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REVIEW ARTICLE

Susac's syndrome – the crucial role of imaging tests for proper diagnosis

Joanna Roskal-Wałek[1,2,A-D], Jerzy Mackiewicz[3,C,E-F], Łukasz Wypchło[4,2,B], Michał Biskup[1,B-C], Dominik Odrobina[5,2,C,E-F]

[1] *Department of Ophthalmology, Voivodeship Regional Hospital, Kielce, Poland*
[2] *Jan Kochanowski University, Kielce, Poland*
[3] *Department of Vitreoretinal Surgery, Medical University, Lublin, Poland*
[4] *Department of Imaging Diagnostics, Voivodeship Regional Hospital, Kielce, Poland*
[5] *Ophthalmology Clinic Boni Fratres Lodziensis, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract

Introduction. Susac's syndrome (SS) is a rare, autoimmune-mediated endoteliopathy characterized by a clinical triad of encephalopathy, branch retinal artery occlusion, and sensorineural hearing loss. SS is also characterized by a neuroimaging triad consisting of white matter lesions, grey matter lesions, and leptomeningeal enhancement on magnetic resonance imaging (MRI). Considering the rarity of SS, as well as certain similarity to other, more frequent neurological diseases, such as multiple sclerosis (MS), this syndrome is sometimes incorrectly diagnosed and treated.

Objective. The aim of the study is to present the current state of knowledge on SS, with particular consideration for the differential diagnostics between SS and MS, using the latest available imaging techniques, such as brain MRI, optical coherence tomography (OCT), OCT angiography (OCTA) and fluorescein angiography (FA).

Review methods. The major electronic databases (PubMed, Google Scholar) were searched manually in order to identify the relevant studies published on SS.

Brief description of the state of knowledge. Distinguishing SS from MS is a diagnostic challenge. In the majority of cases, patients with SS do not present the complete clinical or neuroimaging triad, and a delay in making the correct diagnosis exposes the patient to the occurrence of complications, resulting from the development of the underlying disease, or/and the application of improper treatment. In the case of SS the results of brain MRI and FA are essential for making the correct diagnosis as they may reveal pathognomonic changes.

Sumary. Imaging examinations, such as brain MRI, FA, and OCT complement each other, due to which the diagnosis of SS may be simpler, irrespective of the stage of the disease.

Key words

magnetic resonance imaging, optical coherence tomography, fluorescein angiography, multiple sclerosis, Susac's syndrome

INTRODUCTION

Susac's syndrome (SS) is a rare autoimmune disease during which the occlusion of microvessels in the brain, retina, and inner ear occurs. Occlusion of the vessels leads to the occurrence of a characteristic triad of symptoms, i.e. encephalopathy, visual disturbances associated with branch retinal artery occlusion (BRAO), and hearing loss, respectively [1–7].

SS mainly concerns the Caucasian population, and most frequently occurs between the ages of 20–40, with male to female ratio 1:3.5. However, reported cases indicate that SS may also concern persons within a wider age range from 7–72 years of life [1–9]. Seifert-Held et al. were the first to provide data concerning the epidemiology of SS among the population of Central Europe. According to these data, the incidence of this disease over a five-year period was 0.148/100,000, whereas the annual incidence of SS is 0.024/100,000 [10]. Nevertheless, it is presumed that the frequency of the occurrence of SS is underestimated [11]. The diagnosis of SS based exclusively on the triad of clinical symptoms is inappropriate, and there is great variability with regards to its presentation. The classic triad of symptoms occurs in only 13%-20% of patients and the intensity of triad components varies, which additionally hinders the diagnosis [1–7]. In addition, the symptoms may raise suspicion of other, more frequently diagnosed disease entities, such as multiple sclerosis (MS). SS is one of the most important diseases that should be included in the differential diagnosis of MS, especially due to the similarities in the clinical image and changes observed in brain magnetic resonance imaging (MRI) [12–21].

The wide range of imaging techniques currently available, such as brain MRI, fluorescein angiography (FA), optical coherence tomography (OCT), and OCT angiography (OCTA), allow the recognition of anatomical and physiological correlations underlying the pathology of SS [2, 22–37]. MRI and FA both enable the imaging of pathognomonic changes for SS [2]. Some characteristic features in imaging tests have been proposed as biomarkers which can be useful in monitoring disease activity and detection of SS relapses [5, 15, 22, 23, 37]. The right diagnosis is the key to proper

Address for correspondence: Joanna Roskal-Wałek, Department of Ophthalmology, Voivodeship Regional Hospital, Grunwaldzka 45, 25-736 Kielce, Poland
E-mail: joanna.roskal.walek@wp.pl

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treatment. Preliminary reports indicate that the treatment of misdiagnosed MS may lead to the exacerbation of SS [17–20].

OBJECTIVE

The aim of the study is to present the current state of knowledge on SS, with particular consideration of the differential diagnostics between SS and MS, using the latest available imaging techniques, such as brain MRI, OCT, OCTA and FA.

MATERIALS AND METHOD

In February 2022, an extensive manual search was made through the major electronic databases (PubMed, Google Scholar) in order to identify relevant studies published on SS. The following search terms were used: 'Susac syndrome', 'Susac syndrome, multiple sclerosis', 'fluorescein angiography', 'brain magnetic resonance', 'optical coherence tomography', 'optical coherence tomography angiography', in different combinations. With regard to MS, the most recent review articles concerning the application of MRI, OCT, and FA in the diagnosis of MS were selected. After compiling a list of potentially relevant articles, the full text of each paper was appraised, with particular emphasis on articles presenting differential diagnostics between SS and MS. A total of 75 compatible research publications were identified and used to compile this review.

STATE OF KNOWLEDGE

Pathogenesis of SS. The pathogenesis of SS still remains unclear. It is believed that SS is the result of immune-mediated endoteliopathy, which leads to the narrowing and occlusion of small vessels, resulting in the occurrence of microinfarctions in the brain, retina and cochlea [1–7].

An assessment of a biopsy of the brain tissue in patients with SS shows the presence of multiple microinfarctions in the grey and white matter, with the loss of axons, neurons and myelin in the affected areas [3, 12, 21, 38]. Brain MRI findings also provided evidence of myelin damage and widespread microstructural changes in SS patients [39]. Other changes observed in brain biopsy include occlusive endothelial cell (EC) swelling, endothelial proliferation of pre-capillary arterioles, with thickening of the vessel walls and minimal non-specific periarteriolar inflammatory cell infiltration [3, 12, 21, 38]. These changes are similar to those observed in juvenile dermatomyositis [40].

