Original Article

Investigation of clinical profile of Behçet's syndrome-related versus idiopathic branch retinal vein occlusion

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Purpose: To compare the long-term results of the patients with branch retinal vein occlusion (BRVO) secondary to Behçet's syndrome (BS) with the patients with unknown etiology. **Methods:** Medical records and optical coherence tomography (OCT) imaging results of the patients with BRVO secondary to BS and with unknown etiology were reviewed retrospectively between 2016 and 2018 at a single center. The anatomical location of the BRVO, involvement of the macula, application of laser photocoagulation, and intravitreal injection were evaluated. **Results:** Twenty-eight eyes of 23 patients with BRVO secondary to BS as the study group and 22 eyes of 19 idiopathic BRVO patients as the control group were included in the study. The mean duration of follow-up after the development of BRVO was 74.6 ± 57.4 months in the study group and 63.6 ± 59 months in the control group. The rate of bilaterality, macular involvement, and application of laser photocoagulation was not statistically significantly different between the groups. However, the frequency of injection requirement was significantly lower in the patients with BRVO secondary to BS in comparison to the control group (P = 0.009). **Conclusion:** Although the treatment of BRVO is laser photocoagulation and intravitreal injection of anti-VEGF agents or dexamethasone implant, the patients with BS might respond very well to systemic immunomodulatory agents in case of BRVO. Thus, rearrangement of the immunomodulatory treatment before starting intravitreal injections should be considered in the patients with BRVO secondary to BS.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_217_20

Quick Response Code:

Key words: Behçet's syndrome, branch retinal vein occlusion, immunomodulatory treatment, intravitreal injection, laser photocoagulation

Behçet's syndrome (BS) is a chronic, immuno-inflammatory multisystemic disease with unknown etiology.[1] Relapsing orogenital ulcers, skin lesions, uveitis, arthritis, vascular involvement are the main characteristic finding of the disease. In some patients neurological and major vessel involvement might also be observed.[2] Colchicine, steroid, and immunomodulatory drugs are the mainstay treatment modalities and utilized according to the severity of disease and the location of involvement.[3] Ocular involvement in BS might be as anterior, posterior, or panuveitis and posterior involvement is related to a worse prognosis.[4] Vasculitis, retinitis, or optic nerve involvement can be seen as the involvement of the posterior segment. Retinal vein occlusion in form of vasculitis is one of the possible clinical finding in BS.[4]

Retinal vein occlusions are the second most frequent vascular disease of retina and can lead to severe visual loss.[5] Branch retinal vein occlusions (BRVO) are more common than the central retinal vein occlusion.[6] BRVO is most commonly observed in the sixth decade in hypertensive patients, however, when it is encountered in younger patients inflammatory, hematologic and cardiovascular diseases should be investigated.[7] Despite a good prognosis, macular edema (ME) is the main reason for visual disturbance and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents or dexamethasone implant are the current treatment options. In the presence of retinal ischemia, argon laser photocoagulation might be preferred according to the extent of ischemia.[8]

To date, only two studies have reported the rate of BRVO in BS.[4,9] In their study, Ozdal *et al*. have found that 15 (5.8%) of 257 eyes of patients with BS had BRVO[4] and Tugal-Tutkun *et al*. reported it as 6.6% in 1,567 eyes.[9] However, they did not evaluate the clinical course and therapeutic response of this pathology in detail. Here, we compared the clinical profile of the BRVO patients with BS and hypertensive BRVO patients in terms of macular involvement, history of laser photocoagulation, bilaterality, the location of involvement, and the rate of intravitreal anti-VEGF injection.

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Received: 01-Feb-2020 Revision: 25-Mar-2020
Accepted: 05-Jun-2020 Published: 20-Aug-2020

Cite this article as: Ucar D, Mergen B, Gonen B, Ozguler Y, Seyahi E, Hamuryudan V, *et al*. Investigation of clinical profile of Behçet's syndrome-related versus idiopathic branch retinal vein occlusion. Indian J Ophthalmol 2020;68:1876-80.

Methods

The medical records of 23 BRVO patients with BS and 19 patients with idiopathic BRVO who visited Behçet-Uveitis and Retina Clinics (respectively) of the Department of Ophthalmology in Cerrahpasa Medical Faculty between 2016 and 2018 with a new or older diagnosis of BRVO were investigated retrospectively. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Cerrahpasa Ethics Committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Age, gender, and duration of follow-up were recorded as demographic data.

