Susac syndrome

A differential diagnosis for demyelination

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ABSTRACT

متلازمة سوساك هي اعتلال الأوعية الدقيقة لسبب غير معروف. ربما بسبب تأثير المناعة الذاتية على الشعيرات والشرايين السابقة للشعيرات للدماغ، وشبكية العين، والأذن الداخلية. وغالبا مايتم تشخيصها بشكل خاطئ على أنها التهاب الدماغ والنخاع المنتشر الحاد، أو التصلب المتعدد. نستعرض في هذه المقالة حالة شاب يبلغ من العمر 25 عاماً مصاب بمتلازمة سوساك ومجموعة ثلاثية من المشاكل الصحية (اعتلال دماغي، ومشاكل بصرية، وسمعية) على مدى عامل كامل. أظهرت أشعة الرنين المغناطيسي إحتشاء في الدماغ، واكتناف ثقفي فيوي مركزي مدعوم بانسداد متفرع للشرايين الشبكية وذلك في تصوير الأوعية الشبكية فلوريسين. أغلبية المرضى المصابين بمتلازمة السوساك لاتستمر معهم الاعتلالات والمشاكل السريرية هذه في البداية. في النهاية، يتطلب من الأطباء وأطباء الشعة توخي الحذر لدى المرضى المصابين بأي من هذه المشاكل الثلاثية والحذر عند تشخيصهم في التصوير المغناطيسي للاعتلال العصبي القطعي. يجب متابعة هؤلاء المرضى لمضاعفات لاحقة لانسداد في شريان الشبكية ممكن أن تحدث لهم، حتى وإن كانت اختبارات العيون لديهم طبيعية.

Susac syndrome is a microangiopathy of unknown origin, probably autoimmune, affecting capillaries and precapillary arterioles of the brain, retina, and inner ear. It is often misdiagnosed as acute disseminated encephalomyelitis or multiple sclerosis. We report the case of a 25-year-old male with Susac syndrome who developed the clinical triad of encephalopathy, visual and hearing problems over the course of a year. The characteristic MRI findings including central corpus callosal involvement and brain infarctions were supported by branch retinal arterial/arteriolar occlusions on fluorescein retinal angiography. Most patients with Susac syndrome will not have the complete clinical triad initially. A very high index of suspicion is required by the clinician and radiologist in patients with any component of the clinical triad so as not to misdiagnose the MRI findings for demyelination. Even if initial ophthalmologic examinations are normal, these patients should be followed up for later development of branch retinal artery occlusions.

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Susac syndrome is a microangiopathy of unknown origin, probably autoimmune, affecting the precapillary arterioles of the brain, retina, and inner ear.[1] Susac syndrome has characteristic MR imaging findings including central corpus callosal involvement and features of infarctions, which is supported by branch retinal arterial/arteriolar occlusions in fluorescein angiography (FA). Most patients will not have the complete clinical triad at initial presentation and may take 2 weeks to 2 years for the triad to develop. Even if the initial funduscopic and fluorescein angiographic examinations of the retinal arteries/arterioles are normal, the patients with these characteristic MRI findings and clinical symptoms should be followed up by ophthalmologic examinations for later development of branch retinal artery occlusions. Cerebral angiography is not indicated as the larger vessels evaluated by angiography will be normal. Aggressive treatment may prevent sequelae, and early diagnosis requires a high index of suspicion on the part of the radiologist and referring physician.

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The educational objective of this article is to make the physician aware of this rare syndrome, which could be misdiagnosed and treated as the much more common demyelinating disease entities by the unwary.

Case Report. A 25-year-old white male with no significant prior illness presented with diffuse headache, behavioral changes including frequent outbursts of laughter, photophobia, and hearing loss. The patient was admitted to the neurology service and one gram daily intravenous (IV) methylprednisolone (SoluMedrol, Pfizer Inc., New York, NY, USA) was initiated. Extensive blood and CSF studies were performed. The CSF studies revealed a glucose of 66, protein of 201, white blood cells of less than one, 0 red blood cells, and negative cultures. The CSF was also negative for oligoclonal bands. An electroencephalogram showed features of encephalopathy. Brain MRI showed large T2/FLAIR hyperintense lesions in the splenium and large round "snow ball" like lesions in the anterior body/genu of corpus callosum and also in the dorsal brain stem. Linear "spoke wheel" pattern lesions were also present in the anterior corpus callosum (**Figure 1A**). There were multifocal periventricular, deep, and subcortical white matter lesions (**Figure 1B**). The left middle cerebellar peduncle also showed hyperintense lesions. Post gadolinium images showed partial enhancement of the splenial lesion and also multifocal leptomeningeal enhancement most prominent in the cerebellum (**Figure 1C**). Many of the lesions showed diffusion restriction including the periventricular white matter and splenium of corpus callosum lesions (**Figure 1D**). Cervical spine MRI was normal. The presumptive diagnosis at this time was acute disseminated encephalomyelitis (ADEM). At this point, the ophthalmology service was not involved. He was treated with intravenous steroids (one gram of methylprednisolone per day for 5 days) and 5 days of plasma exchange, and over the next 48-72 hours showed a significant improvement in his mental status (appropriate speech, improved alertness, and orientation), and in his ataxic gait. His hearing remained permanently impaired, and an audiogram showed the hearing loss to be sensorineural in nature. He was discharged home after a brief stay in the rehab hospital on 60 mg of prednisone (generic), which was tapered over the following 3 months. However, in the ensuing 6 months, the hearing loss progressed, with associated tinnitus and dizziness. He received another course of high dose one gram IV methylprednisolone daily for 5 days, and was discharged on 60 mg of oral (PO) prednisone to be tapered over the next 3 months. A repeat brain MRI showed significant interval

