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## Two Sisters with Leukoencephalopathy, Hearing Loss and Retinopathy: A Familial Case of Susac's Syndrome?

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### Authors' contributions

*This work was carried out in collaboration between all authors. Authors AG and MDB conceived and assembled the final version of the manuscript; they also have full responsibility for the work, had access to the data, and controlled the decision to publish. Author FG collected clinical data and drafted the manuscript. Authors SP, FC, SF and FF collected clinical data and revised the manuscript. Author SM revised the manuscript for important intellectual contents. Authors AB and CL performed and described the immunological analysis and revised the manuscript.*

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**Case Study**

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## ABSTRACT

**Aims:** Susac's syndrome is a rare clinical entity characterized by encephalopathy, sensorineural hearing loss and retinopathy caused by immune-mediated arteriole occlusion in the brain, retina and inner ear. No familial cases have been reported. We describe here the cases of two sisters who were seen at our Department for subacute neurological symptoms suggestive of a multifocal central nervous system disorder associated to hearing impairment and clinical or subclinical involvement of visual function.

**Presentation of Cases:** The first case presented with a two-years history of progressive paraparesis, gait ataxia and cognitive dysfunction started at age 46; she also suffered from epileptic seizures since childhood and bilateral visual loss occurred between age 37 and 38. Her sister, aged 44, had a long-standing history of headache followed by sudden-onset bilateral hearing loss at age 35, which did not recover, and an acute episode of right-sided face paresthesias nine years later. Brain MRI showed multiple T2-hyperintense supratentorial lesions involving the corpus callosum in both sisters, with "snowball" appearance in the older one. Serum anti-endothelial cell antibodies assay was positive in the youngest patient.

**Discussion and Conclusion:** After exclusion of other possible options, a diagnosis of Susac's syndrome looked probable for both sisters. Further studies investigating the pathogenesis and the genetic background of the disease are needed.

*Keywords: Susac's syndrome; familial cases; differential diagnosis; anti-endothelial cell antibodies.*

## 1. INTRODUCTION

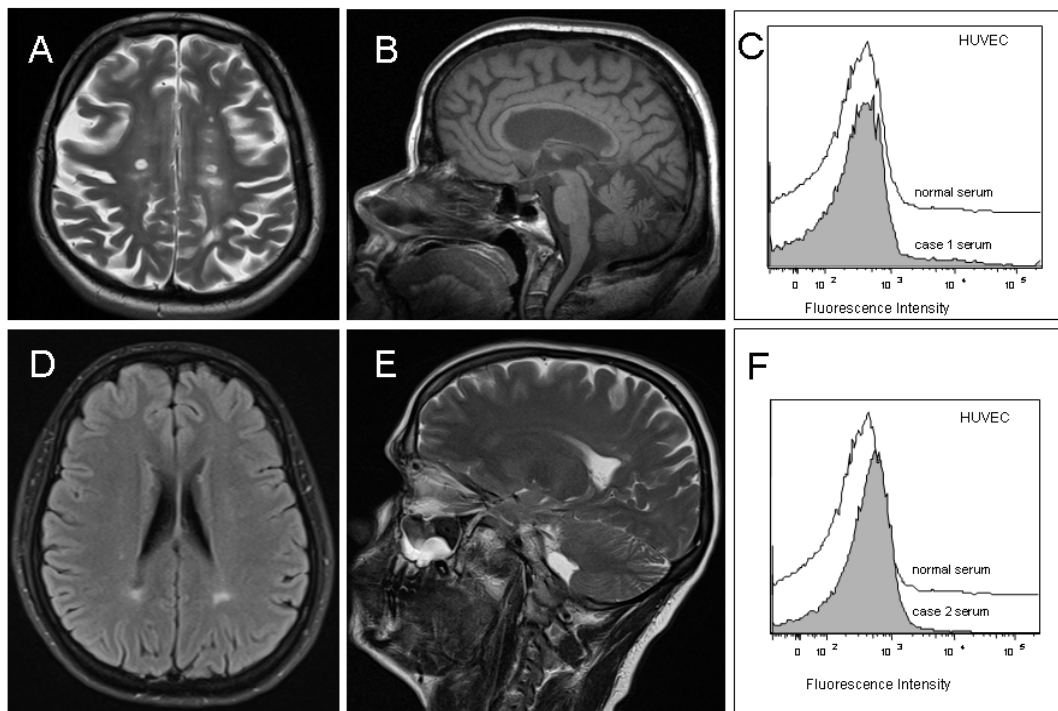
Susac's syndrome is a rare clinical entity characterized by encephalopathy, sensorineural hearing loss and retinopathy caused by immune-mediated arteriole occlusion in the brain, retina and inner ear. No familial cases have been reported. We describe here the cases of two sisters who were seen at the Neurology Unit, Policlinico G. Rossi, Azienda Ospedaliera Universitaria Integrata Verona, Italy for subacute neurological symptoms suggestive of a multifocal central nervous system disorder associated to hearing impairment and clinical or subclinical involvement of visual function.

