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REVIEW ARTICLE

Review for Diagnostics of the Year: Multimodal Imaging in Behçet Uveitis

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ABSTRACT

Behçet disease is a chronic relapsing multisystem inflammatory disorder. Ocular involvement is characterized by a bilateral recurrent non-granulomatous panuveitis and retinal vasculitis. Posterior segment findings vary during the course of the disease, in parallel with the relapsing and remitting intraocular inflammation. Structural alterations occur with increased disease duration. Fluorescein angiography is the gold standard in revealing the extent and severity as well as the leaky and/or occlusive nature of retinal vasculitis. Multimodal imaging using color fundus photography, fluorescein angiography, and optical coherence tomography is essential in visualizing diagnostic features, detecting structural changes, and monitoring disease activity and response to treatment in patients with Behçet uveitis.

Keywords: Behçet uveitis, fundus fluorescein angiography, indocyanine green angiography, multimodal imaging, optical coherence tomography

INTRODUCTION

Behçet disease is a chronic multisystem inflammatory disorder, first described as a distinct entity by Hulusi Behçet in 1937.[1] The disease is significantly more common in the Mediterranean basin and Far and Middle Eastern countries, especially along the ancient "Silk Road".[2] The highest prevalence rate of the disease has been reported in Turkey (420 per 100,000).[3] Although its etiopathogenesis has not yet been clarified, a dysregulation of both innate and adaptive immune systems is implicated.[4] It is believed that environmental agents may trigger an enhanced and dysregulated immune response that results in systemic vasculitis in immunogenetically susceptible individuals.[4,5] The underlying pathology of Behçet disease lesions is a perivascular inflammatory infiltration of the veins, capillaries, and arteries of all sizes and a thrombotic vasculopathy.[1]

Behçet disease primarily affects young adults around 30 years of age.[1] The eye is the most commonly involved vital organ and may be affected in up to 90% of patients depending on the clinical origin of the study.[6] Ocular involvement is characterized by a bilateral recurrent non-granulomatous panuveitis and retinal vasculitis. A minority of patients may have isolated anterior uveitis or unilateral involvement.[7] Posterior segment involvement has been reported in 50-93% of patients with ocular disease, and recurrent inflammatory attacks may lead to severe retinal damage and visual loss.[7–10] Therefore, identification of posterior segment involvement has a very important prognostic value.

Posterior segment findings vary during the course of the disease because of the relapsing and remitting nature of intraocular inflammation. Based on the disease duration and disease activity various fundus findings may be seen, including diffuse vitreous cells and haze, optic disc hyperemia, optic disc infiltration,

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papillitis, neuroretinitis, neovascularization of the disc, superficial retinal infiltrates or full-thickness necrotizing retinitis; inflammatory sheathing of retinal vessels, occlusion of major or peripheral retinal veins or rarely arteries, retinal hemorrhages, retinal neovascularizations; retinal edema, exudative retinal detachment, and macular edema as signs of active disease; and partial or complete atrophy of the optic disc, gliotic sheathing of retinal vessels, ghost vessels, diffuse retinal atrophy, macular atrophy, scarring, or hole formation as signs of structural damage.[7–10]

Multimodal imaging is essential in visualizing diagnostic features, assessing disease activity, monitoring response to treatment, and detecting structural changes in patients with Behçet uveitis (Figure 1 and Figure 2).

COLOR FUNDUS PHOTOGRAPHY

Spontaneous resolution of acute inflammatory signs is a diagnostic feature of Behçet uveitis.[11] Therefore, photographic documentation helps both differential

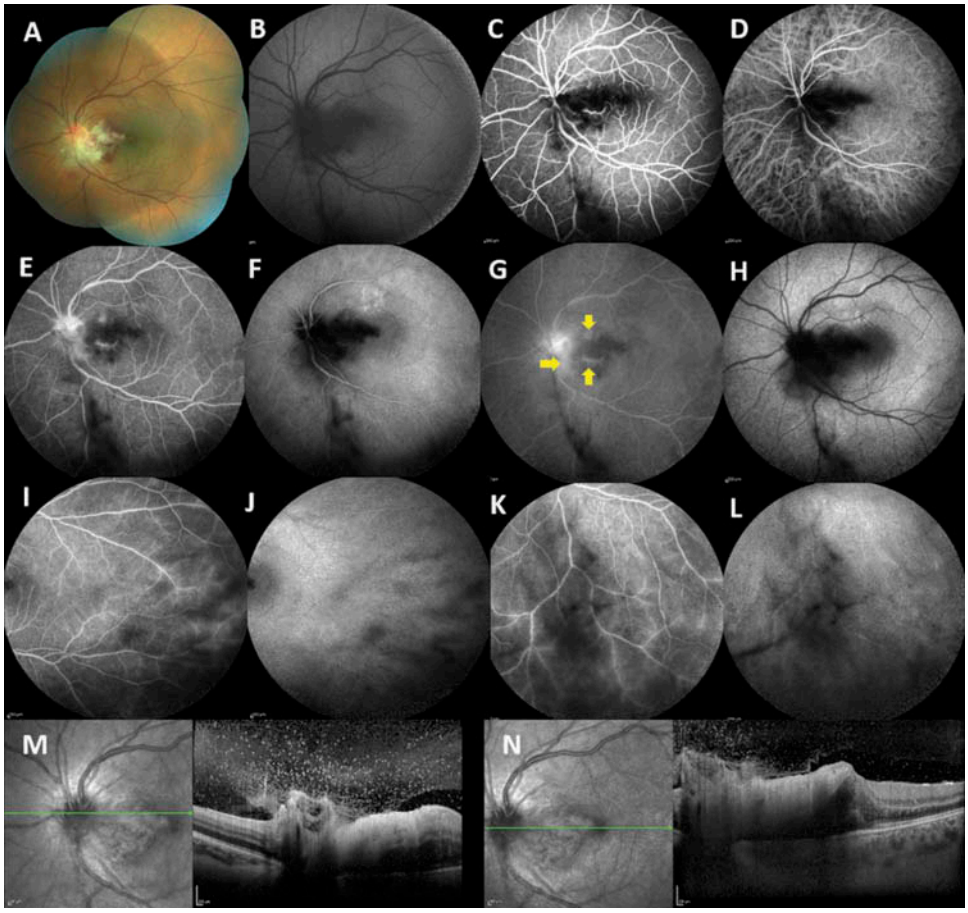

FIGURE 1. Multimodal imaging was performed in a 25-year old male patient with a history of Behçet disease for 5 years who presented with acute visual blurring in the left eye. His visual acuity was 20/20 in the right eye and 20/200 in the left eye and he had 4+ anterior chamber cells in the left eye. Montage color fundus photograph of the left eye (A) shows papillitis, retinal infiltration, edema, and hemorrhages inferior and temporal to the optic disc extending to the fovea; fundus autofluorescence imaging (B) shows hypoautofluorescence of the involved area due to blockage. Dual fluorescein (C, E, G, I, K) and indocyanine green (D, F, H, J, L) angiography was performed. Fluorescein angiographic frame of the posterior pole at 23 seconds (C) shows hypofluorescence of the inferior temporal quadrant of the optic disc, hypofluorescence of the inflamed retina, and leaky small vessel branches and dilated capillaries within the involved area. At 7 min (E) and 24 min (G) increased leakage causes a blurry hyperfluorescence of the inflamed vasculature (marked by arrows only at the 24-min frame). There is also hyperfluorescence of the optic disc and minimal leakage from the tips of venular branches of the arcades. Indocyanine green angiography of the posterior pole shows a dark hypofluorescence of the infiltrated retina (D) surrounded by a halo of lighter hypofluorescence in late frames (F, H) corresponding to the area of retinal edema. Late phase (8–9 min) fluorescein angiography of the temporal (I) and inferior (K) retina reveals leakage from the distal venular branches whereas indocyanine green angiography does not provide any additional information. Also note vitreous opacities and bands causing blockage in both fluorescein and indocyanine green angiographic frames. Spectral-domain optical coherence tomography B-scan through the optic disc in the left eye demonstrates a dense cellular infiltration of the posterior vitreous, a hyper-reflective mass of inflammatory infiltration on the surface of the optic disc, and hyper-reflective thickening and shallow detachment of the retina temporal to the disc (M). A combined depth imaging scan though the fovea demonstrates vitreous infiltration as well as some shadowing beneath the hyper-reflective and thickened papillomacular bundle area (N). Also note the loss of retinal layers (smudge effect) in the nasal half of the macula and the presence of a foveal detachment.

