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Fulminant Susac syndrome—a rare cause of coma: The history of the fatal course in a young man

Hajar Andour[1], Soufiane Rostoum[1], Yassine Regragui[2], Meriem Fikri[1], Mohamed Jiddane[3] and Firdaous Touarsa[1]

Abstract

Susac syndrome is a rare microangiopathy of indeterminate etiology, presumably autoimmune, characterized by a triad of encephalopathy, sensorineural hearing loss, and branch retinal artery occlusions occurring predominantly in women. The onset and progression patterns are multiple, mainly of three modes. Fulminant evolution is exceptional, rarely reported across literature. We report through this case a Susac syndrome in a young man in whom evolution was fatal. Magnetic resonance imaging is essential to raise the diagnosis and for follow-up, with almost pathognomonic findings, all the more useful as the clinical triad is usually incomplete and as the encephalopathy is the most limiting of the symptoms.

Keywords

Susac syndrome, magnetic resonance imaging, encephalopathy, fulminant

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Introduction

Susac syndrome is an infrequent inflammatory disease of central nervous system (CNS). The pathophysiology involving CD8+ lymphocyte cells is now well established.[1] The autoimmune mediation is at the origin of a vasculopathy affecting the small vessels of the brain, inner ear, and retina. This results in the triad of an encephalopathy of variable severity, exceptionally fatal, a sensorineural hearing loss and branch retinal artery occlusions, usually incomplete, making diagnosis challenging.[2] However, some magnetic resonance imaging (MRI) features are characteristic, particularly the involvement of corpus callosum and their details.[3] We display through this case the main symptoms, the currently established pathophysiology, as well as imaging keys to set the accurate diagnosis and rule out the differential ones as we skim over the essentials of therapy especially in severe cases as ours.

Case report

A 29-year-old man with a history of deafness from childhood presented to emergency department with severe headaches and confusion for 3 days. Visual disorders were also reported but difficult to assess in this condition in particular because of communication difficulties and the absence of evident complaining.

Neurological examination showed a temporospatial disorientation. Ophthalmologic examination was performed but incomplete due to patient's prostration. A fundoscopic examination with retinal fluorescein angiography was scheduled as soon as improvement occurred.

The diagnosis of hearing loss went back to the young age and has been reported according to family as a perception disorder, but undocumented, with no hearing prosthesis. The opinion of an otolaryngologist was requested—this one ruled out obvious involvement of the outer and middle ear and confirmed bilateral sensorineural deafness without the possibility of immediate additional examinations.

Cerebrospinal fluid (CSF) analysis showed a slight elevated protein level (0.57 g/L) with a totally lymphocytic

[1]Department of Neuroradiology, Specialty Hospital, Rabat, Morocco
[2]Department of Anesthesiology and Reanimation, Ibn Sina Hospital, Rabat, Morocco
[3]Head of Department of Neuroradiology, Specialty Hospital, Rabat, Morocco

Corresponding Author:
Hajar Andour, Department of Neuroradiology, Specialty Hospital, Hay Riad, Rabat 10100, Morocco.
Email: hajarandour1@gmail.com

