Case Study

Two sisters with leukoencephalopathy, hearing loss and retinopathy: a familial case of Susac's syndrome?

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 history; anti-endothelial cell antibodies
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.

Case Reports

Case 1. In March 2013 a 48-years old woman, was admitted to our Department 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 she also started to notice a bilateral hearing impairment. At that time she underwent a brain MRI showing multiple round-shaped supratentorial T2-hyperintense lesions that were judged as not correlated to the patient symptoms. In 2011 she was admitted to another institution for subacute appearance of walking difficulties. The neurological examination showed paraparesis and gait ataxia, mild dysarthria, hyperreflexia and bilateral Babinski sign. A brain MRI was repeated, which was unchanged compared to the previous one. The patient refused to undergo further investigations.

At the time of our first evaluation, the neurological examination confirmed the paraparesis and gait ataxia reported two years before, worsened to the point that the patient needed bilateral assistance for ambulation. Moreover, she had developed cognitive dysfunction. Suspecting 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. However, 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 (Figure 1A). Brain atrophy was seen, particularly affecting the corpus callosum (Figure 1B). The 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. Serum NMO-IgG assay was negative. Tests for lysosomal enzymes and rheumatologic blood screening were normal. 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 (Figure 1C).

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. At that time 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. BAERs were absent bilaterally. Rheumathological blood work-up resulted negative. She took steroids without benefit. After this event, recurrence of headache attacks were 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. Brain MRI was unchanged compared to the 2004 scan (Figure 1D and 1E), while spine MRI was negative. 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. Blood diagnostic work-up was normal except a weak positive anti-nuclear antibody titer (1:80). 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 (Figure 1F).

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 1200 RPM 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).

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 erythematosus, 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 underdiagnosed condition, with many cases likely misdiagnosed as MS.

**Conclusion**

After exclusion of other possible options, Susac’s syndrome is the probable diagnosis for both sisters reported in the present paper. 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. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

**References**

1. Susac JO. Susac's syndrome: the triad of microangiopathy of the brain and retina with


Figure legend

**Figure 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 375 vs 283) but not with case 1 serum (298 vs 283). Representative example 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.