Use of ultra-wide field retinal imaging and optical coherence tomography angiography in the diagnosis of incomplete Susac syndrome

Carmen Alba-Linero[1*], John Paul Liscombe-Sepúlveda[2*], Victor Llorenç[3], Joan GiraltJosa[3] and Alfredo Adán[3]

Abstract

Purpose: To describe clinical findings through ultra-wide field (UWF) images and optical coherence tomography angiography (OCT-A), in Susac's syndrome (SS).

Methods: SS patients were retrospectively analyzed in a single center. Clinical features, ultra-wide-field retinographies (UWF-PR), UWF fluorescein angiographies (UWF-FA), and optical coherence tomography angiography & *en face* (OCT-A/EF) were reviewed.

Results: Twelve eyes from six patients with a mean follow-up of 35.66 months ± SD 36.88 were included. UWF-PR showed areas of retinal whitening and cotton-wool spots in all the eyes after acute attack. Segmentary mid peripheral arteriolitis could be observed in five eyes by UWF-FA in acute and convalescent stages. OCT-A revealed capillary density changes in all of the affected eyes. During the acute phase there was a well-preserved superficial capillary network, while deep retinal plexus showed a lower density in the affected areas. OCT-A/EF revealed deep retinal plexus drop-out and surrounding edematous retina in acute attacks, becoming atrophic over time. Conversely, superficial plexus was much less affected. Perifoveal reperfusion was seen in seven eyes after the acute attack.

Conclusions: UWF-PR/FA and OCT-A/EF might be helpful to stablish an early diagnosis and to monitor SS progression.

Keywords

Arterial occlusive disease, choroidal/retinal inflammation, immunology, posterior uveitis, techniques of retinal examination, uveitis, Susac's syndrome

INTRODUCTION

First published in 1979, Susac syndrome (SS) is an uncom- mon disease characterized by the clinical triad of branch retinal artery occlusions (BRAOs), encephalopathy and sensorineural hearing loss.[1,2] Although its etiology remains unclear, symptoms are attributed to a pauci-inflammatory occlusive endotheliopathy affecting the non-fenestrated retinal, cochlear, and cerebral vasculature.[3–5] the asynchronous clinical presentation and the similaritie with other disorders with multi-systemic involvement.[6,7] As no specific biological markers have been identified, the diagnosis of SS is based on the clinical and multimodal findings that include multiple BRAOs, commonly bilat- eral, and sometimes accompanied by leakage on fluores- cein angiography (FA) during acute attacks. Some typical funduscopic signs such as yellow deposits in proximal arteriolar walls (Gass plaques) have been described.[8] Even though, typical findings in brain MRI and sensorineural hearing loss in audiology tests are associated to SS presen- tation, the early setting of the disease does not always present with the complete diagnostic triad.

In recent years, the introduction of ultra-wide field (UWF) imaging systems have permitted to assess the reti- nal posterior pole and periphery in a variety of diseases, being able to capture a retinal field up to 200°.[9] The added capability to register UWF fluorescein angiography (FA) has shown an advantage in the diagnosis and follow-up of vascular retinal diseases.[10] On the other hand, the use of optical coherence tomography angiography (OCT-A) has been widely accepted as a diagnostic tool for assessing the superficial and deep capillary plexuses of the retina in many conditions.[11]

We present a case series of patients with different clini- cal presentations of SS and a retrospective analysis with the aim of describing the utility of UWF retinal imaging systems and OCT-A in the diagnosis and follow-up of patients with suspected incomplete SS.

PATIENTS AND METHOD

A case series of six patients with confirmed diagnosis of SS was retrospectively analyzed. Using images acquired with ultra-wide field retinal imaging system (Optomap, Optos PLC, UK), optical coherence tomography (OCT) and OCT-A (Angioplex, Cirrus 5000, Carl Zeiss Meditech, Inc. CA, USA), we observed the findings and correlated them with clinical symptoms and findings in visual field (Humphrey 24-2 SITA fast, USA), brain MRI and audiometry, taken at baseline and the following visits during the first 12 months.

Optical coherence tomography (OCT) is a non-invasive technique for cross-sectional tissue imaging. A scanning OCT beam allows for acquisition of cross-sectional images of the tissue structure. OCT-A is a fast imaging tool, detecting streaming blood, thereby allowing to construct an image of the retinal vasculature; in contrast to “classical” fluorescein angiography (FA) it is dye-free, and therefore lacks significant side effects associated with the fluorescein injections. This allows the in situ, high-resolution visualization of the individual vascular layers, OCT-A visualizes the superficial, the deep and the choroidal vascular network; even the middle capillary plexus can be identified, OCT-A and OCT-A / EF have helped in the diagnosis and monitoring of retinal vascular disease.[12]

Ultra-widefield (UWF) imaging is also a useful technique in the diagnosis of vascular and inflammatory diseases of the retina since sometimes the funduscopic examination can pass unnoticed findings and is a reliable tool to be able to compare over time in an objective way. Similar to standard field retinal angiography, FFA involves intravenous injection of fluorescein, after which up to 200° synchronic retinal images are sequentially obtained.

