

# Pattern and causes of visual loss in Behçet's uveitis: short-term and long-term outcomes

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## Abstract

**Background** To analyze the pattern and causes of visual loss in patients with Behçet's uveitis and to report on the short-term outcome at 6 months and at last follow-up visit. Also, to analyze the pattern of visual acuity changes in eyes with and without macular involvement at the specified time points.

**Methods** This is a retrospective cohort study of a single-center in an academic practice. Fifty-three patients with Behçet's uveitis evaluated between 2004 and 2014 were included. Data on patients diagnosed with Behçet's uveitis were entered retrospectively into a database and analyzed.

**Results** Included were 93 eyes with Behçet's uveitis involving the posterior segment. Frequencies of  $\leq 20/50$  and of  $\leq 20/200$  VA at presentation were 23.7% and 37.6%, respectively. Retinitis, macular inflammatory infiltrate, and dense vitritis were significantly associated with worse vision. Eyes with macular atrophy and macular inflammatory infiltrate sustained the worst logMAR VA at presentation (1.87 and 1.73, respectively) compared to eyes with cystoid macular edema and epiretinal membrane (0.76 and 0.63, respectively). Eyes with no macular involvement had the best VA at presentation. Mean difference in logMAR VA between presentation and the specified time points was greatest for eyes with macular inflammatory infiltrate.

**Conclusions** Behçet's disease affected mostly young males with a male-to-female ratio of 4.8:1. Panuveitis and posterior uveitis were the predominant forms and they were intrinsically associated with sight-threatening potential and breadth of

ocular complications for which aggressive immunosuppressive therapy was essential.

**Keywords** Behçet's disease · Behçet's uveitis · Panuveitis · Posterior uveitis

## Introduction

Behçet's disease (BD) is a multisystemic inflammatory disorder that is most prevalent in countries along the ancient "Silk Road". The eye is the most commonly involved vital organ, and the typical form of involvement is a relapsing remitting panuveitis and retinal vasculitis. Behçet's uveitis can be singled out among uveitides for its aggressive phenotype, characterized by explosive episodes of sight-threatening occlusive retinal vasculitis. It is frequently treatment refractory, and despite the step change improvement in visual prognosis, it remains a leading inflammatory cause of blindness in the working age group [1–3].

Several studies [1, 2] extensively reviewed the ocular manifestations of Behçet's uveitis. Macular pathologies that were described included cystoid macular edema (CME), macular atrophy, macular hole, macular ischemia, and epiretinal membrane (ERM). However, the impact of such sight-threatening complications on visual acuity (VA) in the acute phase and in the long-term follow-up was not adequately addressed.

In the present study, we aimed to analyze the pattern and causes of visual loss at presentation in eyes with Behçet's uveitis and to report on the short-term outcome at 6-month intervals and at last follow-up visit. Additionally, we specifically analyzed the different forms of macular pathologies at presentation and the pattern of VA changes in eyes with and without macular involvement at the specified time points.

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## Methods

We reviewed the medical records of 53 consecutive patients with uveitis secondary to BD who were treated at the Uveitis and Ocular Immunology Service of the Ophthalmology Department, Hadassah Medical Center, from 2004 to 2014. Data collection for the purpose of the study was approved by the institutional review board.

At the initial visit a detailed history was obtained from each patient, including onset of ocular complaints and systemic symptoms. A complete ocular examination was performed at each visit, including Best-corrected Snellen's VA of all affected eyes, slit-lamp biomicroscopy, tonometry, and indirect ophthalmoscopy. Vision of counting fingers, hand motion, light perception (LP), and no LP were recorded as 20/2000 and 20/20 000, 20/100000, and 20/200000, respectively. As the lines on the Snellen's VA chart follow a geometric progression, logMAR (log of the minimum angle of resolution) notation was used to compute the change in VA. VA of  $\leq 20/200$  was defined as severe visual loss (SVL), VA of  $>20/200 - \leq 20/50$  was defined as moderate visual loss (MVL) and VA of  $\geq 20/40$  was defined as good VA (GVA).

For the purpose of this study, a data form was prepared. Demographic data, including age at onset of uveitis, age at diagnosis with BD, age at presentation to the uveitis clinic, gender, ethnic background, and extraocular clinical manifestations of BD, were noted from the medical files of each patient. Ophthalmologic data recorded were laterality and type of uveitis (in accordance with standardization of uveitis nomenclature (SUN) working group) [4], ocular findings, ocular complications, VA at presentation, at 6-month interval and at last follow-up visit, immunosuppressive therapy administered (excluding colchicine treatment which was administered by the patients' dermatologists or rheumatologists) and the follow-up period. Binocular indirect ophthalmoscopy (BIO) score (vitreous haze) was ranked using an ordinal scale ranging from 0 to 4+ according to Nussenblatt et al. [5].

All of the formerly mentioned demographic data, extraocular manifestations and ocular signs at presentation were analyzed with relation to the three subgroups defined by VA at presentation (SVL, MVL, and GVA). In addition, logMAR VA at presentation, at 6 months and at last follow-up was analyzed for the three subgroups. Furthermore, we looked at changes in logMAR VA at the different time points mentioned previously, in eyes with and without macular involvement. Macular involvement was divided into macular atrophy (including eyes with macular hole), macular inflammatory infiltrate, ERM, and CME. In eyes with macular atrophy and another pathology, the cause was considered macular atrophy. In eyes with CME and another pathology (excluding macular atrophy), the cause was considered CME. The difference in logMAR VA between presentation and six months and between presentation and last follow-up visit was analyzed for all the subgroups of macular pathologies.