## 2. CASE REPORTS

### 2.1 Case 1

In March 2013 a 48-years old woman, was admitted to the Neurology Unit for worsening of a gait disturbance started in 2011. Her previous medical history included epilepsy and severe bilateral visual impairment (blindness in the left eye and light perception in the right one) The patient and her family reported that she had an uveitis in the right eye in 2003 and a retinal detachment in left eye in 2004 for which she underwent a fluoresceine angiography (FA); however, no medical reports were available to confirm the diagnosis. In 2004 the patient also started to notice a bilateral hearing impairment and in 2011 she developed subacute walking difficulties with subsequent progressive worsening.

At the time of our first evaluation, the neurological examination showed paraparesis and gait ataxia, mild dysarthria, hyperreflexia and bilateral Babinski sign. The patient needed bilateral assistance for ambulation. Moreover, she had developed cognitive dysfunction.



**Fig. 1. A) T2-weighted axial brain MRI scan of case 1 showing multiple lesions with “snowball” appearance predominantly involving the corpus callosum. B) T1-weighted sagittal brain MRI scan of case 1 showing significant corpus callosum thinning, ventricular enlargement and brainstem/cerebellum atrophy. C) and F) Flow cytometric analysis of serum anti-endothelial cell antibodies. The presence of anti-endothelial antibodies was revealed by the increase of fluorescence intensity of Huvec cells treated with patients’ sera compared to the fluorescence intensity of cells treated with normal serum. Fluorescence intensity is significantly greater in cells treated with case 2 serum than in control (mean fluorescence intensity 375vs283) but not with case 1 serum (298vs283). Representative examples of three independently performed experiments are shown. D) Fluid-Attenuated Inversion Recovery axial brain MRI scan of case 2 showing bilateral irregular lesions in the posterior corpus callosum. E) T2-weighted sagittal brain MRI scan of case 2 showing an ill-defined lesion in the left posterior corpus callosum**

Considering the hypothesis of a primary progressive form of multiple sclerosis (MS), a lumbar puncture was done and CSF analysis showed high IgG index (2.57,  $n.v < 0.70$ ) and positive oligoclonal bands. Serum NMO-IgG assay was negative. Tests for lysosomal enzymes and rheumatologic blood screening were normal (Table 1). Testing for Optic Atrophy 3 (OPA3) gene mutations, which cause a mitochondrial disease compatible with the clinical phenotype of the presented case, was negative. Serum anti-endothelial cell antibodies (AECA) assessed by flow cytometric analysis (see below) resulted negative

(Fig. 1). A 3T brain MRI detected multiple T2-hyperintense lesions with “snowball” appearance, which were not suggestive of typical MS lesions, involving the infratentorial and supratentorial white matter and corpus callosum (the appearance of such lesions was not significantly different compared to the previous MRI scans obtained in 2011 and 2004). Brain atrophy was seen, particularly affecting the corpus callosum (Fig. 1). Cervical spine MRI showed three discrete T2-bright foci spanning over one vertebral segment. None of the brain and cord lesions enhanced after gadolinium. Visual evoked potentials were not recordable. Motor evoked potentials showed bilaterally delayed central conduction time both at lower and upper limbs. Brainstem auditory evoked responses (BAERs) were absent on the right side. Audiometric examination revealed a subtle left sensorineural hypoacusis. In August 2013 the patient started anti-platelet treatment with aspirin 100mg daily. At last follow-up visit of May 2014 she did not report new symptoms and the neurological examination was stable.