Computerized perimetry is useful to detect and monitor dysfunctional insulted retinal areas in a quantitative manner. In conjunction with structural imaging techniques, visual field imaging provides functional information that must be correlated with anatomic damage in the monitoring of vascular diseases of the retina.[13]

In SS, cerebral involvement affects certain areas, and a neuroimaging triad of white matter lesions, deep gray matter, lesions, and leptomeningeal disease is seen, that is why the study of neuroimaging using magnetic reso- nance is key, mainly in suspicious cases where the clinic is not complete.[14]

Definitive diagnosis of SS was made based on presenting two symptoms of the full clinical triad or characteristics lesions in neuroimaging during initial evaluation. All patients had visual field testing, MRI, and FA in the first visit.[14]

All patients received an intravenous methylprednisolone dose of 1 g per day for three consecutive days after the acute setting of SS. A taper-off treatment with a dose of 0.5 to 1 mg/kg/day of oral prednisone was prescribed later on. After initial methylprednisolone pulses, four patients were treated with a dose of 2.5 mg/kg of cyclophosphamide, two patients with a dose of 0.5 g/kg of monthly immunoglobulins, two patients with a dose of 100 mg/day of azathioprine, and one patient required plasmapheresis after several relapses. In three cases with previously prescribed antiplatelet drugs we decided to maintain them as an adjuvant therapy.

Data about age at presentation, gender, best corrected visual acuity (BCVA) using Snellen scale, ear, ocular or neurological manifestations, and implemented treatments were collected.

All patients were followed by a multidisciplinary team, including ophthalmologists, neurologists, otologists and internal medicine specialists. Extraocular examinations were ordered at discretion of the implicated specialists and treatment was agreed among them and the patient. Informed consent was obtained from included patients. All the methods adhered to the tenets of the declaration of Helsinki.Results

Twelve eyes from six Caucasian patients (three males and three females) were included. Mean age of SS diagnosis was 43 ± 10.7 years. Previous medical records revealed bilateral

Table 1. Demographic and clinical symptoms in Susac's syndrome.

Patients	Age (yrs.)	Sex	Ethnicity	Baseline symptoms	Symptoms during follow-up
1	48	F	Caucasian	Scotoma/ Personality changes	Headache/Hypoacusia
2	60	M	Caucasian	Hypoacusia/Headache/Cognitive impairment	Headache/Aphasia
3	41	M	Caucasan	Scotoma/Headache	Headache/Personality changes
4	49	F	Caucasian	Hypoacusia/Headache	Cognitive impairment/Personality changes
5	30	M	Caucasian	Scotoma	No[1]
6	30	F	Caucasian	Scotoma/ Hypoacusia	Headache

F: female; M: male.
[1]MRI with typical lesions.

glaucoma under topical treatment in two patients. Three patients had previous history of retinal occlusive vasculitis with a suspected diagnosis of primary antiphospholipid syndrome and were under antiplatelet therapy. None of the patients presented the complete SS triad initially, although three of them developed it during the follow-up period, with a mean time of 5 months after the initial setting.

Clinical symptoms

The most common symptoms at presentation were unilateral visual scotoma in four patients, sensorineural hearing loss in three patients, and headache in two of them. All cases had bilateral ocular involvement at the end of the follow-up period. Simultaneous bilateral ocular symptoms were present in three patients. Only two eyes from different patients presented altered BCVA of counting fingers and no light perception, respectively.

Four patients showed clinical neurological involvement at presentation and one during the follow-up time. Neurological symptoms included severe headache, personality changes, cognitive impairment and aphasia. Permanent sensorineural hearing loss was detected in four cases.

Demographic results and clinical symptoms are summarized in Table 1. Clinical signs are described in Table 2.

Brain magnetic resonance imaging

MRI showed multiple round T2-weighted lesions in the white matter in four patients. Two of them presented typical lesions around the corpus callosum, and a lesion near the Turkish saddle was found in one of them. Typical SS findings in brain MRI with no clinical neurological manifestation were found in only one patient.

Ultra-wide field retinal imaging

UWF images showed retinal whitening or cotton-wool spots, sparing the fovea in all but two eyes during the setting of SS in pseudocolor retinographies (Figure 1). The most frequent location of retinal infarction was the inferior-temporal branch in 10 eyes. Few subtle hyper-fluorescent geographic areas were found, probably due to fluorescence transmission in the acute and convalescence phases in recently symptomatic eyes, as well as in some of the fellow eyes. In five eyes from three patients a segmentary hyper-fluorescent pattern in mid-peripheral arteriolar branches was observed in Ultra-Wide-Field fluorescein angiography (Figure 2). Those segmentary arteriolitis foci did not coincide necessarily with whitening retinal areas on UWF images, and they tend to persist in some eyes during convalescent stages, even after intensive immunomodulatory treatment.