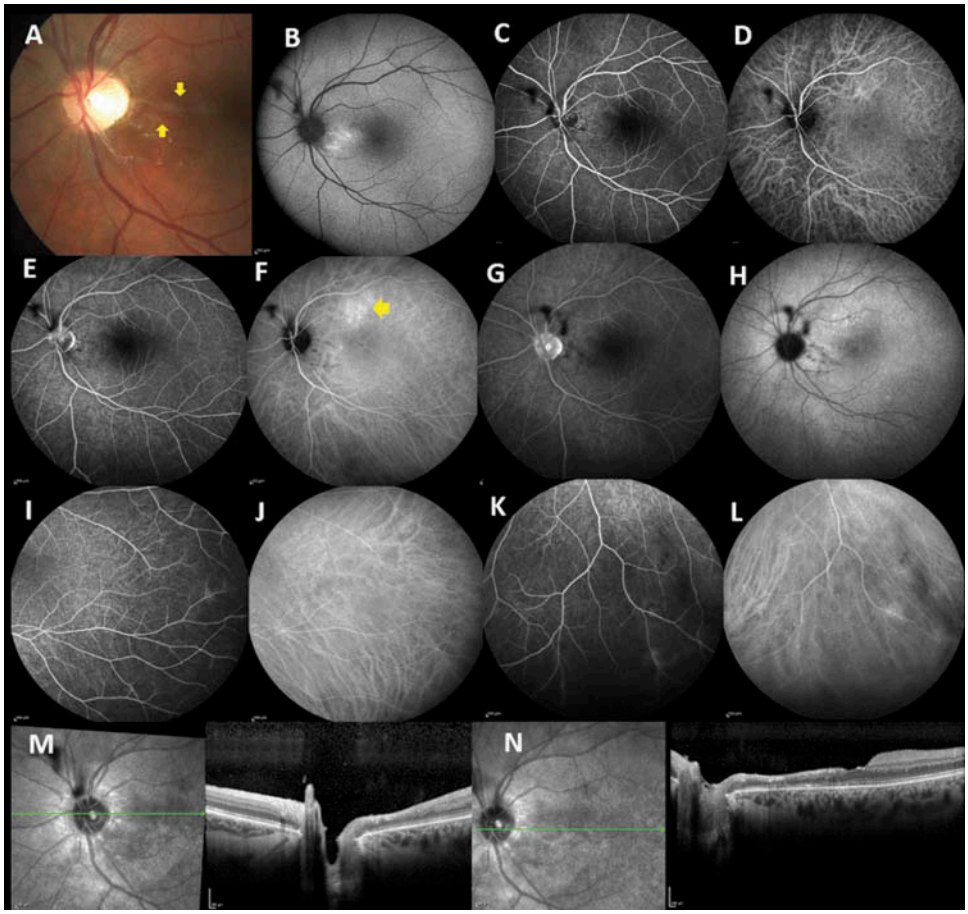

FIGURE 2. Multimodal imaging was performed in the same patient as in Figure 1 following 2 months of anti-inflammatory treatment. His visual acuity increased to 20/60. Color fundus photograph at a 30-degree view (A) shows temporal pallor of the optic disc, ghost vessels indicated by arrows, scattered tiny white deposits in the wake of the retinal infiltration, and sheathing of the inferior temporal retinal artery and vein. Fundus autofluorescence imaging (B) shows hyperautofluorescence in the papillomacular bundle area. Fluorescein angiographic frames of the posterior pole at 1 (C), 6 (E), and 23 (G) min show no filling of the ghost vessels, no vascular leakage, and hypofluorescence of tiny deposits. There is only minimal focal leakage from the temporal (I) and inferior (K) peripheral retinal vessels at 9 min. Indocyanine green angiography of the posterior pole shows a hyperfluorescent area indicated by an arrow at the 6-minute frame (F) which does not show up on fluorescein angiography. Scattered hyperfluorescent dots are seen in the peripheral frames at 9 min of indocyanine green angiography (J, L). Optical coherence tomography scans show resolution of optic disc edema and prepapillary vitreous infiltration (M), and thinning of the papillomacular bundle area with atrophy of inner retinal layers, hyperreflective dots, irregular thinning of the outer nuclear layer, and disruption of outer retinal layers (N).

diagnosis and monitoring of disease activity.[12] The grade of vitreous haze may be documented photographically. In most cases of Behçet uveitis, inflammatory cells seem to be freely distributed in the vitreous gel. Sometimes a cloud of cells may be seen in front of the posterior pole. As the vitreous haze starts to clear with anti-inflammatory therapy, white pearl-like precipitates may accumulate on the surface of the inferior peripheral retina or posterior hyaloidal face. These precipitates are seen as early as 4–5 days after the onset of the uveitis attack and disappear in a couple of weeks without any sequelae.[11] Documentation of this sequence of vitreous cellular infiltration–precipitation helps to differentiate Behçet uveitis from intermediate uveitis (Figure 3). Furthermore, inferior pearl-like precipitates appear as small white deposits, usually arranged in a linear pattern on the surface of the retina, whereas snowball opacities are larger mobile collections in the vitreous.[11] Superficial retinal infiltrates also resolve within a few days, even without treatment, and do not leave any visible chorioretinal scars.[8,11,12] Photographic documentation of the transient nature of retinal infiltrates is also helpful in differentiating Behçet uveitis from other etiologies that may present with cotton-wool spots or superficial or full-thickness retinal inflammatory lesions.[11–13]

FLUORESCEIN ANGIOGRAPHY (FA)

It has been shown that posterior segment involvement may occur in Behçet patients in the absence of any apparent clinical findings.[9] Fluorescein angiographic findings of optic disc staining and peripheral retinal

