

# Susac syndrome – clinical insight and strategies of therapy

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**Abstract.** – Susac syndrome is an uncommon autoimmune microangiopathy characterized mainly by neurological disorders and, to date, 304 clinical cases have been described. The background of this syndrome is an immune-mediated endotheliopathy that affects the microvasculature of the brain, retina, and inner ear resulting in encephalopathy, hearing loss, and branch retinal artery occlusions. However, the cause and the pathogenesis of this microangiopathy remain unclear. Magnetic resonance imaging, retinal fluorescein angiography, and audiography findings enable the diagnosis of this syndrome. In this review, we have demonstrated the epidemiology and pathology of Susac syndrome with detailed description of clinical signs, diagnostic procedures and therapeutic possibilities.

*Key Words:*

Susac syndrome, Autoimmune microangiopathy, Clinical diagnosis, Treatment.

## Introduction

Susac syndrome is a rare autoimmune disease described for the first time in 1979 and named after neurologist J.O. Susac<sup>1</sup>. The characteristic clinical triad of this disease includes encephalopathy, hearing loss, and branch retinal artery occlusions. However, the most common presentation is encephalopathy, which usually at the onset manifests as a headache<sup>2,3</sup>. The classic triad is pathognomonic for Susac syndrome, but the three elements are not always present at the same time<sup>4</sup>. In the literature, many other names of this syndrome are used, which are acronyms of the main symptoms (e.g. SECRET syndrome – small infarcts of cochlear, retinal, and encephalic tissues)<sup>5,6</sup>.

## Pathology

The pathogenesis of this syndrome is unknown, but an autoimmune background is sus-

pected. The mechanisms, which have been already described, include an autoimmune damage and inflammation-related occlusion of the microvessels in brain, retina, and inner ear<sup>1,2,7-10</sup>. It is considered as an autoimmune microangiopathy, since only the precapillary arterioles (< 100 µm) are affected<sup>11-13</sup>. Some of the symptoms resemble the catastrophic antiphospholipid syndrome and this pathology should be considered during the differential diagnosis<sup>13</sup>.

## Course of the Disease

The clinical course of Susac syndrome is a self limiting, fluctuating or relapsing and in some patients the residual neurological sequela is observed. The mild disease, which is easily controlled with medications, usually do not cause serious damage and the recovery with little or no residual disease is reported. However, the exacerbations can be also present and may lead to complete deafness, blindness, dementia and spastic gait<sup>2,7</sup>.

Unfortunately, many cases are underdiagnosed because not all clinical signs are present at the onset of the disease. The symptoms usually develop between several weeks and up to 2 years<sup>14,15</sup>. Moreover, many organs are affected, so they mimic other disorders<sup>3</sup>. In consequence, the diagnosis may be delayed for many months even years, whereas an immediate treatment can halt the disease progression and prevent future disability<sup>8</sup>.

## Epidemiology

Susac syndrome predominantly affects young women aged 20-40 years old (a female predominance of 3 to 1)<sup>4,7,9</sup>, but this disease can occur at any age (also in children, adolescences and adults over 50 years old)<sup>4</sup>. It can affect all races and has been described in the European (French, German, Spanish, and English patients), Asian (Chinese) and American populations<sup>6,16-19</sup>. Till date, about 304 cases have been reported; howev-

er, the real prevalence remains unknown<sup>20</sup>. This is due to the lack of all symptoms characteristic for Susac triad at the beginning of the disease and slow development of pathologic changes in the brain, retinal and cochlear vessels. Infection factors preceding the onset of Susac syndrome may initiate the symptoms<sup>5,8,9,21</sup>.

### **Clinical Signs**

At the beginning of this disease headache and non-specific neurological symptoms are present (subacute encephalopathy). Later, usually acute full-developed encephalopathy occurs, which manifests as headache, impaired cognition and memory, vertigo, dysarthria, ataxia, or corticospinal tract dysfunction, hemiparesis, mood changes and cognitive deficits<sup>11,15</sup>. Headache is a usual prodromal symptom and is observed in more than 50% of the patients. The headache is often severe, unrelenting and generalized and may mimic migraine and presage the encephalopathy<sup>2,16,22</sup>.