Optical coherence tomography angiography

OCT-A revealed capillary density changes in all of the affected eyes. During the acute phase there was a well-preserved superficial capillary network (mean 13.8 ± 2.7 mm^{-1}), while deep retinal plexus showed a lower density in the affected areas. Right after the acute phase, reperfusion of the peri-macular capillary bed was visible in the superficial plexus of seven eyes (baseline mean perfusion index = 0.34 ± 0.07, at 2 weeks 0.37 ± 0.07). The qualitative changes in OCT-A can be seen in Figure 3 and the quantitative changes and reperfusion changes are reflected in Figure 4. A progressive decrease in the density of the deep capillary plexus and subtler in the superficial plexus (mean perfusion index at 18 months = 0.33 ± 0.01) was observed during the following months in the convalescence stage.

The data on the evolution in terms of vascular density and perfusion over the months are represented in Figure 5 and collected in Table 3.

These findings correlated well with OCT en-face (OCT-EF) analysis of the inner retinal, which showed struc- tural hyper-reflective areas at the acute phase, becoming hypo-reflective in the following months. These images also correlated to edematous and atrophic areas respectively in OCT B-scans. Areas with a decreasing deep capillary density were also observed in the fellow asymptomatic eyes of some patients during the convalescent stage (Figure 6).

Prognosis

BCVA remained stable after the acute phase in all eyes. The course of the disease was monocyclic in two patients and polycyclic in four patients. However, new areas of decreasing capillary density in the deep retinal plexus and subsequent atrophic patches were detected in OCT-A images in

Table 2. Clinical signs observed in different imaging techniques in Susac's syndrome.

Patients	Eye	VA	UWF-PR	UWF-FA	OCT-A	OCT-EF	Visual field	CMR
1	OD	CF	Retinal whitening, Optic nerve pallor	Isofluorescent retinal areas, Segmentary arteriolitis	Superficial plexus low density Deep plexus absent	Hyperreflectivity (acute phase)	Total anular defect	Multiple lesions
	OS	1.0	Optic nerve pallor Retinal whitening	Isofluorescent retinal areas, Segmentary arteriolitis	Superficial plexus low density Deep plexus absent	Evolution to hyporeflective areas (atrophy)	Superior paracentral defect	
2	OD	1.0	Retinal whitening	Isofluorescent retinal areas,	Superficial plexus low density/reperfusion Deep plexus absent	Hyperreflectivity (acute phase)	Superior defect	Solitary lesion
	OS	1.0	Retinal whitening, Cotton-wool-spots	Isofluorescent retinal areas,	Superficial plexus low density/reperfusion Deep plexus absent	Hyporeflectivity (atrophic)	Superior defect, Paracentral defect	
3	OD	1.0	Retinal whitening optic nerve pallor	Isofluorescent retinal areas, Segmentary arteriolitis	Superficial plexus low density/reperfusion Deep plexus absent	Hyperreflectivity (acute phase)	Paracentral defect	Multiple lesions
	OS	1.0	Retinal whitening, optic nerve pallor	Hypo-isofluorescent retinal areas, Segmentary arteriolitis	Superficial plexus low density/reperfusion Deep plexus absent	Evolution to hyporeflectives areas (atrophy)	Paracentral defect	
4	OD	1.0	Retinal whitening, Cotton-wool-spots	Hypo-isofluorescent retinal areas	Superficial plexus low density/ Deep plexus absent	Hyperreflectivity (acute phase)	Superior paracentral defect	Peri- callous lesions
	OS	1.0	Retinal whitening	Hypo-isofluorescent retinal areas,	Superficial plexus low density/reperfusion Deep plexus absent	Evolution to hyporeflectives areas (atrophy)	Superior defect	
5	OD	1.0	Anodyne	Hypo-isofluorescent retinal areas, Segmentary arteriolitis	Superficial plexus low density/reperfusion Deep plexus absent	Hyporeflectivity (atrophy)	Normal	Multiples lesions, peri- callous lesions
	OS	1.0	Anodyne	Isofluorescent retinal areas,	Superficial plexus low density/reperfusion Deep plexus absent	Hyporeflectivity (atrophy)	Normal	
6	OD	NPL	Retinal whitening	Isofluorescent retinal areas,	Superficial plexus low density/ Deep plexus absent	Hyperreflectivity (acute phase)	Total anular defect	Multiple lesions, peri-turkish saddler lesions
	OS	1.0	Retinal whitening	Isofluorescent retinal areas,	Superficial plexus low density/ Deep plexus absent	Evolution to hyporeflective areas (atrophy)	Superior defect	

three patients. Those findings suggest subclinical acute or persistent ischemia during the follow-up. Previous diagnosed visual scotomas persisted during the convalescence phase of the disease and a mean defect increase was seen.

Discussion

SS remains a rare entity characterized by the triad of hearing loss, encephalopathy and brunch retinal artery case series presented the classical SS triad at the initial setting, half of them completed it in a mean period of 5 months. The asynchronous presentation of the variety of symptoms and signs possibly posed a challenge to discriminate SS from other occlusive vasculitis or prothrombotic conditions.