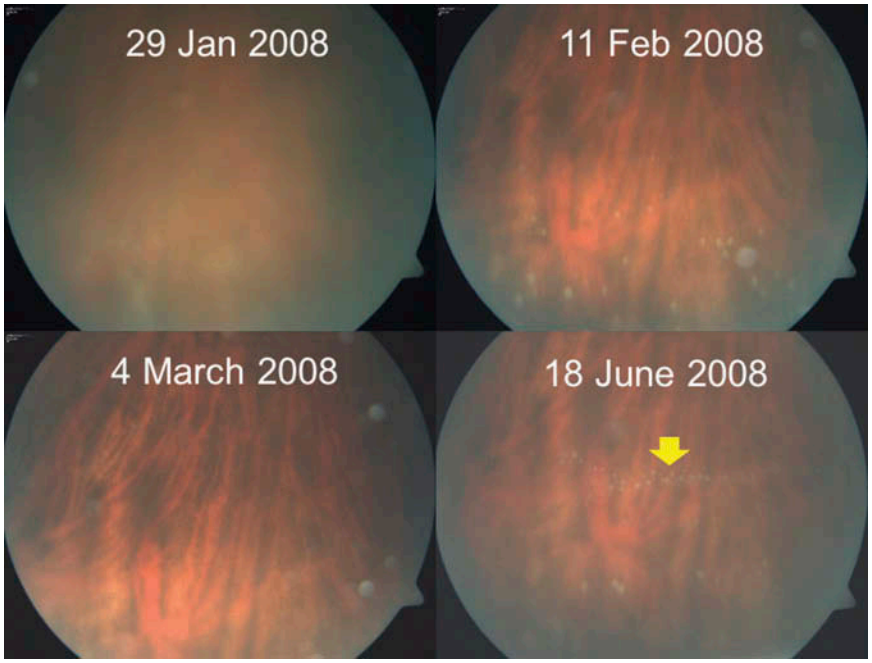

FIGURE 3. Serial color photographs of the inferior retina in the right eye of a patient with Behçet uveitis show a blurred image and limited view of the retina due to vitreous haze during a posterior uveitis attack in January 2008; the appearance of scattered pearl-like precipitates after resolution of vitreous haze 2 weeks later; subsequent resolution of precipitates in March; and linear (arrow) and a few scattered precipitates in June that appeared following another posterior uveitis attack.

capillary leakage have been reported to develop before obvious ophthalmoscopic signs of retinal vasculitis appear.[9]

Fluorescein angiography is the gold standard to detect and monitor both the leaky and occlusive nature of retinal vasculitis in Behçet uveitis.[9,12,14–18] Fluorescein angiographic signs of inflammatory activity include engorgement and increased tortuosity of retinal veins, staining of vessel walls, leakage from large and small retinal vessels, staining of the optic disc, and leakage from the optic disc, macular and retinal capillaries.[12,14,15] A fern-like diffuse capillary leakage is

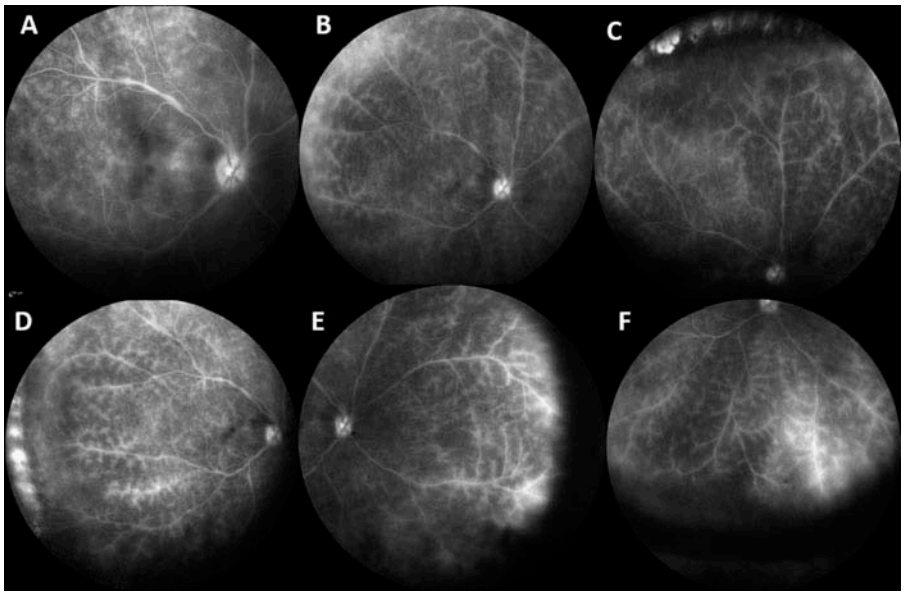

FIGURE 4. Late-phase fluorescein angiography of the right eye of a patient with Behçet uveitis during clinical remission shows staining of the optic disc, perifoveal ring of leakage, and staining of the superior temporal vein in 55-degree (A) and 102-degree (B) view of the posterior pole (A). Wide-field fluorescein angiography reveals diffuse fern-like leakage in superior (C), temporal (D), nasal (E), and inferior (F) retina.

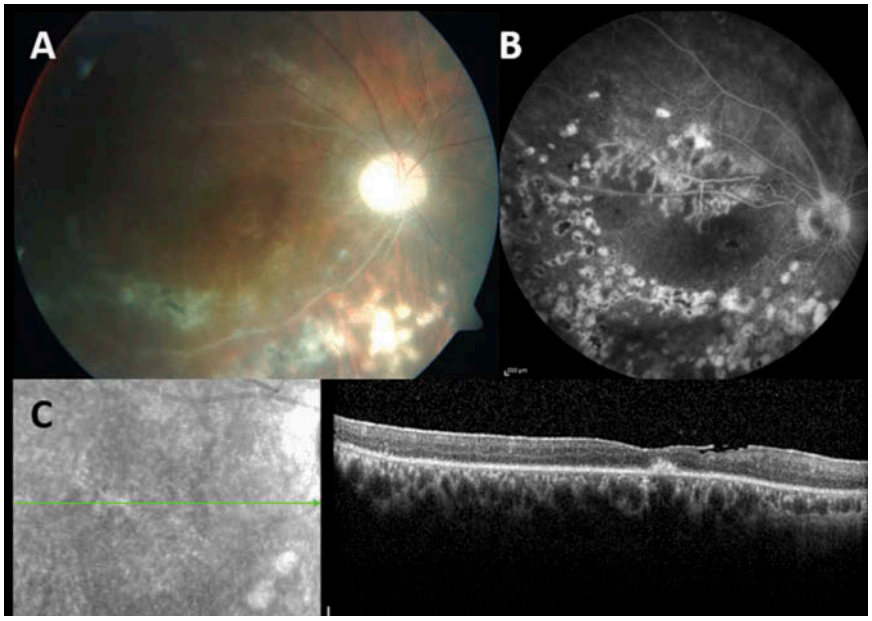

FIGURE 5. Color fundus photograph of the right eye of a patient with Behçet uveitis shows partial optic atrophy, atrophic macula, ghost vessels, and laser scars inferiorly (A). Late-phase fluorescein angiography shows extensive macular ischemia and dilated leaky capillaries superiorly (B). Spectral-domain optical coherence tomography B-scan through the fovea shows diffuse retinal thinning, an epiretinal membrane, loss of outer retinal architecture, and a hyper-reflective focal elevation above the retinal pigment epithelium corresponding to a spot of pigment accumulation.

the most frequent FA finding of Behçet uveitis and may be the only sign of persistent inflammation in the posterior segment during clinically quiescent periods[12,13] (Figure 4). The occlusive nature and extent of retinal vascular involvement can also be shown by FA (Figure 5 and Figure 6). This is essential for detecting and monitoring occlusion of large retinal vessels, capillary nonperfusion, vascular rearrangements, shunt vessels, and neovascularizations.[12,13] Differentiation of retinal neovascularizations from vascular rearrangements and shunt vessels guides the therapeutic approach with laser photocoagulation.[19] Similarly, FA is crucial to identify the mechanisms involved in the development of disc neovascularization in Behçet patients. When disc neovascularization is associated with diffuse capillary leakage—that is, persistent inflammation rather than extensive capillary nonperfusion—laser photocoagulation is contraindicated and intensive medical therapy is required[20] (Figure 7).

