# Susac syndrome misdiagnosed as multiple sclerosis with exacerbation by interferon beta therapy

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## Abstract

Susac syndrome is a rare autoimmune disorder characterised by the clinical triad of encephalopathy, retinopathy (branch retinal artery occlusions) and hearing loss. The diagnosis of Susac syndrome may be difficult initially, and it is not uncommon for patients with Susac syndrome to be misdiagnosed with multiple sclerosis. In this case report, we describe a patient who was diagnosed as having multiple sclerosis for three years, with further deterioration after starting treatment with interferon beta-1a. The patient had the triad of encephalopathy, branch retinal artery occlusions and sensorineural hearing loss. She had the classic magnetic resonance imaging appearance, with normal magnetic resonance imaging of the spinal cord and absence of oligoclonal bands in the cerebrospinal fluid. Our patient responded well to treatment with a combination therapy and discontinuation of interferon beta-1a. Our observations raise awareness about the importance of the early and correct diagnosis of Susac syndrome, which usually affects young patients, with an excellent prognosis if treated aggressively at an early stage of the disease. Susac syndrome is underdiagnosed and is not uncommonly misdiagnosed as multiple sclerosis. Susac syndrome is a great mimicker of multiple sclerosis, and establishing diagnostic criteria for this syndrome is very useful. In any patient presenting with a progressive disabling neurological disorder associated with callosal lesions and/or hearing loss, and/or visual loss especially in women, Susac syndrome should be suspected.

## Keywords

Susac syndrome, multiple sclerosis, branch retinal artery occlusion, sensorineural hearing loss, corpus callosum, microangiopathy

## Introduction

Susac syndrome (SS) is a rare autoimmune disorder that was first described in 1979 by an American neurologist named John Susac.<sup>1</sup> It is characterised by the clinical triad of encephalopathy, retinopathy (branch retinal artery occlusions; BRAOs) and hearing loss. The diagnosis of SS may be difficult initially, and it is not uncommon for patients with SS to be misdiagnosed with multiple sclerosis (MS).<sup>2</sup> In this case report, we report a case of SS that was misdiagnosed as MS for three years, with deterioration in the patient's condition following the initiation of immunomodulatory therapy for MS. We also elaborate on cardinal clinical and paraclinical features that suggest a diagnosis of SS rather than MS.

## **Case report**

A 45-year-old woman presented at our neurology clinic; she had previously been healthy until

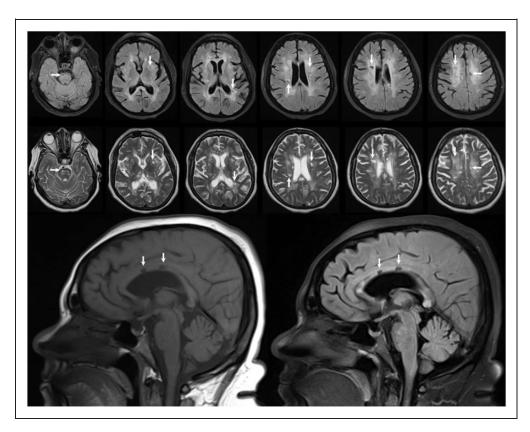
three years earlier, when she developed progressive vertigo, right ear hearing loss and painless blurring of vision. She also developed episodes of behavioural, cognitive and mood changes including depression and memory loss. Among other symptoms, she developed paresthesia in her four limbs and had difficulty walking with imbalance which started 10 months prior to presentation. She also had three attacks of tonic–clonic seizures, an altered level of consciousness and slurred speech. Her past medical, surgical and social history were unremarkable. She was diagnosed as having MS

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**Figure 1.** Magnetic resonance imaging at 3 Tesla showing periventricular white matter, basal ganglia and subcortical lesions, which are high signal intensity on both T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Some of these lesions are showing cavitation and slight diffusion restriction. There are also high signal intensity foci with cavitary lesions in the corpus callosum. In addition, there are multiple parenchymal hemosiderin deposits representing sequelae of a previous microbleed.

and was treated with pulse steroid therapy (1 g of intravenous methylprednisolone per day for five days) followed by the initiation of interferon beta-1a therapy. Her condition deteriorated further for a few months following the initiation of interferon therapy, with a worsening of her visual and auditory symptoms.