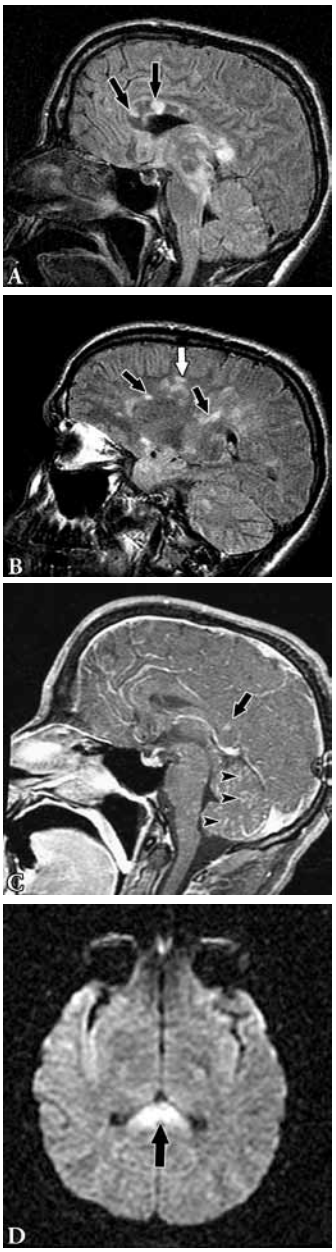

Figure 1 - Patient MRI showing **A)** Sagittal FLAIR MRI at initial presentation shows multiple hyperintense small and large callosal microinfarctions with characteristic round "snowball" like lesions (arrows) in the anterior corpus callosum. Note the linear "spoke wheel" pattern hyperintense lesions in the anterior corpus callosum in between the snowball like lesions. **B)** Parasagittal FLAIR MRI shows periventricular, deep (black arrows) and subcortical (white arrow) white matter hyperintense lesions. **C)** Post contrast sagittal T1W MRI shows partial enhancement of the corpus callosal splenial lesion (arrow). Also, note the leptomeningeal enhancement, which is most prominent in the cerebellum (arrowheads). **D)** Axial diffusion weighted MRI shows diffusion restriction in the splenium of corpus callosum lesion (arrow).

reduction of the multifocal lesions with resolution of the parenchymal and leptomeningeal enhancement. Noticeably the enhancement of the splenial lesion had resolved and appeared hypointense in postcontrast T1 weighted images (**Figure 2**). The diffusion restriction had also resolved. He was successfully tapered off of the oral prednisone and symptoms remained stable until one year after initial presentation, when he again developed a headache, gait instability, blurred vision, photopsias, and worsening personality changes. He was admitted, and the ophthalmology service was consulted. On examination, his visual acuity was 20/25 in the right eye and 20/20 in the left eye with normal color vision and mildly constricted confrontational fields. Pupils were equal, and reactive to light without a relative afferent papillary defect. Ocular motility was normal. The MRI at this time showed increased multifocal acute and chronic lesions including the white matter and corpus callosum. The T1 weighted images showed multiple small central callosal holes (**Figure 3A**), which was highly suggestive of microinfarcts instead of demyelination. There was new diffusion restricting lesions in the splenium of corpus callosum, cerebellum, and right middle cerebellar peduncle. There were new small scattered nodular multiple leptomeningeal and parenchymal foci of enhancement (**Figure 3B**). Cerebral digital subtraction angiogram was normal. Funduscopic exam and FA showed multiple areas of retinal ischemia bilaterally consistent with compromised branch retinal artery blood flow. The cervical spine MRI was again normal. A diagnosis of Susac's syndrome was made. He received 5 days of high dose steroids, 5 days of IV immunoglobulin (IG), and was started on mycophenolate mofetil (CellCept, Genentech, San Francisco, CA, USA) 500 mg PO twice per day, which was titrated to a target dose of one gram 3 times per day as an outpatient. He was also placed on 60 mg PO prednisone daily at discharge with the plan to taper over 6 months. He remained on CellCept one gram 3 times per day and prednisone 20 mg daily. His visual and mental status symptoms have remained stable, however, he had worsening ataxia. The hearing loss never improved, and he underwent a cochlear implant several months later. At the time of manuscript submission, his neuro-immunologist was considering starting monthly cyclophosphamide (Cytoxan, Bristol-Myers Squibb, Princeton, NJ, USA) infusions due to inefficacy of the current oral therapy.

