

A review and update on the Ophthalmic implications for Susac's Syndrome

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Abstract

Susac's syndrome is a rare condition presumed to be immune mediated and resulting in occlusion of small arterial vasculature principally of the brain, inner ear and retina. Clinically the syndrome manifests as a pathognomonic triad of encephalopathy, hearing loss and branch retinal artery occlusion. Early recognition and diagnosis is important as delayed treatment may be profound and result in deafness, blindness, dementia and neurological deficit. The plethora of imaging technology, including Magnetic resonance imaging, fluorescein angiography for the retina, optical coherence tomography (OCT) and OCT-angiography allows deeper and more discrete anatomical-physiological correlation of underlying pathology, early diagnosis and imaging biomarkers for early detection of relapse during follow up. The purpose of this review is to highlight the current clinical classification of Susac's syndrome, available investigations, treatment and care pathway.

Keywords: Susac's Syndrome; Treatment; Branch Retinal Artery Occlusion; OCT angiography; Fluorescein angiography

A review and update on the Ophthalmic implications for Susac Syndrome

Introduction

Susac's syndrome is a rare condition first described in 1979 by neurologist J.O Susac . There is no published incidence of Susac's Syndrome but a period prevalence of 0.148 per 100 000 has been estimated in a central European population above the age of 19 ⁶⁶. The majority of published case reports and case series mainly involve Caucasians from Europe and North America. ^{44; 68} The age range of disease onset is between 7 to 70 years with a mean age of 30.5 years and the ratio between female and male is 3:1. ^{23; 39; 59}

Susac's syndrome is presumed to be immune mediated resulting in occlusion of small arteries, predominantly in the brain, inner ear and retina, giving rise to the pathognomonic triad of encephalopathy, low to mid frequency sensory hearing loss and visual disturbances from branch retinal artery occlusion. Affected patients may develop either or all of the above features over weeks to months. ¹⁴ A review of case reports have found that a complete triad is found only in 13 percent of diagnosed cases at the onset of disease. ¹⁴ Hence, cases which do not fulfil the complete triad remain a diagnostic challenge

The multifocal infarction of Susac's Syndrome may result in potentially irreversible end organ damage leading to neurological deficits, hearing loss and visual impairment. Early recognition of pathognomonic signs and prompt treatment may help prevent permanent function loss. ⁶⁸ The development of imaging technology in modern medicine, including Magnetic resonance imaging, fluorescein angiography for the retina, optical coherence tomography (OCT) and OCT-angiography allows deeper and more discrete anatomical-physiological correlation of underlying pathology, early diagnosis and imaging biomarkers for early detection of relapse during follow up. The purpose of this review is to highlight the current clinical classification of Susac's syndrome, available investigations, treatment and care pathway, with particular reference to the experience in a tertiary ophthalmic unit in the United Kingdom.

Pathophysiology

Although the exact pathophysiology of Susac's Syndrome remains unclear, it is thought most likely to be immune mediated, targeting endothelial cells of the brain eye and inner ear. ^{3; 62}

Endothelial cell injury is thought to be secondary to derivatives of complement-activating IgG1 subclass, anti-endothelial cell antibodies (AECAs).^{14; 23; 36} It is not known if AECAs are a consequence or cause of the pathologic process of Susac's syndrome. Clinically, there are no specific serological markers for Susac's syndrome and AECAs titres which were previously found to be higher in patients with Susac's disease were only found in 25% of the disease study population in a study by Jarius et al.³⁵

Studies from brain biopsies have found unspecific changes of focal microangiopathic and/or gliotic changes such as arteriolar wall proliferation, lymphocytic infiltration and thickening of basal lamina^{14; 29}. Evidence that the pathological pathway of Susac's Syndrome maybe associated with complement pathway was further disputed by brain biopsy series performed by Hardy et al which did not show evidence to support complement deposition.²⁹ In this study, only one out of three brain biopsies showed C4d deposition in microvasculature but similar immunoreactivity was noted in the control samples. Interestingly, all cases showed T cell inflammation in small to medium sized vessels, which were also reported in previous cases.^{21; 28; 29} This highlights the current prevailing trend of thought that the immune element of the disease is likely driven by T lymphocytes.