At this stage, she visited our neurology clinic for the first time for a second opinion. Detailed central nervous system examination showed an encephalopathic woman with aggressive behaviour and labile mood. Her vital signs and systemic examinations were normal. Ophthalmological examination showed diminished visual acuity (20/30 in both eyes) and pallor of the optic disks bilaterally. Fluorescein angiography showed BRAO in the superior temporal artery. She also had diminished hearing in her right ear. She was wheelchair bound mainly due to dizziness and vertigo, but her strength was normal in all of her limbs. Her motor, sensory and cerebellar examination was normal. Magnetic resonance imaging (MRI) at 3 Tesla demonstrated periventricular white matter, basal ganglia and subcortical lesions, which were high signal intensity on both T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Some of these lesions showed cavitation and slight diffusion restriction. There were also high signal intensity foci with cavitary lesions in the corpus callosum. In addition, there were multiple parenchymal hemosiderin deposits representing sequelae of a previous microbleed (Figure 1). MRI of the whole spine and cerebral arteriography were normal (Figure 2). Cerebrospinal fluid (CSF) examination showed a slightly elevated protein at 0.7 g/L with no cells and absence of oligoclonal bands. A full laboratory work-up including tests for connective tissue disease, vasculitis, brucella, syphilis and paraneoplastic syndrome was unremarkable. An audiogram showed a mild bilateral sensorineural hearing loss (Figure 3).

With the confirmation of cerebral, cochlear and retinal involvement, a diagnosis of SS was made. In addition, the diagnosis of MS was excluded, and interferon therapy was discontinued. She was given a second course of pulse steroid therapy (1g of intravenous methylprednisolone per day for five days) followed by oral prednisolone at 1 mg/kg/day with gradual tapering. She was also started on azathioprine 100 mg/day. Despite the advanced clinical and radiological stage of the disease, fortunately, the patient showed a good response with an improvement of all clinical parameters including cognitive, visual, cochlear, motor and behavioural aspects. She was seen in the clinic two months following discharge from the hospital walking and satisfied. She is currently on a small dose of steroids (5 mg of prednisolone daily) and azathioprine (150 mg daily). In addition, she was given aspirin, carbamazepine and atorvastatin.



Figure 2. Magnetic resonance imaging of the spine showing normal features.

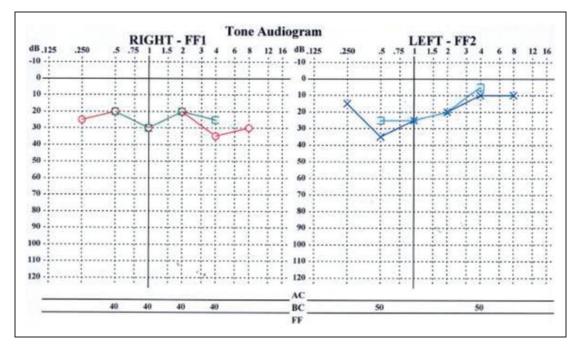


Figure 3. Audiometry showing a mild bilateral sensorineural hearing loss.

# Discussion

The pathogenesis of SS remains unknown. However, it is believed to be an autoimmune disorder leading to endothelial inflammation and causing occlusion of the microvessels in the brain, retina and inner ear. In this disorder, only the precapillary arterioles with a size less than 100  $\mu$ m are affected. The pathogenesis involves swelling of the endothelial cells and the basal membrane, leakage and lymphocytic infiltration of the vessel wall, and luminal deposition of the thrombotic material causing occlusion of the vessel<sup>3</sup> (Figure 4).

It is well known that autoimmune disorders are usually more prevalent in women, and SS was similarly found in several studies to be more common in women, with a male to female ratio of 1:3.5. It affects young patients aged 20–40 years, but it can occur at any age, including children, adolescents and adults over 50 years of age. It can affect all races including American, European and Asian populations.<sup>4</sup> To the best of our knowledge, this is the first case of SS reported from Saudi Arabia. To date, less than 400 cases have been reported in the literature.<sup>5</sup> The exact prevalence remains unknown. However, this disorder could be underdiagnosed and puzzling. Using Google search, the term 'Susac syndrome' yielded a total of 44,600 results, which is much less than the term 'multiple sclerosis', which yielded a total of 22,700,000 results.