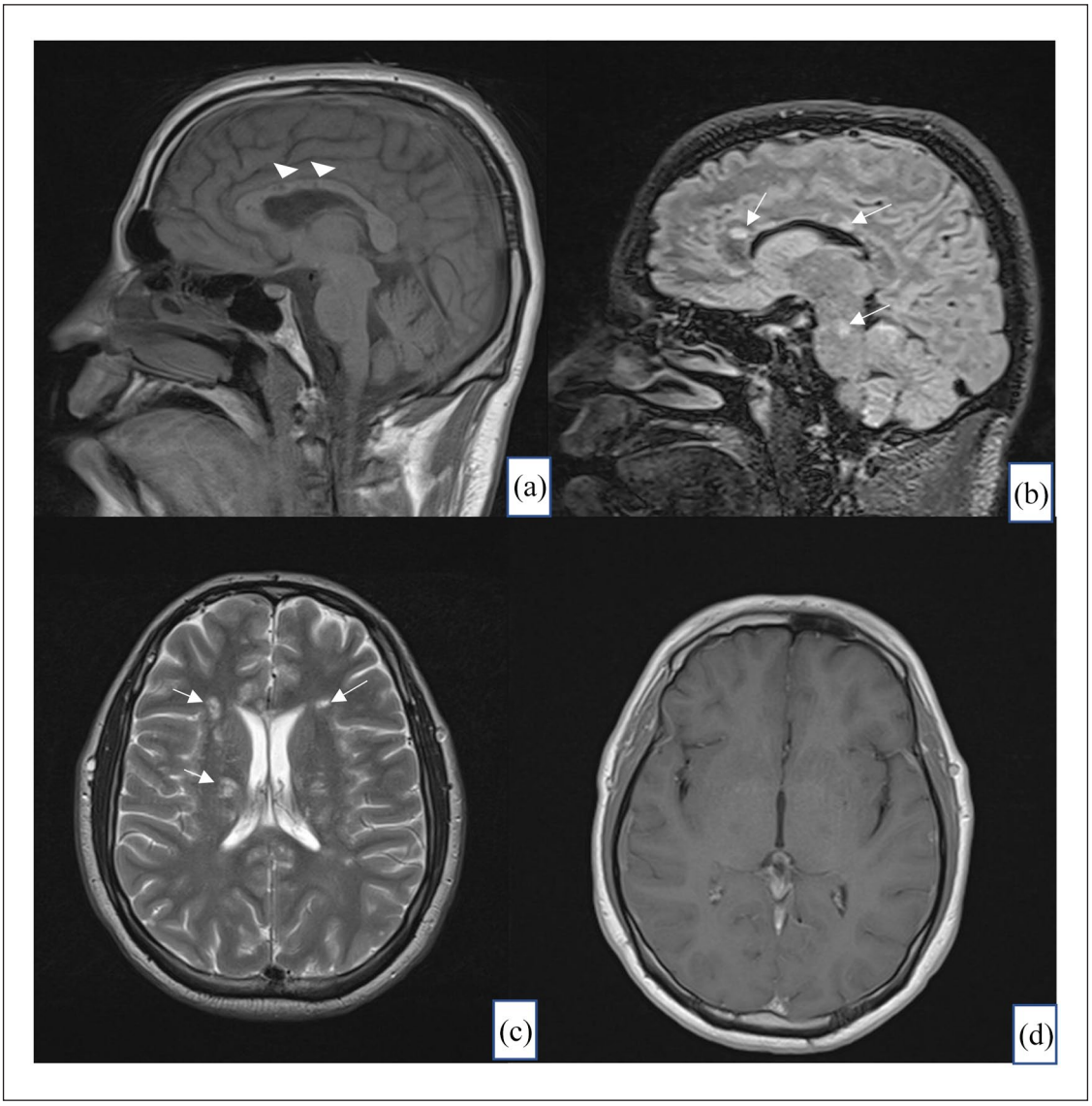

Figure 1. Brain MRI according to sagittal T1 (a), sagittal FLAIR (b), axial T2 (c) and axial T1 with Gadolinium injection (d) showing small lesions in corpus callosum (a; arrowhead) in hypersignal FLAIR including in the midbrain (b; arrows), periventricular (c) with no contrast enhancement at gadolinium injection (d).

pleocytosis of 15 leukocytes/mm^3. The glucose level was normal at 0.6 g/L recorded concomitantly with a glycemia of 1.28 g/L. The screening of oligoclonal bands was negative. Other laboratory tests were all unremarkable. Blood screening for infections and common vasculitis was performed but was also negative.

The angio-computed tomography (CT) was normal. A brain MRI was performed and showed multiple small lesions central in the corpus callosum, periventricular in the hemispheres, in the deep gray nuclei, and in the midbrain low intensity on T1-weighted sequences. The same lesions corresponded to high-signal abnormalities on T2 and fluid attenuated inversion recovery (FLAIR)-weighted sequences with no restriction on diffusion-weighted imaging (DWI). There was no enhancement on T1 post-contrast sequences. In light of this clinical presentation, a Susac syndrome was evoked (Figure 1(a)–(d)). During hospitalization, neurological status worsened and a second MRI was decided and this one revealed more extensive lesions (Figure 2(a)–(e)). Close monitoring and corticosteroid therapy, consisting of 1 g per day of intravenous methylprednisolone for 5 days, were instituted associated with a pulse of intravenous immunoglobulin at a dosage of 2 g/kg with less than 3 days of overlap between the two therapies; however, the patient became unconscious with the onset of respiratory distress which required his transfer to intensive care where he was intubated. His clinical condition was rapidly complicated by sepsis limiting the use of immunosuppressive drugs and death occurred 10 weeks later.