Other mechanisms such as idiopathic vasospasm, hypercoagulopathy, viral infection have been proposed but there has been no proven correlation.^{9; 30; 52; 64}

Clinical signs and symptoms

The clinical triad of Susac's syndrome included acute encephalopathy, hearing loss and branch retinal artery occlusion (BRAO). A Study by Jarius et al of 20 patients diagnosed with Susac's syndrome found that 72% of cases presented with encephalopathy at initial clinical presentation, 20% with hearing loss and 24% with visual disturbances. Of these, 64% had residual neurological deficits such as 'mild psycho-organic syndrome' 'disorientation' 'fatigability' 'cognitive impairment ranging from mild to severe' and 'memory loss'. 24 % of patients had residual motor symptoms such as 'spasticity', 'paresis', ' spastic hemi or tetraparesis' and ' brainstem symptoms such as dysarthria, dysphagia, internuclear ophthalmoplegia and ataxia. 84% had residual auditory deficits including hyperacusis and tinnitus and 72% had residual visual impairment in the form of scotomas.³⁵

Rennebohm et al proposed two clinical subsets of the disease, the first with predominant neurological symptoms and the second with recurrent BRAO, but without active

neurological symptoms and minimal or no abnormalities on MRI brain scan. The second type may recur over periods of years without accrument of neurological deficits.⁵⁷

There is a large variation in the presentation of natural history of Susac's Syndrome. The same authors (Rennebohm et al) also proposed three major clinical courses:(a) monocyclic; fluctuating disease which self limits after 2 years and does not recur; (b) polycyclic; relapsing disease beyond 2 years; (c) variation with severity of symptoms, with no clear remission. ⁵⁹

Neurological characteristics

Typically, patients present with non specific neurological symptoms such as generalised or migraine-like headaches which may later progress to encephalopathy, with impaired cognition, vertigo, ataxia, dysarthria, hemiparesis, mood and cognitive deficits. Headache may occur up to 6 months before onset of the other symptoms. 75% of patients present with neuropsychiatric symptoms such as personality changes and paranoia.[3]

Auditory Characteristics

Patients may present with nonspecific clinical symptoms such as tinnitus, hearing loss or peripheral vertigo. Low-to mid-frequency hearing loss are typical for patients with Susac's syndrome. ⁶¹

Ocular Characteristics

Patients present with symptoms associated with retinal ischemia secondary to branch retinal artery occlusion or vasculitis. This may manifest as visual field loss as an altitudinal defect or central or paracentral scotoma. Occasionally, if the infarct is in the far periphery of the retina, patients may be asymptomatic. Occasionally, Susac's patients may have visual aura with their migraine-like headaches. Some patients may be too ill with encephalopathy to notice or report visual symptoms, despite this, ocular assessment is paramount if Susac's syndrome is suspected, even in asymptomatic patients.

Fundoscopy may reveal Gass plaques (originally known as retinal arterial wall plaques). These are yellow refractile lesions, simulating emboli. It was thought that Gass plaques were caused by an immune mediated localized reaction in the retina artery wall. They may be present in any location along the retinal arteries, and are not limited to the arteriolar bifurcation (in comparison to Hollenhorst plaque of cholesterol). Anecdotally Gass plaques

are common in the acute stages of the disease and their appearance fluctuates with disease activity, with eventual disappearance.¹⁵ However, Gass plaques are characteristic but not pathognomonic of Susac's Syndrome and may be seen in a few other rare retinal disorders such as Eale's disease and lymphoma. (Figure 1)

In addition, affected retina may show sectoral whitening, typical of ischemia from BRAO, but such changes may be transient.^{16; 25} Very rarely, neovascularisation and vitreous haemorrhage may occur as a result of retina ischemia.

Retinal peripheral arterio-arterial (A-A) collaterals is one of the newly described findings of Susac's Syndrome. A report of 11 patients with Susac's syndrome with available fundoscopic photographs found 10 patients with A-A and 1 with arterio-venous collaterals in and late in disease course.¹⁷

Role of Imaging modalities

The plethora of imaging technology such as Magnetic resonance imaging, fluorescein angiography for the retina, optical coherence tomography (OCT) and OCT-angiography can now deliver discrete information of the anatomical-physiological correlation of underlying disease pathology. This facilitates early diagnosis as well as monitoring of disease remission or detection of relapses.