The clinical presentation of SS is variable, ranging from a very subtle to a quite extensive disease.

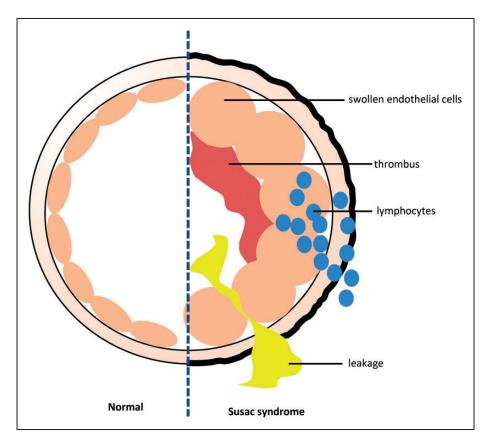


Figure 4. Diagram showing the possible pathogenesis of Susac syndrome that involves swelling of the endothelial cells and the basal membrane, leakage and lymphocytic infiltration of the vessel wall, and luminal deposition of the thrombotic material causing occlusion of the vessel.

It typically starts as subacute encephalopathy with headache and non-specific neurological symptoms. Later, other manifestations develop including impaired cognition, memory loss, vertigo, dysarthria, ataxia, corticospinal tract dysfunction, hemiparesis and mood changes. Other features include seizures and psychiatric disorders with personality changes and paranoid behaviours (75% of patients).<sup>6</sup> Although SS is classically characterised by the clinical triad of encephalopathy, retinopathy (BRAOs) and hearing loss, the concomitant appearance of the triad is relatively rare, which often leads to the initial misdiagnosis. The visual symptoms include a sudden visual loss or blurred vision, with visual field abnormalities depending on the affected region and the number of arterial occlusions. The hearing loss may be mild or very severe, unilateral or bilateral, depending on the area of infarction. Most of the published cases in the literature demonstrated loss of lower frequencies on pure tone audiometry.4,7

MRI is the neuroimaging modality of choice for diagnosing SS. However, findings on MRI can mimic other neurological disorders such as MS and acute disseminated encephalomyelitis (ADEM). In SS, MRI demonstrates numerous multifocal high signal intensity lesions on T2-weighted and FLAIR images in the white and grey matter. Involvement of the grey matter would differentiate SS from MS (which is usually limited to white matter) but not from ADEM (which can involve both the white and grey matter). The characteristic shape of the lesions in SS is a punched-out appearance in the corpus callosum, the centrum semiovale, internal capsule, periventricular white matter, brainstem and cerebellum, demonstrating microinfarcts. The central callosal holes are considered pathognomonic for SS in the presence of an appropriate clinical setting. When lesions of the corpus callosum are observed, the suspicion of SS should be high, especially when there are coexisting ophthalmological or auditory abnormalities.<sup>8</sup> In addition, diffusion tensor imaging typically shows widespread fibre impairment.9 Ultrahigh MRI at 7 Tesla has been reported to be a useful tool for understanding the pathogenesis of SS and distinguishing MS lesions from SS lesions in terms of the perivascular localisation, the presence of a hypointense ring and the frequency of CSF isointense lesions.<sup>10</sup>

Fluorescein angiography is a useful examination, which may show BRAO, and in many cases enables the final diagnosis to be made. However, BRAO may not be seen in the early stages of the disease. In the acute presentation of the disease, BRAO may appear with Gass plaques, which are retinal refractile arterial wall plaques at the mid segments of the retinal arterioles, and it may also be accompanied by a multifocal

Table	1.	Diagnostic	criteria	for	Susac	syndrome.
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1	The presence of characteristic MRI features of SS (cranial MRI – hyperintense, multifocal, round small lesions, at least one of them in the corpus callosum ('snowball') in T2 (or FLAIR) weighted sequences)		
2	Encephalopathy (new cognitive impairment and/or behavioural changes and/or new focal neurological symptoms and/or new headache)		
3	Retinopathy (BRAOs or arterial wall hyperfluorescence in fluorescein angiography or characteristic signs of retinal branch ischaemia in funduscopy or spectral domain optical coherence tomography)		
4	Vestibulocochlear involvement (new tinnitus and/or hearing loss and/or peripheral vertigo with classic findings on audiogram of sensorineural hearing loss)		
5	Woman between the ages of 20 and 40 years		
6	Pregnant or one year postpartum		
Probal	te SS: 1–4 must be present ble SS: one and two of 2–6 must be present le SS: one and one of 2–6 must be present		

