OCULAR MANIFESTATIONS OF SUSAC SYNDROME

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ABSTRACT

Objective/Purpose
Susac syndrome is a rare condition characterized by the triad of encephalopathy, sensorineural hearing loss and visual disorders caused by branch retinal artery occlusions. To date, only a few reviews, small series and case reports are published. Clinical presentation, clinical course, general workup and therapy is described in 10 patients with Susac syndrome.

Methods
A retrospective observational study of patients diagnosed with Susac Syndrome between 2005 and 2019 at the Ghent University Hospital (tertiary referral centre) is conducted. A total of 10 patients were studied with special attention for the ophthalmological aspect. All medical records, including ophthalmic, neurologic and otorhinolaryngologic files, were reviewed. Finally, we compared our results with the contemporary knowledge and available literature.

Results
Only 10% of patients initially presented with a full clinical triad and finally 50% evolved into one. Encephalopathy was present in all cases. Branch retinal artery occlusions were present at first ophthalmologic visit in 90% of patients. Fluorescein angiography (FFA) is essential in both diagnosing and monitoring Susac syndrome and may show signs of disease activity, such as arterial wall hyperfluorescence, in the presence of a normal dilated fundoscopy. OCT may show a typical patchy retinal nerve fibre layer thinning and be helpful in the differential diagnosis. Aggressive and prolonged treatment with immunosuppressants, without premature tapering, is absolutely needed in the management of Susac syndrome.

Conclusions
The rarity of the disease and the variability of clinical presentation and disease course makes a diagnosis of Susac syndrome challenging. If Susac syndrome is suspected, a full neurologic, ophthalmologic and otorhinolaryngologic work-up with NMR brains, FFA and audiometry is essential. Further investigation is necessary to have more insights in the disease and to establish treatment guidelines and improve outcomes.
INTRODUCTION
Susac syndrome is a rare condition, first described by the neurologist John Susac in 1979. [1] It is a microangiopathy that typically affects the arterioles of the brain, retina and inner ear, leading to a triad with encephalopathy, sensorineural hearing loss and visual disorders caused by retinal arterial branch occlusions. [2] Early recognition, diagnosis and treatment is important to delay disease progression and prevent irreversible damage. [3]

Demographic data
A prevalence of 0.14 per 100,000 in a central European population above the age of 19 years is reported. [1,4] The overall incidence is not known. [2,3] Typically, the syndrome starts at a mean age of 30.5 years with a typical range between 20 and 40 years old, but it is described between the age of 7 and 70 years. [1,2,5] Ratio female to male is 3:1. [2,3,5,6,7] There is no racial preference. [3]

Pathophysiology
To date, the exact pathophysiologic process is unknown. Presumably, it is an autoimmune mediated endotheliopathy which leads to a microangiopathy and subsequent vessel occlusion with ischemia, mainly affecting the precapillary arterioles of the retina, inner ear and brain. Probably, this reaction is mediated by anti-endothelial cell antibodies (ACEA), derivatives of the complement activated IgG1 subclasses. ACEA’s may also be elevated in other inflammatory diseases and titers are found to be raised in only 25% of patients with Susac syndrome. It is unclear whether these antibodies are a cause or a consequence to the disease process. [1,2,8,9,10] Other described pathophysiologic mechanisms are idiopathic vasospasms, hypercoagulopathy and viral infections. However, evidence is lacking. [2,11,12]

Clinical presentation
Clinically, patients present with a typical triad of an acute or subacute encephalopathy, sensorineural hearing loss and visual disorders caused by branch retinal artery occlusions (BRAO). Both clinical presentation and course are highly variable. Only in 13% of cases all aspects of the triad are present at initial presentation. [1,8]
Generally, at presentation, encephalopathy is present in 67%, BRAO in 40% and sensorineural hearing loss in 37% of patients. Average time from onset to the full triad comprises 21 weeks, but may last up to 10 years. In the end, up to 85% of patients evolve into the full triad and therefore absence of a full triad does not exclude a possible diagnosis of Susac syndrome. [3,8,13,14]

Based on the disease course, 3 major groups are described: monocyclic, polycyclic and a chronic course. The monocyclic group has a fluctuating clinical course, but is self-limiting over a period of 2 years. Recurrences after a period of 2 years are reported in the polycyclic group and patients with a chronic course have no clear remission at all during any point in the disease course. [7] A monocyclic course is most common and reported in 54% of cases. A polycyclic course and a chronic progressive course are present in respectively 42% and 4% of cases. [8]

If a patient presents with a BRAO and / or sensorineural hearing loss, but does not develop an encephalopathy within 2 years after onset, it is very likely they will not develop any neurological problems in the future, nevertheless, NMR brains may show some abnormalities (typical callosal lesions). These patients typically present with recurrences over years and thus usually follow a polycyclic course. [3,7,8]

a. Ocular characteristics

Ocular symptoms may vary. Patients may be asymptomatic or may present with photopsias, decreased visual acuity, visual field deficits and / or visual aura such as scintillating scotomas with migrainous headaches. If visual field defects are present, most commonly altitudinal defects and / or black or grey (para)central scotomas are reported. If small peripheral areas of retina are affected, when the area of retinal ischemia is too far in the periphery or when patients have a severe encephalopathy, they may not report any visual disorders. [3,12,14-16]

b. Neurological characteristics

Encephalopathy may be variable and patients may present with acute or subacute forms and it may range from very mild to very severe. [3,8,17]

Headache is known as the most common prodromal symptom and it may be present during several months as a single sign. Especially in the early stages, Susac syndrome may be misdiagnosed as
migraine and in 40% of cases migraine type headache is reported as one of the presenting symptoms. A severe migrainous or oppressive headache is present at any point during the disease course in 80% of patients. Headache may become chronic and exacerbations during Susac syndrome are seen. [2,3,6,8,14,16-19]