It was suggested that injury to the endothelium which occurs in the course of SS may be the result of circulating antibodies (anti endothelial cell antibody-ACEA). However, this hypothesis has been questioned because AECAs are detected in only 25% of patients with SS, and no relationship is observed between their titres and the severity of the disease [2, 41, 42]. Currently, based on the presence of these antibodies the diagnosis of SS is not recommended [2]. A study by Gross et al. throws new light on the pathogenesis of SS. The results of their study suggest that SS is an endoteliopathy in which T CD8 + lymphocytes recognize an unknown antigen on the endothelial cells, leading to its damage and the development of small ischaemic foci and microhaemorrhages [42].

One hypothesis concerning the pathophysiology of the disease is a parainfectious mechanism involving the presentation of a viral antigen on the endothelium after a viral infection [11, 42]. Recently, Venditti et al. have reported a case of SS after a COVID-19 infection [43]. However, based on the literature review, the infectious agent does not seem to play the main role in SS [1, 42].

It is also presumed that hormonal and immunological changes related with pregnancy, as well as a transient condition associated with a hypercoagulable state, may reveal the disease or cause aggravation of SS. It is estimated that 5% of cases of SS occur in association with pregnancy [44]. The recurrence of SS is also reported in patients receiving hormone replacement therapy, which additionally emphasizes the effect of hormones in the pathophysiology of SS [45].

Coagulation disorders may also modify or play a role in the pathogenesis of the disease. In patients with SS, protein S deficiency and factor V Leiden mutations have been reported, and anticardiolipin antibodies and a lupus anticoagulant detected; however, it is uncertain whether they are pathogenic for SS [46, 47].

A genetic basis of SS has also been considered, however, so far, it is impossible to identify a gene responsible for this syndrome [48].

Clinical symptoms of SS. SS is characterized by a classic clinical triad in the form of encephalopathy, retinopathy (BRAO), and hearing loss [1–7].

At the disease onset, patients frequently have symptoms related to the central nervous system. It usually starts as a sub-acute encephalopathy with headache and non-specific neurological symptoms. Headaches may precede the symptoms of encephalopathy by several months. Later, other symptoms develop, including impairment of cognitive functions, memory loss, dizziness, dysarthria, ataxia, cortico-spinal tract dysfunction, or hemiparesis. Other symptoms include seizures and mental disorders, with personality disorders and paranoid behaviour which are underemphasized [1–7, 12, 17, 49].

Visual symptoms mostly result from BRAO. Patients with SS and BRAO may report visual field defects with or without reduced visual acuity. Patients may also report positive visual phenomena, scintillating scotomas, or photopsia. It should be kept in mind that the BRAO of peripheral arteries may be asymptomatic. Moreover patients with encephalopathy may be unable to report visual impairment [1–7, 12, 17].

Hearing loss, however, may be of an acute or sub-acute type, often precipitous at onset with a typically rapidl progress, sometimes resulting in complete deafness in either one or both ears [1–7, 12, 17, 50]. Important otologic symptoms of SS are also tinnitus and dizziness. Audiometric assessment usually reveals an increasing pattern of sensorineural hearing loss within the range of low and medium frequencies, resulting from damage to the structures of the inner ear [50].

SS or MS-differentiation. At disease onset, the classic triad of symptoms of SS is absent in 87% of patients, with full manifestation of SS observed within several months, and in some cases complete manifestation of SS lasted more than two years [1]. Frequently, this incomplete manifestation of SS leads to an initially incorrect diagnosis [13, 14, 17–21]. The scope of disease entities with which SS should be differentiated is wide [1, 50, 51] (Tab. 1).

Table 1. Differential diagnosis of SS

Demyelinating Central nervous system (CNS) disease	Multiple sclerosis, acute disseminating encephalomyelitis (ADEM), Neuromyelitis optica (Devic's disease)
Vasculitic, connective tissue, and autoimmune disease	Antiphospholipid antibody syndrome, Systemic lupus erythematosus, Poliarteritis nodosa, Behçet disease, Churg-Strauss syndrome, Dermatomyositis, Eales disease, Limbic encephalitis, Primary CNS vasculitis, Sarcoidosis, Sjögren syndrome, Takayasu Disease, Vogt-Koyanagi-Harada syndrome, Wegener granulomatosis
Infectious CNS disease	Lyme disease, Tuberculosis, Creutzfeldt-Jakob disease, Syphilis, Toxoplasmosis, Viral encephalitis, Progressive multifocal leukoencephalopathy
Malignancy	Primary CNS lymphoma, CNS metastases, Paraneoplastic syndrome
Mitochondrial diseases	Lactate acidosis and stroke-like episodes (MELAS)
Psychiatric diseases	Psychotic disorders
Otolaryngological diseases	Cogan syndrome, Ménière s disease, sudden sensorineural hearing loss
Cerebrovascular disease	Transient ischaemic attack, stroke, Cerebral autosomal dominant Arteriopathy with subcortical infarcts and Leukoencephalopathy (CADASIL)
Others	Migraine, Cryoglobulinemia

Source: Patel et al.[50], mod.

MS is probably the most frequent misdiagnosis of SS [12, 17–21, 28]. Both MS and SS more commonly affect younger adults and share a female preponderance. Moreover similarities in the clinical image and observed MRI changes make correct diagnosis a challenge [12, 13].

The misdiagnosis of MS instead of SS is especially important in relation to the applied treatment. Previous reports indicate that treatment of misdiagnosed MS may lead to exacerbation of SS [17–20]. Drugs such as interferon beta-1a or natalizumab have been reported to worsen the course of SS [17–20]. In the described cases of the exacerbation of the symptoms of SS after treatment with interferon beta-1a, an improvement was observed after discontinuation of this drug [17, 18, 20]. It is presumed that the treatment for MS may aggravate the course of SS as a result of changes which occur in the immune system under the effect of the treatment applied in MS [12].

With respect to the reported case of the exacerbation of incomplete SS after natalizumab there is some doubt [19]. The results of the study by Gross et al. indicated that natalizumab-anti-α4 integrin monoclonal antibody could prevent binding CD8+ T cells onto a human brain microvascular endothelial cell, and may be helpful in treating SS where CD8 + T cells adhere to central nervous system microvessels and polarize granzyme B, which most likely results in the observed endothelial cell injury. The off-label use of natalizumab in four SS patients in a study by Gross et al. was associated with decreased disease severity [42]. Recently, it has been reported that glatiramer acetate, which can greatly enhance the CD8+ T cell response, used in the treatment of misdiagnosed MS, can lead to the exacerbation of SS [20]. Conversely, TNF inhibitors, such as infliximab which are beneficial in SS, may worsen the progression of MS, where they are contraindicated [52].