MRI: magnetic resonance imaging; SS: Susac syndrome; FLAIR: fluid-attenuated inversion recovery; BRAO: branch retinal artery occlusion. From Kleffner et al.,<sup>13</sup> with permission.

distinctive staining of the vessels. The changes are usually bilateral, dominate early, or may occur later in the course of the disease.<sup>11</sup> Optic coherence tomography is an additional useful tool for the diagnosis, and it shows a severe and distinct retinal or retinal nerve fibre layer damage that is more severe than in MS.<sup>12</sup>

Other important investigations include an audiometry, laboratory studies and CSF analysis. The audiometry will typically show sensorineural hearing loss involving the low and mid-frequency tones. Laboratory studies may be indicated in some patients, including patients with suspected connective tissue disorders, antiphospholipid antibody syndrome, or vasculitis. The CSF analysis typically shows an elevated protein and a variable degree of lymphocytic pleocytosis. CSF oligoclonal bands are usually absent, which helps in differentiating SS from MS.<sup>4,7</sup>

The diagnosis of SS may be difficult initially, and a high index of suspicion must be present (Table 1).<sup>13</sup> The classic triad of SS is absent in 97% of patients at the time of onset of symptoms. This clinical triad may become complete after a delay of months to more than two years. There are several differential diagnoses including MS, ADEM, systemic lupus erythematosus, antiphospholipid syndrome, vasculitis, stroke, complicated migraine, sarcoidosis, neuro-Behçet disease, Marchiafava–Bignami disease and cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.<sup>14</sup>

To date, there are no treatment guidelines for SS, and most strategies used are based on clinical experience, case series and case reports. The initial treatment of the acute presentation of SS should be aggressive and includes intravenous methylprednisolone (1000 mg daily for five days) followed by oral steroids (1 mg/kg daily). Oral steroids should be tapered slowly guided by the type and course of the disease and clinical response. A commonly used strategy is to give a high dose of steroids for two to four weeks then tapering 10-15% every two weeks down to 10-15 mg every morning. After six months, a slower tapering (2.5 mg every month) is used until the medication is stopped. Intravenous immunoglobulins pulsed every four weeks for several months can be useful in severe cases. The long-term treatment is usually an immunosuppressive medication including cyclophosphamide, mycophenolate mofetil, rituximab, or azathioprine. In addition, aspirin should be added to the treatment to reduce the procoagulopathic state. Patient education should be provided regarding the side effects of immunosuppressive therapy, the risk of infertility and the possible need for vaccination. For patients with severe hearing loss, cochlear implants may be useful for improvement of the quality of life.<sup>15</sup> Further studies are needed into the optimal treatment of SS.

Our patient was misdiagnosed as having MS for three years and was treated with interferon beta-1, with deterioration in her condition. This clinical deterioration could be either worsening of the underlying disease or autoimmune dysregulation due to the medication. Our experience is similar to that of Laird et al.<sup>16</sup> who reported a 23-year-old man with SS who was initially misdiagnosed as having MS with exacerbation of the disease by this medication.

## Conclusion

We described a patient who was diagnosed as having MS for three years, with further deterioration after starting treatment with interferon beta-1a. The patient had the triad of encephalopathy, BRAO and sensorineural hearing loss. She had the classic MRI appearance with normal MRI of the spinal cord and absence of oligoclonal bands in the CSF. Our patient responded well to treatment with a combination therapy and discontinuation of interferon beta-1a. Our observations raise awareness about the importance of the early and correct diagnosis of SS which usually affects young patients, with an excellent prognosis if treated aggressively at an early stage of the disease. SS is underdiagnosed and is not uncommonly misdiagnosed as MS. SS is a great mimicker of MS, and establishing diagnostic criteria for this syndrome is very useful. In any patient presenting with a progressive disabling neurological disorder associated with callosal lesions, and/or hearing loss, and/or visual loss especially in women, SS should be suspected.

#### **Conflict of interest**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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