**Table 1. Most relevant diagnostic blood and cerebrospinal fluid tests performed in the presented cases**

Test	Case 1	Case 2	Normal range
<b>Blood</b>			
C reactive protein	3.3mg/l	4.1mg/l	<5mg/l
Rheumatoid factor	11U/ml	10 U/ml	<15U/ml
Antinuclear antibodies	Negative	Positive1:80	Negative
Anti-ENA antibodies	Negative	Negative	Negative
Anti-neutrophil cytoplasmic antibodies	Negative	Negative	Negative
Lupus anti-coagulant	1.14	0.86	<1.20
Anti-cardiolipin IgG	8.3U/ml	N/A	<20u/ml
Anti-beta2-glicoprotein IgG	6.4U/ml	N/A	<20U/ml
Anti-aquaporin4 antibodies	Negative	Negative	Negative
Vitamin B12	583pg/ml	N/A	193-982pg/ml
Folates	3.1ng/l	N/A	3.0-15.0ng/l
TSH	1.86mU/l	2.74 mU/l	0.35-4.00mU/l
Lysosomal enzyme activity assay	Normal	N/A	Lab reference range
Very long chain fatty acids	Normal	N/A	Lab reference range
Anti Borrelia B. antibodies	Negative	Negative	Negative
<b>Cerebrospinal fluid</b>			
Protein	0.33g/l	N/A	0.15-0.45g/l
Leucocytes	1/mcl	N/A	<5/mcl
Oligoclonal bands	Positive (CSF restricted)	N/A	absent
Ig G index	2.57	N/A	<0.7
Anti-HSV antibodies	Negative	N/A	Negative
Anti Borrelia B. antibodies	Negative	N/A	Negative

## 2.2 Case 2

In April 2013 the 44-years-old sister of the patient described above, was referred to our Department because of a subacute episode of paresthesias in the right side of the face occurred two months earlier, which resolved with a non-steroid anti-inflammatory drug course. In 2004 she had a sudden-onset bilateral sensorineural hearing loss preceded by

headache. She took steroids without benefit. After this event, recurrence of headache attacks was consistently reported by the patient.

At our first observation the neurological examination showed severe bilateral hearing loss and subtle cognitive impairment. Audiometric examination revealed a severe bilateral sensorineural hearing loss.

A blood diagnostic work-up including blood cell count, liver and renal function, and rheumatologic markers was normal except a weak positive anti-nuclear antibody titer (1:80) as shown in the Table. Since the clinical picture suggested the possibility of a mitochondrial disease, genetic testing for MTTL1 mutations was performed, which resulted negative. Serum AECA assay gave a positive result with the same technique used for the older sister (Fig. 1F). Brain MRI detected multiple small ill-defined T2-hyperintense foci in left frontal and periventricular regions with partial involvement of the posterior corpus callosum and no enhancement after gadolinium; no relevant changes were noted compared to a previous MRI performed in 2004. (Figs. 1D and 1E). Spine MRI was negative. BAERs were absent bilaterally. Motor, visual and somatosensory evoked potentials were normal. Electroretinogram oscillatory potentials were absent in right eye. The patient underwent a FA showing mild bilateral chorioretinal dystrophy. In August 2013 she started aspirin 100mg daily and immunosuppressive treatment with azathioprine 150mg daily, given the positive AECA assay. At last follow-up visit in May 2014 the patient reported no new symptoms and the neurological exam was unchanged.

*Flow cytometric analysis of AECAs in patients' serum.* Huvec cells (Promocell, Heidelberg, Germany) were cultured in Endothelial Cell Growth Medium (Promocell) in a 6 wells plate (BD Biosciences, San José, CA, USA) and used between 6th and 8th passages. Cells were pre-incubated in Phosphate Buffer Saline (PBS) with 10% patient's serum for 30 minutes at 4°C. A pool of normal sera was used as control (Life Technologies, Carlsbad, CA, USA). Cells were then detached with accutase, washed with PBS at 1200RPM for 5 minutes. 100000 cells were stained with allophycocyanin (APC)-conjugated anti-human IgG antibody (Jackson Immuno Research, West Grove, PA, USA) for 30 minutes at 4°C, washed with PBS and acquired on a FACSCanto 2 (BD) and analysed with FlowJo software (Treestar, Ashland, OR, USA).

### 3. DISCUSSION

The two cases reported here show a combination of different degrees of hearing loss, visual system involvement, and brain abnormalities that—taken together—suggest a diagnosis of Susac's syndrome [1]. This condition is a rare immune-mediated endotheliopathy leading to the occlusion of precapillary arterioles of brain, retina and inner ear. Pathological studies reveal endothelial microangiopathy with arteriolar wall proliferation, lymphocytic infarction and basal lamina thickening in the involved tissue [2]. The presence of serum AECA in some patients further supports the hypothesis of an autoimmune pathogenesis. [3]

Susac's syndrome affects women more than men and the age of onset is most frequently between 20 and 40 years. The typical triad of encephalopathy, visual disturbance and hearing loss occurs simultaneously in around 13% of cases at disease onset. Neurological symptoms and signs frequently include (≥20% of cases) cognitive changes (predominantly memory loss and confusion), psychiatric disturbance, headache, gait ataxia, and pyramidal signs. The clinical course may be monophasic, relapsing-remitting or—rarely—progressive (<5% of cases). Audiometry shows sensorineural hearing loss with preferential involvement

of middle and low tones. CSF analysis may reveal mild pleocytosis and oligoclonal bands [3].