Regarding the differential diagnosis between SS and SM, ophthalmological examination and the use of imaging tests: brain MRI, FA, OCT are of particular importance for the correct diagnosis (Fig. 1–4, Tab.2).

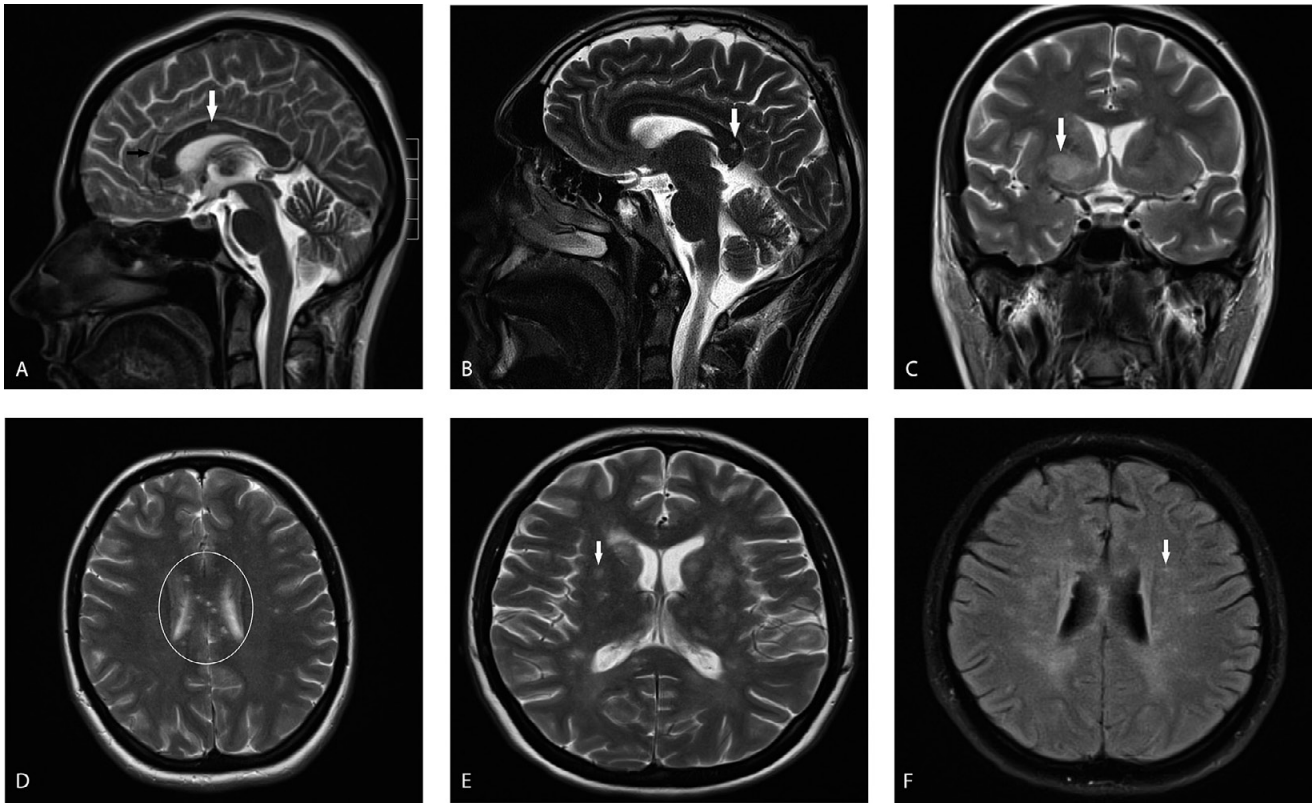

Figure 1. Characteristic MR imaging findings from selected patients with SS. A. Sagittal T2 sequence showing 'snowball lesion' (white arrow) in the central part of the corpus callosum and radial 'icicle' lesions (black arrow) arising from the roof of the callosum. B. Sagittal T2 sequence showing single 'snowball lesion' (white arrow) in the corpus callosum. C. Coronary T2 sequence showing a thalamic lacune (white arrow). D. Axial T2 sequence showing 'string of pearls' (marked by a circle) – punctate hyperintensities in white matter. E. F Axial T2 and axial FLAIR sequence showing typical punctate hyperintensities (white arrow) in periventricular white matter