Other reported neurologic symptoms are the following: confusion, cognitive impairment, dementia, short-term memory loss, behavioural and personality changes, emotional disturbances, vertigo, ataxia, dysarthria, aphasia, upper motor neuron signs, hemiparesis, agitation, apathy, psychiatric disturbances with psychosis and paranoia, attention deficit, imbalance and gait abnormalities, seizures, disorientation, numbness / sensory disturbances, sphincter dysfunction with fecal and urinary incontinence and urinary retention, nausea, vomiting, oculomotor dysfunction and diplopia. Neuropsychiatric symptoms, such as personality changes and paranoia, are reported in up to 75% of cases. [1,3,8,16,18-20]

c. Auditory characteristics
Hearing loss may be acute and severe or insidious and mild. Most commonly, a bilateral asymmetric sensorineural hearing loss for low to medium frequencies on audiometry is present. Other reported symptoms are tinnitus, peripheral vertigo and vestibular nystagmus. [1,8,17]

Ophthalmological findings
If Susac syndrome is suspected, a dilated fundoscopy and fluorescein angiography (FFA) is mandatory, also in the absence of any visual disorders. When dilated fundoscopy is normal, FFA remains indispensable for diagnosis, follow-up and monitoring of disease activity. Preferably, ultrawide field FFA is used over conventional FFA, because of a better possibility to evaluate the periphery. [3,6,18,20]

a. Dilated fundoscopy: branch retinal artery occlusions and Gass plaques
Fundoscopy typically reveals multiple branch retinal artery occlusions without any intraocular inflammation. Multiple retinal arterioles, unilateral or bilateral, may be affected. A central retinal artery occlusion is very rare. As a consequence of arteriolar occlusions the following signs may be present: focal retinal whitening, boxcar segmentation, arteriolar narrowing, cotton wool spots, optic disc hyperemia and optic disc pallor, perivascular sheathing and peripheral capillary closure.
Occluded arterioles may reperfuse over time or evolve into ghost vessels or arterial silver wiring. Retinal peripheral arterio-arterial collaterals may develop and when this is seen in a young patient with a history of BRAO, it is very suggestive for Susac syndrome. [1-3,15,21-25]

Gass plaques or retinal arterial wall plaques are yellow refractile lesions and are very similar to emboli. They represent areas of lipid deposits as a consequence of slow accumulation into the damaged vessel wall due to an immune mediated localized reaction. They are frequently present in the acute stage and are evanescent. In contrast to emboli / Hollenhorst plaques, Gass plaques may be located anywhere along the retinal arteries and especially at sites other than bifurcations. They are characteristic, but not pathognomonic for Susac syndrome and are also seen in other retinal diseases such as primary vitreoretinal lymphomas, Eales, toxoplasmosis, arterial macroaneurysms and acute retinal necrosis. [15,17,22]

b. **Fluorescein angiography (FFA)**

Arterial wall hyperfluorescence (AWH) is known as a typical feature of Susac syndrome. This may be present in nonperfused retinal arterioles, but may as well be seen in seemingly uninvolved vessels. Egan et al stated that this finding indicates a diffuse endotheliopathy. AWH at a distance from an occluded arteriole is pathognomonic for Susac syndrome and may be helpful in differentiating Susac syndrome from other vasculitic processes. Persistence of AWH is suggestive for persistent subclinical activity. AWH may evolve into a BRAO, however, frequently they do not. Retinal veins may also be involved in the disease process. [2,15,22]

Previously, it was thought that choroidal circulation was not affected, but segmental staining of choroidal vessels and dark dots, representing small circumscribed areas of choriocapillaris perfusion, can be seen on late indocyanine green angiogram (ICG) sequences. [26]

c. **SD-Optical Coherence Tomography / Optical Coherence Tomography - angiography**

Optical coherence tomography (OCT) is an essential tool in the diagnosis of Susac syndrome. OCT facilitates the quantification of both the retinal nerve fiber layer (RNFL) thickness and the macular volume. It helps in differentiating Susac syndrome from other retinal vascular diseases and multiple sclerosis. [27,28]
Susac syndrome typically affects the retinal microvasculature without choroidal vascular damage. As a result, there is a thinning of the inner retinal layers without damage to the outer nuclear and photoreceptor layers. A characteristic morphological pattern of often severe and patchy RNFL thinning is seen; whereas several sectors of RNFL thickness shows severe damage, other sectors remain completely normal. A loss of foveal delineation may occur. Occluded arterioles may reperfuse after initiation of treatment and this may result in a normal appearing FFA. However, once inner retinal thinning has occurred and is observed on OCT, no recuperation in retinal thickness is to be expected. This emphasizes the added value of OCT. [13,27,28]

As known, the classic ocular manifestation of MS is an optic neuritis which results in thinning of the RNFL, typically slightly enhanced on the temporal quadrant. In contrast to patients with Susac syndrome, there is an evenly distributed thinning of the RNFL without a loss of foveal delineation. Furthermore, in Susac syndrome, the RNFL thinning is found to be most pronounced in the nasal quadrants. RNFL thinning in MS accumulates over time and becomes more severe especially in later stages of the disease. In early stages of MS and in clinically isolated syndrome (CIS), when differentiation of Susac syndrome is most important, RNFL thinning is barely detectable. Unfortunately, it stays unclear at which time point OCT starts to show abnormal findings in patients with Susac syndrome whereby the differential diagnosis remains a challenge. [27,28]

OCT angiography (OCTA) is a new diagnostic imaging tool, allowing noninvasive assessment and follow-up of retinal tissue damage over time. Both superficial and deep retinal vascular plexuses may show damage as a result of vascular non-perfusion and this may be more precisely demonstrated by OCTA than FA. OCTA allows a more precise anatomical - functional correlation and assessment of retinal vascular diseases are more accurate due to the development of a retinal microvasculature map. However, imaging with OCTA is limited to the posterior pole and it cannot detect vascular leakage or vessel staining, thus disease activity may be missed. So, despite the development of OCTA, FFA is still needed for both evaluation of the periphery and detection of disease activity. [13,25,29]

d. Visual field examination / microperimetry

Visual field deficits correspond to the areas of retinal artery occlusion and RNFL thinning on OCT subsequently correlates with the presence of abnormalities on visual fields. Thirty percent of cases
have central field defects and/or extensive peripheral field loss and this is known to be permanent. However visual field examinations and microperimetry have low sensitivities as OCT may also be abnormal even when the visual field/microperimetry remains normal. This suggests that OCT is a significantly more sensitive tool for monitoring retinal injury in Susac syndrome. [27]

**MRI brains**

MRI demonstrates widespread abnormalities in the grey matter, white matter and leptomeninges, predominantly supratentorial, but infratentorial lesions are also seen. [17,19]