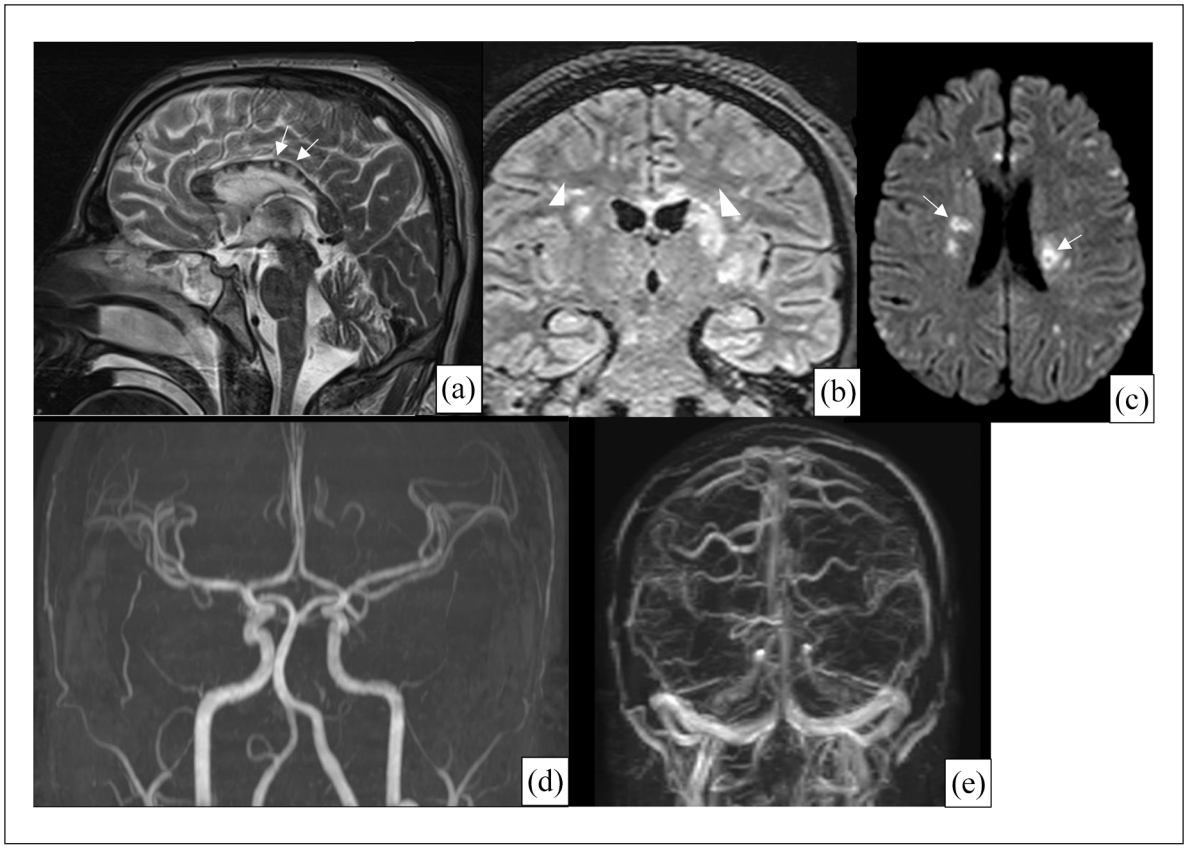

Figure 2. Second brain MRI performed in front of worsening symptoms showing extensive increased size and number lesions with the same characteristics on sagittal T2 (a; arrows) and coronal FLAIR (b; arrowhead)–weighted images, some of which with a restriction on diffusion-weighted images (c; arrows) and with no abnormalities at angiographic sequences (d, e).

Discussion

First described in 1979 by Susac, this syndrome is also known under the acronyms of SICRET standing for Small Infarcts of Cochlear, Retinal and Encephalic Tissues or RED-M for Retinopathy, Encephalopathy, and Deafness associated Microangiopathy. It is a rare vasculopathy, presumably autoimmune, affecting brain, inner ear, and retina predominantly in women, with an average age between 23 and 40 years, but seems to be underdiagnosed with increasingly main features recognized.[4–6]

The clinical classic triad of encephalopathy, BRAO (Branch Retinal Arteries Occlusions), and hearing loss is pathognomonic but rarely complete at the onset. Cerebral symptoms could be severe, migraine-like headaches with aura or psychiatric symptoms (depression, maniac access, or psychotic disorders). Disorientation and confusion are common features of these encephalic disorders in serious cases[7] but rarely lead to obtundation, thus could be probably a factor of poor outcome, especially as encephalopathy is the most limiting symptom. Likewise, they mask other triad elements as we found to be the case in our patient.