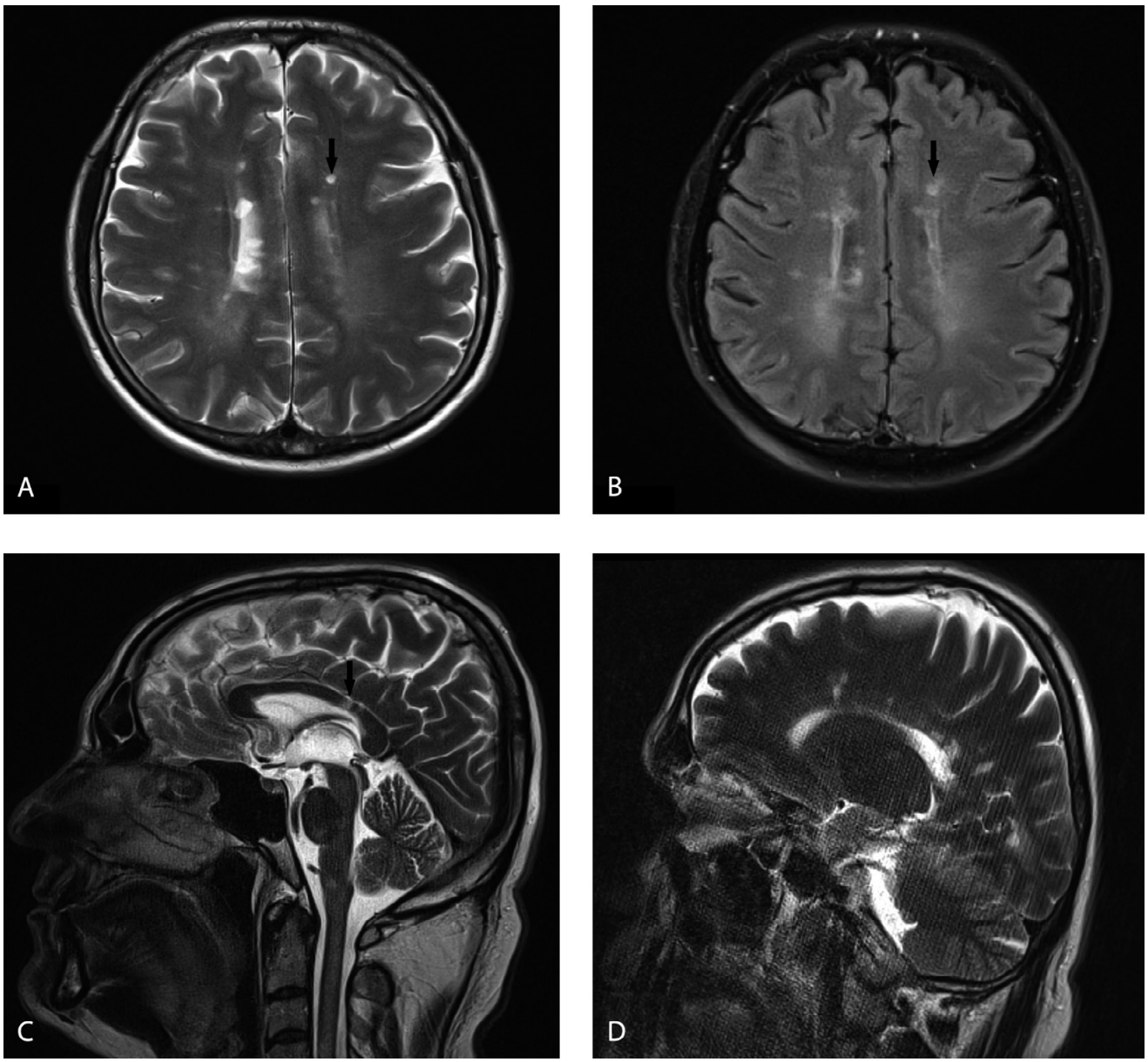

Figure 2. Characteristic MR imaging findings from selected patients with MS. A. B. Axial T2 and FLAIR images showing ovoid hyperintensities in the white matter (black arrow). C. Sagittal T2 image showing demyelinating lesions in the corpus callosum which are in contact with the undersurface of the callosum (black arrow). D. Sagittal T2 image showing Dawson's fingers – lesions that propagate centrifugally along the medullary venules and are arranged perpendicular to the lateral ventricles (extending radially outwards).

Brain MRI. Despite the clinical triad, SS is also characterized by a neuroimaging triad consisting of white matter lesions, grey matter lesions, and leptomeningeal enhancement (LME) in magnetic resonance imaging (MRI) [2, 25]. It is believed that the observed changes are the result of the obstruction of small arterioles of a diameter smaller than 100 μm [33, 53].

These microinfarctions can cause T2 hyperintense lesions at any area of the brain. In the encephalopathic form of SS, the involvement of the corpus callosum is always seen. Microinfarctions in the central part of the callosum in sagittal FLAIR and T2-weighted sequences cause the appearance of a 'snowball'. 'Spoke' or radial 'icicle' lesions arising from the roof of the callosum are also commonly identified on this sequences (Fig. 1A-B). Diffusion sequences may also reveal hyperdense changes of the internal capsule, resembling a 'string of pearls' [1–3, 7, 12, 25] (Fig. 1D). The presence of these changes affecting the central part of the corpus callosum is pathognomonic for SS.

Focal white matter lesions, which are hyperintense on T2-weighted scans, are among the pathological hallmarks of MS, and MRI is an irreplaceable part of the diagnostic work-up of patients with suspected MS [54, 55]. In patients with few lesions, there is a particularly increased risk of misdiagnosis based on MRI. Lesions observed in MRI patients with SS can mimic demyelinating lesions; however, demyelinating lesions in MS are commonly larger and have an ovoid appearance (Fig. 2A-B) while lesions observed in SS are punctate and smaller (Fig. 1D-F). However, larger thalamic lacunes due to involvement of lenticulostriate perforators can be observed in SS [12, 54] (Fig. 1C).

In MRI, SS shows a strong predilection to affect the corpus callosum (Fig. 1A-B). In SS, the corpus callosum

is affected in its central part while its periphery is spared, while in MS, changes are observed on the under surface of the corpus callosum and in the callososeptal interface (Fig. 2C). Affecting the deep grey matter is typical of SS, but rare in MS. Frequently, after going through the acute phase of SS, a generalized atrophy of the brain, cerebellum, and the corpus callossum is observed in MRI [2, 3, 5, 7, 12].

Patients with SS are more likely to present LME then MS patients. Coulette et al. reported an association between an increase in the number of regions of LME and clinical relapses in patients with SS; the authors suggested that LME could therefore become an interesting biomarker to monitor disease activity [23]. In the study by Engish et al., LME was also correlated with SS severity [37]. Bellanger et al. note that LME is a key feature of SS, but is only sporadically shown on post-contrast T1-weighted images (T1-WI, and the use of post-contrast fluid-attenuated inversion recovery (FLAIR) may be more sensitive. They assessed the MRI results for patients with SS. LME was observed on all post-contrast FLAIR, contrary to post-contrast T1-WI (17/17 (100%) vs. 15/19 (79%), $p < 0.05$) [24].

Ultra-high-field strength (7-T) MRI, which allows for a more accurate assessment of the morphology of the lesions, provides a new tool for differential diagnosis between MS and SS. Callosal lesions in SS are hyperintense in the centre and surrounded by a ring-like signal extinction on 7-T T2-weighted images and are more hypointense than MS lesions. Moreover, 7 Tesla MRI reveals that white matter lesions in SS are less often located in a perivenular location, unlike the MS lesions [56].

Another feature that may be helpful in the differential diagnosis between MS and SS is the presence of changes in the spinal cord, which are a feature of MS, and may be a predominant site of demyelination. In SS patients, lesions in the spinal cord a very rare [12].

Ophthalmic symptoms. Both SS and MS patients may report visual disturbances. Visual symptoms are frequent in MS, with retrobulbar optic neuritis definitely being the most common cause of their occurrence. Patients with retrobulbar optic neuritis in the course of MS typically complain of monocular visual blurring, pain concomitant to eye movements, colour vision disturbances. Other ocular manifestations of MS include pars planitis, peripheral vasculitis, ocular motility dysfunction manifested as nystagmus or diplopia [3, 12, 57]. Patients with SS have visual disturbances mostly resulting from BRAO; however, nystagmus in cases of SS have also been described [58].