A variety of differential diagnosis arise in front of presumptive SS: neurodegenerative diseases, such as multiple sclerosis, or autoimmune diseases such as antiphospholipid

syndrome, systemic lupus erythematosus, sarcoidosis and occlusion.[15,16] Even though none of the patients in our

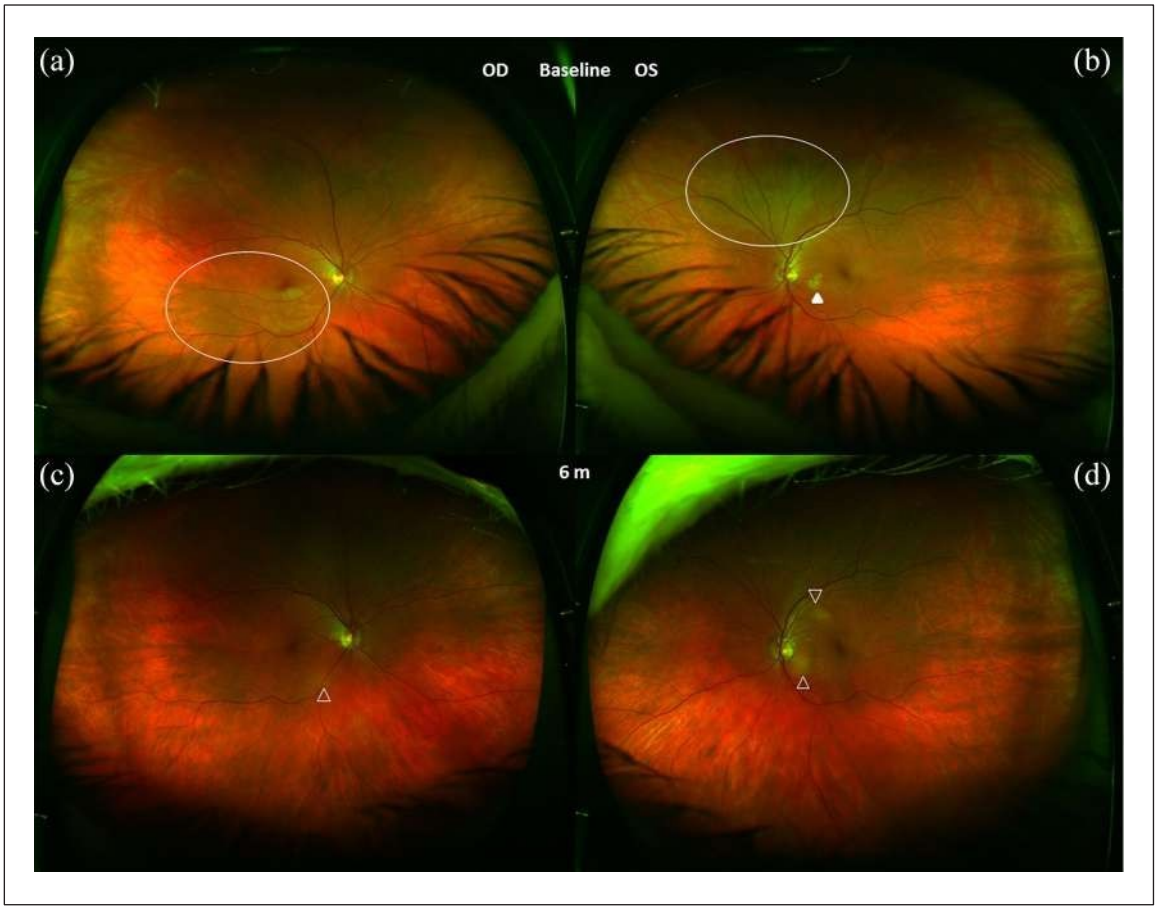

Figure 1. Ultra-wide field retinal images in a patient with Susac's syndrome. Retinal whitening (white circle) was found in the right eye after an acute attack perceived as migraine, photopsias and relative scotoma (a). In the fellow eye, superior retinal whitening (white circle) and cotton-wool-spots (filled arrow) were discovered (b). After 6 months and several methylprednisolone and cyclophosphamide pulses, the infarcted area appeared almost normal (empty arrow) in the right eye (c), but two small retinal lesions could be appreciated in the left eye (empty arrows) (c).