The patients without any history of disease other than hypertension as a possible etiology for BRVO were included as the control group. The patients with any kind of vasculitis other than BS were excluded from the study. BRVO patients with BS who had no other ocular pathology were included as the study group. The patients with coexisting pathologies that might mask the effect of BRVO on best corrected visual acuity such as cataract, corneal pathologies, additional retinal pathologies, glaucoma were excluded from the study. BRVO patients with BS who showed retinal capillary leakage in seemingly uninvolved areas of the retina were also excluded from the study. Diagnosis of BS was made according to the International Study Group for Behçet's Disease.[10]

The types of systemic involvement (arthritis, deep vein thrombosis, etc.) and the types of coexisting uveitis (anterior, intermediate, posterior uveitis, or panuveitis) in patients with BS at the presentation of BRVO were recorded. The average time between the disease onset and the presentation of BRVO was also recorded for BRVO patients with BS.

The diagnosis of BRVO was made according to the clinical findings and with the help of fundus fluorescein angiography (FFA) Visucam 500 (Carl Zeiss Meditec, Jena, Germany) and optical coherence tomography (OCT) (Cirrus HD-OCT software version 4.0; Carl Zeiss Meditec, Inc., Dublin, CA, USA). Laser photocoagulation was performed in the patients with ischemia in FFA and applied only to the ischemic area. Decision of laser photocoagulation was made following the same schedule in both groups. Presence of macular edema was investigated with OCT imaging [Fig. 1]. In case of macular edema, intravitreal anti-VEGF agents (ranibizumab, aflibercept) or dexamethasone implant were applied to the patients in the control group. However, among patients with BS, in case of macular edema, corticosteroids and immunosuppressive agents (such as azathioprine, cyclosporine, infliximab) were preferred first. According to the severity of involvement, the dose and the intervals of the immunosuppressive agents were adjusted, or another agent was added or switched. Intravitreal injection was considered if there is no response within 1 month of follow-up. The location of BRVO was detected according to the FFA images [Fig. 2] and classified as the involvement of superior or inferior retinal vascular branches. All the diagnosis and treatment decisions were made by a single ophthalmologist (D.U.). Bilateral involvement was evaluated as sequential bilateral involvement in time. Patients were also evaluated for the presence of any neovascularization on the retina, iris, angle, or optic disc.

The normal distribution of the groups was tested with a Shapiro–Wilk test. For the comparison of the rates of two independent groups Mann–Whitney U test was used and for two dependent groups, the Wilcoxon signed rank test was used. For the comparison of the ratios, a Chi-square test or a Fisher's exact test were utilized. *P* values below 0.05 were accepted as statistically significant. SPSS version 20.0 was used for all of the statistical analysis.

Results

The results are summarized in Table 1. Twenty-eight eyes of 23 BRVO patients (19 M/4 F) with BS and 22 eyes of 19 idiopathic BRVO patients (9 M/10 F) were included in the study. There were significantly more male patients among Behçet patients ($P = 0.02$). The mean age of the patients with BS was 41.5 ± 10.1 years while the mean age of those with idiopathic BRVO was 61.1 ± 7.8 years ($P < 0.0001$). The mean duration of follow-up in the BS group was significantly longer than that found in the idiopathic group (74.6 ± 57.4 months versus 63.6 ± 59 months ($P < 0.00001$)). The average time between the diagnosis of BS and onset of BRVO was 4.3 ± 7.5 years.

As shown in Table 1, laser photocoagulation was performed in 20 eyes (71.4%) in the patients with BS and in 14 eyes (63.6%) in the idiopathic BRVO patients ($P = 0.56$). All the BRVO patients who had laser photocoagulation had ischemic BRVO, while the others had non-ischemic BRVO. The frequency of macular involvement in terms of edema or atrophy was similar in both groups. Rate of intravitreal injection for macular edema was found to be significantly lower in BS group (3 eyes; 10.7%) compared to idiopathic group (10 eyes; 45.4%), ($P = 0.009$). Among BRVO patients with BS, management with systemic immunosuppressive agents alone was found to be sufficient for the treatment of macular edema in 21 (75%) of 28 eyes, in 3 eyes (10.7%) intravitreal injection was required within 1 month of follow-up because of poor response to systemic treatment. Among the remaining patients with BS, macular edema was not present in 1 (3.6%) of 28 eyes and macular atrophy was present in 3 (10.7%) of 28 eyes at the first visit due to previous attacks of macular edema secondary to BRVO. These 3 patients had missed the opportunity for injection or immunosuppressive treatment because of the atrophy that had developed in their macula at the time of presentation.