## Statistical analysis

Statistical analysis was performed using SPSS version 20 (IBM Corp., Armonk, NY, USA). Descriptive statistics are given as the mean and standard deviation for quantitative variables, as N and percent for qualitative variables. SA value of  $p < .05$  was considered as significant. All  $p$  values assumed two-tailed.

For all ratio variables baseline differences between the groups negated using a one-way ANOVA. For all nominal variables differences between the groups negated using a Chi-square test.

For comparison between the three VA severity subgroups at each time point and for comparison between the macular pathologies subgroups we used one-way ANOVA followed by post hoc test (Bonferroni), comparing each group to another one.

Kaplan-Meier curve was constructed to display SVL as a function of time.

## Results

### Demographic and extraocular clinical characteristics of patients with Behçet's uveitis

Included were 53 patients: men 44 (83%), women nine (17%), 70% of Palestinian ethnicity, 28% of Sephardic and 2% of Ashkenazi Jew origin. Mean age at presentation to the uveitis clinic was 27 years (median 26, range 10–49 years), 83% of the patients were  $\leq 35$  years. No patient was identified to have onset of uveitis at 50 years or older. The mean age at which the eye problem started was 25.8 years. The time interval between the diagnosis of the intraocular inflammation and referral to the uveitis clinic was 282 days (9 months) (Table 1). A statistically significant correlation was demonstrated between gender and level of visual loss at presentation; however, it was not significant for the ethnic background. Although that patients in the group with SVL were diagnosed and presented to our clinic at a younger age in comparison to patients with initial better vision, their presentation to the uveitis clinic, however, came with a considerable delay following diagnosis (Table 1). The results did not achieve conventional statistical significance. The disease started in the pediatric age group ( $\leq 16$  years of age) in four patients (7.5%) (three males, one female) at a mean age of 13.8 years (range between 10 and 16 years). Uveitis was the trigger to diagnose BD in 66% of patients. Mean follow-up time was 40 months (median 29, range 6–156).

At presentation, all patients had recurrent oral ulcers, 25 patients (47%) had genital ulcers, 17 (32%) had arthritis, and 13 (25%) had skin lesions. Two patients (4%) had lower leg thrombophlebitis, one had myocarditis (2%), one (2%) had epididymitis, and one (2%) had CNS parenchymal involvement. Statistically significant correlation between extraocular

**Table 1** Demographic features and extraocular clinical manifestations in 53 patients (93 eyes) with Behçet's uveitis and comparison of proportions between the three subgroups defined by visual acuity at presentation

Variable	SVL N = 35	MVL N = 22	GVA N = 36	p-value
Gender, Male	29 (83%)	14 (64%)	33 (92%)	.027
Ethnicity Palestinian	26 (74%)	17 (77%)	23 (64%)	.475
Genital Ulcers	14 (40%)	12 (55%)	18 (50%)	.518
Skin lesions	7 (20%)	4 (18%)	10 (28%)	.627
Arthritis	11 (31%)	6 (27%)	13 (36%)	.777
Thrombophlebitis	0 (0%)	0 (0%)	4 (11%)	.037
Myocarditis	1 (3%)	0 (0%)	1 (3%)	.728
Epididymitis	1 (3%)	0 (0%)	1 (3%)	.728
CNS involvement	0 (0%)	2 (9%)	0 (0%)	.037
Mean age at presentation to uveitis clinic (SD)	26.87 (8.72)	28.50 (5.76)	27.26 (9.98)	.782
Mean age at diagnosis with BD (SD)	24.49 (7.78)	27.27 (6.73)	26.92 (10.15)	.376
Mean interval between diagnosis and referral to uveitis clinic in months (SD)	408.5 (871.0)	224.8 (362.7)	171.6 (376.3)	.245

CNS central nervous system, SVL severe visual loss, MVL moderate visual loss, GVA good visual acuity

manifestations and level of VA loss at presentation was demonstrated for thrombophlebitis and CNS involvement (Table 1).

The disease fulfilled all the diagnostic criteria of Behçet's Research Committee of Japan [6] (oral, genital ulcers, ocular inflammation, skin lesions) and was complete in seven (13%) patients, whereas in 46 patients (87%) it was incomplete: 24 had three major criteria and 22 patients had two major criteria (all had oral ulcers and uveitis).

Uveitis was bilateral in 40 patients (75.5%) and unilateral in 13 patients (24.5%). Of the unilateral cases, seven patients evolved to becoming bilateral within a mean period of 20.7 months (range 6–96). Thus, eventually at last follow-up, only six patients remained unilateral (11%).