Lesions are most frequently seen at the corpus callosum, periventricular areas, centrum semiovale and subcortical regions. In addition, deep grey matter (70%), basal ganglia and thalamus (70%), cerebellum (50%), cerebellar peduncles (70%) and brainstem (30%) may also be involved. Callosal lesions are considered pathognomonic for Susac syndrome, however, in recent reports 20% of patients didn’t have callosal involvement, suggesting that this finding may not be mandatory for the diagnosis of Susac syndrome after all. [16,17,19,20,30,31]

Lesions are typically small (3-7mm), round, numerous and multifocal with predominantly white matter T2 and FLAIR hyperintensities, that preferentially involve the center of the corpus callosum. Those callosal lesions are present in the acute phase and are called ‘snowballs’. Linear defects may also be present and are called ‘spokes’. In the late phase, these lesions cavitate and form small central ‘punched out’ black holes, seen as hypointensities on T1-weighted images. Hyperintense lesions extensively involving the internal capsule may be recognized as a ‘string of pearls’ appearance on diffusion weighted imaging (DWI). Those lesions represent numerous punctate arteriolar microinfarcts. String of pearls and snowballs are relatively specific for Susac syndrome. General atrophy of the corpus callosum, cortex and cerebellum are seen in severely affected patients as late sequelae. Conversely, resolution of white matter lesions is rare, however, has been reported. [17,18]

**Diagnosis**

Recently, the European Susac Consortium developed diagnostic criteria for Susac syndrome to help both experts and physicians in making a correct diagnosis and thereby prevent delayed treatment initiation. [32]
A definite diagnosis is present when there is a full triad with both brain, retinal and vestibulocochlear involvement. Brain involvement is defined as behavioural changes, new cognitive impairment, new headache and / or new focal neurologic symptoms. The headache must be migrainous or oppressive and may not precede any other symptoms for more than 6 months. Headache of the trigemino-autonomic type is excluded. MRI findings must also be typical and show hyperintense, multifocal, round small lesions in the corpus callosum on T2 and FLAIR sequences. Retinal findings must include branch retinal artery occlusions and a fundoscopy, fluorescein angiography and OCT is mandatory for the diagnosis. Vestibulocochlear involvement is determined by tinnitus, peripheral vertigo and / or sensorineural hearing loss. Only one of these findings suffices for having vestibulocochlear involvement. Importantly, sensorineural hearing loss must be confirmed by an audiogram and vestibular vertigo by caloric testing and vestibular evoked myogenic responses. [32] When only 2 of 3 aspects of the full triad are present, a probable diagnosis of Susac syndrome is made. If only some findings of the triad may be heralded, we conclude to a possible diagnosis. [32]

**Differential diagnosis**

Susac syndrome is a very rare condition and because of the heterogenous, variable and non-specific presentation, a broad differential diagnose must be considered. Although, Susac syndrome is a vascular disorder and multiple sclerosis is a demyelinating disease, multiple sclerosis is probably the most frequent misdiagnosis of Susac syndrome due to overlap in clinical presentation and patterns of MRI pathology. However, this is a very important misdiagnosis, partly because of a different treatment strategy. Interferon beta, frequently used in treating MS, has been shown to worsen Susac retinopathy. On the other hand, TNF inhibitors which may be used in treating Susac syndrome, are contraindicated in patients with MS. [1,3,28]

Other differential diagnosis includes other demyelinating diseases (acute disseminated encephalomyelitis (ADEM)), auto-immune diseases (Behcet, SLE), vascular diseases (atherosclerosis, primary angiitis of central nerve system), intravascular lymphoma and infectious encephalitis. However, in all of these cases branch retinal artery occlusions are very rare and therefore an important clue towards Susac syndrome. If presentation is mainly with vertigo and fluctuating hearing loss, a misdiagnosis with Menière disease is not uncommonly seen. [14,19,33]
From the ophthalmologist viewpoint however, the FFA picture is quite typical and not easily mistaken for other disease underlying the strength of a multidisciplinary approach in the diagnosis of Susac syndrome.

**Therapy**
Currently, there are no randomized controlled trials for the treatment of Susac syndrome and therefore it is based on small series and case reports. This is mainly due to the variable clinical course of the disease and the rarity. Treatment strategy is individualized and adapted to the severity of the disease, both neurologically and ophthalmologically. [17]

Early and aggressive therapy, but also for a long enough time, is needed to control the disease and to prevent irreversible damage and relapses. Studies have already shown that immunosuppressive therapy is the cornerstone in the treatment of Susac syndrome, however, the exact therapy and the appropriate treatment duration remains elusive. Various combinations of the following are used: steroids, cyclosporine, cyclophosphamide, intravenous immunoglobulins (IVIG), methotrexate, mycophenolate mofetil, azathioprine and plasmapheresis. [16,17]

According to the most recently published guidelines, the following treatment schemes may be applied, mainly adjusted to the severity of the central nervous system damage.
If an extremely severe or a severe encephalopathy is present, it is advised to start with high-dose pulsed intravenous methylprednisolone of 1 gram during 3-5 days followed by a high dose oral prednisone (60-80mg or 1mg/kg) for four weeks and a consequent slow taper. In addition IVIG, cyclophosphamide, mycophenolate mofetil, tacrolimus or rituximab are added.
If a moderate encephalopathy is present, high-dose pulsed IV methylprednisolone followed by high dose oral prednisone is also recommended. In addition, IVIG, mycophenolate mofetil or rituximab are added to therapy.
A mild encephalopathy may be treated with pulsed IV methylprednisolone, however, initiation of high dose oral prednisone is also a good alternative. IVIG, mycophenolate mofetil or rituximab must also be added to the treatment scheme.
Independently of the severity of the disease, in most cases a duration of therapy of at least 2 years is needed. After discontinuation of treatment, a follow-up duration of another 2 years is recommended to monitor the clinical stability. [3]

If patients present with mainly recurrent branch retinal artery occlusions, therapy must not be as aggressive as with a primary encephalopathy. The following is proposed: high-dose pulsed IV methylprednisolone followed by high dose oral prednisone and consequent slow tapering, in combination with IVIG or mycophenolate mofetil. Therapy must be tailored to serial FFA results and the presence of encephalopathy. If clinical stability is achieved, prednisone may be slowly tapered. IVIG may be tapered after 6 months and mycophenolate mofetil after 6 to 12 months. In refractory cases or if there is insufficient clinical improvement, cyclophosphamide and rituximab may be used as an alternative. [17]