None of the patients in both groups had any relapse of BRVO during their follow-up. None of the BS patients showed neovascularization on the disc, angle, or iris but 7 eyes (25.0%) showed retinal neovascularization. The most common associated uveitis type was posterior uveitis (7/28, 25.0%) followed by panuveitis (6/28, 21.4%) and anterior uveitis (2/28, 7.1%) at the presentation of BRVO, whereas 13 (46.4%) eyes did not show any signs of uveitis. The associated systemic involvement at the presentation of BRVO is shown in Table 2. The most common systemic involvement was arthritis (5/28, 17.9%) and deep vein thrombosis (5/28, 17.9%).

The mean LogMAR equivalent of best corrected visual acuity (BCVA) in the study group was 0.8 ± 0.9 at first visit and 0.4 ± 0.6 at last visit ($P = 0.16$). The mean LogMAR equivalent of BCVA in the control group was 0.38 ± 0.5 at first visit and 0.17 ± 0.2 at last visit ($P = 0.17$). No significant difference was present between the mean initial BCVA between two groups ($P = 0.70$) and mean last visit BCVA of two groups ($P = 0.45$).

Table 1: Demographic and clinical characteristics of the study groups

	Behçet BRVO *n*=23	Idiopathic BRVO *n*=19	*P*
Mean age±SD (years)	41.5±10.1	61.1±7.8	<0.00001
Gender (Male:Female)	19:4	9:10	0.02
Mean duration of follow-up±SD (months)	74.6±57.4	63.6±59	<0.00001
Presence of laser photocoagulation, *n* (%)	20/28 (71.4)	14/22 (63.6)	0.56
Macular involvement, *n* (%)	26/28 (92.9)	20/22 (90.9)	1.0
Frequency of injection, *n* (%)	3/28 (10.7)	10/22 (45.4)	0.009
Involvement of inferior half, *n* (%)	19/28 (67.9)	5/22 (22.7)	0.002
Bilateral involvement, *n* (%)	5/23 (21.7)	3/19 (15.8)	0.71

Table 2: The associated systemic involvement in BRVO patients with Behçet's syndrome at the presentation of BRVO

Systemic involvement	*n* (%)
Arthritis	5/28 (17.9%)
Deep vein thrombosis	5/28 (17.9%)
Papulopustular lesions	3/28 (10.7%)
Arthralgia	2/28 (7.1%)
Erythema nodosum	1/28 (3.6%)
Genital ulcer	1/28 (3.6%)

When the location of BRVO was investigated, inferior half was involved significantly more frequently in the BS group (19 eyes; 67.9%) compared to that found in the idiopathic group (5 eyes; 22.7%), (P = 0.002). There were similar number of patients with bilateral involvement in both groups (5 patients; 21.7% versus 3 patients; 15.8%), in BS and idiopathic group, respectively (P = 0.51).

Discussion

Although BRVO is more frequent in older age and in the patients with systemic vascular disorders such as hypertension, diabetes mellitus, and hyperlipidemia, it is also associated with systemic vasculitides such as systemic lupus erythematosus, sarcoidosis and BS.[11] Despite unclear etiology, since it is a vascular thrombotic event, the pathology can be explained with Virchow's triad: venous stasis, hypercoagulability, and vascular endothelial injury.[12] Vasculitic nature of BS might explain its tendency to develop BRVO via vascular endothelial injury. However, despite this possible explanation, the clinical profile of branch retinal vein occlusion in BS has not been studied in detail. Its frequency has been reported to be between 5.8 and 6.6% in the patients with BS who had ocular involvement.[4,9] In our study, we have shown that the involvement of inferior retinal vascular branches was more frequent in the patients with BS in comparison to the patients with idiopathic BRVO. The different location of involvement might be related to a different mechanism underlying the endothelial injury due to BS. Endothelial injury in BS has been related mostly with inflammation. However, since vascular thrombosis in BS has been observed in almost 40% of the patients,[13] an extensive prothrombotic state due to *thrombophilic factors* (such as factor V Leiden mutation,[14,15] deficiency in protein C, protein S and antithrombin,[16-19] increased levels of anticardiolipin antibody,[20-23] increased serum lipoprotein-A,[24] *alterations in platelet activation*, (increased mean platelet volume,[25] etc.) and *other coagulation mechanisms* (decreased fibrinolysis,[26,27] increased thrombin activatable fibrinolysis inhibitor,[28] etc.) has been suggested as a possible explanation.