In the diagnostics of SS, fundus examination and FA are irreplaceable. In the fundus examination in patients with SS, BRAO and Gass plaques can be observed (Fig 3. A-B). BRAO reflects microinfarction observed in the brain in patients with SS [1–8, 53]. Gass plaques observed in fundus examination during SS are yellow deposits, most often located at the mid-segment of the retinal arterioles, and not at arteriolar bifurcations, as is the case of typical cholesterol embolism (Hollenhorst plaques). These plaques were attributed to atheromatous deposits from the slow extravasation of blood lipids into the arterial wall at the sites of arterial wall damage. Gass plaques in SS are frequently observed at the acute stage of the disease and may change together with the activity of the disease, and subsequently disappear. Gass plaques also occur in other disorders, such as Eales' disease and lymphoma, and their presence may suggest SS; however, this is not a pathognomonic symptom. Gass plaques are not visible in FA [2, 34, 35].

Other symptoms observed in eye fundus examination include the presence of 'cotton wool' spots, presence of arterio-arterial collaterals, neovascularization on the optic disc, macular oedema; there are also reports concerning extensive intraretinal haemorrhages and veno-venous collaterals [2, 5]. Zur et al. reported retinal microaneurysms which can indicate ischemic retinal damage, as new ocular finding in SS [59].

Fluorescein angiography. FA is an invaluable examination in the evaluation of patients with SS [22, 60]. It should be noted that BRAO affecting peripheral branches may be overlooked in an ophthalmological examination. As many as 99% of patients undergoing FA showed the presence of BRAO, which emphasizes the diagnostic value of the ophthalmological examination and FA in suspected cases of SS [1]. Widefield FA can be epecially useful which allows assessment of peripheral retina. Turczyńska et al. analyzed the widefield FA results of 20 patients with incomplete or complete SS. Vascular changes in the posterior pole were seen in 64.7% and in the peripheral retina in 82.4%. The authors conclude that widefield FA of the peripheral retina has a key role in cases of suspected SS as it confirms the diagnosis and enables assessing disease activity [22].

One of the most important imaging findings which can be seen only in FA is arteriolar wall hyperfluorescence (AWH) [2] (Fig.3 C-D). AWH is the result of a characteristic leakage and indicates damage to the tight junctions and the integrity of the vessel wall. AWH may be observed at the site of BRAO, but also at the site of damage to the vessel wall where BRAO has not yet occurred. AWH may be present even when the patient is asymptomatic and has no changes in fundus examination [2–5, 34].

The occurrence of retinopathy in a patient with MS is one of the main red flags which suggest a diagnosis other than MS [61]. Patients with SS experience BRAO, which is not a characteristic feature of MS; thus, this is a differentiating symptom which should be sought for in FA when the diagnosis of SS is suspected, even in patients without visual symptoms, or when the examination of the fundus of the eye seems normal [2, 12]. In the case of uveitis during MS, the change most frequently observed in FA is multifocal elongated retinal perivenous 'sheathing' with focal vascular leakage [62]. AWH at the site of BRAO is non-specific for SS, and should also be an incentive for the consideration of the presence of other factors responsible for the development of vessel inflammation. AWH located at a distance from BRAO is confirmatory for SS and is non-typical for other inflammations of the vessels [2]. Recently, Van Oevelen et al. published a report showing an evolving distally shifting pattern of AWH in patients with SS [63].

FA plays an invaluable role not only in the diagnostics, but also in the monitoring of the activity of SS [2, 8, 35]. A previous study by Mallam et al. demonstrated the persistence of AWH despite the resolution of clinical symptoms, which suggests persistent subclinical activity [35].

Optical coherence tomography. OCT examination is also a useful diagnostic tool in the differentiation between SS and MS [26–28, 64, 65]. In a study by Brandt et al. the results of