Brain MRI usually shows multiple hyperintense lesions on T2-weighted images in supratentorial and infratentorial white matter with round-shaped “snowball” appearance, typically involving the corpus callosum, which is frequently thinned with or without whole brain atrophy [4]. Absence of spinal cord lesions is a typical feature, although symptoms and signs suggestive of spinal cord involvement (e.g. myelopathic sensory disturbance and/or pyramidal signs and urinary dysfunction) are not infrequent [3]. FA typically reveals segmental non-perfused retinal arterioles and staining of the arteriolar wall; in some cases arterial constriction, leakage and perivascular sheathing can also be observed. The presence of Glass plaques are characteristic for branch retinal artery occlusion (BRAO) that is pathognomonic of Susac’s syndrome [5].

Differential diagnosis includes MS, acute disseminated encephalomyelitis, vasculitis, lupus erythematosus, Behcet’s disease, sarcoidosis, Sjogren syndrome, Lyme disease, viral infections, malignancy, mitochondrial disorders, and cerebrovascular disease, which were ruled out in the two cases described, based on clinical picture and work-up results. In the first case presented the contemporary presence of sensorineural hearing loss and encephalopathy (cognitive changes) with brain MRI showing typical snowball lesions—particularly involving the corpus callosum—is suggestive of Susac’s syndrome. Although presence of spinal cord lesions on MRI and CSF oligoclonal bands are not typical findings, they do not exclude the diagnosis. Unfortunately, it was not possible to determine the presence of BRAO on the FA done at visual disturbance onset. However, the severe irreversible visual impairment presented by the patient makes unlikely the reported diagnosis of uveitis and retinal detachment. In the second case severe bilateral sensorineural hearing loss, neurological symptoms (sensory disturbance, headache and cognitive impairment) and MRI findings support the diagnosis of Susac’s syndrome, although the chorioretinal dystrophy observed on FA is not suggestive of retinal arteriole occlusion.

AECAs were positive in the serum of the youngest sister, although the diagnostic relevance of this finding is limited given the low sensitivity and specificity of the assay in the context of Susac’s syndrome [6].

In autoimmune disorders (e.g. rheumatoid arthritis, lupus erythemathosus, etc.) it is relatively frequent to observe cases who have a positive familial history for the disease. This is likely due to a shared multifactorial genetic background providing a predisposition to a given clinical condition in presence of certain environmental triggers. The genetic component of autoimmune diseases is also suggested by gender effect (females are significantly more affected than males, as observed in Susac’s syndrome) and is substantiated by case-control, linkage and genome-wide association studies. Current evidence points at genes implicated in immune system modulation (e.g. major histocompatibility complex, cytokines, and chemokines genes) as the most likely candidates for autoimmune disorders. However, no familial cases of Susac’s syndrome have been reported so far and no genetic studies exist. This may be at least in part explained by Susac’s syndrome being a rare and under diagnosed condition, with many cases likely misdiagnosed as MS.

#### **4. CONCLUSION**

After exclusion of other possible options, Susac's syndrome is the probable diagnosis for both sisters reported in the present paper. This condition should be included in the

differential diagnosis of clinical triad of encephalopathy, retinopathy, and hearing loss. Early diagnosis of the syndrome is enabled by the combination of the ophthalmologic, audiometric, and brain MRI features. No specific treatment exists although it is reported that early immunosuppressive or immunomodulatory therapy may reduce sequelae and improve recovery [3].

Future research should further investigate the pathogenesis and the genetic background of the disease to elucidate its etiology and improve treatment.

## CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

## ETHICAL APPROVAL

Not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Susac JO. Susac's syndrome: the triad of microangiopathy of the brain and retina with hearing loss in young women. *Neurology*. 1994;44(4):591-593.
2. McLeod DS, Ying HS, McLeod CA, Grebe R, Lubow M, Susac JO, Luty GA. Retinal and optic nerve head pathology in Susac's syndrome. *Ophthalmology*. 2011;118(3):548-552.
3. Dorr J, Krautwald S, Wildemann B, et al. Characteristics of Susac syndrome: a review of all reported case. *Nat Rev Neurol*. 2013;9(6):307-16.
4. Susac JO, Murtagh FR, Egan RA, et al. MRI findings in Susac's syndrome. *Neurology*. 2003;61(12):1783-1787.
5. Egan RA, Hills WL, Susac JO. Gass plaques and fluorescein leakage in Susac syndrome. *J Neurol Sci*. 2010;299(1-2):97-100.
6. Jarius S, Kleffner I, Dörr JM, et al. Clinical, paraclinical and serological findings in Susac syndrome: An international multicenter study. *J Neuroinflammation*. 2014;11:46.

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