### Ocular signs at presentation

Posterior uveitis and panuveitis were the predominant types of ocular inflammation observed at presentation, occurring in 51% and 49%, respectively. There were no cases of isolated anterior uveitis. Vitritis was the most commonly observed sign in 85 eyes (91.4%) (Total number of eyes = 93, men = 76 eyes, women = 17 eyes). Retinitis was the second most frequently observed sign in 56 eyes (60%). Retinal vasculitis was observed in 38 eyes (40.8%) and papillitis in 21 eyes (22.6%). Macular inflammatory infiltrate (Fig. 1) was observed in 12 eyes (13%). Hypopyon was observed at presentation in only two eyes (2%) while anterior uveitis was noted in 37 eyes (40%) (Table 2). A statistically significant correlation was demonstrated between retinitis and the level of visual loss at presentation: it was observed in 94% of eyes with SVL in comparison to 64% of eyes with MVL and 25% of eyes with GVA ( $p < .001$ ). Similarly, a positive correlation was noted between macular inflammatory infiltrate and VA loss as it was observed

in 29% of eyes with SVL vs 9% of eyes with MVL ( $p < .001$ ). It was not observed in eyes with GVA. Also, the higher the mean BIO (binocular indirect ophthalmoscopy) score at presentation, the greater the level of VA loss ( $p = .035$ ) (Table 2).

### Ocular complications at presentation

CME (Fig. 2) was the most common complication encountered in 31 eyes (33.3%). There was no correlation with the level of VA loss at presentation as it was observed in 37%, 32%, and 31% of eyes in SVL, MVL, and GVA subgroups, respectively. Macular atrophy (Fig. 3) was observed in 15 eyes (16%) while optic atrophy (Fig. 3) was seen in nine eyes (10%) and both statistically significantly correlated with VA loss ( $p < .001$ ,  $p = .017$ , respectively) (Table 2). ERM was noted in 9 eyes (10%). Ocular hypertension was observed in 13 eyes (14%) while cataract was observed in 7 eyes (8%).

Additional complications noted at presentation included optic disc neovascularization (NVD) in 11 eyes (12%) and neovascularization elsewhere (NVE) in eight eyes (9%) of which five eyes had NVD and NVE concomitantly, whereas three eyes had NVE alone. Vitreous hemorrhage developed in three eyes (3%), of which two eyes had NVD and NVE and one eye had NVE. Retinal tear, branch retinal vein occlusion (BRVO) and macular hole (Fig. 4) were each seen in two eyes (2%). BRVO was statistically significantly correlated to MVL (Table 2).

### Visual acuity at presentation and its evolution 6 months later and at last follow-up

At presentation, mean logMAR VA was 0.85, improving to 0.49 at the 6-month interval. At last follow-up, it was 0.57 (Fig. 5a, Table 3). After excluding eyes with limited visual



**Fig. 1** (Left) Color fundus photograph of the left eye of a young man with severe posterior uveitis showing white macular infiltrate with associated retinal hemorrhages and blurry appearance of the optic disc because of vitreous hemorrhage from optic disc neovascularization. Vascular tortuosity and sheathing is also noted along the vascular arcades and small white retinal infiltrate is noted temporal to fovea with

small retinal hemorrhages adjacent to it. (Right) Fluorescein angiogram demonstrating hyperfluorescence of small blood vessels, vascular arcades and optic disc compatible with optic disc neovascularization. Hypofluorescence is noted in the areas of the macular infiltrates and also in the areas of blocked fluorescence by the vitreous hemorrhage

potential at presentation because of macular atrophy, macular hole, and optic atrophy (15 eyes: 13 in the SVL subgroup and two eyes in the MVL subgroup), mean logMAR VA was

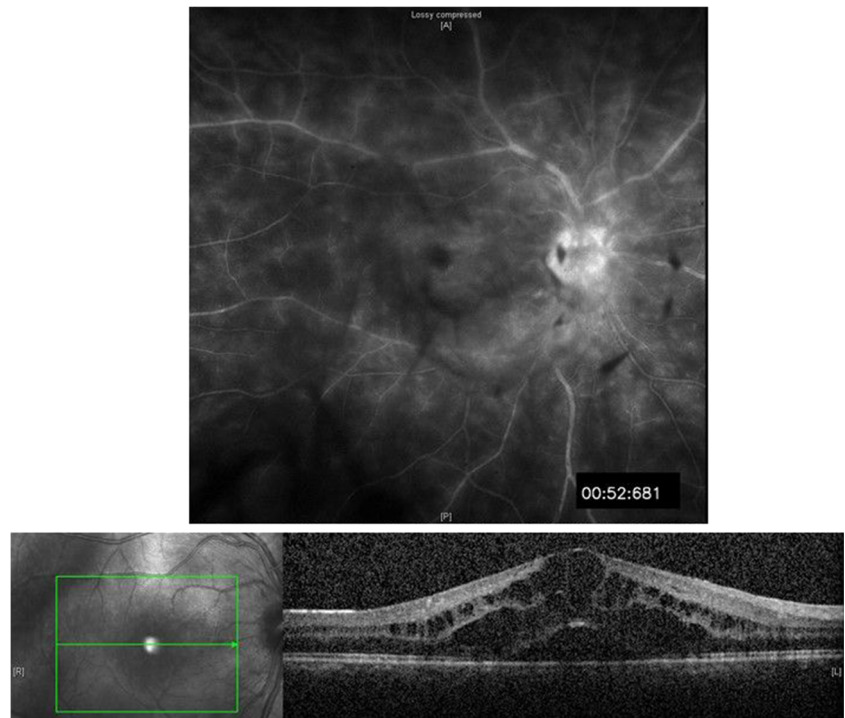
0.64 at presentation improving to 0.32 at the 6-month interval. At last follow-up, it was 0.36 (Fig. 5b, Table 4). Kaplan-Meier survival plot for SVL is shown in Fig. 6.