Encephalopathy is frequently associated with psychiatric disorders and the neuropsychiatric symptoms may dominate even in 75% of patients<sup>11,15</sup>. The most common symptoms are personality change, bizarre and paranoid behavior. These symptoms are accompanied by multifocal neurologic signs, which usually distinguish the encephalopathy from a true psychiatric illness. Transient paresthesias and hemiparesis may precede the encephalopathy and can be misdiagnosed as the transient ischemic attacks. Bilateral extensor plantar responses and pseudobulbar speech can be present, but seizures and myoclonus may also occur<sup>15,16</sup>.

Even the visual or hearing disorders are characteristic for Susac syndrome, the co-existence of cochlear or ophthalmological symptoms ranges only 40% of patients<sup>11,15,20</sup>. Visual disorders can be present as sudden visual loss or the blurred vision and diminished visual field. They vary depending on the region or the number of arterial occlusions, e.g. the infarctions in the posterior pole result in an impaired vision, while the occlusion in peripheral region of the retina cause very subtle changes or is asymptomatic<sup>1,9</sup>.

The otolaryngological symptoms vary depending on the place of infarction. The cochlear end-arteriole occlusion at the apex cause cochlear hearing loss usually for low to moderate frequency tones<sup>22,23</sup>. If pathologic changes are present of the membranous labyrinth, they cause prominent jerk nystagmus<sup>7,9,11</sup>. The hearing disorders may

be mild and subacute or very severe. They may be unilateral or bilateral and may spontaneously withdraw. However, permanent hearing loss is also reported, mainly if it is acute and not promptly treated. All of the symptoms usually develop gradually, sometimes over a period of two years<sup>14,15</sup>.

### **Diagnosis**

The diagnosis of Susac syndrome is based on the clinical presentation, laboratory tests and imaging studies.

### **Magnetic Resonance Imaging (MRI)**

MRI is the neuroimaging study of choice. It demonstrates microinfarctions (Figure 1), which are the main histopathologic changes<sup>5,21</sup>. They have a punched-out appearance and are present in corpus callosum, the centrum semiovale, internal capsule, periventricular white matter, brainstem, and cerebellum<sup>1,3,5,7,8,10,24</sup>. The callosal lesions are characteristic for Susac syndrome and may be present in the genu, corpus, and splenium of the corpus callosum. However, the central localization is very suggestive of this disease<sup>3</sup>. The lesions are usually bilateral and their diameters are about few millimeters, but sometimes they can cross 1 cm<sup>9</sup>.

Sagittal T1-weighted images demonstrate multiple, small, low-signal-intensity abnormalities that are present during the subacute or late phase of disease. These lesions (called “snowball lesions”) corresponded to the high-signal-intensity abnormalities seen on the T2-weighted MRI image and they spare peripherally<sup>4,18,22,24</sup>. The lesions enhance during the acute stage in 70% of patients. Their rapid cystic transformation and involvement of the basal ganglia are also present<sup>9</sup>. If the encephalopathy is severe, atrophy will ensue in the chronic phase. As encephalopathy abates, white matter lesions typically diminish (really disappear), but atrophy becomes evident. The cranial nerves are not involved in Susac syndrome<sup>16</sup>.

The parenchymal or leptomeningeal lesions may show enhancement on contrast material. The leptomeninges are affected in one-third of patients and the changes in this area are probably associated with headaches. The deep gray matter involvement (basal ganglia and thalamus) is present in 70% of cases. The small cortical microinfarctions in the cortex, the white matter and leptomeninges may be invisible in MRI, but they are identified in a brain biopsy. In some reports, the



**Figure 1.** *A*, Midline sagittal unenhanced T2-weighted MRI: hypointense lesions (*arrowheads*) in corpus callosum. *B*, Midline sagittal unenhanced T1-weighted MRI: hyperintense lesions in corpus callosum (*arrowheads*).

lesions in the right side of the internal capsule are correlated with spastic gait<sup>4</sup>. However, the association between MRI findings and the intensity of clinical manifestations of encephalopathy is not entirely clear<sup>4,23</sup>. Moreover, the snowball-like lesions are characteristic, but not pathognomonic for Susac syndrome<sup>2</sup>. Regardless this fact, MRI is very useful and bring forward the final diagnosis, mainly if the typical triad of symptoms are not present<sup>25</sup>.

### **Cerebral Arteriography**

In Susac syndrome, precapillary arterioles (< 100  $\mu\text{m}$ ) are involved, which are beyond the resolution of arteriography. Thus, cerebral arteriography findings are almost always normal<sup>20</sup>.

