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Case Report

Susac Syndrome: Report of Four Cases and Review of the Literature

Tai Hung Do, Christiane Fisch, and François Evoy

Summary: Susac syndrome is a rare disease of unknown pathogenesis. It is caused by a microangiopathy affecting the arterioles of the brain, retina, and cochlea, giving the classic clinical triad of subacute encephalopathy, visual loss secondary to retinal branch occlusions, and sensorineural hearing loss. The features of four cases of this syndrome are presented. MR imaging, retinal fluorescein angiography, and audiography findings enable diagnosis. Early therapy may reduce sequelae and improve recovery.

Susac syndrome is a rare disease attributed to a microangiopathy involving the arterioles of the brain, retina, and cochlea. This syndrome was first described by John O. Susac in 1979 in two young women presenting with the classic clinical triad of subacute encephalopathy, retinal arteriolar branch occlusions, and sensorineural hearing loss (1). Since then, approximately 60 cases have been reported in the medical literature (2). Surprisingly, to our knowledge no article on this syndrome has been published in the radiologic field. Rapid diagnosis is important for early therapy, and imaging is mandatory. The radiologist plays an important role when the disease is suspected and helps orient the investigation. Four cases of Susac syndrome are presented with special emphasis on imaging findings and review of the literature.

Case Reports

Case 1

A 36-year-old woman presented in January 1996 with vertigo, ataxia, vomiting, visual impairment of the left eye, hearing loss in the left ear, and weakness on the left side of her body. Routine laboratory studies were normal.

Cerebral MR imaging showed multiple small foci of high signal intensity in the periventricular white matter, corpus callosum (Fig 1A), centrum semiovale bilaterally, left posterior arm of the internal capsule (Fig 1B), and right middle cerebellar peduncle. The aspect and distribution of these lesions favored the diagnosis of multiple sclerosis. No improvement of visual or hearing symptoms was noted after treatment with intravenous corticotherapy. There was mild improvement of neurologic symptoms.

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Despite interferon therapy introduced at the end of January 1996, the patient presented in February with confusion and personality changes. Visual and hearing deficits were noted on the right side. The patient was disoriented, with inappropriate speech and loss of memory. Laboratory findings disclosed increased CSF protein level (2.33 g/L) and a positive rheumatoid arthritis test. Cerebral CT and angiography findings were normal. Repeat MR imaging was unchanged. Ophthalmologic examination disclosed bilateral visual field deficits more pronounced on the left. The ophthalmoscopic examination showed multiple retinal arteriolar branch occlusions. Severe bilateral deafness led to hearing prosthesis. An open cerebral biopsy in March 1996 showed small foci of ischemic cortical necrosis. On follow-up, only mild improvement of memory occurred. During the years that followed, important hearing sequelae affected her living condition.

Case 2

A 33-year-old man treated with migraine prophylaxis complained of pulsatile headache in June 2000 with vertigo, ataxia and diminished attention span and memory. On physical examination, the patient was subfebrile with nuchal rigidity, dysmetria, and adiadococinesia. He was confused, somnolent, and disoriented and had incoherent speech. Laboratory tests showed elevated white cell count and proteinorachia (2.53 g/L).

Brain CT and angiography were normal. The first MR imaging study showed leptomeningeal enhancement in the interpeduncular area (Fig 2A). Foci of high T2 signal intensity were noted in the corpus callosum and periventricular white matter (Fig 2B). Acute disseminated encephalomyelitis was suspected. Leptomeningeal biopsy revealed areas of capillary hyaline thrombi with perivascular inflammatory cells, suggesting a microangiopathy (Fig 2C).

A few days before neurologic deterioration, the patient complained of hearing problems. Audiometric evaluation revealed bilateral low-frequency sensorineural hearing loss and impaired discrimination. The patient had no visual complaint. Because of suspicion of Susac syndrome, an ophthalmologic evaluation was performed. Retinal fluorescein angiography showed peripheral retinal arteriolar branch occlusions in the left eye (Fig 2D).

Neurologic deterioration was noted on July 3, with hemiparesis and increased ataxia. At repeat MR imaging, multiple small high T2 lesions had appeared in the centrum semiovale, periventricular white matter, posterior arm of the internal capsule, thalamus (Fig 2E), cerebral peduncles, and white matter of the cerebellum. Enhancement of some lesions in the cerebellum, the corpus callosum, and the posterior arm of the internal capsule followed gadolinium injection (Fig 2F). Leptomeningeal enhancement had disappeared.

Neurologic status improved after corticosteroid therapy. There was some residual cognitive impairment affecting memory and concentration. The third MR imaging study showed marked decrease in cerebellum and cerebral signal intensity anomalies. Some small residual nodular enhancement was noted in the corpus callosum. The patient was transferred to a rehabilitation center. Good evolution with important cognitive improvement occurred. He was able to return to work with a hearing prosthesis.