**Table 2** Ocular findings at presentation in 93 eyes with Behçet's uveitis and comparison of proportions between the three subgroups defined by visual acuity at presentation

Ocular Signs	SVL N = 35	MVL N = 22	GVA N = 36	p-value
Hypopyon	1 (3%)	1 (5%)	0 (0%)	.479
Anterior uveitis	17 (49%)	8 (36%)	12 (33%)	.394
RAPD	3 (9%)	0 (0%)	0 (0%)	.077
Posterior synechiae	0 (0%)	1 (5%)	0 (0%)	.196
CME	13 (37%)	7 (32%)	11 (31%)	.828
Macular atrophy	13 (37%)	2 (9%)	0 (0%)	<.001
ERM	6 (17%)	0 (0%)	3 (8%)	.097
Macular inflammatory infiltrate	10 (29%)	2 (9%)	0 (0%)	<.001
Retinitis	33 (94%)	14 (64%)	9 (25%)	<.001
Papillitis	10 (29%)	3 (14%)	8 (22%)	.421
Optic disc atrophy	7 (20%)	2 (9%)	0 (0%)	.017
Optic disc neovascularization	6 (17%)	2 (9%)	3 (8%)	.466
Retinal vasculitis	19 (54%)	9 (41%)	10 (28%)	.076
Retinal neovascularization	5 (14%)	1 (5%)	2 (6%)	.313
Vitreous hemorrhage	2 (6%)	0 (0%)	1 (3%)	.484
Retinal tear	1 (3%)	0 (0%)	1 (3%)	.728
BRVO	0 (0%)	2 (9%)	0 (0%)	.037
Macular hole	1 (3%)	1 (5%)	0 (0%)	.479
Ocular Hypertension	6 (17%)	3 (14%)	4 (11%)	.763
Cataract	3 (9%)	2 (9%)	2 (6%)	.847
BIO score Mean (SD)	1.07 (1.07)	0.52 (0.50)	0.57 (0.95)	.035

RAPD relative afferent pupillary defect, CME cystoid macular edema, ERM epiretinal membrane, BRVO branch retinal vein occlusion, BIO binocular indirect ophthalmoscopy, SVL severe visual loss, MVL moderate visual loss, GVA good visual acuity

**Fig. 2** Fluorescein angiogram (above) of the right eye showing hyperfluorescence of blood vessels and of the optic disc compatible with retinal vasculitis and papillitis. Hypofluorescent areas are secondary to blocked fluorescence from the scattered vitreous opacities. Spectral-domain optical coherence tomography (below) shows marked cystoid macular edema with intraretinal and subretinal fluid

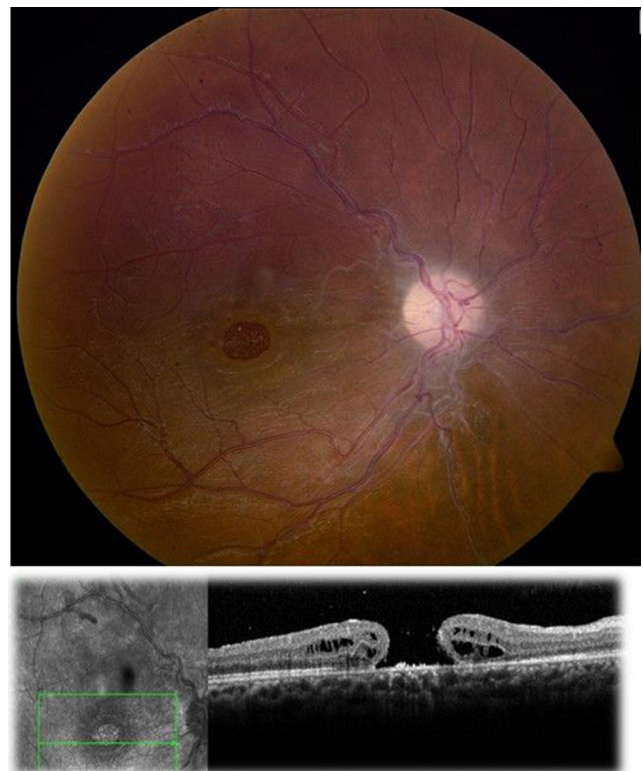


Severe visual loss at presentation was observed in 35 eyes (37.6% of all eyes) of 33 patients (28 men, five women), and 84.8% of patients were men. The most common causes for

SVL were CME and macular atrophy, each was encountered in 13 eyes (37% of SVL eyes). Macular inflammatory