Ocular disorders like visual blurring are present when the posterior pole of retina is involved, while they can be totally asymptomatic if arterial occlusions are peripheral. Fundoscopic examination shows sometimes an ischemic edema, with possible Gass plaques and cotton wool spots. Retinal fluorescein angiography is the ophthalmic test to confirm arteriolar branch occlusions and capillary leaks compatible with a vasculopathy. Usually there is no uveitis or hemorrhage as was the case during our patient's initial screening.[8]

Hypoacusis attributed to infarctions in the cochlear apex is often acute, bilateral, and asymmetrically associated with vestibular hyporeflexia. Audiometry reveals a perception hearing loss predominantly in low frequency range.[9]

The pathophysiology of Susac syndrome, which has long been the subject of controversy, is now much more clarified. The main mechanism of this neuroinflammatory disease is an oligoclonal expansion of terminally differentiated activated $CD8^+$ cells (CTL). The resulting endotheliopathy causes vascular leakage and small ischemic lesions primarily in the corpus callosum, inner ear, retina, and cerebellum. This mechanism constitutes the primum movens for new investigations concerning therapeutic opportunities.[1] Disseminated cortical anatomic microlesions under MRI resolution capacities explain the impressive symptoms of diffuse encephalopathy contrasting with the absence of

Table 1. Useful differential criteria at imaging and biology in SS, MS, and ADEM.

	SS	MS	ADEM
Imaging	- Central involvement of corpus callosum - No medullary involvement - Deep gray matter lesion - Possible parenchymal enhancement with miliary appearance in cerebellum - Possible leptomeningeal enhancement	- Peripheral fibers and perpendicular to CC, ependymal undersurface - Presence of spinal cord lesions - No deep and gray matter lesions - Enhancement of active areas of inflammation	- No involvement of callososeptal interface - Possible spinal cord involvement - Gray matter and cortical involvement—Deep juxtacortical lesions more than periventricular - Possible enhancement in active lesions
CSF analysis	- No OBCs - High protein level in CSF analysis with discrete pleocytosis	- Oligoclonal bands - Unlikely high protein level or high count cell in CSF	- Unlikely OCBs - Less frequent high protein levels and pleocytosis than SS

SS: Susac syndrome; MS: multiple sclerosis; ADEM: acute disseminated encephalomyelitis; CSF: cerebrospinal fluid; OBC: oligoclonal bands; CC: Corpus Callosum.

radio-clinical correlation. Cerebral and retinal capillary leak phenomena are a presumed cause of the enhancement on injection of gadolinium at the beginning of the acute phase and of their reversibility.

Although the clinical triad of encephalopathy, hearing loss, and BRAO is pathognomonic for SS, it could take several years before getting complete. Other examinations are not specific; angio-CT and arteriography are normal. CSF analysis generally shows predominantly lymphocytic pleocytosis with the absence of oligoclonal bands invalidating multiple sclerosis (MS), but a normal number of cells in CSF is still possible in Susac Syndrome (SS). Brain MRI is thus a cornerstone for the diagnosis, revealing lesions of the white matter, involving the periventricular regions, the semi-oval center, the subcortical region, and the corpus callosum. The involvement of corpus callosum is almost pathognomonic with numerous small well-limited lesions (3–7 mm) becoming confluent as they enlarge ($>$7 mm) taking an appearance of "wheel spoke" or "snowball" or "stalactite" at the central fibers. These abnormalities are in hyposignal on T1 sequences and hypersignal on T2 and FLAIR-weighted sequences. On follow-up imaging, callosum lesions are taking a punched-out appearance representing micro-infarctions. Infratentorial lesions are less common than supratentorial ones and are observed in the cerebellum, followed by the brainstem and middle cerebellar peduncles as was the case in our patient. The important radiological features of SS, very useful for differential diagnosis are lesions of deep gray basal ganglia and thalamus. They could be encountered in 70% of cases, suggesting extensive lenticulostriate arteries lesions when taking the appearance of "giant lacunes." Gadolinium enhancement can be seen in active lesions as well as some cases of hypersignal at DWI in early lesions. Leptomeningeal enhancement is a very relevant differential criterion appearing in 30% of cases on post-gadolinium T1 sequences[10,11] and in 100% of cases on post-gadolinium FLAIR sequences emphasizing the importance of their use.[12]