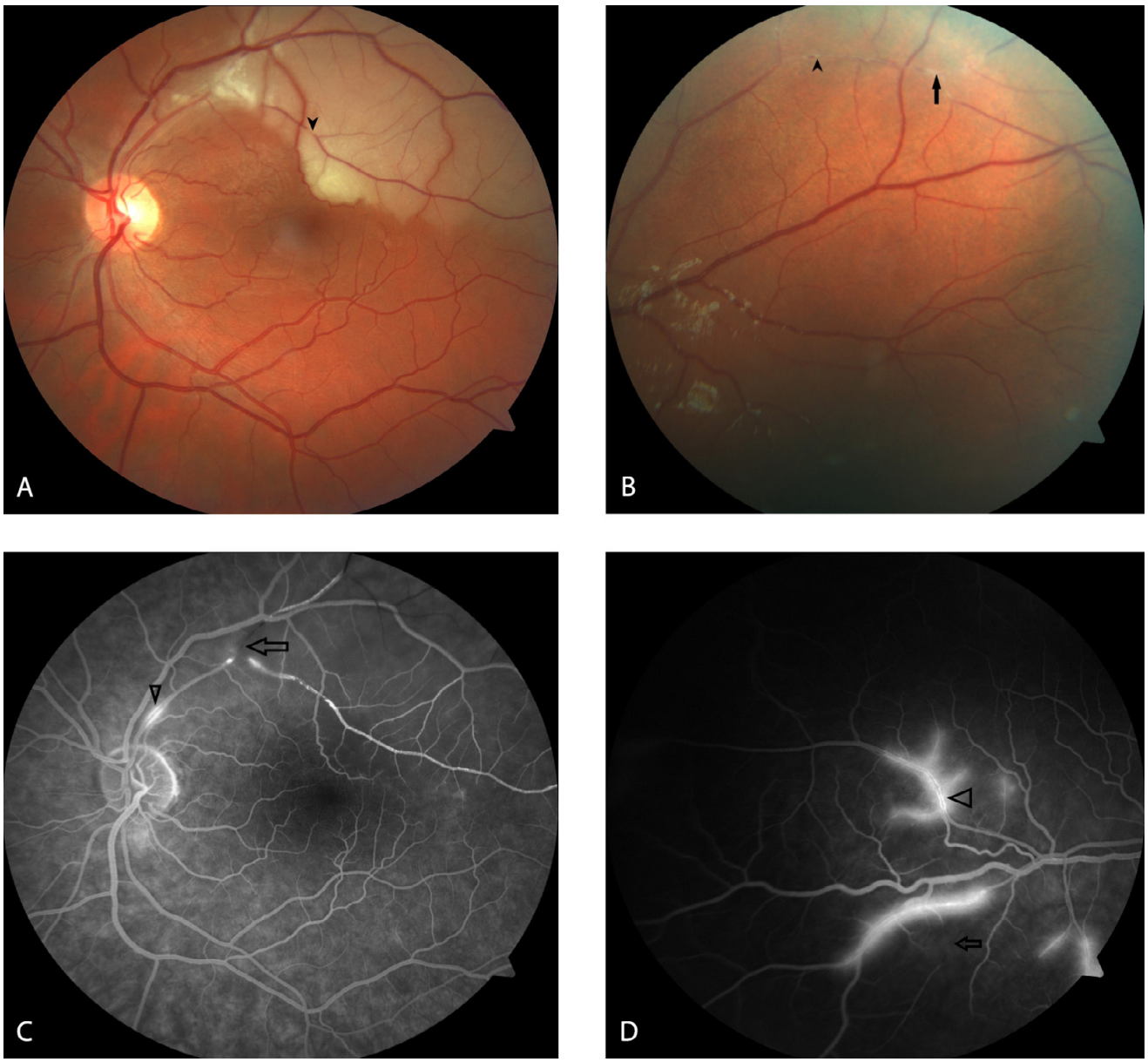

Figure 3. Fundus photography and fluorescein angiography imaging findings from selected patients with SS. A, B. Color fundus image showing branch retinal artery occlusion with Gass plaque (arrowheads) and sheathing around the vessel wall (arrow). C, D. Fluorescein angiography showing branch retinal artery occlusion (arrow) and arteriolar wall hyperfluorescence (arrowhead)

OCT examination were compared between patients with SS and those with relapsing-remitting form of MS (RRMS) with or without optic neuritis, as well as with a control group. The study showed patchy reductions of the peripapillary retinal nerve fibre layer and the total macular volume, compared with patients with RRMS and healthy controls. The most important difference between SS and RRMS was the character of retinal nerve fibre layer thickness (RNFLT) damage, which may be useful in the differentiation between these two diseases. In contrast to patients with MS, in those with SS the decrease in RNFLT was more severe and showed a sectoral character, which is compatible with segmental involvement of retinal arterioles in SS. OCT of patients with MS showed dispersed thinning of RNFLT, which was slightly intensified in the temporal quadrant after optic neuritis [27].

However, it should be noted that in this study, patients with RRMS, as well as those with SS, had diagnoses confirmed after several months, or even years; therefore, the described changes do not apply to the initial stages of these diseases [27]. Nevertheless, OCT provides supplementary diagnostic information for FA, especially at later and chronic stages of the disease, when there may not be more BRAO or other vascular pathologies detected by FA. According to the stage of the disease, OCT and FA provide specific, supplementary diagnostic information in SS [2, 28].

In a study by Bernard et al., OCT examination in patients with SS also demonstrated the thinning othe retinal nerve fibre layer, which was inherently patchy and more clearly displayed in the nasal quadrants; loss of the normal foveal shape was also observed, which is atypical of MS. In addition, the scope and range of abnormalities detected in OCT were correlated with the degree of advancement, severity of the disease, and the results of visual field examinations [26]. In a study by Ringelstein et al. a patchy thinning of the retinal

Table 2. Changes in imaging studies in the course of SS and MS.

Imaging tests	Susac Syndrome	Multiple Sclerosis
MRI		
Corpus callosum involvement	Central	Peripheral
Deep grey matter involvement	Common	Uncommon
White matter lesions	Punctate	Ovoid
Leptomeningeal enhancement	Common	Uncommon
Spinal cord lesions	Rare	Common
OCT Character of RNFLT damage	Sectoral	Dispersed
OCTA	Vascular hypoperfusion within macular area in both superficial and deep capillary retinal plexus; VD decrease; Deep retinal plexus drop-out in acute attacks, becoming atrophic over time; Superficial plexus less affected; Unaffected choriocapillary vasculature	VD decrease; Alterations of the choriocapillaries
FA	BRAO AWH Normal choroidal circulation	Multifocal elongated retinal perivenous 'sheathing' with focal vascular leakage; Cystoid macular oedema in uveitis associated with MS
Fundus examination	Gass plaques, BRAO, cotton-wool spots, tiny peripheral hemorrhages, retinal arterio-arterial collaterals, neovascularization on the optic disc, retinal microaneurysms *Absence of intraocular inflammation associated with occlusion of retinal arterioles	Optic neuritis, retinitis, uveitis, pars planitis, peripheral vasculitis * The most common ophthalmic manifestation of MS is retrobulbar neuritis and in these cases a fundus examination typically reveals no changes

MRI - magnetic resonance imaging; OCT - optical coherence tomography; OCTA - optical coherence tomography angiography; FA - fluorescein angiography; RNFLT - retinal nerve fibre layer thickness; VD - vascular density; BRAO - branch retinal artery occlusions; AWH - arterial wall hyperfluorescence.

nerve fibre layer, ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform layer was observed, compared to the corresponding sectors in eyes with RRMS and the control group. No changes were observed in the outer nucleus layer and photoreceptor layer, suggesting a retinal but not choroidal vascular pathomechanism [28], which was also confirmed by indocyanine angiography [66].

The above-mentioned studies confirm that OCT is a useful diagnostic tool in SS and helps to differentiate it from MS [26–28, 65].

Optical coherence tomography angiography. García-Serrano et al. reported that the use of OCTA proved to be very helpful in the diagnosis of SS, before clear cerebral ischaemic changes appeared in brain MRI. OCTA generates images of a medium resolution of 8–10 μm, showing impaired blood supply to small calibre vessels (<100 μm), and may supplement other imaging techniques, such as MRI, in which endothelial changes at early stages of the disease may not be visible [33].

Recently, single reports have been published concerning changes in OCTA in patients with SS. These studies demonstrated an unaffected choriocapillaris vasculature and both superficial and deep retinal vascular plexuses damage characterized by vascular non-perfusion, which corresponds to the topography of BRAO [30, 31]. Todorich et al. described a case of SS with BRAO, where typical for BRAO hyperreflectivity of the inner and middle retinal layers was observed, characteristic of acute ischaemia [32]. The consequence of past BRAO may be the thinning of inner layers of the retina observed in OCT in patients with long-lasting SS [26–28]. In a study by Alba-Linero et al., OCTA revealed deep retinal plexus drop-out and surrounding edematous retina in acute attacks, becoming atrophic over time. Superficial plexus was much less affected [67]. Wirth et al. reported that even clinically unaffected eyes of SS patients showed poorer vascular parameters in OCTA [68].

In the case of SS described by Azevedo et al., in OCTA examination a decrease in vascular density (VD) was observed in both the superficial and deep plexus. After several months, an improvement in VD was noted. The researchers hypothesized that a change in vascular flow associated with the activity of the disease was responsible for these changes. Inflammation of the vascular vessels may lead to a lower vascular flow due to the narrowing of the vessel [31]. Mastropasqua et al. described a case of SS, where after the application of treatment, OCTA images also disclosed an increase in VD [69].

