anti-VEGF agents is an option to stop the neovascularization, much better in combination with fotocoagulation.

In complicated cases with NVG it is indicated to apply treatment algorithm.

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