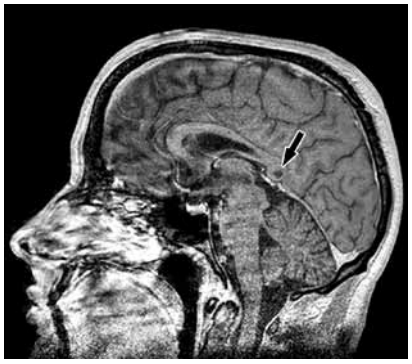

Figure 2 - Sagittal postcontrast T1W MRI at 6 months follow-up shows disappearance of contrast enhancement and the hypointense signal of the lesion in the splenium of corpus callosum (arrow).

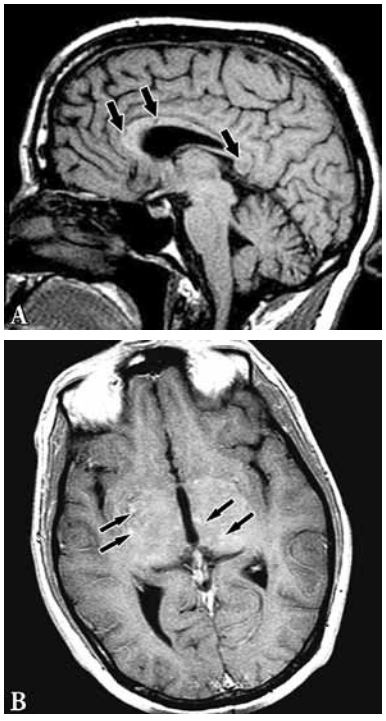

Figure 3 - Patient MRI showing: **A**) Sagittal T1W MRI one year after the initial study shows multiple small "central callosal holes" (arrows). **B**) Post contrast axial T1W MRI shows new small scattered nodular multiple foci of enhancement (arrows).

Discussion. Susac syndrome is a microangiopathy of unknown origin, probably autoimmune, affecting the capillaries and precapillary arterioles of the brain, retina, and inner ear. Microinfarctions have been shown to be the basic pathology in brain biopsy; and endothelial changes that are typical for antiendothelial cell injury have been implicated.[1] John O. Susac first described the syndrome in 1979.[2] Various acronyms have been in use for the syndrome including RED-M for retinopathy, encephalopathy, deafness-associated microangiopathy,[3] SICRET for small infarcts of cochlear, retinal,

and encephalic tissue,[4] and retinocochleocerebral vasculopathy.[5,6]

More than 200 cases have been reported. Women in their third and fourth decades of life are predominantly affected with a male:female ratio of 1:3. The mean age is 28 years with a range of 9-58 years.[6] Up to 97% of patients do not have the complete clinical triad at initial presentation. There can be a delay of weeks to more than 2 years for the triad of encephalopathy, retinopathy, and sensorineural hearing loss to manifest. However, partial clinical forms of the syndrome may occur. Headache is the most common complaint and may be the major presenting feature of the syndrome. The encephalopathy may include confusion, memory and/or psychiatric disturbances. Clinically, Susac syndrome may be misdiagnosed as migraine since the patients usually present with headaches and may have photopsia and scintillating scotoma. The rapid onset of dementia may mimic Creutzfeldt-Jakob disease and profound encephalopathy developing over a short period may mimic herpes simplex encephalitis.[1] Patients with tinnitus and hearing disturbance may also be clinically suspected as having Ménière disease.