Fluorescein angiographic findings may also have prognostic implications. In patients with active Behçet uveitis, FA findings of disc neovascularization, macular window defect and macular ischemia indicate a poor visual prognosis.[14] Another study evaluating the risk and prognostic factors for poor visual outcome in Behçet uveitis showed that diffuse retinal vasculitis confirmed by FA was more frequent in patients with visual acuity ≤ 20/200 compared to patients with visual acuity > 20/200 at the time of last remission (93.6% versus 77.4%).[21] Although this difference was not statistically significant, the mean number of ocular attacks per year was significantly higher in the former group.[21] Kim et al.[16] have recently shown that posterior pole involvement, the degree of retinal vascular leakage, optic disc hyperfluorescence, and macular leakage were significantly associated with worse

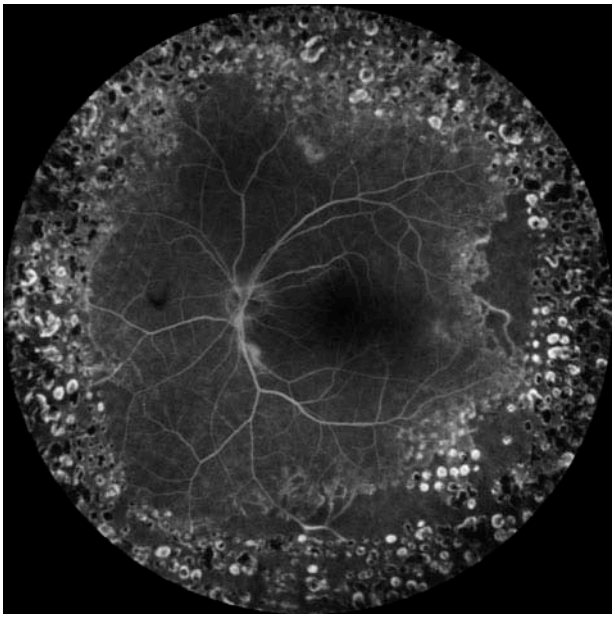

FIGURE 6. Wide-angle (102 degrees) fluorescein angiography of the left eye of a patient with Behçet uveitis during clinical remission shows 360 degrees of peripheral laser photocoagulation scars and areas of nonperfused retina posterior to the laser scars in the temporal and inferior quadrants.

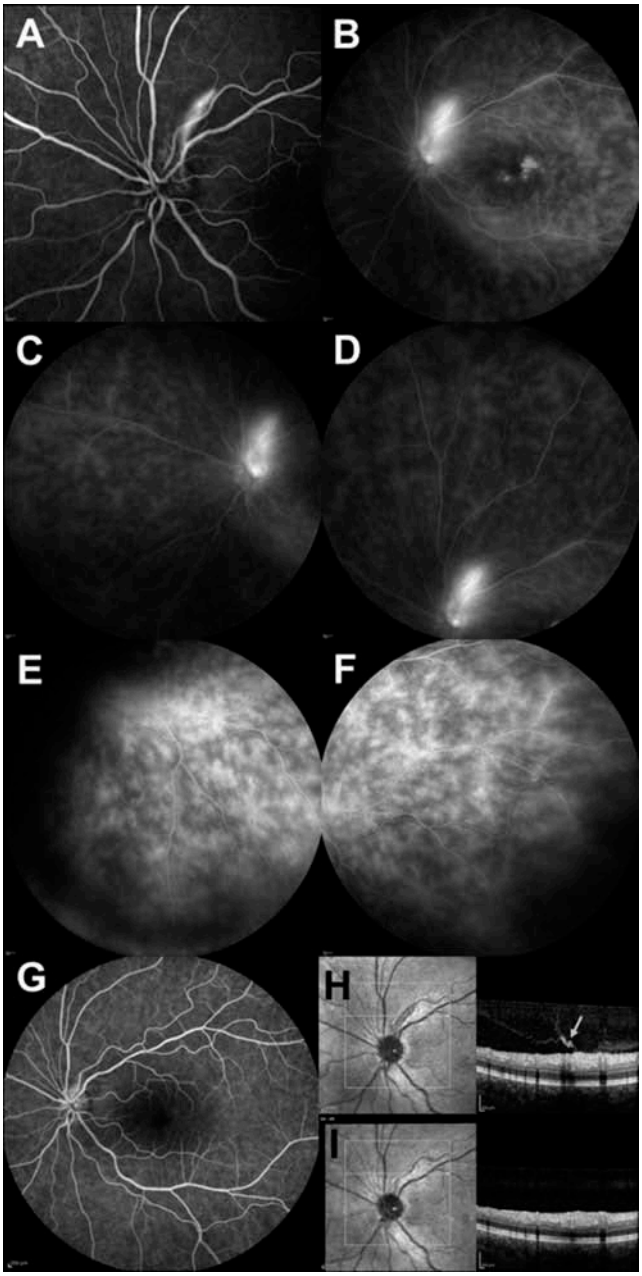

FIGURE 7. Early-phase fluorescein angiography of a female patient with Behçet uveitis shows early filling of neovascularization arising from the optic disc (A). Late-phase fluorescein angiography of the posterior pole shows optic disc staining and profuse leakage from neovascular tuft, a petaloid fluorescein pattern associated with cystoid macular edema, retinal vascular staining of temporal venous arcades, and diffuse capillary leakage (B). There is diffuse capillary leakage without retinal ischemia in the nasal (C), superior (D), inferior (E), and temporal (F) late-phase peripheral sweeps of the angiogram. Fluorescein angiography taken 2 months after institution of interferon alfa-2a therapy shows complete regression of the disc neovascularization, cystoid macular edema, and vascular leakage (G). Optical coherence tomography shows hyper-reflective cross-sectional views of the neovascular tuft anchored to the detached posterior hyaloid (arrow) (H); using the auto-rescan feature, spectral-domain optical coherence tomography confirms regression of the neovascularization after therapy (I).

visual acuity in Behçet patients.[16] The authors proposed an angiographic classification and grading of Behçet retinal vasculitis based on location, extent, and severity of retinal vascular leakage and suggested that the use of FA classification and grading might be clinically significant in terms of patients' visual prognosis and therapeutic approach.[16] Kang and Lee.[15] used an FA scoring system previously described by Tugal-Tutkun et al.[22] to evaluate the long-term progression of retinal vasculitis in Behçet patients. The authors reported that the FA score was significantly reduced during the quiescent phase compared to the active phase; however, the high FA scores found during activation did not significantly change with each activation during long-term follow-up.[15] They suggested careful monitoring of FA findings and early detection with prompt treatment of active inflammation in order to preserve vision.[15]

Although FA is crucial in monitoring response to treatment and is routinely used in clinical practice (Figure 8), FA findings have rarely been included as an outcome measure in clinical trials of Behçet uveitis. Keino et al.[17] reported that infliximab was effective in reducing both ocular inflammatory attacks and background retinal vascular and disc leakage in refractory Behçet uveitis over 1 year of treatment. The same authors evaluated the effect of infliximab over 4 years, and showed that the mean background retinal vascular and disc leakage scores decreased at the end of each 1-year treatment period.[18]