Initially, it was stated that all patients needed long-term prophylactic antithrombotic or anticoagulation therapy, however, recent studies concluded that this was not effective. Despite intake of aspirin, recurrent BRAO’s were frequently seen. In addition, serious hemorrhagic complications were reported in patients with warfarin intake. [3,17]

**Prognosis and follow-up**

Early recognition and correct diagnosis with prompt, aggressive and sustained treatment, results in a better prognosis with improved outcomes, however, irreversible damage is commonly described. Delayed and suboptimal treatment as premature rapid tapering, is known to result in poor outcomes. Residual symptoms range from very mild to very severe and are directly linked to a correct approach. Nevertheless, in a few cases, spontaneous remission is seen. [1,3]

Visual and auditory deficits are most commonly permanent and encephalopathy may be more reversible. It is estimated that half of patients for the most part recover, however, another 50% remain to have mild to moderate neurologic problems. [2,17]
Due to the variable course and the recurrence risk after remission, even after multiple years, long term management with serial ophthalmological, auditory and neurological / MRI brain evaluations are needed. [1,3]

Purpose
We aim to describe the clinical presentation, clinical course, diagnosis and treatment of Susac syndrome by studying a group of 10 patients followed at the Ghent University Hospital. We compare our results with the literature and try to have more insights in the disease and treatment of the disease, with special attention for the ophthalmological aspect.
METHODS

We performed a retrospective, observational study of all currently diagnosed Susac patients with ophthalmologic follow-up at the Ghent University Hospital (tertiary care centrum, Belgium). In total, we collected 10 patients. We conducted a retrospective search through all medical records since first presentation at the Ghent University Hospital to December 2019. Follow-up ranges back to January 2005.

We conducted this study in co-operation with the Department of Neurology and the Department of Otorhinolaryngology of Ghent University Hospital. Ethics approval was obtained from the institutional Ethics Committee by the Department of Neurology. At the department of Neurology, there are 11 patients with a diagnosed Susac syndrome in follow-up, however the ophthalmologic follow-up of this one extra patient is at another hospital in Belgium. Because of a lack of ophthalmological data, we decided to exclude this patient from our study.

First of all, we performed a systematic literature search through PubMed and MeSH using the following search terms: susac and ophthalmology, susac and OCT, susac and treatment, susac and gass plaques / arterial wall plaques, susac and diagnosis, susac and fluorescein angiography, susac and multiple sclerosis.

Relevant articles were selected based on the content of the title and/or abstract and study design. Initially, we searched for review articles, but because the literature is not very elaborate, case series were also included. Articles older than 2000 were excluded.

Subsequently, all patient records of the department of Ophthalmology, Otorhinolaryngology and Neurology were studied. We collected all the available and relevant data of all patients within each department. We focused on the ophthalmological aspect of Susac syndrome and therefore all ophthalmic examinations were reviewed. In this thesis, we describe the clinical presentation, clinical course, additional investigations, treatment and prognosis of all studied patients, with special attention for the ophthalmological aspect.

Finally, we compared our results with the current literature and we tried to establish a correct and updated approach for the diagnosis, therapy and follow-up of patients with Susac syndrome.
RESULTS

Demographic data
The mean and median age at diagnosis is respectively 38.9 years and 35 years, but ranges from 27 to 69 years old. Out of 10 patients, there are 6 females and 4 males. The delay in time between onset of symptoms and diagnosis is estimated to range from months to years, however, concrete data are missing. Mean and median duration of follow-up is respectively 3.3 years and 3.6 years and ranges from 9 months till 15 years. A summary table is attached at the end of results. (Table 1).

Clinical presentation
Clinical presentation is strongly variable. Only 1 patient (10%) initially presented with the full triad of an encephalopathy, hearing loss and visual disorders. All patients (100%) had an encephalopathy at first presentation and in 50% of cases it was isolated. Three patients had additional hearing problems and only one had associated visual symptoms. None of the patients presented with isolated auditory or visual symptoms. Subsequently, 5 patients (50%) evolved into a complete triad over the course of 2 days to 4 months. One patient continued to have isolated neurological symptoms during the full disease course. Three patients (30%) did not develop any ocular symptoms, however, only one patient had a completely normal ocular investigation.

<table>
<thead>
<tr>
<th>SYMPTOMATOLOGY</th>
<th>At presentation (n=10)</th>
<th>During disease course (n=10)</th>
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<tbody>
<tr>
<td>Full triad</td>
<td>1</td>
<td>5</td>
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<tr>
<td>Isolated encephalopathy</td>
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<td>1</td>
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<td>Isolated visual disorders</td>
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<td>Encephalopathy and hearing problems</td>
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</table>

a. Neurology
At presentation, all patients had an encephalopathy, ranging from mild to severe. Most commonly reported neurological symptoms were the following: confusion (n=4), cognitive or personality changes (n=6), gait instability (n=5), fatigue (n=3) and paresthesia (n=4). Headache was present in
7 patients and frequently as one of the presenting symptoms. A typical migrainous headache was present in 3 patients, all of them were female.

An extended neurological work-up was performed in all patients. All patients underwent MRI brains with T1, T2, fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI), both axial and sagittal, and with use of gadolinium. Lesions in the corpus callosum, which are considered to be pathognomonic for Susac syndrome, were present in every patient. Other observed lesions included leptomeningeal involvement, both (sub)cortical deep white and gray matter lesions, supra- and infratentorial lesions, cerebellar and brainstem lesions. The typical snow balls, punched out and spokes lesions were also noticed in some patients.

b. Otorhinolaryngology

At presentation, 4 patients had hearing loss and/or tinnitus. Another 4 patients developed hearing loss and/or tinnitus in the following days to months (range: 2 days – 6 months) and 1 patient subsequently developed nonspecific (noise intolerance) hearing symptoms 8 months after presentation. Only 1 patient developed no ear symptoms at all. Audiometry was aberrant in 9 out of 10 patients, with hearing loss in the low – mid frequencies except for 2 patients with high frequency loss. Interestingly, the one patient with the normal audiometry was not asymptomatic and had complaints of subjective hearing loss and tinnitus.