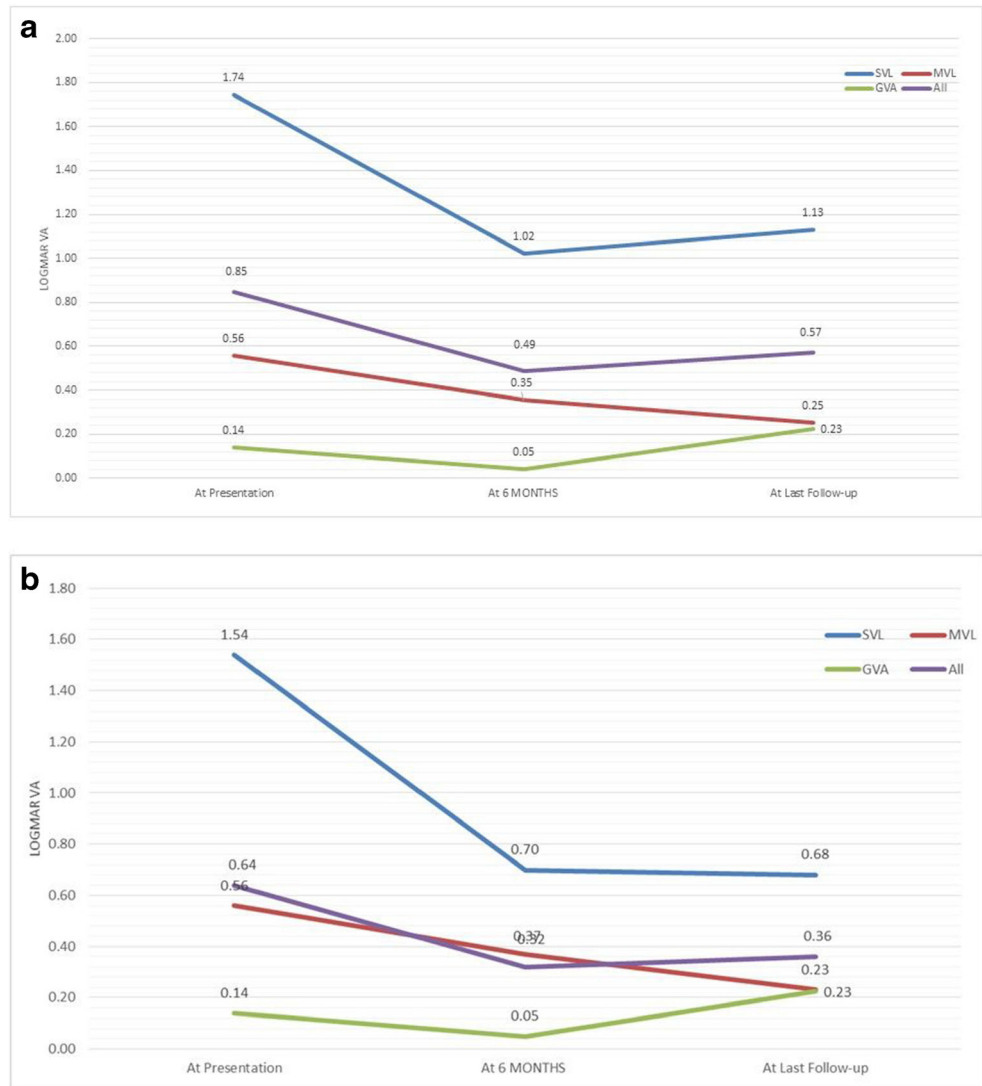


**Fig. 3** Color fundus photograph (above) of the left eye of a young woman showing optic disc pallor with diffuse vascular sheathing and some ghost vessels. Hard exudates are also noted in the center of the macula from a recent attack of neuroretinitis. Spectral-domain optical coherence tomography (below) shows pan-retinal atrophy and small intraretinal cystoid spaces



**Fig. 4** Color fundus photograph (above) of the right eye of a young female showing mild optic disc pallor with diffuse vascular sheathing and macular hole which is also illustrated as a full-thickness macular hole in the spectral-domain optical coherence tomography (below)

**Fig. 5 a** The graph shows logMAR visual acuity at presentation in all eyes, in eyes with severe visual loss (SVL), moderate visual loss (MVL), and good visual acuity (GVA). Changes in logMAR visual acuity are also shown at 6 months and at last follow-up visit. **b** The graph shows logMAR visual acuity at presentation in all eyes (excluding eyes with limited visual potential at presentation because of macular atrophy, optic atrophy, and macular hole), in eyes with severe visual loss (SVL), moderate visual loss (MVL), and good visual acuity (GVA). Changes in logMAR visual acuity are also shown at 6 months and at last follow-up visit



infiltrate was observed in 10 eyes (29%), while optic disc atrophy was seen in seven eyes (20%). Eventually, 20 eyes (57.1% of SVL eyes) remained with SVL at last follow-up.

Eleven eyes (31.4%) improved to  $\geq 20/40$  and four eyes (11.4%) improved to VA of  $>20/200 - \leq 20/50$ .

**Table 3** LogMAR visual acuity at presentation, at six months and at last follow-up visit in the three subgroups defined by visual acuity at presentation

LogMAR VA/Group	SVL N = 35	MVL N = 22	GVA N = 36	p-value
At presentation <sup>a</sup>	1.74 (0.51)	0.56 (0.12)	0.14 (0.13)	$p < .001$
At 6 months <sup>b</sup>	1.02 (0.90)	0.35 (0.45)	0.05 (0.17)	$p < .001$
At last follow-up <sup>c</sup>	1.13 (1.02)	0.25 (0.27)	0.23 (0.40)	$p < .001$

SVL severe visual loss, MVL moderate visual loss, GVA good visual acuity

<sup>a</sup> SVL > MVL and GVA. MVL > SVL

<sup>b</sup> SVL > MVL and GVA

<sup>c</sup> SVL > MVL and GVA

**Table 4** LogMAR visual acuity at presentation, at six months and at last follow-up visit in the three subgroups defined by visual acuity at presentation after excluding eyes with limited visual potential at presentation (eyes with macular atrophy, optic atrophy, and macular hole)

LogMAR/Group	SVL N = 22	MVL N = 20	GVA N = 36	p-value
At presentation <sup>a</sup>	1.54 (0.51)	0.56 (0.12)	0.14 (0.13)	$p < .001$
At 6 months <sup>b</sup>	0.70 (0.80)	0.37 (0.45)	0.05 (0.17)	$p < .001$
At last follow-up <sup>c</sup>	0.68 (0.87)	0.23 (0.26)	0.23 (0.40)	$p < .01$