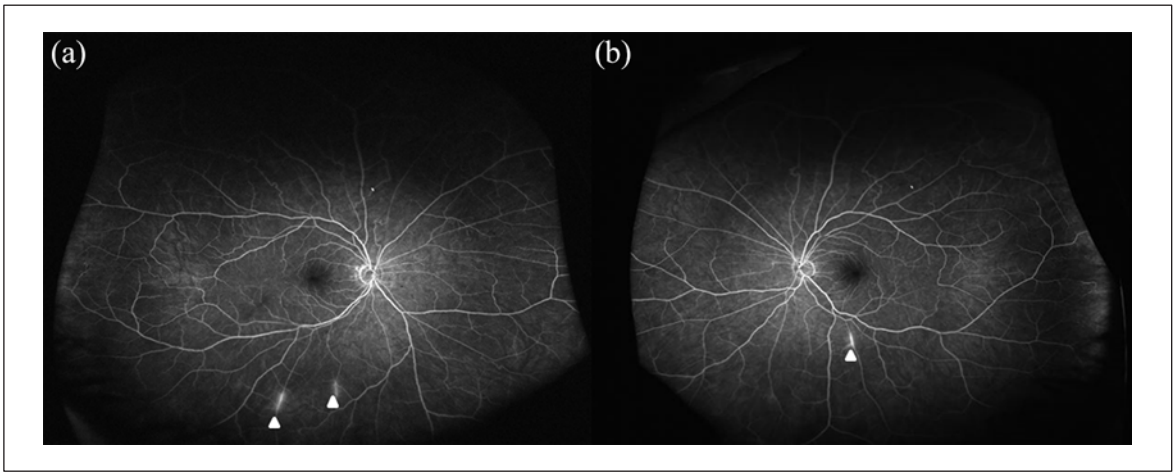

Figure 2. Ultra-wide field fluorescein angiography in a patient with Susac syndrome. Arterio-venous phase of the angiogram revealed mid-peripheral segmentary arteriolitis (filled white arrows) in the right (a) and left eye (b) after an acute attack treated with a high dose of methylprednisolone. Isofluorescence of the retinal occluded vessels was visible despite several retinal infarcts 3 weeks prior.