### **Fluorescein Angiography**

In the disease, retinal irregularities may be detected during ophthalmoscopy examination or fluorescein angiography<sup>6,23</sup>. Fluorescein angiography is a useful examination in evaluating the branch retinal artery occlusions (BRAO), which in many cases enables the final diagnosis (Figure 2). The changes are usually bilateral, may dominate at the onset of the disease or may occur later in the clinical course. Even BRAO is not seen at the very onset of Susac syndrome, the fluorescein angiography should be repeated, because the occlusions may develop later in the course. If the occlusions

are in the posterior pole they usually cause acute visual disorders. If they are localized peripherally, the patient may be asymptomatic<sup>2,15,26</sup>.

In acute episodes the characteristic fundus picture of the BRAO can be as associated with Gass plaques (retinal refractile arterial wall plaques at the mid segments of the retinal arterioles) and the multifocal fluorescence<sup>23,26</sup>. It is suggested that this multifocal distinctive staining of the vessels is pathognomonic for Susac syndrome<sup>26</sup>.

### **Videoelectroencephalography**

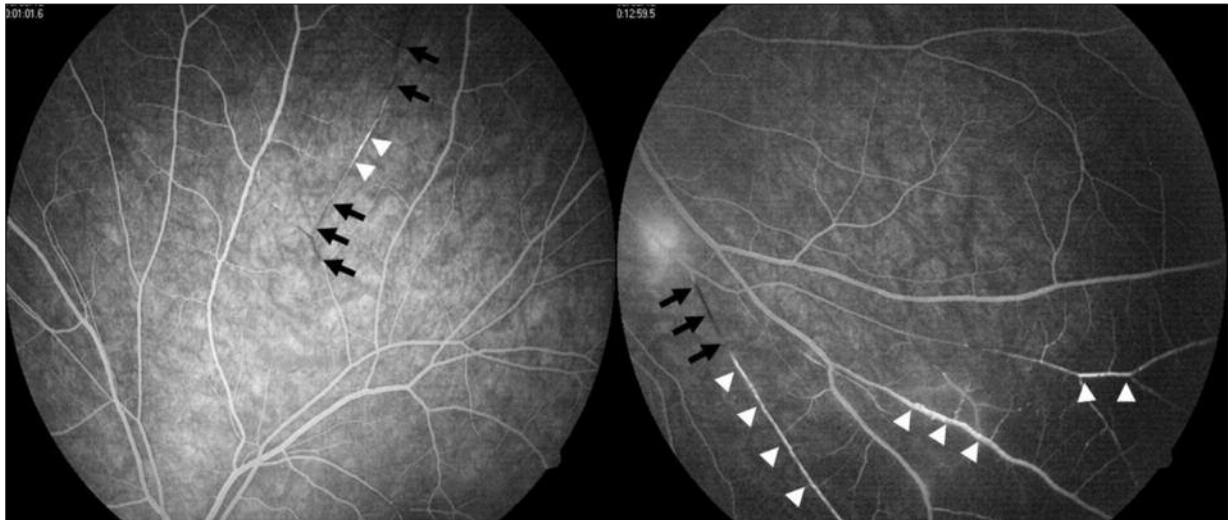
VideoEEG may reveal improper notation with the delta waves, which are suggestive of encephalopathy<sup>27</sup>. Even this examination is not specific and contributes little to the diagnosis, it is often done in the presence of neurological symptoms and can indicate the presence of encephalopathy. In the literature generalized slowing with no epileptiform activity is described and it attributes to the widespread vascular involvement<sup>20</sup>.

### **Audiometry**

The sensorineural hearing loss involves mainly the low and mid-frequencies tones<sup>23,26</sup>.

### **Laboratory Studies**

Laboratory studies are negative for antinuclear antibodies (ANA), cANCA, pANCA, hepatitis panel, Epstein-Barr polymerase chain reaction,



**Figure 2.** Fluorescein angiography, demonstrating the occlusion of a retinal artery (*arrows*) and leakage of the vessel wall (*arrowheads*).

cardiolipin antibodies, and herpes infection. In some cases, antiphospholipid and/or anti-endothelial cell antibodies may be elevated and can cause the endothelial cell injury<sup>2</sup> or the symptoms similar to the catastrophic antiphospholipid syndrome<sup>13</sup>.