Also, in the case of MS, there appear reports concerning the use of OCTA. The studies are scarce although they indicate that patients with MS show retinal vascular alterations [70–72]. Studies demonstrate the possibility of using the measurement of VD as a new marker for monitoring disease activity [70]. At present, there are insufficient studies concerning the use of OCTA in both disease entities in order to assess whether there are any differences, and of what type concerning both diseases. Nevertheless, OCTA examination may provide new information concerning pathophysiological mechanisms in both MS and SS, with particular consideration for vascular dysfunction.

Clinical image. The differences between MS and SS, apart from those observed in imaging examinations, also concern the clinical image and results of laboratory tests. Headache occurs in approximately 80% of patients with SS; however, this is not a typical symptom of MS [12, 49]. Moreover, headache belongs to the main red flags indicating a diagnosis other than MS [61]. The features of encephalopathy in SS, such as observed cognitive disorders, confusion or mental and personality changes occur in about 75% of patients with MS, but rarely occur at the beginning of the disease [2, 12]. While tinnitus, sensorineural hearing loss and dizziness

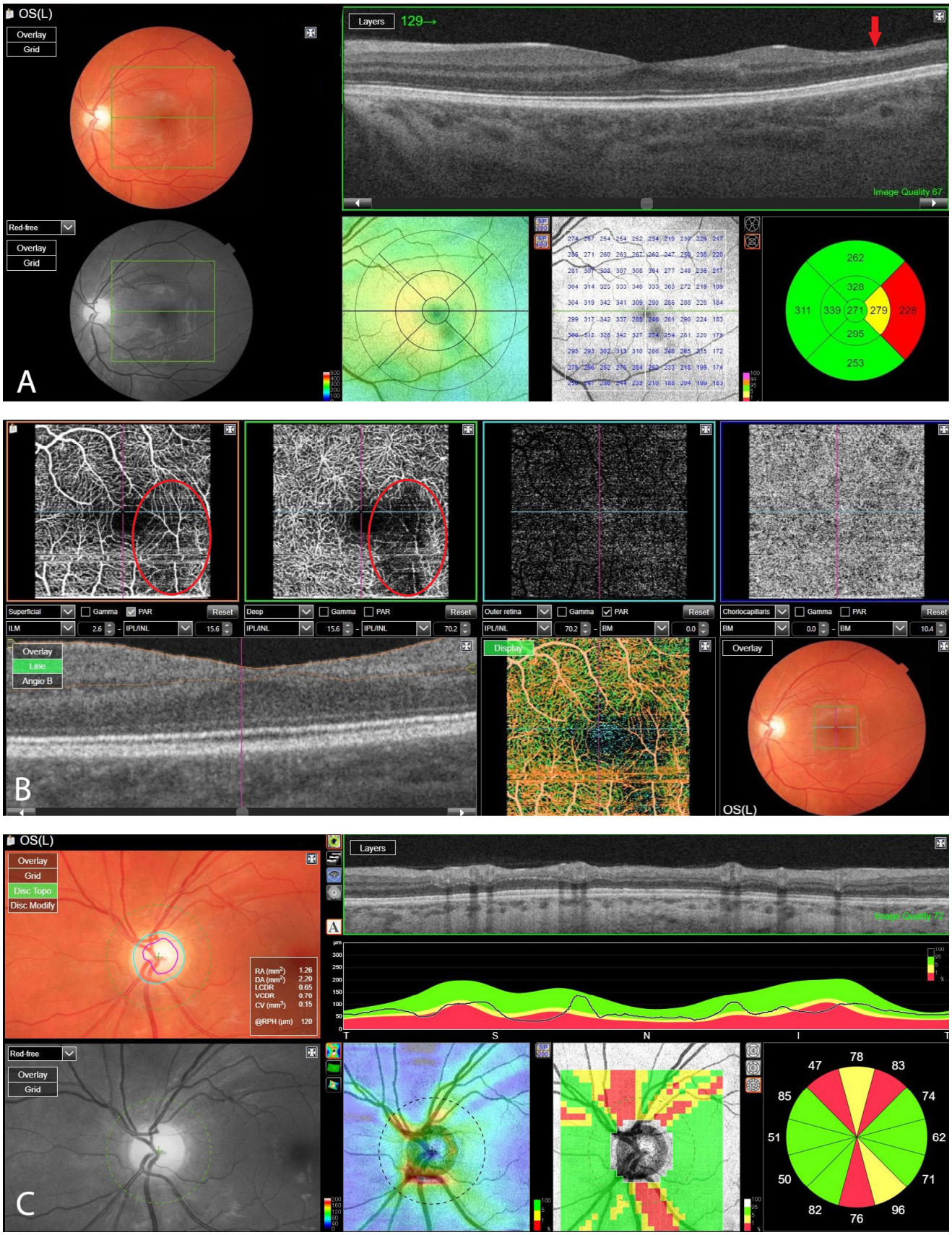

Figure 4. OCT imaging findings from SS patient performed several months after initial presentation. A. OCT image showing atrophic thinning of the inner retina (arrow). B. OCTA image of the left eye revealing mainly affected deep retinal plexus (ischaemic areas marked by a circle). C. OCT image showing sectoral retinal nerve fibre layer thickness decrease.

Table 3. European Susac Consortium (EuSaC) diagnostic criteria for Susac Syndrome.

Brain involvement	i) Symptoms and clinical findings: cognitive impairment and/or behavioural change and/or focal symptoms and/or new nature of headache ii) Imaging: Typical findings on cranial MRI — hyperintense, small, diffuse, circular lesions; at least one in corpus callosum on T2 images (or FLAIR)	To fulfil 1, at least one of the clinical findings and the typical MRI findings have to be documented.
Retinal involvement	i) Clinical findings and symptoms not required ii) BRAOs or AWH in retinal fluorescein angiography or characteristic symptoms of retinal branch ischaemia in fundoscopy/ SD-OCT examination	To fulfil 2, at least one BRAO or AWH in fluorescein angiography or characteristic signs of retinal branch ischaemia in funduscopy or corresponding damage in OCT has to be documented.
Vestibulocochlear involvement	i) Symptoms and clinical findings: new onset or change in tinnitus and/or hearing loss and/or peripheral vertigo ii) Examination of inner ear function: hearing loss confirmed by audiogram; vestibular vertigo supported by specific diagnostics	To fulfil 3, at least one of the clinical findings must be present and hearing loss or vestibular vertigo must be supported by specific investigations of the inner ear function.
Definite		Each criterion (1; 2; 3) with subcriteria (i; ii) has to be met
Probable		2 of 3 have to be met
Possible		1 of 3 criteria met