White matter lesions are more prominent than those in grey-matter, and hence the lesions are often misdiagnosed as MS. The characteristic involvement of central fibers of corpus callosum should guide the radiologist to consider the possibility of Susac syndrome. Corpus callosal involvement is usually present with the microinfarcts being typically small but may be large and "snowball" like. There can be linear white matter T2/FLAIR hyper intensities ("spoke wheel" pattern), which extend from the callosal septal surface to the superior margin of the corpus callosum. Later "central callosal holes" develop and can be considered pathognomonic of this syndrome in the correct clinical setting. Other rare conditions like Marchiafava-Bignami disease and viral encephalitis can cause these lesions. Deep grey matter involvement of the basal ganglia and thalamus can be identified in the brain MRI in up to 70% of patients. In contrast to Susac syndrome, the callosal involvement in MS and ADEM is on the undersurface of the corpus callosum at the calloso-septal interface. Also, leptomeningeal enhancement, which occurs in 33% of patients with Susac syndrome, is not a feature of MS or ADEM. The "string of pearls" finding on MRI, which represents involvement of the internal capsule with multiple microinfarcts, which is always associated with the multiple corpus callosum lesions, can be very helpful when present on diffusion weighted imaging. This is associated with long-tract signs clinically.[7] Rarely, conditions like metastasis could be considered with the leptomeningeal and parenchymal areas of enhancement.

The MR imaging usually fails to identify the small cortical microinfarctions, even though all brain biopsies show microinfarctions in the cortex as well as in the white matter and leptomeninges. The brainstem and cerebellum are often involved. Diffusion restriction of the microinfarcts can occur, which is a valuable indicator of the syndrome, but it is noteworthy that aggressive demyelinating lesions could also sometimes produce diffusion restriction.[1,6] Variable parenchymal enhancement can occur in Susac syndrome, yet not to be confused with the larger open ring enhancement pattern seen in demyelinating syndromes like tumefactive MS or ADEM. A recent article[8] stated that in 7 Tesla MRI, 92% of MS plaques had a small central vein whereas only 54% of the white matter lesions of Susac syndrome did so. Also, MS plaques in that study showed a small hypointense rim in 41%, whereas only 4% of Susac syndrome lesions showed this feature. Moreover, the CSF isointense lesions within the central part of corpus callosum frequently seen in Susac syndrome were not commonly demonstrated in MS.

The retinopathy in Susac syndrome consists of retinal arterial or arteriolar branch occlusions with patchy areas of retinal infarcts, which can cause sudden onset of impaired vision, photopsia, black spots, and scintillating scotoma. The classic findings seen on FA include multifocal areas of hypoperfusion through branch retinal arteries with hyperfluorescence of the vessel walls, and 'leakage'. These abnormalities may occur in proximal, mid-range, or distal segments of the branch retinal arteries.[9] The branch retinal artery occlusion mirrors the brain microinfarctions, and may be considered the ocular equivalent of the microinfarction seen in MRI as per Susac et al.[1]

Microinfarctions can also affect the cochlea and semicircular canals. The apical portions of the cochlea, which are supplied by end arterioles of the inner ear are affected and manifest as sensorineural hearing loss with lower tones being altered first on audiometry. The hearing loss may be mild and insidious or can occur acutely. Tinnitus and vertigo are also common complaints, and a prominent jerk nystagmus could suggest infarction of the membranous labyrinth.[1]

Aggressive immunotherapy includes oral prednisone, pulses of methylprednisolone, IV immunoglobulin, methotrexate, cyclosporin A, cyclophosphamide, and mycophenolate mofetil, and low dose aspirin. For unrelenting cases that are not adequately responding to conventional therapies, plasmapheresis could be considered. Different anecdotal treatment algorithms for encephalopathy and branch retinal artery occlusions/hearing loss without encephalopathy have

been proposed. All of these treatments are based on a dermatomyositis treatment model.[10,11] Intratympanic methylprednisolone injections in a patient's regimen have shown initial improvement, but may eventually relapse and progress to deafness.[12]

In conclusion, Susac syndrome is a microangiopathy/endotheliopathy of unknown origin, probably autoimmune, affecting the capillaries and precapillary arterioles of the brain, retina, and inner ear. The diagnosis is made by identifying the characteristic MRI pattern, especially those in central fibers of the corpus callosum accompanied by a partial or complete clinical triad of encephalopathy, visual, and hearing problems and fundus or retinal fluorescein angiographic findings of branch retinal artery/arteriolar involvement. A very high index of suspicion is required on the part of the clinician and radiologist to diagnose Susac syndrome in patients with any component of the clinical triad. Even if the initial ophthalmologic examinations are normal, these patients should be followed up for later development of branch retinal artery occlusions.

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CASE REPORTS

Case reports will only be considered for unusual topics that add something new to the literature. All Case Reports should include at least one figure. Written informed consent for publication must accompany any photograph in which the subject can be identified. Figures should be submitted with a 300 dpi resolution when submitting electronically or printed on high-contrast glossy paper when submitting print copies. The abstract should be unstructured, and the introductory section should always include the objective and reason why the author is presenting this particular case. References should be up to date, preferably not exceeding 15.