Systemic

Susac et al has described a neuroimaging triad which consists of 1. White matter lesions; 2. Deep grey matter lesions; 3. Leptomeningeal enhancement and 4. Involvement of the corpus callosum in all cases. Typically, lesions on magnetic resonance imaging (MRI) using T2/fluid attenuated inversion recovery have been described as hyper intense, multifocal and round (snowball appearance). The lesions are caused by arteriolar infarction in the callosum, and over time cavitate and develop into the appearance of a 'hole'.^{39; 69}

Pure-tone or speech audiogram may favour low or mid-tone frequencies and peripheral vertigo may be confirmed by caloric testing of the vestibular organ, vestibular evoked myogenic potentials or nystagmography.³⁹

Ophthalmic investigations

Fluorescein Angiography (FFA)/ Indocyanine angiography(ICG)

Fluorescein angiography demonstrates characteristic changes of Susac's syndrome in wall of arterial retinal vasculature with unexplained encephalopathies, whereas ICG is normal. Fluorescein angiography typically reveals an unusual leakage pattern of arterial wall as demonstrated by hyperfluorescence (AWH) which may occur either far away from occluded arteriole or in normal vessels (Figure 1b). The prevalence of AWH in Susac's Syndrome is not known, but the presence of AWH located away from a BRAO is pathognomic for Susac's Syndrome.¹⁵ A previous study by Mallam et al demonstrated the persistence of AWH despite resolution of clinical symptoms, which suggest persistent subclinical activity.

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Optos wide field angiography may be used to monitor disease activity. In particular, wide field angiography allows monitoring of vasculitis, as a proxy of subclinical activity, in the far periphery.(Figure 2).

All patients will require an FFA or wide field angiography if Susac's syndrome is suspected even in normal fundoscopy as this imaging modality is key in aiding diagnosis and future treatment monitoring.

OCT/OCT A

The use of OCT/OCTA for monitoring of disease

The advent of optical coherence tomography has allowed intricate evaluation of the anatomy of the retina down to 3um. Further, OCT angiography is a novel and non-invasive approach that allows volumetric retinal and choroidal blood flow analysis and hence allows detailed analysis of retinal microvasculature at discrete levels of the retina. This facilitates differentiation of various retinal vascular diseases from characteristic morphological patterns of injury to the inner retina.

The use of OCT in defining retinal nerve fibre layer (RNFL) abnormalities in other neurological diseases is well established. Studies have investigated the use of imaging markers using parameters such as RNFL thickness, macular volume (MV), and ganglion cell and inner plexiform retinal layer abnormalities as surrogate markers for evaluating disease activity and therapeutic response in multiple sclerosis.^{22; 56} For example. RNFL atrophy is more profound in secondary progressive MS than in relapsing remitting and clinically isolated syndrome.^{12; 31} OCT findings may therefore be complementary in demonstrating disease pathology and impact in varying time and space to assist in the

confirmation of diagnosis of Susac's syndrome when the clinical findings have resolved or have been equivocal.

Case reports analysing spectral domain OCTs in patients with Susac's syndrome have described thinning of discrete inner retina layers such as RNFL, inner nuclear layer layers and undulations of the outer plexiform layers, thought to be secondary to swelling of bipolar cells. In the same report, the authors have also described a characteristic bilateral temporal macular atrophy with thinning of the inner retinal layers.¹ Outer retina findings were found to be normal. Such changes were reported to persist even in recovery or in FFA and funduscopy negative patients. These observations suggest subclinical 'scarring' which persists despite inactive disease and successful treatment and may function as a complementary diagnostic modality to FFA. (Table 1)

Findings using spectral domain OCT (TR Vue XR, Avanti, Optovue, United States and DRI Swept source OCT triton, Topcon apan) revealed vascular hypoperfusion within macular area in both superficial and deep capillary retinal plexus which corresponded to clinical topography of BRAO both on funduscopy and FFA. Again, the choriocapillaris was normal. A study by Azevedo et al demonstrated that during the follow up of the patient, post treatment with pulsed intravenous steroids, the use of OCTA and documentation of vascular density index allowed subclinical analysis of disease activity and reinitiating of treatment prior to clinical onset.⁴