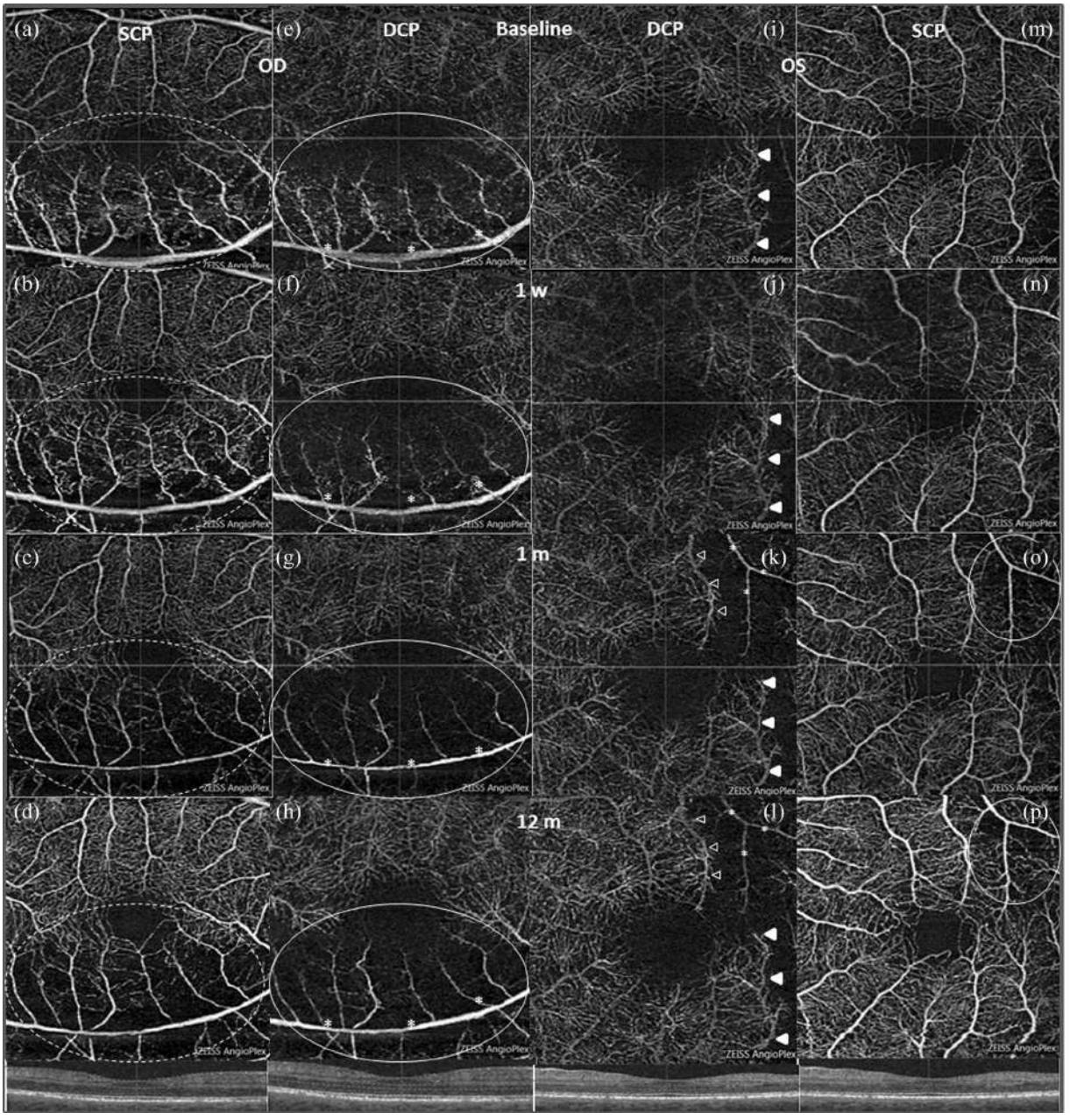

Figure 3. Optical coherence tomography angiography (3 × 3 frame) in a patient with Susac syndrome. Progressive loss of capillary density in the superficial retinal plexus (SRP) after an acute attack in the right eye (dashed circle) (a–d). Deep retinal plexus (DRP) was extremely scarce during the acute attack and disappeared over time (white circle). Note projection artifacts from the overlying SRP (asterisks) (e–h). Absence of DCP was also appreciated in the fellow asymptomatic eye (filled arrows), and increased during the follow-up (empty arrows). SRP is only slightly affected in the left eye (white circle) (m–p). The images correspond to baseline (a,e,i,m), 1 week (b,f,j,n), 1 month (c,g,k,o) and 12 months (d,h,l,p).

Behçet's disease, all of which can present with similar neurological manifestations.[17,18] In our case series the main prior presumptive diagnosis was antiphospholipid syndrome in three patients. In the context of a diagnosed systemic vasculitis, as antiphospholipidic syndrome, the presumptive Susac's should be attributed to the underlying condition. However, in the case of two of our patients, internal medicine work-up suspected an antiphospholipific