Source: Kleffner et al. [74]).
MRI – magnetic resonance imaging; FLAIR – fluid-attenuated inversion recovery; BRAOs – branch retinal artery occlusions; AWH – arterial wall hyperfluorescence; SD-OCT – spectral domain optical coherence tomography

may occur in MS due to changes affecting the brainstem or the auditory pathways, the symptoms usually disappear within days or months, even without corticosteroid treatment [12]. Bilateral tinnitus and hearing loss in MS are very rare, and are a subsequent 'red flag' suggesting a diagnosis other than MS, e.g. SS or Cogan's syndrome [61]. With respect to sensorineural hearing loss, currently there are no clinical or audiometric findings that are diagnostic for SS.

Skin involvement in the form of livedo reticularis occurring in some patients with SS in the case of primarily diagnosed MS should be an incentive for considering a diagnosis other than MS [61, 73].

Laboratory tests. Also, laboratory analysis of the cerebrospinal fluid shows differences between SS and MS. As many as 90% of patients with MS have oligoclonal bands in the cerebrospinal fluid, while in the case of patients with SS this is only 4%. Analysis of the cerebrospinal fluid in patients with MS demonstrates a normal or slightly elevated level of protein, whereas in patients with SS the examination shows an increase in protein concentration, and relatively often mild pleocytosis, usually lymphocytosis [7, 12].

Proposed criteria for the diagnosis of SS. Vishnevskia-dai et al. proposed criteria for diagnosing SS which might be helpful in diagnosing patients at an early stage of the disease. According to the researchers, there are three categories of the disease: suspected, incomplete, and complete SS. At the stage of suspicion of the disease, the risk of arteriosclerosis and coagulopathy should be excluded, while one of the three main symptoms (triad) occurs, as well as one of the following factors: female aged between 20–40 without risk factors for occlusive arterial disease, female within one year of pregnancy, occurrence of typical MRI lesions in the corpus callosum or periventricularly. Incomplete SS is characterized by the occurrence of two out of three symptoms of the triad, and complete SS – with three symptoms of the triad [6]. Kleffner et al. proposed a more detailed diagnostic criteria for SS [74] (Tab. 3).

Recently, Egan verified the criteria of diagnosing SS proposed to-date. The researcher recommended that during preliminary evaluation, patients should have an obligatory visual field testing, FA, and brain MRI. Audiograms should be performed in patients complaining of hearing loss or tinnitus. Egan emphasized that even when the clinical triad and neuroimaging triad are not completely observed, the occurrence of changes in the central part of the corpus callosum in MRI and AWH in FA examination in normal looking retinal arterioles far from BRAO, speak for the definitive, and not as previously postulated, probable diagnosis of SS [2].

Treatment of SS. Sufficiently early correct diagnosis is essential for undertaking proper treatment. At present, steroids are applied in the first-line treatment of SS. In addition, the following drugs are have been applied in the treatment of SS: azathioprine, mycophenolate mofetil, methotrexate, rituximab, immunoglobulin cyclophosphamide, plasmapheresis [1–7, 9, 47]. There are also promising monoclonal antibodies that have been released or will soon be released for the treatment of SS, specifically: natalizumab, ocrelizumab, alemtuzumab, daclizumab, adalimumab and infliximab [2, 47]. In the course of SS, treatment with anti-platelet and anti-clotting drugs was used primarily, while currently there are no such indications [2, 53]. In patients with hearing loss, it is possible to obtain a considerable degree of improvement using cochlear implants. At an acute phase of hearing loss and tinnitus attempts are undertaken to apply dexamethasone injections into the tympanic membrane [1–7, 50].

Rennebohm et al. proposed recommendations concerning treatment of SS considering the component of the clinical triad which is most dominant in the clinical image, differentiating treatment for SS between that which should be implemented in the case of SS with domination of symptoms on the part of the central nervous system, treatment of SS with prevalence of changes concerning the retinal vessels, and treatment of SS in which the dominant symptom is hearing disorders [75].

Prognosis of SS. The prognosis in SS is good if treatment is started sufficiently early which, considering the diagnostic difficulties, is rarely possible. SS may take its course in three ways: monocyclically (with several fluctuations, and ultimately resolves within one or two years), polycyclically (with remissions, which may last more than two years), chronically (without remissions, for more than two years) [1,

3, 7]. A catastrophic course of SS was reported in association with the use of cannabis [16].

Early diagnosis and treatment in patients with SS reduces the risk of complications of the disease. To-date, the observations carried out indicate that the disease is diagnosed too late, which ultimately leads to the impairment of cognitive functions in approximately 50% of those with SS. The consequences of encephalopathy occur in 60–70% of patients, and as with visual disorders, in most of them, these consequences are moderately intensified. Sensorineural hearing loss in SS is most often reversible, whereas in some cases it requires the provision of a cochlear implant [5, 7, 50].

After making a preliminary diagnosis, the patient should be re-evaluated after one month, and subsequently after three months, performing a check-up examination of the visual field, brain MRI and FA. In the case when a patient complains of new symptoms, all the above-mentioned examinations should be carried out. In the case of occurrence of hearing loss, repeating an audiogram is recommended. Medical management is insufficient when new alterations are revealed in MRI, visual field defects are observed, or AWH in FA. When no new changes are found in MRI, FA and the visual field are stable, it may be presumed that the patient is in remission, and may gradually discontinue treatment. However, the patient should be carefully observed for any disease recurrence [2].

CONCLUSIONS

It should be kept in mind that in the majority of cases, patients with SS do not present the complete clinical or neuroimaging triad, and a delay in making the correct diagnosis exposes the patient to the occurrence of complications, resulting from the development of the underlying disease, or/and application of improper treatment. Imaging examinations, such as brain MRI, F, and OCT, complement each other, due to which the diagnosis may be simpler, irrespective of the stage of the disease. The use of imaging techniques may not only contribute to the correct diagnosis, but also facilitate monitoring of the course of the disease and the detection of recurrences. These clinical tests are complementary and some are confirmatory in the diagnosis of SS when the clinical triad is incomplete. It should be borne in mind that the ophthalmic examination may be of particular importance in the diagnosis, which emphasizes the role of interdisciplinary cooperation in making a correct diagnosis of SS.

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