Several diagnoses could be evoked in front of such signal abnormalities, but the most prevalent and plausible are those of MS and acute disseminated encephalomyelitis (ADEM); however, radiological features are different.[3] Although corpus callosum could be involved at any part, lesions are more likely to be central in Susac syndrome relatively sparing periphery and unlikely to affect the undersurface or callososeptal interface which is more a feature of MS. Deep gray lesions are an important radiological finding in SS, not met in MS. They involve different sites than those observed in ADEM, which is more frequent in children and where these lesions are mainly of thalamic site. Moreover, leptomeningeal enhancement reported in literature is another differential feature that is sometimes seen in SS but is not occurring either in MS or in ADEM.[7] The main differential imaging findings are summarized in Table 1.

Criteria for the diagnosis of SS had been proposed. They include clinical and paraclinical items for each organ of the triad. Thus, according to symptoms and paraclinical findings, the diagnosis of SS can be definite, probable, or the most probable.[13] In the case of our patient, as hearing loss goes back to childhood and as the ophthalmologic examination could not be performed due to altered consciousness, the diagnosis of SS is probable, especially in front of complete typical criteria of brain involvement.

Although different reports summarize the evolution of Susac syndrome in three general patterns which are monocyclic with an active period $\leqslant$2 years, polycyclic with alternating phases of remission over a period of more than 2 years, and chronic continous,[14] the natural history of SS is still not well elucidated. Indeed, because of its scarcity, all studies concerning this syndrome are retrospective, and the most complete one concerns 304 patients[2] whose average duration of follow-up did not exceed 46 months, whereas some exacerbations or relapsing of the disease was reported years after the onset. The underestimation of this polycyclic natural history calls into question the true frequency of the monocyclic mode.[15]

Follow-up of SS should be adapted to each case, the major criterion determining its frequency is the stability or no of the patient. It will be based according to the presented symptoms on brain MRI, fundoscopic examination, nay retinal angiography, visual field, audiogram, and, in the ultimate case, a lumbar puncture, if deemed necessary.

Evolution of brain MRI images has been reported to not have a correlation with the clinical symptomatology and does not allow the prediction of later exacerbations. In successfully treated patients, a normalization of DWI within 3 months and a decrease in hypersignal T2-FLAIR lesions over time have been remarked with a possible late atrophy of corpus callosum. Fatal course is exceptional, reported in literature no more than 3 times to date, where the only man's death was more related to levamisole's effect rushing evolution.[16] To our knowledge, this is the first case of a young's man death by Susac syndrome occurring with no history of drug addiction. Imaging findings in the fatal syndrome seem to not show a different appearance apart from extensive lesions with restriction on DWI and possible enhancement.

Fatal course is invariably due to encephalopathy with few reported cases of death in the literature.[16,17] It occurs in around 12 weeks which raises the question of the need to intensify therapy in this period in front of a worsening outcome. Furthermore, studies are required as there is no consensus about therapy in SS with controversies over the choice of molecules in the "acute phase."

Conclusion

Susac syndrome is a potentially fatal inflammatory disorder of CNS with a characteristic clinical triad usually incomplete, thus highlighting the importance of radiological findings in the diagnosis. Brain MRI is the imaging modality of choice in the presence of neurological manifestations, with characteristic callosal lesions. Differential diagnoses are variable, but they can be excluded by a summary based on clinical arguments, laboratory tests, and imaging results. The evolution is generally benign; however, a fatal course is not exceptional and requires aggressive therapy.

Author contributions

All authors participated actively to elaboration of this scientific document:

The first author, who is the correspondent one: wrote the text, communicated with the intensive care unit and followed the course of the patient.

The second author contributed to set the diagnosis and to write the manuscript.

The third author was the intensive care physician directly responsible for the case.

The other authors set the diagnosis and the latest one, in addition, corrected the manuscript.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

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ORCID iD

Hajar Andour https://orcid.org/0000-0003-0736-386X

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