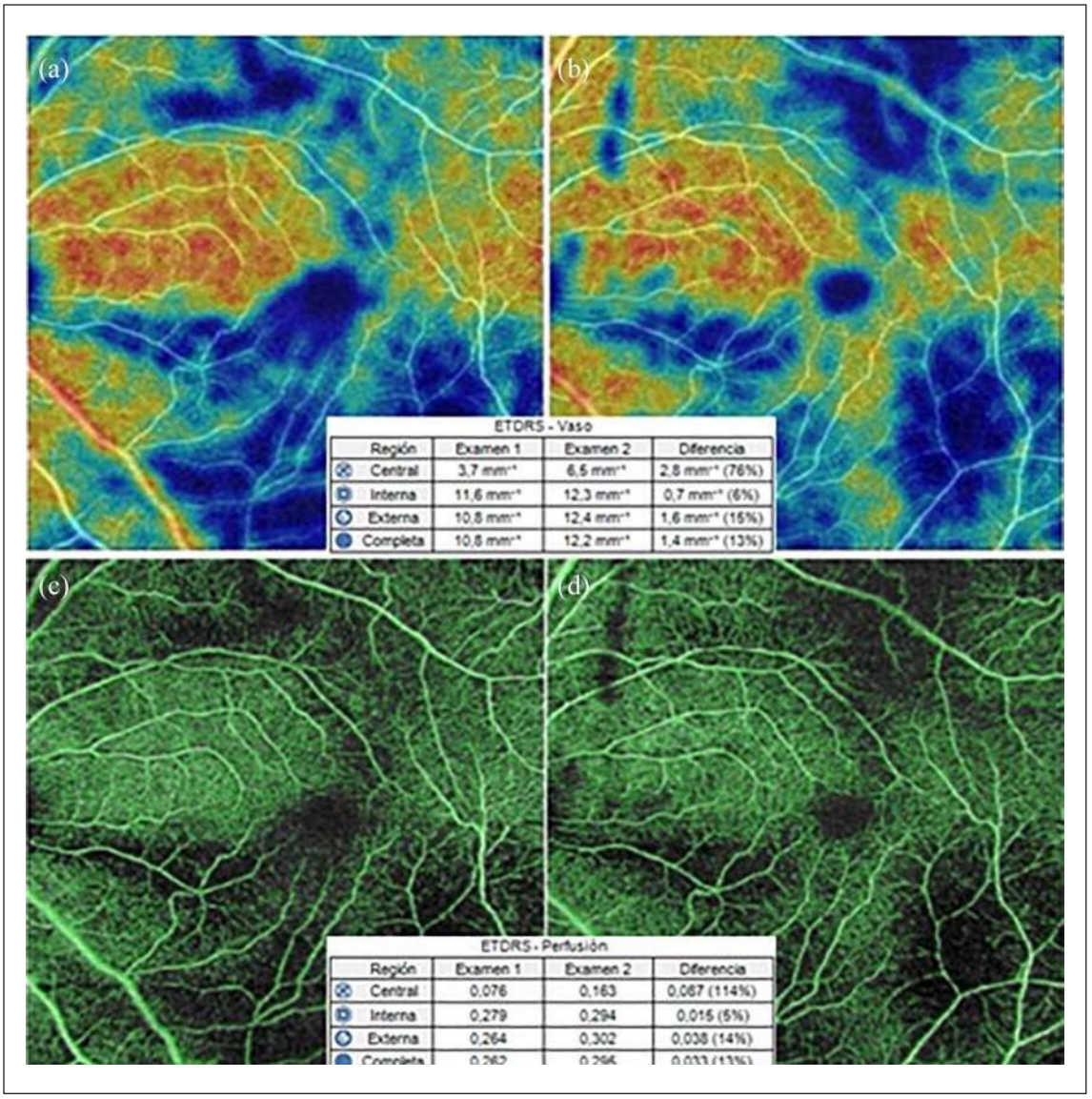

Figure 4. Optical coherence tomography angiography in Susac's syndrome. Quantitative analysis of the superficial capillary plexus. Vascular density during acute attack (a) and 2 weeks later (b). Perfussion during the acute attack (c) and 2 weeks later (d). Note the increase in central vascular density (76%) and central reperfusión (114%).

syndrome based on erratic slightly elevated anticardiolipin antibody titters over normal limits and, in the context of retinal occlusive vasculitis. Anticardiolipin antibodies can be found elevated in many infectious and non-infectious uveitis with occlusive retinal vasculitis, as well as in healthy controls. Thus, slightly raised anticardiolipin antibodies in uveitis is extremely unspecific.

Other autoimmune diseases such as sarcoidosis usually accompany other signs of ocular inflammation such as vitritis, chorioretinitis or granulomatous inflammation in the anterior chamber.

Magnetic Resonance Images can help us in early diagnosis in certain cases thanks to the visualization of microinfarctions in the central portion of *Corpus Callosum* in sagittal sections FLAIR and T2, lesions resemble "snowflakes" that subsequently evolve to black holes and central-callous atrophy. These injuries have a size of 3 to 7 mm, and suggest precapillary occlusion of small size below 0.1 mm diameter. Hyperdense images are also recognized in diffusion in internal capsule that take the form of "necklace of pearls." The presence of such images associated with injuries center-callous is unequivocally pathognomonic of Susac's syndrome.[14] Almost all of our patients presented multiple lesions in magnetic resonance images, being the corpus callosum the most frequent localization. This can help us to discern between brain injuries in Susac's Syndrome with respect to those of multiple sclerosis or Behcet's disease.

The advantages of UWF retinal photographs and fluorescein angiography seemed to be useful tools to reveal injured or ischemic retinal areas.[19,20] UWF photographs revealed wide areas of retinal whitening and the pres- ence of cotton-wool spots in one or both eyes during the acute attacks. Nevertheless, concurrent atrophic retinal areas were not visible in UWF retinal photographs or UWF-FA exams.

Early arterial times in UWF-FA revealed hypo-fluorescence areas around occluded vascular branches only in a

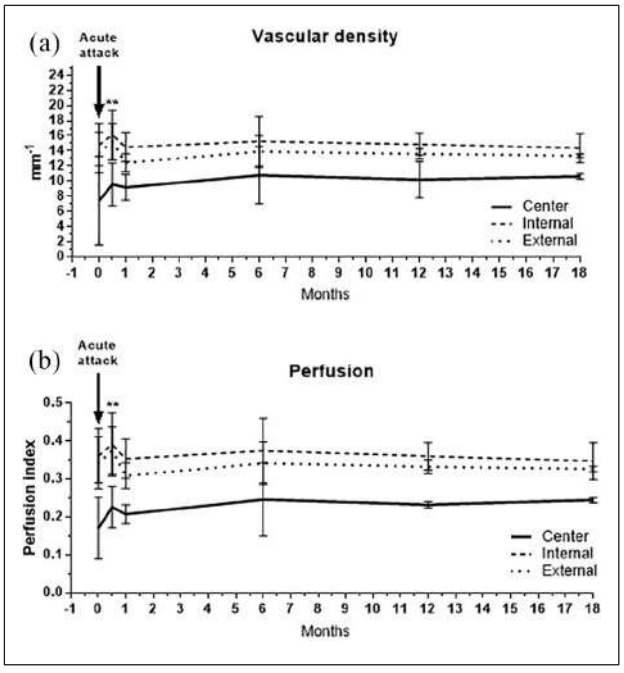

Figure 5. Vascular density and perfusion evolution after acute attack in Susac's syndrome.

few eyes. Conversely, other authors described hypo-fluorescence at infarcted zones.[21] A relatively preserved superficial retinal plexus could explain the dye transit in infarcted areas. UWF-FA offered an advantage revealing mid-peripheral segmentary arteriolitis in three patients. These areas did not necessarily correspond to Gass plaques or retinal whitening areas. Gass plaques are characteristic but not pathognomonic of SS and may be seen in a few other rare retinal disorders such as Eales disease and lymphoma.[21] Furthermore, this segmentary arteriolar staining persisted after intensive treatment, so its value as an activity biomarker was not clear. In our opinion, mid-peripheral segmentary arteriolitis, if present, can be a distinctive sign for early SS diagnosis. Even though, other pro-thrombotic conditions, as antiphospholipid syndrome, can be easily confused with SS, it is typically characterized by the lack of vasculitis (if a biopsy is possible), thus the finding of arteriolitis in UWF-FA could be a clue for early SS recognition.