Ocular presentation

Symptoms

Initially, only 2 patients reported ocular symptoms, but due to the delay in referral to a tertiary centre between first symptoms and first visit, 6 patients eventually had visual disorders at the first ophthalmological consultation. At presentation, 2 patients were not able to cooperate because of their neurological condition, however during follow-up their neurological condition improved and subsequent anamnesis was possible. In the end, 7 patients reported visual disorders at some point during the disease course and all of them described a central or paracentral scotoma. Other reported ocular symptoms included blurry vision and/or grayish haze (n=6), floaters (n=4) and photopsias (n=2).
Visual acuity
In most cases, visual acuity was not compromised. Typically, there was a visual acuity of 1.0.
One patient had a reduced visual acuity up to 0.8 due to retinal ischemia in the macular region. Once the disease activity was extinguished, the visual acuity recovered to 1.0, however with remaining difficulties.
Another patient had a visual acuity of 0.05 at one point during follow-up. This was due to a severe subcapsularis posterior cataract, as a result of prolonged corticosteroid use. After phaco-emulsification the vision recovered and fluctuated between 0.7 and 1.0. This fluctuation was not correlated to the retinal function and/or recurrences of Susac syndrome.

Anterior segment
At presentation, anterior segment was unremarkable in all cases. As previously stated, during follow-up one patient developed a significant subcapsularis posterior cataract in both eyes. A phaco-emulsification was performed with a good postoperative result and a recovery of vision. The same patient also developed a steroid response with a spike in intra-ocular pressure (IOP). Topical therapy with timolol was started and IOP was thereby controlled. Treatment with corticosteroids did not need any adjustments.

Fundoscopy and fluorescein angiography
A dilated fundoscopy and fluorescein angiography was performed at each ophthalmological consultation in every patient. Retinal vascular occlusions were observed in 90% of patients. In our study, only one patient (10%) had a completely normal fundoscopy and fluorescein angiography at the first visit and during further follow-up.

At presentation, vascular stops were bilateral in 7 patients and eventually all affected patients evolved into bilateral and multiple vascular stops. (fig 1) In the acute phase, focal retinal whitening and edema, cotton wool spots and intraretinal bleedings as a result of infarction, were observed. Other ophthalmic findings included the following: delayed vascular filling and patchy choroidal filling, arteriolar narrowing, boxing

Figure 1: multiple arterial vascular occlusions superior and inferior on FFA with areas of AWH along the vessels
signs and boxcar segmentation, perivascular sheathing, silver wiring, ghost vessels and fibrotic vessels.

Gass plaques were not seen in all patients (n=6) (fig 2). Their presence fluctuated strongly and correlated with disease activity. Arterial wall hyperfluorescence, both in occluded and normally appearing vessels, was found to be characteristic (fig3). In a minority of cases, staining of blood vessels was accompanied by leakage and diffusion into the adjacent retinal tissue. Also, all but every AWH evolved into a branch retinal arterial occlusion. Vascular reperfusion of some vessels after initiation of immunosuppressive therapy and during remission was seen in every patient. In one patient a distinctive arterio-arterial (AA) collateral was seen in the macular region. (fig 4)

Figure 2: A Gass plaque along a vessel in the nasal quadrant on fundoscopy

Figure 3: AWH without vessel occlusion on FFA

Figure 4: superotemporal AA collateral on fundoscopy

Significant peripheral ischemia was seen in 4 patients and chronic follow-up, despite absence of disease activity, was needed to monitor and prevent ocular complications. To date, additional therapy was not necessary and neovascularization was not seen.

Optical coherence tomography

Optical coherence tomography of the macular region was performed at each consultation in every patient. As previously stated, in our study one patient did not have any ocular damage in both eyes, including a normal fundoscopy, fluorescein angiography and normal findings on OCT. The remaining 9 patients and subsequently 18 eyes, all had ocular involvement at one point during the clinical course. At initial investigation, 5 eyes had inner retinal atrophy and another 5 eyes subsequently developed atrophy. At presentation, inner retinal edema as a consequence of retinal infarction, was present in 2 eyes. It is noteworthy to mention the patchy distribution of the inner retinal atrophy in all affected eyes. Loss of foveal delineation was seen in 2 eyes.
It is interesting to notice that in one eye, a small pigment epithelial detachment with the clinical picture of a central serous chorioretinopathy was present. Luckily, it was small and located in the periphery of the macular region. We may assume this was in part due to the intake of steroids, necessary in the management of Susac syndrome. No extra treatment was necessary and a spontaneous recovery was seen. In the remaining 19 eyes, no abnormalities were detected on the level of the outer retina.

Visual field examination
Goldmann perimetry was performed in 60% of patients and one other patient (10%) had an automated visual field (Humphrey). Visual field examinations were mainly taken during the early stages of follow-up (mostly 2011 - 2016) and thereafter, they were taken very sporadically.

A (peri)-central sensitivity drop and (para)-central scotomas were present in respectively 8 (57%) and 4 eyes (29%). A quadrantanopia was seen in 3 eyes. No altitudinal defects were documented. These findings were found to be fairly consistent during follow-up. General contraction of peripheral borders was present in 4 eyes, however, in half of these cases there was a very strong variation during follow-up and the reliability of this finding is therefore questionable.

In most cases, visual field examination was congruent with the retinal findings and areas of branch retinal artery occlusions. One patient had great difficulties to reliably perform a visual field examination with variable results during follow-up that weren’t always found to be congruent with the retinal findings. On the other hand, it is remarkable that anything but every area of branch retinal artery occlusion was reflected on the visual field examinations.

Differential diagnosis
Because of the rarity of the disease and the variable clinical presentation, Susac syndrome may be missed, especially in the early stages. Important differential diagnoses at initial presentation in the neurology and NTE departments in our centre were MS (n=4), migrainous headache with or without visual aura (n=2) and benign paroxysmal positional vertigo (BPPV) (n=2). One patient was initially misdiagnosed with Menière disease. The initial differential diagnosis in other patients included ADEM, infectious encephalitis and primary CNS angitis.
However, close collaboration between the neurology and the ophthalmology department in our hospital leading to a very low threshold fluorescein angiography examination in patients with clinical symptoms suspicious for Susac syndrome, remarkably improved and accelerated the diagnosis.