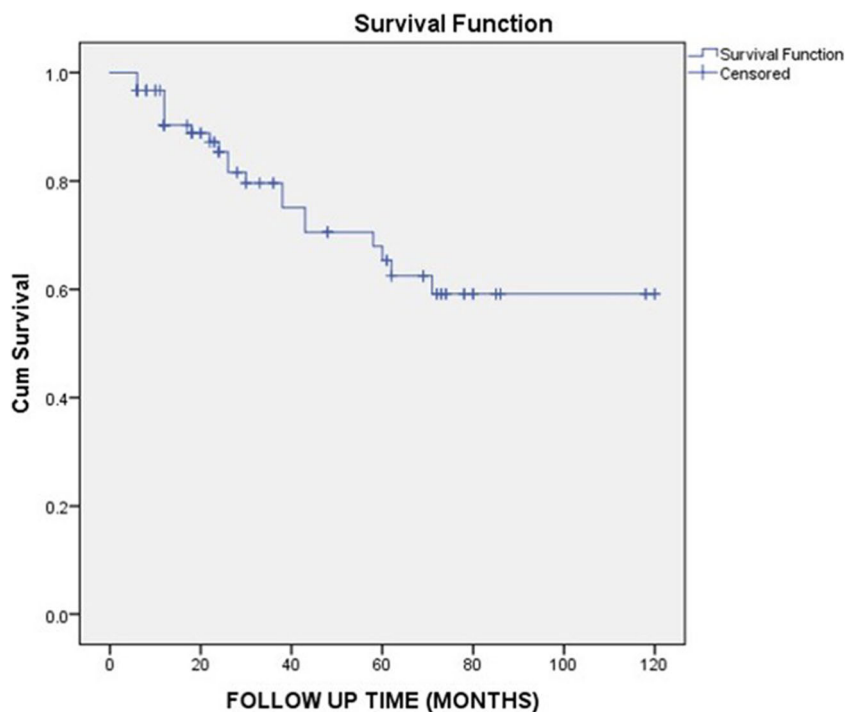
SVL severe visual loss, MVL moderate visual loss, GVA good visual acuity

<sup>a</sup> SVL > MVL and GVA. MVL > SVL

<sup>b</sup> SVL > GVL

<sup>c</sup> SVL > MVL and GVA

**Fig. 6** Kaplan-Meier survival curve showing the percentage of eyes suffering from severe visual loss over time



Moderate visual loss at presentation was encountered in 22 eyes (23.7% of all eyes) of 16 patients (11 men and five women). CME was seen in seven eyes (32% of MVL eyes) whereas macular atrophy, optic atrophy and macular inflammatory infiltrate were each observed in 2 eyes (9%). Only 5 eyes (22.7%) remained with MVL at last follow-up, one eye (4.5%) sustained SVL and the majority of 15 eyes (68.2%) improved to 20/40 or better.

Good visual acuity was observed in 36 eyes (38.7%) at presentation. CME was observed in 11 eyes (30.5% of GVA eyes). However, macular atrophy, optic atrophy, and macular inflammatory infiltrate were not observed in any of the eyes. At last follow-up, 27 eyes (75%) kept GVA of 20/40 or better, seven eyes (19.4%) developed MVL, and two eyes (5.6%) sustained SVL.

**Visual acuity changes in eyes with and without macular pathology**

We further analyzed changes in logMAR VA in eyes with and without macular involvement (Table 5). Eyes with macular atrophy and macular inflammatory infiltrate sustained the worst logMAR VA at presentation (1.87 and 1.73, respectively) compared to eyes with CME and ERM (0.76 and 0.63, respectively). Eyes with no macular involvement had the best VA at presentation (0.37). The mean difference in logMAR VA between presentation and 6 months and between presentation and last follow-up was greatest for eyes with macular inflammatory infiltrate (−1.07 and −1.20, respectively). The smallest change in logMAR VA was observed for eyes with no

**Table 5** LogMAR visual acuity at presentation, difference in logMAR visual acuity between presentation and 6 months and between presentation and last follow-up in eyes that did not have macular involvement at presentation (Non), in eyes with cystoid macular edema (CME), in eyes with macular atrophy, in eyes with epiretinal membrane (ERM), and in eyes with inflammatory infiltrate

Macular Involvement	Non N = 37	CME N = 31	Atrophy N = 15	ERM N = 4	Infiltrate N = 6	p-value
LogMAR VA at presentation <sup>a</sup>	0.37 (0.40)	0.76 (0.66)	1.87 (0.61)	0.63 (0.92)	1.73 (.65)	p < .001
LogMAR VA difference from presentation to 6 months <sup>b</sup>	−0.15 (0.35)	−0.35 (0.63)	−0.50 (0.69)	−0.53 (0.65)	−1.07 (1.10)	p < .05
LogMAR VA difference from presentation to last follow-up <sup>c</sup>	−0.15 (0.35)	−0.26 (0.78)	−0.15 (0.67)	−0.48 (0.83)	−1.20 (0.91)	p < .01