Visual disturbance in BRVO is mostly related to macular edema. The rate of macular edema in BRVO over a 1-year period has been reported as 5–15%.[29] The mechanism of macular edema in BRVO has been linked to the increased hydrostatic pressure due to occlusion in the vein according to the Starling's law. VEGF and interleukin-6 (IL-6) secretion due to the ischemia secondary to venous occlusion has been hypothesized to contribute to the macular edema in BRVO by breaking the blood–retina barrier and increased vascular permeability.[30] Thus, in case of macular edema, the main treatment approach includes the intravitreal injection of anti-VEGF agents (bevacizumab,[31] aflibercept,[32] ranibizumab[33]) to decrease the VEGF levels or dexamethasone implant[34] (Ozurdex®; Allergan, Inc, Irvine, CA, USA) to decrease inflammatory cytokine levels (IL-6 etc.). Anti-VEGF agents have been thought to act by preventing the increase in vascular permeability and decreasing the neovascularization which in turn would decrease macular edema.[7] In our study, the BRVO patients with BS had lower rates of injection in comparison to the control group. In the BRVO patients with BS, since the etiology is a systemic vasculitis disorder, we preferred to rearrange the systemic immunomodulatory agents including corticosteroids in 21 (75%) of 28 eyes. These agents reach the posterior segment for exerting their anti-inflammatory effects on macular edema. Because BS is a systemic disease, we considered BRVO development as a vascular activity and aimed to suppress it systematically. Thus, the necessity of intravitreal injections might have decreased. However, in the idiopathic group, since the disease does not show a vasculitic pattern, utilization of immunomodulatory agents is not preferred due to different pathogenetic mechanism.

BCVA in both groups were found to remain unchanged statistically. These results might show that anti-VEGF treatment combined with laser photocoagulation of ischemic retinal areas in ischemic BRVO patients might prevent BCVA loss over time. However, in the BRVO patients with BS, laser photocoagulation combined with systemic immunomodulatory treatment (+/- intravitreal injection) might prevent BCVA loss over time.

Presence of retinal ischemia in BRVO is shown with the help of FFA imaging. BRVO patients are divided into two groups: (1) ischemic BRVO, (2) non-ischemic BRVO. In the case of ischemic BRVO, argon laser photocoagulation of ischemic retinal areas is indicated in the treatment to prevent the release of VEGF

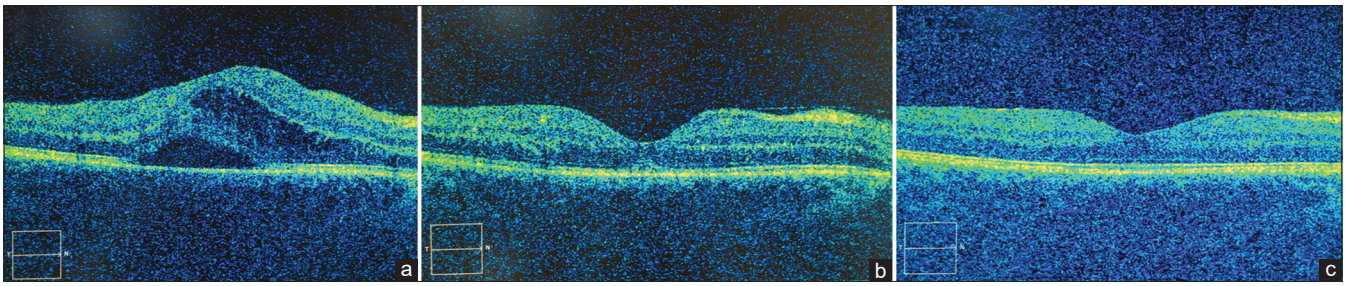

Figure 1: OCT image of macular edema due to BRVO in a patient with BS (a) and regression of the edema 1 month after adding 60 mg/day methylprednisolone plus 150 mg/day azathioprine (b). OCT image of the same patient 6 months after the development of BRVO showed no recurrence even after withdrawing the steroid by tapering its dose (c)