Cerebrospinal fluid (CSF) examination usually reveals a high spinal fluid protein in the range of 0.1 g/l to 3 g/l. In some cases, mild pleocytosis (frequently lymphocytic) is present. Sometimes an elevated IgG concentration and increased IgG index with the presence of oligoclonal bands are detected and may suggest multiple sclerosis (but the presence of oligoclonal bands and/or intrathecal IgG does not exclude a diagnosis of Susac syndrome). CSF analysis is nonreactive for the Venereal Disease Research Laboratory (VDRL) test and other viral and bacterial tests<sup>2,20</sup>.

### **Differential Diagnosis**

At the early stages of Susac syndrome usually the characteristic triad is not present suggesting other disease regarding affected organ<sup>3,8</sup>. Because encephalopathy is usually present at the onset of this disease, it should be differentiated from neurological disorders. Differential diagnoses based on MRI findings should include thromboembolic stroke, chronic encephalitis, lupus erythematosus, Ménière's disease, meningeal carcinomatosis, aseptic meningitis, systemic lupus erythematosus, Behçet's or Lyme disease, complicated migraine, ADEM (acute disseminated encephalomyelitis), multiple sclerosis and

psychiatric disorders (schizophrenia). The other diseases such as sarcoidosis, tuberculosis, syphilis and lymphomas have to be ruled out.

The radiological findings usually resemble the changes in multiple sclerosis and this disease is commonly recognized at the early stages of Susac syndrome<sup>29</sup>. Nevertheless, in neurological disorders the changes are larger and extend from the peripheral regions (the undersurface of the corpus callosum) to the deep layers (from the periventricular extension into the deep white matter). Conversely, in Susac syndrome peripheral sparing of these lesions is observed and the specific central localization of brain lesions in corpus callosum is very suggestive of this vasculopathy<sup>3</sup>. Moreover, in Susac syndrome the clinical course is usually fluctuating with recurrent attacks (sometimes self-limiting)<sup>11,14,15</sup>, while in neurologic diseases (e.g. multiple sclerosis, acute disseminated encephalomyelitis, cerebral infarction), the course is progressive and prolonged<sup>22,30,31</sup>. In multiple sclerosis, hearing loss and BRAO are usually not present<sup>32</sup>.

The visual disorders are usually present in Susac syndrome and they should be differentiated with Cogan syndrome and primary CNS lymphoma<sup>11,15</sup>. However, in mentioned disease usually uveitis is present, while retinal vasculitis is characteristic for Susac syndrome. Sensineural hearing loss should be distinguished from meningitis and central nervous infections. The detection of microorganisms in cerebrospinal fluid examination is very helpful for a final diagnosis.

The abnormalities of arteries at the base of the brain should also be considered as one of the causes of hearing loss<sup>2,16</sup>. The involvement of leptomeninges is probably associated with headaches. It should be differentiated from migraine and encephalopathy<sup>4</sup>.

### Treatment and Management

Susac syndrome should be treated early and aggressively. In cases when immediate administration of immunosuppressive therapy was implemented, recovery was almost complete.

However, even a good effect of immunosuppression is observed, the best treatment still needs to be defined.

The treatment regularly starts with intravenous methylprednisolone (followed by oral steroids) and intravenous immunoglobulins (IVIG) pulsed every four weeks for several months (Table I). Such treatment is mainly recommended if the encephalopathy is not present and the recurrent BRAO with or without hearing loss dominate. The implementation of glucocorticosteroids is very beneficial and they should be considered as