<sup>a</sup> Atrophy and Infiltrate > Non, CME, and ERM

<sup>b</sup> Infiltrate > Non

<sup>c</sup> Infiltrate > Non, CME, and Atrophy

**Table 6** Comparison of the frequencies of the different macular pathologies between the present study and other studies from Turkey, Tunisia, China, and USA

Macular Features	Present Study, 2016	Tugal-Tutkun et al. [6] Turkey 2004	Khairallah et al. [11] Tunisia 2009	Yang et al. [13] China 2008	Kaçmaz et al. [12] USA 2008 *
Number of eyes	93	1567	111	691	142
Macular inflammatory infiltrate	13%	N/A	N/A	N/A	N/A
Macular Atrophy (including macular hole)	18.3%	39.2%	N/A	5.8%	N/A
Cystoid Macular Edema	33.3%	44.5%	19.8%	38.2%	14.4%
Epiretinal Membrane	10%	17%	17.1%	9.6%	11.5%

\*Uveitis involving the posterior segment. N/A: not available

macular involvement ( $-0.15$  at 6 months and at last follow-up).

### Treatment

At presentation, 14 patients were on no systemic therapy (26.4%). However, the majority of the patients (21 patients, 39.6%) were on monotherapy: prednisone in 18 patients (34%), azathioprine in two patients (3.8%), and cyclophosphamide in one patient (1.9%). Fourteen patients were on dual therapy (26.4%): nine on prednisone and cyclosporine (17%), two on prednisone and azathioprine (3.8%), one on prednisone and methotrexate (1.9%), one on cyclosporine and methotrexate (1.9%), and one on prednisone and interferon- $\alpha$  (1.9%). Four patients were on triple therapy (7.5%) with prednisone, cyclosporine, and azathioprine.

At last follow-up visit, nine patients (17%) were on monotherapy: azathioprine in four patients (7.5%), prednisone in two patients (3.8%), whereas methotrexate, cyclosporine, and cyclophosphamide each in one patient (1.9%). Eighteen patients (34%) were on dual therapy: prednisone and azathioprine in nine patients (17%), prednisone and cyclosporine in six patients (11.3%), prednisone and methotrexate in one patient (1.9%), and prednisone and interferon- $\alpha$  in one patient (1.9%). Twenty-one patients (39.6%) were on triple therapy: prednisone, cyclosporine and azathioprine in 13 patients (24.5%), prednisone, cyclosporine, and infliximab in four patients (7.5%), prednisone, azathioprine, and infliximab in three patients (5.7%), and prednisone, cyclosporine, and methotrexate in one patient (1.9%). Two patients (3.7%) were on quadruple therapy with prednisone, cyclosporine, infliximab, and either methotrexate or azathioprine. Three patients (5.7%) were in remission and were on no systemic therapy.

Overall, the percentage of patients receiving prednisone increased between presentation and last follow-up (66% vs. 79%). Also, there was a marked increase in the use of steroid-sparing agents: azathioprine (15 to 57%), cyclosporine (26 to 47%), methotrexate (4 to

11%), and in the use of TNF- $\alpha$  blockers (0 to 17%). No change was noted in the use of interferon- $\alpha$  and cyclophosphamide (2% at initial and at last follow-up visit).

### Discussion

Behçet's uveitis is a sight-threatening condition with serious implications for the patient as its ocular consequences may be irreversibly detrimental. We herein aimed to analyze the pattern and causes of visual loss and the changes in VA over short and long-term follow-up. We further aimed to elucidate the influence of each of the vision-threatening macular features on the final visual outcome in 93 eyes of 53 patients who had a mean follow-up time of 40 months.

In our cohort, patients were predominantly young males with a male-to-female ratio of 4.8:1. They were mostly of Palestinian ethnicity with a mean age of 26 years at first diagnosis with intraocular inflammation. All patients presented with posterior segment involvement in the form of either posterior or panuveitis. Macular involvement (CME, ERM, macular atrophy, macular hole, and macular inflammatory infiltrate) occurred in 60% of eyes at the time of presentation. Uveitis was the trigger to diagnose BD in 66% of patients, emphasizing the role the ophthalmologist plays in bringing attention to this sight-threatening and potentially life-threatening systemic disease that may go undiagnosed if limited to orogenital, joint, or skin manifestations.

Severe visual loss occurred in 37.6% of eyes at presentation. It was secondary to severe inflammation involving the macula in the form of macular inflammatory infiltrate and CME, as well as subsequent to optic and macular atrophy and dense vitreous opacification. SVL occurred more commonly in men than in women. This is comparable to the cohorts reported by Tugal-Tutkun et al. [7] and by Arevalo et al. [8] in which SVL at presentation was present in 41.2% and 38.4% of the eyes, respectively. Despite the prompt use of systemic



immunomodulatory therapy, more than half of those SVL eyes (57%) in our cohort remained with poor vision because of the irreversible structural complications involving the macula and the optic disc. Tugal-Tutkun et al. [7] and Yoshida et al. [9] reported a better visual prognosis for patients who presented in the 1990s than those who presented in the 1980s. Even though our cohort of patients was recruited between the years 2004–2014, a significant proportion of eyes had SVL at first presentation. Patients in our cohort presented to the uveitis clinic with a mean delay of 9 months from the time of diagnosis of uveitis. Eyes with SVL had a remarkably long interval (408.5 days) before presenting to the uveitis clinic, which was almost twice as long the interval at which eyes with MVL and GVA presented. Delay in referral to a tertiary care center or uveitis specialty clinic has been reported to be a risk factor for poor clinical and visual outcomes in uveitis [10], presumably because of the delay in identifying the sight-threatening potential of the inflammation and the delay in the prompt institution of appropriate immunomodulatory therapy. In addition, the EULAR recommendation [11] stated that any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regime that includes azathioprine and systemic corticosteroids; however, 66% of patients in our cohort were either on no therapy or only on monotherapy, resulting in substantial visual loss and guarded visual potential. This emphasizes the preeminent importance of timely and adequately instituted immunomodulatory therapy in Behçet's uveitis. This also highlights the importance of further defining the ocular diagnostic criteria in BD, which is still one of the unmet needs as diagnosis is based on the association of nonspecific uveitis signs with systemic manifestations.