**Treatment**

At present no evidence based therapeutic guidelines are established. In our study, an individualized approach was taken. The treating neurologist coordinated the therapeutic strategy, taking into account the ophthalmological and otorhinolaryngological findings.

As previously mentioned, only one patient did not have any ocular involvement, and she was also the only patient who did not receive any therapy for Susac syndrome. Every other patient received high dose corticosteroids, intravenous (n=8) or peroral (n=1), with subsequent tapering. Steroids were combined with plasmapheresis (n=7) and / or mycophenolate mofetil (Cellcept) (n=8) in most cases. Two patients were started on steroids in monotherapy without any other immunosuppressive agents, but this was insufficient and immunosuppression was subsequently needed.

Due to a lack of clinical improvement, 5 patients (50%) needed a therapeutic adjustment and plasmapheresis and / or rituximab were added. Rituximab was additionally started in 4 patients because of inadequate control with one immunosuppressant (mostly mycophenolate mofetil). In one patient, therapy with steroids, initial plasmapheresis, mycophenolate mofetil and rituximab was insufficient and cyclophosphamide (Endoxan) needed to be added on top of it.

Azathioprine (Imuran) was used in 3 patients. One patient was switched from mycophenolate mofetil to azathioprine during the disease course because of a pregnancy wish, another patient because of a possible side effect with psychological disturbances. In our third patient, azathioprine was started as initial therapy in combination with steroids.

IVIG was not started in any of our patients, mainly because no refund was provided. Prophylactic treatment with aspirin (Asaflow) was started in half of our patients.
During tapering of therapy, eight of our patients had a relapse with clinical deterioration, neurologically and / or ophthalmologically. Relapses were seen if corticosteroids were tapered too quickly. As previously mentioned, two patients were started on steroids in monotherapy, and both had recurrences while tapering treatment. Relapses were also observed with a lowering of the dosage of mycophenolate mofetil or when ceasing treatment with plasmapheresis.

Typically, a maintenance treatment of minimum 2 years duration was applied after clinical stabilisation. Finally, in only one patient a clinical stabilisation was seen during 2 years and treatment could be successfully stopped. The remaining 8 patients were still on immunosuppressive therapy at the end of follow-up.

**Prognosis and follow-up**

Duration of follow-up ranged from 9 months to 15 years. Seven of our patients tend to have a monocyclic course, however, in 4 of them the duration of follow-up up to now is less than 2 years. One patient has a polycyclic course and the remaining 2 patients, with a follow-up of 7,2 years and 8,7 years, rather have a chronic course with no clear clinical stabilization or remission at all.

Recurrences were present in 9 patients. Time frame of recurrences in which one or more recurrences was seen, ranges from 2 months to 13,4 years with a mean and median of 3,7 and 1,3 years. Number of recurrences ranges from 1 to 11 times with a mean and median number of respectively 4,1 and 4 times. Duration in between recurrences ranges from 1 week to 10 years. The patient with a duration of 15 years of follow-up was lost to follow-up during 6 years, but subjectively no recurrences occurred during this period. This patient had a relapse ten years after the first presentation, shortly followed by another relapse.

If relapses were encountered, the follow-up interval was shortened. If only subtle signs of disease activity were present, such as a minimal increase in lesions on brain imaging and / or vascular staining on FFA, therapy was not always directly adjusted. Each time, there was an individualized approach in management focused on strict follow-up to allow rapid treatment adjustments if necessary.
At the end of follow-up, residual symptoms were present in every patient. Review of patient files make us believe that every patient had a subjective and significant improvement of the initial burden. But, because of the retrospective nature of this study, it is impossible to specify and quantify this finding.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex (F/M)</th>
<th>Age at diagnosis (y)</th>
<th>Duration of follow-up (years / months)</th>
<th>Involvement neurology / ENT / ophthalmology (*)</th>
<th>Right eye: 1) Fundoscopy / FFA 2) OCT</th>
<th>Left eye: 1) Fundoscopy / FFA 2) OCT</th>
<th>Treatment during disease course</th>
<th>Relapses with tapering of therapy</th>
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<tbody>
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<td>1</td>
<td>F</td>
<td>35</td>
<td>15y (lost to follow-up during 6y)</td>
<td>Neurology, ophthalmology, ENT</td>
<td>1) vascular stops at presentation. No additional vascular stops during FU 2) Thinning RNFL from presentation</td>
<td>1) vascular stops at presentation. No additional vascular stops during FU</td>
<td>- Corticosteroids - Plasmapheresis - Mycophenolate mofetil</td>
<td>Yes</td>
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<tr>
<td>2</td>
<td>M</td>
<td>69</td>
<td>1y2m</td>
<td>Neurology, ophthalmology, ENT</td>
<td>1) vascular stops at presentation. No additional vascular stops during FU 2) normal thickness RNFL at presentation and during follow-up</td>
<td>1) vascular stops at presentation. No additional vascular stops during FU</td>
<td>- Corticosteroids - Plasmapheresis - Mycophenolate mofetil - Rituximab</td>
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<td>M</td>
<td>35</td>
<td>3y</td>
<td>Neurology, ophthalmology, ENT</td>
<td>1) vascular stops at presentation. Relapses with additional vascular stops during FU 2) normal thickness RNFL at presentation and during follow-up</td>
<td>1) vascular stops at presentation. Relapses with additional vascular stops during FU</td>
<td>- Corticosteroids - Plasmapheresis - Rituximab - Azathioprine</td>
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<td>5y7m</td>
<td>Neurology, ophthalmology, ENT</td>
<td>1) vascular stops at presentation. Relapses with additional vascular stops during FU 2) inner retinal edema at presentation - thinning RNFL during FU</td>
<td>1) vascular stops at presentation. Relapses with additional vascular stops during FU</td>
<td>- Corticosteroids - Mycophenolate mofetil</td>
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<td>Age</td>
<td>Diagnosis</td>
<td>Presentation Findings</td>
<td>Follow-up Findings</td>
<td>Treatment</td>
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<td>33</td>
<td>9m Neurology, ENT</td>
<td>1) normal fundoscopy / FFA at presentation and during follow-up</td>
<td>2) normal thickness RNFL at presentation and during follow-up</td>
<td>No treatment</td>
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<td>29</td>
<td>1y4m Neurology, ophthalmology, ENT</td>
<td>1) vascular stops at presentation. Relapses with additional vascular stops during FU.</td>
<td>2) normal thickness RNFL at presentation - thinning RNFL during FU</td>
<td>- Corticosteroids - Plasmapheresis - Mycophenolate mofetil - Rituximab</td>
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<td>M</td>
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<td>1) vascular stops at presentation. Relapses with additional vascular stops during FU.</td>
<td>2) normal thickness RNFL at presentation and during follow-up</td>
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<td>1) vascular stops at presentation. Relapses with additional vascular stops during FU.</td>
<td>2) normal thickness RNFL at presentation and during follow-up</td>
<td>- Corticosteroids - Plasmapheresis - Mycophenolate mofetil</td>
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<td>F</td>
<td>35</td>
<td>8y8m Neurology, ophthalmology, ENT</td>
<td>1) vascular stops at presentation. Relapses with additional vascular stops during FU.</td>
<td>2) normal thickness RNFL at presentation and during follow-up</td>
<td>- Corticosteroids - Plasmapheresis - Mycophenolate mofetil - Azathioprine</td>
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<td>Patient 10</td>
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<td>27</td>
<td>4y3m</td>
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<td>2) Thinning RNFL from presentation</td>
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<td>1) Normal fundoscopy / FFA at presentation. Vascular stops during FU.</td>
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<td>2) normal thickness RNFL at presentation - thinning RNFL during FU</td>
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<td></td>
<td>2) inner retinal edema at presentation - thinning RNFL during FU</td>
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<td>1) Vascular stops at presentation, incl BRAO. No additional vascular stops during FU.</td>
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<td>- Corticosteroids</td>
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<td>- Plasmapheresis</td>
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<td>- Mycophenolate mofetil</td>
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Table 1: Summarizing table of results with patients characteristics.
(* including symptoms and/or any abnormalities on MRI brains, audiometry and/or FFA