Differential Diagnosis

Susac's syndrome often presents with variable symptoms at initial presentation.^{18; 35} Patients have been misdiagnosed with various conditions, for example, acute disseminated encephalomyelitis (ADEM), multiple sclerosis²⁰ and Behcet's disease, therefore often delaying treatment. Although Susac's syndrome is a vascular disorder and multiple sclerosis is a demyelinating disease, symptoms between the two disease often overlap. Further, treatment for multiple sclerosis often involves disease-modifying therapies such as interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab or alemtuzumab and these will not treat Susac's syndrome. Further, Interferon Beta has been shown to worsen Susac's retinopathy.⁴¹ Conversely, TNF inhibitors such as infliximab which appeared to be beneficial in Susac's syndrome may worsen the progression of multiple sclerosis, where they are contraindicated.⁷⁰

There are distinctive MRI findings between Susac's Syndrome, ADEM and MS. MRI lesions in ADEM and MS are found at the under surface and septal interface of the corpus callosum, whilst lesions in Susac's Syndrome are found in the centre of the corpus callosum. Lesions in MS are typically ovoid (Dawson's fingers) and predominantly involves the white matter, but that of Susac's syndrome are round (snowballs) on T2 and fluid-attenuated inversion recovery (FLAIR), 'punched out holes' on T1 hypointensity when chronic and involves both white and grey matter.⁶⁹ Radial 'icicle' or 'spoke' lesions from roof of the callosum are also noted to be characteristic in Susac's syndrome.⁵⁷ Punctate microinfarcts described as 'a string of pearls' appearance in the internal capsule are also seen in Susac's syndrome but not in other diseases.^{32; 69}

Spinal cord involvement is well established in MS but only a single case has ever been reported in Susac's syndrome and the lesions in the case were distinguished by its paracentral and laterally position in the cord (instead of the usual posterolateral position common in MS secondary to demyelination).^{8; 33, 10}

The use of OCT in differentiating diagnosis

OCT provides a non invasive technique allowing instant differentiation between Susac's Syndrome and Multiple Sclerosis. 2 case series comparing changes of Susac's versus relapsing-remitting multiple sclerosis found significant changes in the two diseases. A large case series which evaluated 34 cases (17 with Susac's syndrome) demonstrated patchy thinning of the retinal nerve fiber layer, ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform layer in comparison to corresponding sectors in relapsing-remitting MS.^{6; 60} Another series published 3 patients at different stages of Susac's syndrome: one in sub-acute stage, a second with treated chronic disease with minimal residual neurological deficits, and the last with severe untreated chronic disease and permanent neurological deficits. The patient with the chronic disease demonstrated most severe RNFL thinning. It was noted that 2 of the 3 patients had demonstrated loss of foveal contour on OCT. These findings were demonstrated despite normal visual fields testing. Comparatively, the loss of foveal contour has not ever been described in studies of OCT changes of patients with MS.⁶

Prognosis

Early recognition and treatment may sometimes reverse some of the encephalopathic and visual signs and symptoms, but hearing loss often remains permanent. A review of the outcome of Susac's syndrome in 9 patients by Aubart-Cohen et al found that all patients had permanent hearing loss with mean 34dB(range 15-7-dB).³ Although thought to be self-limiting after several years (range of period differs with individual patients), recurrence after 18 years of remission have been reported.^{52; 53} Hence, there is a need for life long monitoring in patients diagnosed with Susac's Syndrome.

Current Treatment

Systemic

There has been no randomized controlled trials (RCTs) for treatment of Susac's syndrome, although 63 published case reports and series have suggested possible empirical treatment algorithms.^{2; 5; 7; 11; 13; 14; 18; 19; 21; 24; 26; 27; 28; 34; 35; 36; 37; 38; 40; 42; 43; 45; 47; 49; 50; 54; 55; 57; 59; 62; 63; 64; 65; 67; 71; 72; 73; 74; 75; 77} Treatment is often dependent on the expertise and experience of treating clinician and unit. Treatment of CNS-predominant Susac's syndrome is dependent on the severity of the disease (which is guided by severity of encephalopathy clinically, severity of ischemic lesions seen on MRI). In severe cases, patients may be treated with 1g pulsed methylprednisolone for 3-7 days followed by high dose oral steroids or Intravenous immunoglobulins. In extremely severe cases or refractory cases, pulsed cyclophosphamide, mycophenolate mofetil, tacrolimus or plasma exchange are alternative treatments.^{15; 48; 51}