Conventional fundus cameras can capture only 30° to 60° of the fundus at a time and cannot image the entire retina simultaneously. This limited view makes it difficult to correctly locate peripheral lesions and to confirm and/or compare changes over time.[23] An ultra-wide-field (UWF) imaging system (OptosPLC, Scotland, United Kingdom) has recently been introduced and provides 200° of photographic, autofluorographic, and angiographic views of the ocular fundus (Figure 9). Leder et al.[23] conducted a prospective study comparing clinical examination, standard (60°) and UWF imaging to see whether the added information provided by UWF images would alter the management of patients with non-infectious retinal vasculitis. The authors noted a significant difference both in determination of disease activity and disease management with the use of UWF imaging compared with standard imaging. Disease activity was detected in 45% of visits based on clinical examination and standard FA, compared with 68% with clinical examination and UWF imaging. A decision to alter treatment was made in 6% of visits based on clinical examination alone, and in an additional 4% based on standard FA. The use of UWF color images altered the treatment in an additional 14% of visits and the use of UWF FA in 51% of visits.[23]

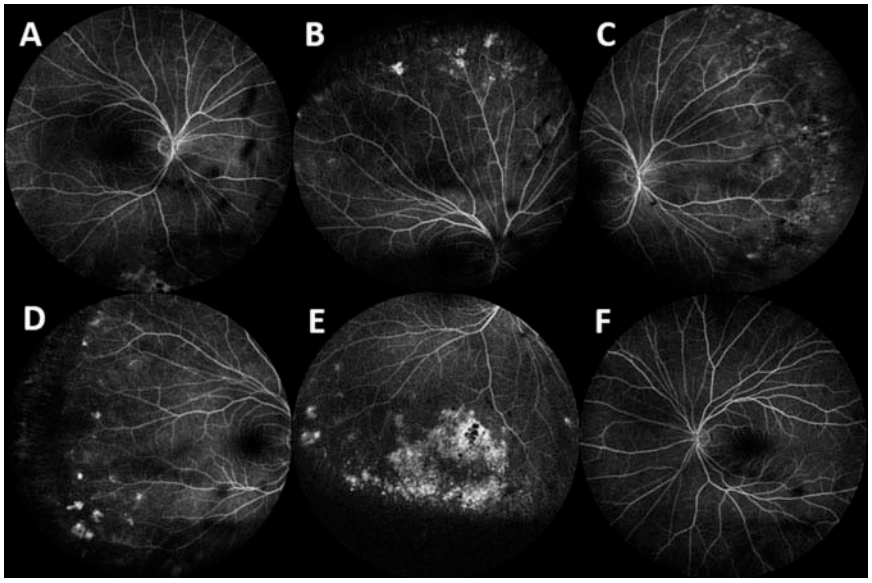

FIGURE 8. Late-phase wide field (102 degrees) fluorescein angiography of a Behçet patient successfully treated with interferon alfa-2a shows no staining of the optic disc in either the right (A) or the left (F) eye. There are typical window defects associated with retinal pigment epithelial changes in the superior (B), nasal (C), temporal (D), and inferior (E) peripheral fundus in the right eye. Only minimal leakage is noted in peripheral vascular branches in the right eye.

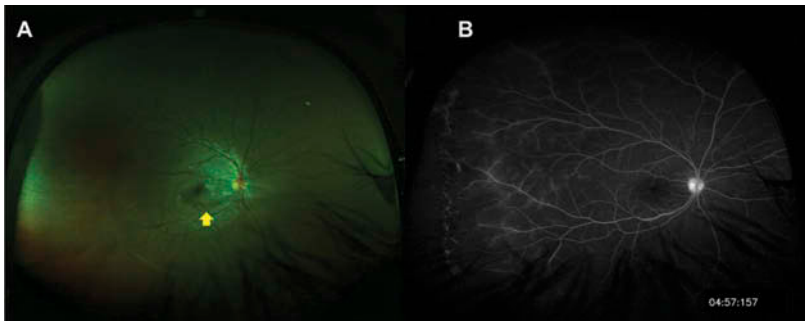

FIGURE 9. Images obtained using the ultra-wide field imaging system (OptosPLC) in the right eye of a patient with Behçet uveitis in clinical remission shows an inferior arcuate retinal nerve fiber layer defect (arrow) in color photograph (A), and staining of the optic disc and vascular leakage in the temporal peripheral retina on fluorescein angiography (B). Eyelashes are blocking the view of the inferior retina.

In many cases of Behçet uveitis, retinal vessels and capillaries anterior to the equator are involved[13] and peripheral leakage, ischemia, and neovascularization may be difficult to detect using conventional fundus cameras. Therefore, visualization of the peripheral retina by an UWF imaging system can make a significant contribution to the diagnosis, monitoring, and treatment of retinal vasculitis in Behçet patients. In a recent study of 20 patients with active retinal vasculitis associated with Behçet disease, UWF retinal imaging revealed additional information that led to a change of management in 80%, and enhanced disease monitoring in 55%, of the patients.[24] Ultra-wide field FA revealed peripheral and posterior changes such as fluorescein leakage from retinal capillaries in 84.8% of patients even in the absence of visual loss or abnormal fundus findings.[24] Peripheral capillary nonperfusion was demonstrated in 66.7%, optic disk leakage in 63.6%, macular leakage in 30.3%, macular edema in 27.3%, and retinal neovascularization in 9.1% of the eyes.[24]

INDOCYANINE GREEN ANGIOGRAPHY (ICGA)

Because Behçet disease is a systemic vasculitis, inflammation of the choroidal vasculature would be expected. Involvement of choroidal vessels has been shown by ICGA in patients with Behçet uveitis. However, ICGA findings reported for Behçet uveitis are nonspecific and include delayed and irregular filling of choriocapillaris, stromal vessel hyperfluorescence, staining of choroidal vascular walls, hyperfluorescent spots, hypofluorescent plaques,

optic disc and diffuse choroidal hyperfluorescence in the intermediate or late phase of ICGA.[25–28] These findings do not have significant correlation with the systemic manifestations of Behçet disease.[25] Bozzoni-Pantaleoni et al. [29] have reported that hypofluorescent lesions in the early and intermediate phases of ICGA that become isofluorescent in the late phase were more frequently found in patients with a shorter disease duration, whereas the finding of large poorly defined hypofluorescent areas that remain hypofluorescent through the late phase of ICGA was associated with increased disease duration. No significant correlation has been shown between FA and ICGA findings, and the latter do not add clinically useful information on disease activity or therapy monitoring. Therefore, it is not necessary to perform ICGA on a routine basis in patients with Behçet uveitis.[12,26] ICGA may be especially useful in differential diagnosis, when primary choroidal inflammatory conditions need to be excluded. It is also useful in confirming the diagnosis of central serous chorioretinopathy that may develop during the course of high–dose corticosteroid therapy in patients with Behçet disease.[12]

FUNDUS AUTOFLUORESCENCE (FAF)

Fundus autofluorescence imaging allows the detection of low-intensity autofluorescence produced by fluorophores (mainly lipofuscin) present in the retinal pigment epithelial (RPE) cells. These fluorophores originate from the photoreceptor outer segments and accumulate in the RPE cells. Their excessive presence in the RPE layer is an indicator of RPE cell dysfunction. Since RPE is involved in most posterior segment inflammations, FAF imaging provides useful information on the metabolic state of RPE that may be indicative of disease activity.[30] The only report on FAF findings in Behçet uveitis is a recent study using the UWF imaging system.[24] In a series of 18 patients (34 eyes), peripheral changes were shown in 82.3%, multifocal hyperfluorescent spots in 55.9%, multifocal hypofluorescent spots in 50%, and hypofluorescent lesions along retinal vessels similar to those described in pigmented paravenous retinochoroidal atrophy in 20.6% of eyes.[24] These abnormalities were more visible with UWF-FAF than with UWF pseudocolor imaging, and FAF revealed significantly more distinct information regarding the number and extension of these lesions. The authors suggested that active retinal vasculitis might induce RPE alterations in the retinal periphery and recommended the use of UWF-FAF in Behçet uveitis.[24] On the other hand, FAF is not expected to be useful in the evaluation of inflammatory retinal lesions or subsequent inner retinal damage at the posterior pole, which primarily determine the visual prognosis in Behçet patients. Therefore, we believe that FAF is not a useful tool for monitoring Behçet uveitis.