**Table I.** Treatment of Susac syndrome.

Medication	Actions/treatment suggestions	Effectiveness
<b>Momptherapy</b>		
GCS orally or iv (mainly methylprednisolone)	The most frequently used medications High-dose iv methylprednisolone during the acute phase may diminish/withdrawal the symptoms Tapering of GCS may lead to a disease recurrence	The first-line therapy Very good response if the treatment is prompt, aggressive, and sustained
Acetylsalicylic acid	An antiplatelet effect by inhibiting the production of thromboxane In low doses diminishes the risk of hemorrhagic complications	Implemented in most studies and usually beneficial
Anticoagulants	Should be considered only in a procoagulant state	Usually effective
Cyclophosphamide	If the symptoms reappeared after glucocorticosteroids reduction A high dose every 4 weeks should be repeated	Effective
Other immunosuppressants (mycophenolate mofetil, rituximab, tacrolimus)	Used in prolong phase or in multisystemic involvement if GCS or CTX is not effective	Response was observed
Intravenous immunoglobulins	Effective in acute and prolong phase Implemented mainly with concomitant GCS	Effective
Nimodipine	Proposed as an adjuvant therapy (antivasospastic and neuroprotective effect is suspected)	No significant efficacy
<b>Combined treatment</b>		
Methylprednisolone iv + IVIG	First-line therapy in acute phase	Effective (no further were reported)
Cyclophosphamide + IVIG	Proposed in acute phase	Very effective
Azathioprine + prednisolone	In long-term immunosuppressive treatment	Partial recovery
Nimodipine + acetylsalicylic acid	Reveal antivasospastic and an antiplatelet effect	Lack of efficacy
<b>Additional therapies</b>		
Plasmapheresis	The rapid removal of disease-causing autoantibodies from the circulation Temper the disease process, but simultaneous medical and immunosuppressive therapy is required for long-term management	Beneficial in some cases May increase the risk of aggravation
Hearing aids and vestibular rehabilitation	If cochleovestibular disturbances are present	Effective as additional therapy
Psychological, eventually psychiatric therapy	In neurologic deficits and psychiatric disturbances	Effective as additional therapy
Cochlear implantation for hearing loss	If bilateral hearing loss is observed	Restore significantly hearing
Hyperbaric oxygen therapy	Reduces the visual sequelae and minimizes ischemic lesions	Improvement in visual field and visual acuity

GCS: glucocorticosteroids; IVIG: intravenous immunoglobulins; iv: intravenous; CTX: cyclophosphamide.

the first-line therapy. (Table I). High dose of methylprednisolone administered intravenously during the acute phase of the disease was reported to cause a definite remission<sup>33</sup>. Nevertheless, in 10% of patients such treatment is not effective and deterioration during oral prednisolone is observed<sup>1,34</sup>. Furthermore, the cease of glucocorticosteroids or their quick tapering led to the relapse. If a recurrence after glucocorticosteroids reduction is present or the onset of the disease is aggressive, a high dose of cyclophosphamide every 4 weeks should be considered<sup>35</sup>. Combined treatment with cyclophosphamide and intravenous immunoglobulins are also very effective<sup>36</sup>. Plasmapheresis can be considered as well. A good response to IVIG often is reported and no further relapses are observed<sup>37</sup>.

It is suggested that after the acute phase the patient should be on immunosuppressive therapy e.g. azathioprine, prednisolone in small doses (5 mg), aspirin, and dipyridamole<sup>38</sup>. If cyclophosphamide is contraindicated, a treatment with azathioprine and prednisolone can be another option of long-term immunosuppression; however, only partial recovery is observed during such therapy<sup>39</sup>. The migraine headaches respond to triptans and topiramate, but the generalized headaches usually are ceased after high doses of intravenous methylprednisolone. The severe hearing loss can be successfully treated with cochlear implants.

In Susac syndrome, also antithrombotic agents should be considered as part of the treatment regimen<sup>2</sup>. The retinal occlusions respond to anticoagulative treatment and arteries recanalizations frequently are observed. The withdrawal (cease) of oral contraceptives and hormonal replacement therapy should be thought, because hormones may aggravate the blockage of blood vessels<sup>2,16</sup>.

In the literature, many combined and additional therapies have been described, which are summarized in Table I. The treatment should be monitored by serial fluorescent angiograms and MRI.

## Conclusions

Susac syndrome is a rare autoimmune disease caused by a microangiopathy affecting the pre-capillary arterioles of the brain, retina, and inner ear. The exact cause of the disease is unknown, but an immune response with microembolization is suspected. Susac syndrome is underdiagnosed, because the disease is rare and not considered

during differential diagnosis. It is often misdiagnosed as multiple sclerosis or varied form of encephalitis. Because the symptoms develop after few months or even years and the characteristic triad is not present at the beginning of the disease, the diagnosis is postponed. Nevertheless, in every case of callosal lesions located centrally within the fiber tracts with relative sparing of the periphery Susac syndrome should be considered. Such localization location should increase clinical suspicion and suggest diagnosis, which should be followed by immediate therapy.

## Conflict of Interest

The Authors declare that there are no conflicts of interest.

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