Ophthalmic

In cases of Susac's retinopathy with CNS involvement, treatment of the CNS disease will take precedence and this often treats the BRAO. However, when patient presents with isolated Susac's retinopathy with BRAO, immunosuppressive treatment can be less aggressive and of shorter duration than that required for those with CNS disease. It is recommended that patients are treated with pulsed IV methylprednisolone 1g for 3 days followed by oral prednisolone (usually over a course of 1 month). IVIG and Mycophenolate Mofetil (MMF) are started early as alternatives in severe or non-responding cases. Serial FFA is required during follow up (up to 3 weekly) and medication tapered once serial angiography has ruled out recurrence of active disease. IVIG and MMF should be continued for a minimum of 6 months. In patients who progress despite the use of

corticosteroid, IVIG and MMF, Cyclophosphamide and Rituximab could be used as an alternative ^{3; 58} .

Long term monitoring with FFA is recommended as BRAO may be recurrent, even when receiving ongoing treatment. Signs of retina ischemia such as vitreous haemorrhage , neovascularisation may also be a sequelae. As a result, patients with residual retinal capillary drop out in the retinal periphery are closely observed for development of neovascularisation, which can be treated with laser photocoagulation. ^{3; 58}

The successful use of local intravitreal steroids (triamcinolone) to treat branch retinal artery occlusions in Susac's syndrome prior to the start of systemic corticosteroids has also been described. However, the main stay of treatment remains systemic immunosuppression. ⁷⁶

A Proposed Care Pathway

With distillation of the literature, response to therapies and with contemporary ocular imaging we present a care management pathway we have adopted.

We monitor Susac's syndrome with EDTRS letter charts, OCT spectralis and optos wide field angiography. We recommend all patients with newly diagnosed and active Susac's Syndrome commence high dose corticosteroids , at a minimum of prednisolone 60mg a day and monitored 2 weekly with wide field angiography during acute phase.(Figure 2, 3) After 2 weeks, a patient is deemed refractory to treatment if there are no clinical improvements and, mycophenolate mofetil (1g BiD) will be added. Rituximab, Cyclophosphamide or IVIG will be considered as third line treatment after a further 4 weeks, and plasma exchange a final resort.

Maintenance therapy should be continued until MRI, FA and visual fields shows signs of stability with no new lesions and the patient remains clinically stable. Treatment can then be tapered over a period of 6 months (Figure 3). Patients will require life long monitoring for disease recurrence even when treatment has been eventually stopped.

In cases where patients present with encephalopathy, CNS disease will need to take precedence and more aggressive treatment may be necessary from the outset.

Conclusion

In conclusion, this review highlights the importance of early recognition of Susac's syndrome, given its varied forms of presentation and the severe consequences of delayed treatment. Ophthalmologists play a pivotal role in assisting diagnosis with pathognomonic fundal and imaging findings such as Gass plaques and AWHs. The role of retina angiography (FFA or wide field angiography) is crucial in the monitoring of ophthalmic disease as it is more sensitive than brain MRI in monitoring Susac's syndrome disease activity. New ophthalmic imaging modalities such as OCT/ OCT angiography and wide field angiography allows for unprecedented detailed documentation of retinal involvement in Susac's Syndrome and monitoring patients for relapse and necessity for treatment.

Literature Search

This literature review of the current article, ' A Review and Update on the Ophthalmic Implications for Susac's Syndrome was performed using Pubmed, from 1975 to 2018, with the search words ' Susac's Syndrome' and 'treatment', 'imaging', 'fluorescein angiography', 'indocyanine angiography' and ' optical coherence tomography'. All case reports and series were included in the search. Non-peer reviewed articles and non English abstracts were excluded.

Disclosure

None of the authors (LZ Heng, R Lee, C Bailey, AD Dick and A Ross) have any financial disclosures, no commercial or similar relationships to members of families or products mentioned in the subject matter in relation to the article.

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