OPTICAL COHERENCE TOMOGRAPHY (OCT)

In eyes with clear optical media, OCT provides a noninvasive investigation of posterior pole lesions, macular edema, and other macular complications in Behçet uveitis.

Cystoid macular edema is the most frequent vision-threatening complication and should be closely monitored by OCT, which provides both high-resolution cross-sectional imaging of the retina and quantitative measurement of retinal thickness. Fluorescein angiography and OCT are two complementary techniques for the detection and follow-up of uveitic macular edema.[31–34] Discrepant results of FA and time-domain (TD) or spectral-domain (SD) OCT imaging have been reported in more than 40% of uveitic eyes.[31,32] Kempen et al.[33] reported only a moderate agreement between macular leakage on FA and macular thickening on TD OCT, probably because these are related but non-identical characteristics of macular edema. Although FA is required to assess the overall activity of uveitis, OCT is superior for demonstrating the distribution of fluid as diffuse, cystoid, and subretinal, thus allowing identification of different patterns of macular edema.[34] Serous macular detachment has indeed become a detectable feature of macular edema only after the advent of OCT.[34,35] Vitreomacular interface abnormalities such as epiretinal membranes can best be visualized by SD OCT.[34,36] Both serous macular detachment and epiretinal membrane have prognostic implications in eyes with uveitic macular edema.[35,36] Furthermore, with the use of high resolution and contrast, SD OCT also allows evaluation of outer retinal layers, especially the junctions between inner and outer segments of the photoreceptors (IS/OS line; ellipsoid zone) and the cone outer segment tips line (interdigitation zone).[37] The integrity of these zones are correlated with visual function and prognosis in eyes with uveitic macular edema.[38]

In Behçet uveitis, an exudative macular detachment may develop at the onset of a severe uveitis attack, whereas cystoid macular edema with or without macular detachment is a sign of persistent intraocular inflammation; OCT enables noninvasive imaging of these pathologies. However, OCT cannot replace FA in monitoring Behçet uveitis because perifoveal or diffuse retinal capillary leakage, as well as macular or peripheral retinal nonperfusion, as the underlying mechanisms of macular edema and visual loss can only be assessed by FA. Atmaca et al.[39] compared macular TD OCT findings with FA findings in 33 eyes of 18 patients with

Behçet uveitis and reported normal OCT scans in 9 eyes with pathological findings on FA.

Optical coherence tomography is also used to detect other macular pathologies such as macular atrophy, hole formation, or scarring that may develop in advanced Behçet uveitis.[37] It has been shown that decreased foveal thickness and disruption of the ellipsoid zone detected by OCT are associated with poor visual function as a result of irreversible damage to the macula in patients with Behçet uveitis.[40–42] Takeuchi et al.[40] analyzed visual acuity, microperimetric changes, and macular thickness in patients with Behçet uveitis without active clinical inflammation or any TD OCT evidence of macular edema. The authors reported that visual acuity, perimetric sensitivity, and macular thickness decreased with increased disease duration.[40] Perimacular occlusive vasculitis resulting in macular thinning was suggested to be relatively more common in patients with a long disease duration than in patients with shorter duration of disease and active leaky vasculitis in the macular area.[40] Unoki et al.[41] analyzed relationships between visual acuity, foveal thickness, and integrity of the IS/OS line (ellipsoid zone) and external limiting membrane (ELM) on SD OCT imaging during clinical remission of Behçet uveitis. They showed that logMAR visual acuity negatively correlated with foveal thickness, and that eyes with intact IS/OS had significantly better visual acuity than those with ill-defined IS/OS whereas the status of ELM did not seem to be associated with visual acuity.[41] Yuksel et al.[42] found a disrupted subfoveal IS/OS line in 24.2% and a disrupted ELM in 28.8% of 66 eyes with inactive Behçet uveitis that underwent SD OCT imaging, and a lower visual acuity in eyes with a disrupted IS/OS line. A decreased central foveal thickness was associated with decreased visual acuity; however, IS/OS integrity, but not central foveal thickness, was an independent variable for visual acuity.[42]

Transient retinal infiltrates are the most commonly seen lesions during exacerbations of Behçet uveitis. The use of OCT has provided insight into the nature of these lesions and their sequelae. SD OCT sections through retinal infiltrates typically show focal retinal thickening, increased hyper-reflectivity with blurring, especially of inner retinal layers, and optical shadowing (Figure 10). There may also be disruption of outer retinal layers. However, in contrast to a focus of retinochoroiditis, such as in ocular toxoplasmosis, there is no focal choroidal thickening beneath the retinal infiltrate and the RPE contour is not affected, that is, there is no inward bowing of the RPE line. In Behçet uveitis, retinal infiltrates rapidly resolve without any apparent retinochoroidal scarring. However, SD OCT sections typically show inner retinal atrophy (Figure 10).[11,12,37] The development of non-glaucomatous localized retinal nerve fiber layer (RNFL) defects has been recently described as sequelae of superficial retinal infiltrates affecting the posterior pole in Behçet uveitis.[11,12,37,43] These papillomacular or arcuate RNFL defects can be easily identified by SD OCT B-scan imaging and may be associated with corresponding visual field loss.[37,43] This finding is a helpful diagnostic clue and indicator of posterior pole involvement in early Behçet uveitis, but localized RNFL defects are not seen in advanced disease with diffuse retinal and optic atrophy.

There are recent studies on SD OCT-based quantitative analysis of vitreous haze in patients with intermediate, posterior, or panuveitis.[44–46] Diffuse vitritis is a constant feature of posterior segment involvement in Behçet uveitis and high-grade vitreous haze is associated

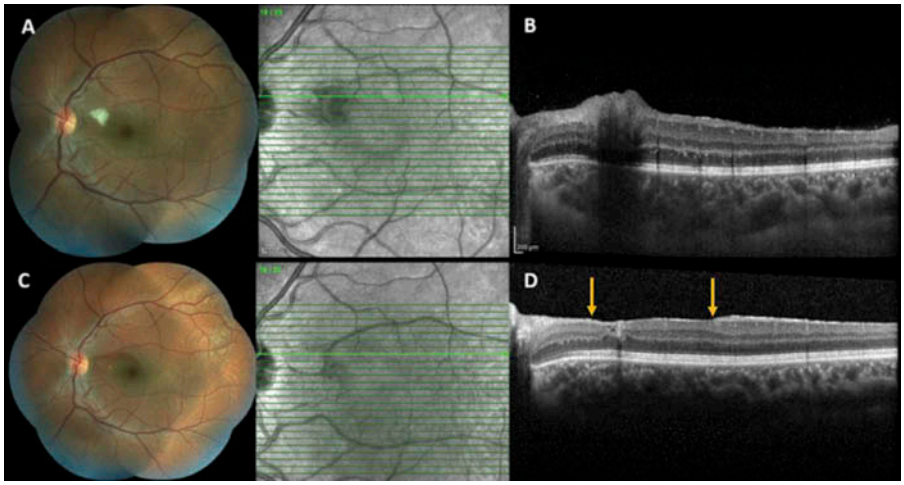

FIGURE 10. Color fundus photograph of the left eye of a patient with an exacerbation of Behçet uveitis shows a retinal infiltrate at the posterior pole (A). Spectral-domain optical coherence tomography B-scan through the infiltrate shows focal thickening and hyper-reflectivity of the inner retina with loss of retinal layers and shadowing beneath the lesion (B). Four months later, color fundus photography shows a focal retinal nerve fiber layer defect as a sequel of the infiltrate (C); and the optical coherence tomography autorescan shows focal disorganization and hyper-reflectivity in the inner retina and loss of the retinal nerve fiber layer (between the two arrows) (D).

with severe retinal inflammation.[11] An objective and reproducible quantification of vitreous inflammation would be extremely useful in monitoring Behçet uveitis.