Moderate visual loss was observed in 23.7% of eyes because of vitritis and CME in the majority of the eyes. It was reversible in most of the eyes, with 68.2% of those eyes improving to 20/40 or better. Visual improvement gained in the first few months after presentation was maintained all through the period of long-term follow-up, again stressing the need for immediate institution and long-term maintenance of aggressive strategy aiming at suppressing the sight-threatening inflammation.

We further analyzed the association between macular pathologies and VA at presentation. Table 6 summarizes the macular pathologies in the present study and compares their frequencies with other big studies from the same geographical areas and other distant countries [7, 12–14]. Macular inflammatory infiltrate was observed in 13% of eyes (83% being in the SVL group). There was, however, no mention of the prevalence of macular inflammatory infiltrates in those studies. Such infiltrates involving the posterior pole were found to be significantly linked to visual loss. This was previously highlighted in the recent publication by Kaburaki et al. [15] on Behçet's disease ocular attack score 24 (BOS24) published by the Ocular Behçet Disease Research Group of Japan. In the

BOS24, out of the six defined parameters, two are used to assess inflammatory signs within the arcades: one assesses posterior pole lesions while one parameter specifically assesses foveal lesions, thus allowing more impact of macular lesions on the overall score of inflammatory signs. Despite the ominous outlook of visual loss in such eyes, visual recovery was so robust indicating that macular atrophy represents a cumulative damage that develops in a gradual manner following severe repeated uveitic attacks. In the study by Tugal-Tutkun et al. [7] the frequency of macular atrophy was high (Table 6) as this complication was documented for eyes not only at presentation but also during the long period of follow-up. Prevalence of CME varied between the studies (14.4% to 44.5%). It was not found to be associated with worse VA in our cohort; it occurred almost equally in the three severity subgroups (37%, 32%, and 31% of SVL, MVL, and GVA eyes respectively). CME is a reactive macular inflammatory response to a myriad of inflammatory stimuli also described in BD eyes with anterior uveitis [7]. Rapid disease control allowed meaningful visual recovery in those eyes.

The severe clinical course in Behçet's uveitis was further supported by the requirement of aggressive therapeutic protocols to control inflammation. There was a significantly increased requirement of triple immunosuppressants (40% compared to 7.5% at presentation) at last follow-up. One third of the patients were on dual immunosuppression. Despite the use of second- and third-line immunosuppressant agents and biologic therapy in 83% of the patients, prednisone remained a needed medication as 79% of patients used it by the last follow-up. Two patients were on quadruple therapy with prednisone, cyclosporine, infliximab, and either methotrexate or azathioprine. These treatment trends indicate, with aggressive steroid and immunomodulatory therapy as proxy indicators of severity, that BD patients clearly have ominous treatment-resistant uveitis.

This study represents the largest reported group of patients with Behçet's uveitis treated in Israel. Ben Ezra et al. [16] reported 30 years earlier (in 1986) on a cohort of 49 patients with uveitis secondary to BD. The authors concluded that, regardless of the type of treatment, 74% of the eyes lost useful vision 6 to 10 years after initial diagnosis. According to the authors, late complications that were not amenable to treatment were the cause of the poor vision or intractable blindness. In our cohort of patients, 24.7% of eyes (23 eyes) had loss of useful vision by the last follow-up and were mostly (87%) in SVL group at presentation. However, the spectrum of ocular complications observed in our cohort was smaller than that reported in previous studies [7, 11, 12], as we have not observed the occurrence of glaucoma, hypotony, retinal detachment, and phthisis bulbi indicating better visual course nowadays with the modern immunomodulatory agents than in the previous decades. Cingu et al. also reported on fewer severe ocular complications in

patients who presented in the early 2000s in comparison to patients who presented in the 1990s, resulting thus in a better 3-year visual outcome [17]. Similarly, Tugal-Tutkun et al. [7] showed a trend for better visual prognosis in patients who presented after 1990, because of the availability and use of new immunomodulators and biologic agents and the more aggressive treatment approach. Taylor SR et al. [18] reported in 2011 that the visual prognosis was improved and that the use of biologic agents was associated with a lower risk of severe visual loss at 5 and 10 years. This was reflected in our cohort, as 57% of eyes (53 eyes) had a final VA of 20/40 or better.

In conclusion, despite the vision-threatening recurrent manifestations of BD in typically young patients, more than a third of eyes sustaining SVL at presentation can be rescued and most eyes with MVL can improve to 20/40 or better. These rates indicate that with appropriate immunosuppressive therapy, progressive decline in the visual functions in BD patients may be avoided or significantly decreased.

#### Compliance with ethical standards

**Funding** No funding was received for this research.

**Conflict of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study (retrospective study) formal consent is not required.

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