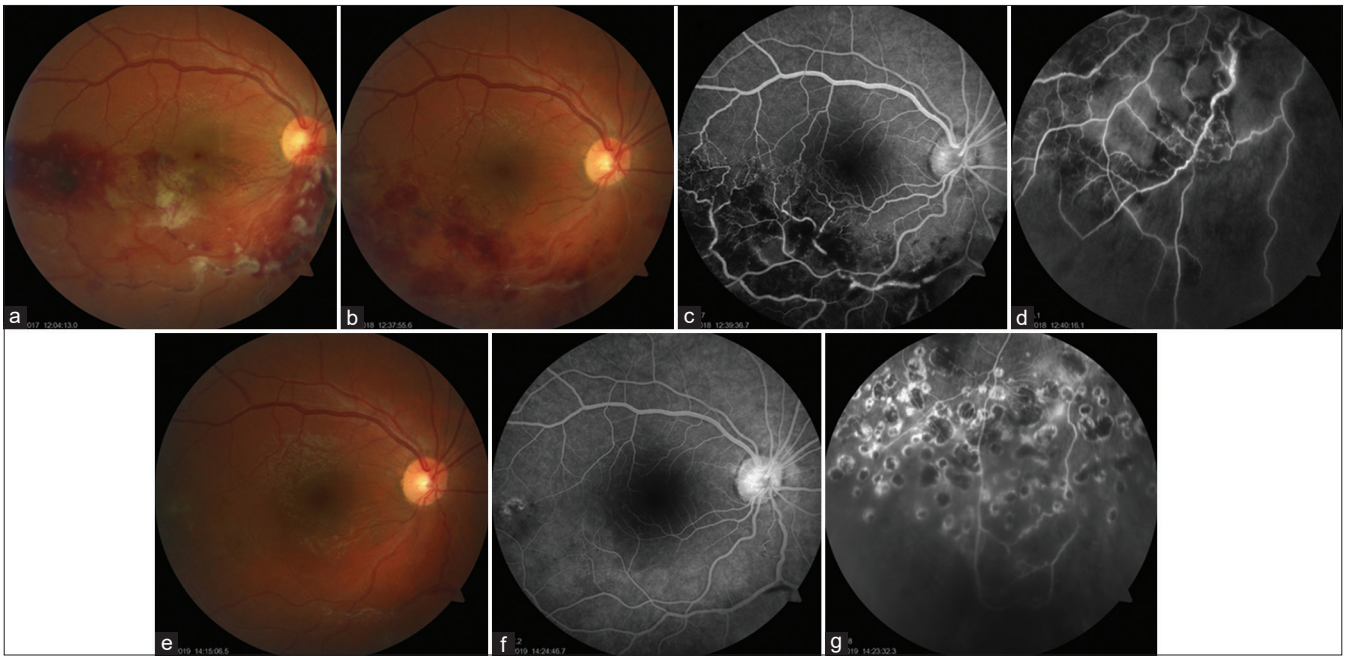

Figure 2: Fundus image of a patient with BRVO secondary to BS (a). Fundus image of the same patient 5 months after the development of BRVO and rearrangement of the immunomodulatory treatment (b). Ischemic regions related to the BRVO were observed at the inferotemporal quadrant in the FFA image of the patient at the 5th-month visit (c and d). Fundus (e) and FFA image (f) of the patient 16 months after BRVO. Laser spots can be observed at the inferotemporal quadrant (g)

from ischemic areas. In this study, no difference was detected between the BRVO patients with BS and the control group in terms of the rate of laser photocoagulation. This result also pointed out that there was no difference in the rate of ischemic BRVO between two groups. It is possible to explain it with the same occlusive result despite different mechanisms of both etiologies. When bilateral involvement was investigated in our study, again no significant difference was detected between two groups. This might be related to systemic vascular involvement of both etiologies. In comparison to 21.7% and 15.8% bilaterality rate over time in our patients, in a systematic review, bilateral involvement rate was reported as 10% for the idiopathic BRVO.[29]

Conclusion

In conclusion, despite the low number of patients and absence of a control group with a different treatment strategy for the patients with BS; in our study, we showed that the BRVO patients with BS might need lower rates of anti-VEGF or dexamethasone implant injection. Rearrangement of systemic immunomodulatory medication in BRVO patients with BS should always be kept in mind. Involvement of inferior retinal half was observed more frequently in the BRVO patients with BS. Further studies with a larger sample size are needed to understand the clinical characteristics of BRVO patients with different etiologies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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