A localized inflammatory vitreous condensation overlying the infiltrated optic disc is typical in Behçet neuroretinitis and SD OCT scans through the optic disc may show a "smoking volcano" picture or may reveal a "mushroom-shaped cloud that caps the plume". Resolution of the disc infiltrate and overlying inflammatory debris can be noninvasively monitored by OCT (Figure 11 and Figure 12).

Enhanced depth imaging (EDI) OCT, which is already being integrated into most commercially available OCT machines, provides *in vivo*, cross-sectional, histologic information on the choroid. There are four publications reporting on choroidal thickness assessment by the EDI mode of SD OCT in patients with Behçet uveitis.[47–50] Ishikawa et al.[47] and Kim et al.[48] reported that subfoveal choroidal thickness was significantly greater during an acute attack of Behçet uveitis than in remission (338±94 versus 267±90 μm and 398±157 versus 356±141 μm in the two studies, respectively).[47,48] Ishikawa et al.[47] reported

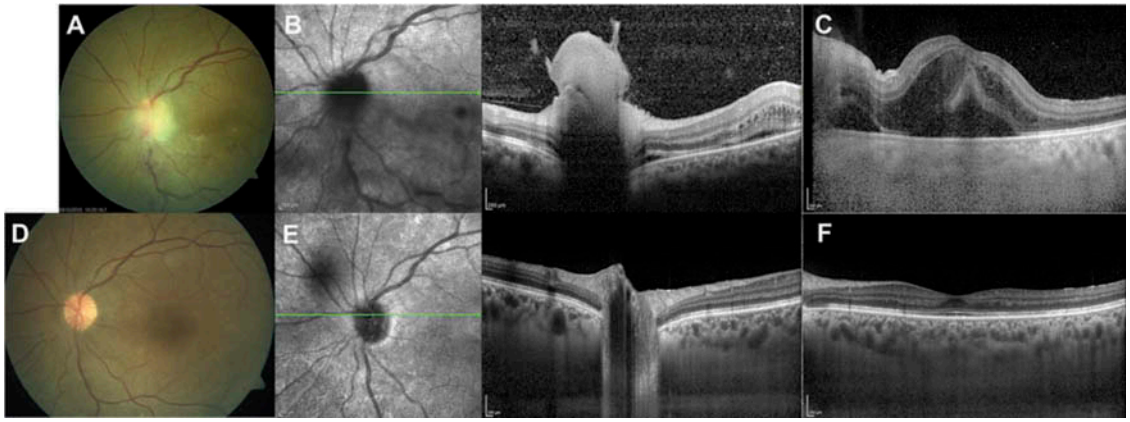

FIGURE 11. Color fundus photograph of the left eye of a 37-year-old female patient with Behçet uveitis shows a localized inflammatory vitreous condensation overlying the infiltrated optic disc and subretinal fluid accumulation at the macula indicating neuroretinitis, as well as retinal infiltration at the inferotemporal disc margin and retinal vasculitis with retinal hemorrhages along the inferotemporal vascular arcades (A). Spectral-domain optical coherence tomography B-scan through the optic nerve head shows a "mushroom-shaped hyperreflective cloud that caps the plume" pattern of hyper-reflectivity of the inflammatory vitreous exudation (B). Optical coherence tomography B-scan through the fovea reveals retinal thickening due to fluid accumulation in the outer retina and serous retinal detachment at the optic disc border and at the fovea (C). After 6 months of therapy, color fundus photograph shows a vital optic disc (D) and the optical coherence tomography scans through the disc (E) and the fovea (F) show complete resolution of inflammation. Visual acuity increased from 20/200 to 20/20 in 6 months.

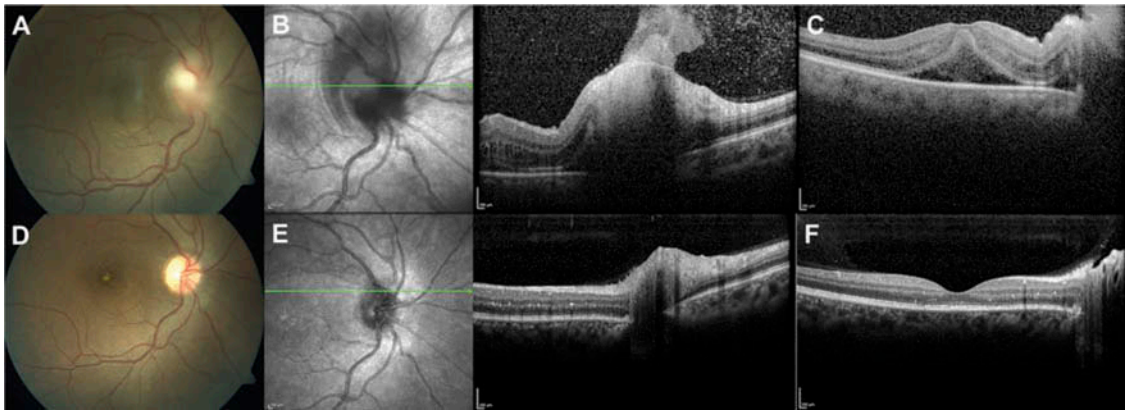

FIGURE 12. Color fundus photograph exemplifying neuroretinitis in the right eye of a 35-year-old female patient with Behçet uveitis shows localized inflammatory vitreous condensation overlying the optic disc and a prominent area of optic disc infiltration superotemporally (A). Spectral-domain optical coherence tomography B-scan passing through the prominent optic disc infiltration shows a "smoking volcano" pattern of hyper-reflectivity of the inflammatory vitreous exudation (B). Optical coherence tomography B-scan through the fovea confirms retinal thickening and juxtapapillary retinal detachment, as well as foveal detachment with cloudy subfoveal fluid (C). After 3 weeks of therapy, color fundus photograph shows temporal pallor of the optic disc and a macular star formation (D), and optical coherence tomography scans through the disc (E) and the fovea (F) show resolution of vitreous infiltration, optic disc edema, and subretinal fluid, and the presence of hyper-reflective dots in the retina. Despite a mild disruption of the ellipsoid and interdigitation zones, visual acuity improved from 20/200 to 20/25.