DISCUSSION

Susac syndrome is a very rare and frequently underdiagnosed disease. It is presumed to be an autoimmune endotheliopathy and as known, in general, autoimmune diseases are more prevalent in females. Similarly, in Susac syndrome a female predominance with a female to male ratio of 3:1 is reported in literature which is congruent with our findings (ratio 3:2).

It is assumed that although it is more prevalent in females, the disease may be more severe in males. In our study, it is remarkable that all patients who needed supplementary immunosuppression with rituximab are males and also, the one patient who presented with a full clinical triad was a male patient. In addition, males tended to have a moderate (n=2) to severe (n=2) encephalopathy and all males evolved into the full clinical triad with recurrences in 3 out of 4 males. On the other hand, all males have a monocyclic course to date, while a polycyclic (n=1) or chronic (n=2) course is seen in 3 females.

Clinical presentation and clinical course

In our study, only 10% of patients initially presented with a full clinical triad which is in accordance with literature. Reviews have shown that 85% of patients evolved into a full triad over an average time of 21 weeks. In our study, this was only the case in 50% of patients and moreover within a shorter range (2 days - 16 weeks).

Comparing our results with the literature, our patients tend to have a more severe presentation. In our study, every patient presented with an encephalopathy, whilst in the literature this is reported in only 67%. Likewise, vascular occlusions were observed in 90% of our patients at the first ophthalmological visit, in studies this finding is reported in only 40% of cases.

As stated in the literature, a migraine-type or oppressive headache may be present in up to 80% of cases and it may be one of the presenting signs of Susac syndrome. We may confirm this finding as 70% of our patients did have a headache, which was of the migraine-type in 43% of cases, and this symptom was already present at first presentation in nearly all of them. In our study, referral with initial misdiagnosis of migraine was present in 20%. This suggests the importance of an extensive investigation, especially if patients present with headache or migraine and subsequently develop other additional symptoms.
MRI brain seems to be very helpful in diagnosing Susac syndrome. As stated in the literature, callosal lesions are a characteristic finding and in all of our patients such typical lesions were present. Moreover, if patients present with mainly neurological signs, it is not unlikely that a misdiagnosis with MS is made and in this case MRI brains may be able to make the differential diagnosis with Susac syndrome because both MS and Susac syndrome have typical and distinct lesions on imaging.

An ophthalmological investigation with fluorescein angiography is absolutely needed once Susac syndrome is suspected, even if no visual disorders are present or when a severe encephalopathy precludes any communication. Vascular stops may definitely be seen in asymptomatic patients. In our review, 70% of patients had visual disorders, but abnormalities were seen in 90% of patients. Also, during follow-up, serial FFA remains mandatory because symptoms are frequently not congruent with findings and some signs, such as AWH, are clearly visible on FFA, but not visible on a dilated fundoscopy and thus disease activity may be missed. On the other hand, FFA helps detecting complications such as ischemia which possibly needs to be treated. This underlines the need of FFA at every follow-up visit, even if no overt disease activity is seen.

On the other hand, OCT is also a very important and additional tool in diagnosing Susac syndrome. Serial follow-up, both in literature and in our study, has shown that vascular reperfusion is not uncommon once immunosuppressive therapy is started and remission is seen. Though, a vascular occlusion results in irreversible atrophy of the inner retina and so, FFA may be normal while OCT is able to demonstrate damage to the retinal tissue.

OCT may also be helpful in differentiating MS from Susac syndrome. Referred patients with initial misdiagnosis of MS was seen in 40% of cases. MS results in an evenly distributed thinning of the retinal nerve fiber layer, in Susac syndrome RNFL thinning is typically patchy and loss of foveal delineation may occur and this was respectively seen in 50% and 10% of eyes in our study.

The added value of a visual field examination for diagnosis and follow-up is questionable because of a very low sensitivity. Paracentral / central scotomas and peripheral defects may be seen and they correspond to the areas of retinal damage but certainly not all areas of damage are reflected on this examination. The combination of fundoscopy, FFA and OCT allow a more
objective, precise and sensitive evaluation of retinal infarctions. Visual field examination however is useful to document and to screen patients for if they comply with legal driving requirements.

**Diagnosis**

Susac syndrome may easily be missed because of the rarity of the disease and the variable clinical course. When Susac syndrome is suspected, a full neurological, ophthalmological and otorhinolaryngological work-up is needed. Both MRI brains and FFA may show typical signs such as callosal lesions and BRAOs and thus be a very important tool for making a correct diagnosis. It is important to notice that even in the absence of symptoms, abnormalities on additional examinations may certainly be observed and may lead to a full triad despite the absence of symptoms.