OCT-A resulted in a feasible and noninvasive tool to detect capillary density loss or decreased perfusion in injured retinal areas. In the superficial retinal plexus, a moderate decrease of the capillary density and perfusion could be measured during the acute attacks. It was followed by early peri-foveal reperfusion in some eyes. Some authors have described restored perfusion in large vessels in absence of reperfusion signs in small capillar- ies.[22] In our series, a vascular density loss persisted at the superficial plexus, but UWF-FA denoted that some residual flow is still present in convalescent or quiescent stages. The deep retinal plexus was observed as the main primarily affected capillary network in SS during acute stages. Injured areas appeared as low to absent vascular density zones, and persisted or progressed during conva- lescent stages. OCT-EF correlated well with vascular changes, since recently infarcted areas appeared hyper- reflective, and structurally edematous. Along convales- cent stages, injured areas became atrophic, highly hypo-reflective and well defined, and seemed to increase in size over time in some eyes. Our results agree with oth- ers in literature, even though there is limited information on OCT-A use in SS.[23,24] OCT-A and OCT-EF frames showed to be useful for assessing the extent of acute or previously injured central retinal areas, as well as helpful to monitor the progression of the disease.

Guidelines for the treatment of SS are still speculative, possibly due to the lack of objective activity biomarkers and the unpredictable course of SS. Even though, systemic corticosteroids and classic immunosuppressive therapy remain as the main treatment. Cyclophosphamide, intravenous immunoglobulins, and rituximab have been used in refractory cases.[25] The use of antiplatelet and anticoagulant therapy is controversial.[26]

In conclusion, SS has an often incomplete and variable presentation, so imaging techniques can be useful for the diagnosis of this disease. UWF-PR can provide detection of inadvertent infarcted areas and UWF-FA can detect peripheral and medial segmental arteriolitis as in our case series. OCT-A is a non-invasive test that will allow us to detect decreased capillary density and perfusion in acute SS cases and subsequent reperfusion after treatment. OCT-A and OCT-A/EF are useful to assess both the extent of the injury and the residual damage from previous outbreaks, being useful in monitoring the disease, although larger studies are needed to determine constant findings that could be used as imaging biomarkers for early diagnosis.[12,26]

Table 3. Mean vascular density and perfusion values of the superficial retinal capillary plexus by OCT angiography (angioplex) at the time of an acute attack and successive follow-up time-points in Susac's syndrome.

	Vascular density (mm^{-1})					Vascular perfusion (perfusion index)				
	Time	Center	Internal	External	Complete	Time	Center	Internal	External	Complete
Mean ± SD	Baseline	7.43 ± 5.91	14.83 ± 2.81	13.80 ± 2.67	13.87 ± 2.69	Baseline	0.17 ± 0.08	0.36 ± 0.07	0.34 ± 0.07	0.34 ± 0.07
Mean ± SD	2 weeks	9.57 ± 2.81	16.10 ± 3.31	15.17 ± 2.40	15.20 ± 2.61	2w	0.23 ± 0.05	0.39 ± 0.08	0.37 ± 0.06	0.37 ± 0.07
Mean ± SD	1 month	9.18 ± 1.72	14.52 ± 1.94	12.42 ± 1.23	12.80 ± 1.16	1m	0.21 ± 0.03	0.35 ± 0.05	0.31 ± 0.03	0.32 ± 0.03
Mean ± SD	6 months	10.78 ± 3.76	15.28 ± 3.27	13.93 ± 2.08	14.15 ± 2.39	6m	0.25 ± 0.10	0.37 ± 0.09	0.34 ± 0.06	0.35 ± 0.06
Mean ± SD	12months	10.20 ± 2.40	14.88 ± 1.47	13.62 ± 0.72	13.78 ± 0.30	12m	0.23 ± 0.01	0.36 ± 0.04	0.33 ± 0.02	0.34 ± 0.01
Mean ± SD	18months	10.63 ± 0.35	14.39 ± 1.94	13.36 ± 0.23	13.48 ± 0.40	18m	0.24 ± 0.01	0.35 ± 0.05	0.33 ± 0.01	0.33 ± 0.01

Figure 6. Optical coherence tomography *en face* analysis of the inner retina (3 × 3 frame) in a patient with Susac syndrome. Hyperreflective (edematous) injured area after an acute attack in the right eye (white circle) (a). An hyporreflective paramacular area (filled white arrows) was observed in the fellow asymptomatic eye, suggesting a previous attack (e). Progressive atrophy of the recently infarcted area in the right eye (white circles) (b, c, d). Increasing atrophy surrounding the macula in the left asymptomatic eye (white empty arrows), in spite of methylprednisolone and cyclophosphamide pulses, suggesting new subclinical attacks (f-h). The images correspond to baseline (a,e), 1 week (B,F), 1 month (c.o). and 12 months (d.h).

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