that the choroidal thickness correlated with clinical scores of inflammation in the anterior and posterior segment of the eye, whereas Kim et al.[48] did not find a significant correlation between choroidal thickness and severity of anterior or posterior segment inflammation or disease duration. Ishikawa et al.[47] showed Behçet cases with irregular filling and dye leakage from the choroidal vessels on ICGA associated with a thickened choroid; these ICGA findings were observed in eyes with or without retinal vascular leakage on FA. However, Kim et al.[48] found a significant association between choroidal thickness and retinal vascular leakage on FA. They also reported that the choroid was thicker than that of healthy control subjects not only during an attack of Behçet uveitis, but also during remission of the disease.[48] Atas et al.[49] reported similar results of a thicker choroid in eyes in remission of Behçet uveitis compared with control eyes, although the difference did not reach statistical significance. However, half of the eyes included in their study had a history of only anterior uveitis and the disease duration showed a wide range (1–20 years).[48] In contrast to these reports, Coskun et al.[50] demonstrated that the choroid was significantly thinner in eyes of Behçet patients with active posterior uveitis in comparison to control subjects. There was no significant difference in the choroidal thickness between eyes with an acute attack of Behçet uveitis and those in remission.[50] Interestingly, Kim et al.[48] reported that there was no significant difference in subfoveal choroidal thickness between the two eyes of Behçet patients with unilateral active uveitis, and the choroid was also found to be thicker than normal in the uninvolved fellow eyes. Although the authors suggested that this finding could be attributed to subclinical choroidal involvement in Behçet disease, we do not think there is enough evidence to support this because only 13 patients with unilateral involvement were compared to 13 control subjects in their study, and the lack of a significant difference between the two eyes may conversely suggest that the choroidal thickness does not change in active Behçet uveitis. Their results need to be confirmed in a larger study. The results of EDI OCT studies are conflicting, probably because of the non-homogenous patient populations studied based on variable definitions of activity and remission as well as variable disease duration. Inherent limitations of the current technology might also have played a role in these conflicting results. Since choroidal thickness shows individual variability, meaningful results can only be obtained by studying large numbers of patients and controls. Although longitudinal follow-up data in the studies reported by Ishikawa et al.[47] and Kim et al.[48] suggested a decrease in choroidal thickness with resolution of intraocular inflammation, the change in the mean thickness seems to be small and may not be clinically meaningful or useful. Central foveal thickness, an automatically calculated OCT parameter, is still more useful for noninvasive monitoring of inflammatory activity in Behçet uveitis (Figure 13).

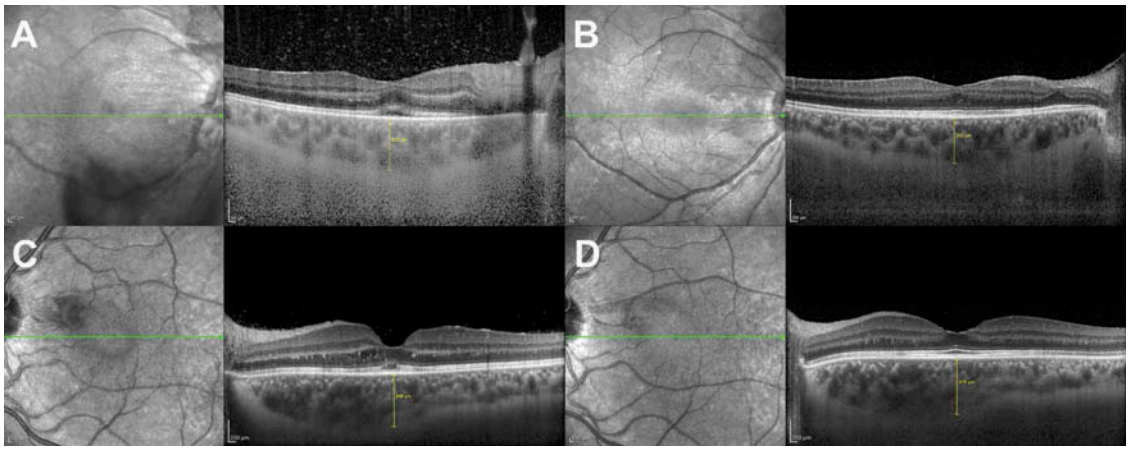

FIGURE 13. Choroidal thickness measurement during a uveitis attack in a 35-year-old female patient with a history of Behçet uveitis for 18 months reveals a subfoveal choroidal thickness of 439 µm on enhanced depth imaging optical coherence tomography B-scan of the right eye (A). There are hyper-reflective dots in the vitreous and retina indicating inflammatory infiltration and shallow subretinal fluid accumulation. Hyper-reflective retinal infiltrate and vitreous condensation cause optical shadowing of underlying structures at the papillomacular bundle. After 15 months of therapy, enhanced depth imaging optical coherence tomography reveals a decrease in subfoveal choroidal thickness to 392 µm (B). There is resolution of inflammation in the retina and vitreous and thinning at the papillomacular bundle with disruption of the inner retinal architecture. Choroidal thicknesses were measured manually using digital calipers provided by the Heidelberg Spectralis device software. Central foveal thickness recorded from the central 1-mm ETDRS grid display on the optical coherence tomography thickness map report decreased from 344 µm to 295 µm. Choroidal thickness measurement on enhanced depth imaging optical coherence tomography B-scan of the left eye of a 23-year-old male patient (the same patient as in Figure 10) with a total disease duration of 4 months reveals a subfoveal choroidal thickness of 449 µm during the acute uveitis attack (C). There are hyper-reflective dots and mild disruption of the ellipsoid and interdigitation zones. After 4 months of therapy, enhanced depth imaging optical coherence tomography shows an increase in subfoveal choroidal thickness to 475 µm (D). There is resolution of retinal inflammation and reinstitution of the outer retinal hyper-reflective lines. Central foveal thickness decreased from 323 µm to 267 µm.

Assessment of the choroidal thickness *per se* provides quantitative information. However, acquiring quantitative and qualitative information on the choroidal structure could enhance our understanding of the pathogenesis of choroidal involvement in uveitis. Unfortunately, currently available SD OCT devices cannot automatically segment the choroid. Optical coherence tomography angiography (OCTA) is an evolving technology that can characterize the vascular morphology of the retinal and choroidal circulation. Currently commercially available OCTA devices can produce *en face* images of the choroid but have a small field of view (either 3×3 mm or 6×6 mm) and there are no data on the use of OCTA in Behçet uveitis. As part of an ongoing prospective observational study we have evaluated in vivo quantitative morphology of the subfoveal choroid in eyes with acute attack of Behçet uveitis using EDI OCT to identify any significant differences between patients and healthy controls. We performed computed light-to-dark ratio analysis on EDI OCT scans using the method previously described by Branchini et al,[51] and thereby segmented the choroid into choroidal stroma and choroidal vessel lumen. Our preliminary results showed that there was no significant thickening or thinning in the choroid during an acute attack of Behçet uveitis compared to controls. However, we demonstrated significant choroidal stromal expansion in eyes with active Behçet uveitis that could indicate inflammatory infiltration in the choroid. (Onal et al, unpublished data). It has been speculated that inflammatory cells start to accumulate in the inner choroidal stroma because blood vessels in Sattler's layer have thinner walls compared with the larger vessels in Haller's layer.[52] We speculate that the stromal expansion may affect the inner choroid and therefore is less likely to cause thickening of the whole choroid in patients with Behçet uveitis.

Optical coherence tomography has revolutionized the qualitative and quantitative assessment of posterior segment pathologies associated with uveitis and has now become a standard ancillary test for detecting and monitoring uveitic macular edema. However, opacity of ocular media due to significant vitreous haze and/or cataract prevents acquisition of optimum images with this excellent instrument.

CONCLUSIONS

Color fundus photography, FA, and OCT are routinely used in multimodal imaging of the posterior segment in patients with Behçet uveitis. Although fluorescein angiography remains the gold standard in monitoring retinal vasculitis, OCT is widely used for noninvasive monitoring of macular edema and OCT-based prognostic features have been defined. Modern imaging devices, especially the introduction of OCT technology, have led to a better understanding of inflammatory lesions and structural changes in the retina and choroid. In addition to the significant contribution of UWF imaging in the diagnosis and monitoring of Behçet uveitis, future developments in wide-field OCT imaging and OCTA may provide valuable information on Behçet uveitis.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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