**Treatment**

The rarity of the disease and the lack of studies are the main cause of a lack of evidence based standardized treatment protocols. Despite the absence of a clear protocol, studies already have shown the importance of rapid and aggressive immunosuppressive therapy, however, duration, dosage and type of immunosuppressive therapy remains unclear.

We have tried to establish a possible treatment protocol, based on the literature and the findings in our study. First, it is very important to appoint a coordinator because of the interdisciplinary nature of Susac syndrome. In our opinion, the neurologist may be a good choice because neurologic problems are present in most cases, important differential diagnoses with migrainous headaches and MS are seen and in general, they are also more familiar with initiation and adjustments of immunosuppressive therapy. A fast and easy communication between the neurologist, ophthalmologist and otorhinolaryngologist is absolutely necessary.

In the acute stage, we propose pulsed high-dose IV corticosteroids with subsequent slow tapering of peroral steroids. At initiation, it seems important to start with intravenous therapy rather than high dose steroids peroral. Almost all of our patients received intravenous therapy primarily with a good initial control of the disease. A subsequent slow tapering of steroids is essential, because otherwise relapses are seen.
Immunosuppressants must be initiated from the start. In our study, we observed that the only 2 patients who were started on steroids in monotherapy, did not have an adequate clinical response and so, immunosuppression needed to be started later in the disease process. Because of a delay in early and aggressive treatment, they had a prolonged active disease course and thus, a higher risk of developing irreversible neurological, ophthalmological and/or otorhinolaryngological damage.

Classic, as a first immunosuppressive agent, mycophenolate mofetil (Cellcept) can be started. In our patients, this was frequently started in combination with plasmapheresis. In the literature, the importance of additional plasmapheresis is unclear, however, in our patients, it resulted in a good clinical response. Nevertheless, we are unable to notify the added value of plasmapheresis to the immunosuppressants.

If inadequate control is present, more aggressive treatment is needed and rituximab may be added as a second immunosuppressive agent and cyclophosphamide as a third. In our study, we have no experience with IVIG because no refund was provided.

We advise a duration of immunosuppressive therapy of at least 2 years after clinical stabilization and without any recurrences during this time frame. During tapering of therapy, a close follow-up is needed and if relapses are seen, therapy must be subsequently adjusted.

It is important to monitor and alert patients for side effects of both steroids and immunosuppressive agents. Infections are not uncommonly seen and this may eventually lead to a tapering or even stop of treatment as was seen in some of our patients. If this is the case, strict follow-up and considering to restart or switch agents is important.

If there is a very mild disease course, delaying treatment is suitable because a spontaneous remission is possible as is reported in literature and is seen in one of our patients. Nevertheless, if postponing therapy is chosen, a strict follow-up is necessary, so if any deterioration or relapse is seen, therapy can be initiated directly and aggressively.

**Conclusion**

Because of the rarity of the disease and the variable clinical course, literature is limited and only a few reviews are published. We tried to establish more insights in the clinical presentation,
clinical course, additional investigations, diagnosis and therapy of Susac syndrome by describing a group of 10 patients who were followed at the Ghent University Hospital, with special attention for the ophthalmologic aspect. We attempted to compare our results with the literature and we tried to propose a treatment protocol based on these findings.

However, we were also limited by deficiencies in patient files due to the retrospective nature of this paper and also the small number of patients with Susac syndrome. Prospective multicenter studies are needed to be able to understand Susac syndrome more precisely and to establish treatment strategies and long-term outcomes.
REFERENCES


**DUTCH RESUME**

**Inleiding**

Susac syndroom is een zeldzame aandoening gekenmerkt door de klassieke triade van een encefalopathie, sensorineurale gehoorsverlies en visuele stoornissen veroorzaakt door retinaal arteriële takocclusies. Klinische presentatie en verloop zijn sterk wisselend en slechts in 13% van de gevallen is een volledige triade bij presentatie aanwezig. Tot op heden is de beschikbare literatuur beperkt. Wij verzamelden een groep van 10 patiënten met de diagnose van Susac syndroom in het UZ Gent en beschrijven de klinische presentatie, het klinische verloop, diagnose en behandeling, met de nadruk op het oftalmologische aspect.

**Method**

Het betreft een retrospectief observationele studie waarbij alle patiënten met de diagnose van Susac syndroom en opvolg in het UZ Gent (tertiair centrum) werden verzameld. In totaal werd een groep van 10 patiënten bestudeerd met speciale aandacht voor het oogheelkundige aspect. Patiëntendossiers van oogheelkunde, neus-keel-oor en neurologie werden volledig bestudeerd. Uiteindelijk vergeleken we onze bevindingen met de huidige kennis in de literatuur.

**Resultaten**

De volledige klinische triade is slechts aanwezig in 10% van de patiënten bij presentatie en in 50% over het volledige ziekteverloop. Een encefalopathie was aanwezig in alle patiënten. Retinaal arteriële takocclusies waren aanwezig in 90% van de patiënten bij de eerste consultatie, hoewel slechts 70% oculaire klachten vermeldde. Fluoresceïne angiografie is essentieel, zowel bij de diagnose als opvolg van Susac syndroom. Arteriële wand hyperfluorescentie, zeker indien aanwezig op een normaal uitzienend vat, is pathognomonisch voor Susac syndroom en duidt op ziekte-activiteit die kan gemist worden bij fundoscopie. OCT toont typisch een onregelmatige verdunning van de retinale zenuwvezel laag. Behandeling met corticosteroïden en immunosuppressiva, zonder vroegtijdige of te snelle afbouw, is noodzakelijk om ernstige sequelen te voorkomen.

**Besluit**

Susac syndroom is een zeldzame aandoening met een sterk variabele klinische presentatie en ziekteverloop wat het stellen van een diagnose bemoeilijkt. Bij vermoeden van susac syndroom is een volledige uitwerking met neurologie, neus-keel-oor en oftalmologie noodzakelijk. NMR hersenen, fluoresceïne angiografie en audiometrie zijn onontbeerlijk. Verder onderzoek naar
Susac syndroom is nodig om meer inzichten te verkrijgen in de aandoening en behandel protocollen te kunnen opstellen.