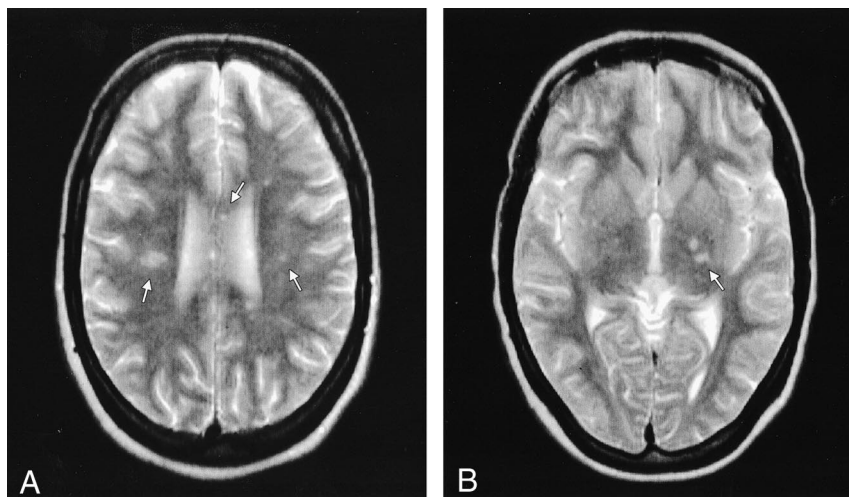


FIG 1. Case 1.

A, Axial T2-weighted MR image shows hyperintense lesions in the periventricular white matter and corpus callosum.

B, Axial T2-weighted MR image shows a small, hyperintense foci in the left posterior arm of the internal capsule.

and had no visual limitation. Follow-up MR imaging showed disappearance of the signal intensity anomalies.

Case 3

A 40-year-old man presented in September 2000 with confusion, headache, and personality changes. On examination, he was alert but disoriented and had incoherent speech. Initially, no complaint was made about visual or auditory symptoms. Ophthalmologic examination was normal. The rest of the neurologic and general physical examination was normal.

Laboratory analysis showed elevated CSF protein level (1.20 g/L) and a slight increase of C-reactive protein. Other laboratory findings were unremarkable. Nonspecific diffuse slowing was noted on an electroencephalogram.

CT and cerebral angiography were normal. Two MR studies were performed during the first week of hospitalization. The initial MR imaging study was normal. The second MR imaging study, 5 days later, showed multiple enhancing punctuate foci in the cerebellum that were more numerous on the left side (Fig 3A). A few T2-weighted hyperintense small lesions could be seen in the genu and splenium of the corpus callosum and in the periventricular frontal white matter (Fig 3B).

An initial presumptive diagnosis of viral encephalitis was made, and therapy with acyclovir was started. During hospitalization, repeat neurologic examination revealed ataxia and increased cognitive impairment. Susac syndrome was suspected. Retinal fluorescein angiography showed retinal arteriolar branch occlusions in the left eye. The audiogram showed moderate to severe sensorineural hearing loss on the left side (Fig 3C). Leptomeningeal biopsy findings were consistent with microangiopathy.

Acyclovir was interrupted, and corticotherapy with solumedrol was started. Significant clinical improvement was noted and confusion resolved. Two days after discharge, the patient was readmitted for aggravation of hearing loss in the left ear. Cyclophosphamide and intravenous immunoglobuline were administered, and prednisone was increased. On follow-up, the patient's condition had improved, but he continued to have slight cognitive impairment and left deafness persisted. There was no functional visual limitation despite the angiographic findings. MR imaging performed 9 months later demonstrated resolution of the enhancing and high T2 signal intensity anomalies and a small area of encephalomalacia from biopsy.

Case 4

A 23-year-old female student was admitted in April 2001 with progressive nonpulsatile headache, vomiting, personality

changes, vertigo, tinnitus, and unsteady gait. Transitory numbness of her left arm had been noted. On examination, she was disoriented, disinhibited, and had diminished concentration. Her mood was labile with inappropriate laughter. She was ataxic and had mild right arm weakness. Routine laboratory findings were normal. The CSF examination demonstrated increased protein level (2.26 g/L).

Cerebral angiography was normal. MR imaging showed several hyperintense T2 lesions in the body and genu of the corpus callosum, the centrum semiovale, the thalamus bilaterally, the mesencephale, the cerebellum, and the left middle cerebellum peduncle (Fig 4A). No enhancement was noted after gadolinium injection.

Audiometry revealed mild bilateral sensorineural hearing loss more pronounced on the right with mild low frequency discrimination impairment. Retinal fluorescein angiography disclosed an inflamed left retinal arteriole with a leaking arteriolar wall (Fig 4B).

Diagnosis of Susac syndrome was made, and treatment with corticosteroids, antiplatelets, and intravenous gamma-globuline was given. Cognitive and neurologic improvements were noted. A second MR imaging study showed a decrease in size of the hyperintense lesions, particularly in the thalamus, the corpus callosum, the cerebellum, and the left middle cerebellar peduncle. The patient was discharged from the hospital.

In June 2001, she was readmitted with recurrent confusion and diminished bilateral visual acuity. Increased lesions at retinal fluorescein angiography were noted bilaterally. Repeat MR imaging showed increase in size and number of the hyperintense lesions in the thalamus and cerebellum (Fig 4C). New lesions were noted in the caudate nucleus and pons. Several punctuate enhancing lesions were shown after gadolinium injection in the superior portion of the cerebellum. Treatment was adjusted by introduction of Procytox (Baxter Corporation, Mississauga, Ontario, Canada), with a good outcome.

Discussion

In reference to the original description by Susac in 1979 of two women who presented with encephalopathy, retinal arteriolar branch occlusions, and deafness, Hoyt proposed in 1986 the eponym "Susac's syndrome" (3). Mass et al suggested the acronym RED-M: retinopathy, encephalopathy, deafness associated microangiopathy (4, 5). Schwitter et al used another acronym, SICRET: small infarcts of cochlear, retinal, and encephalic tissues (6). Petty

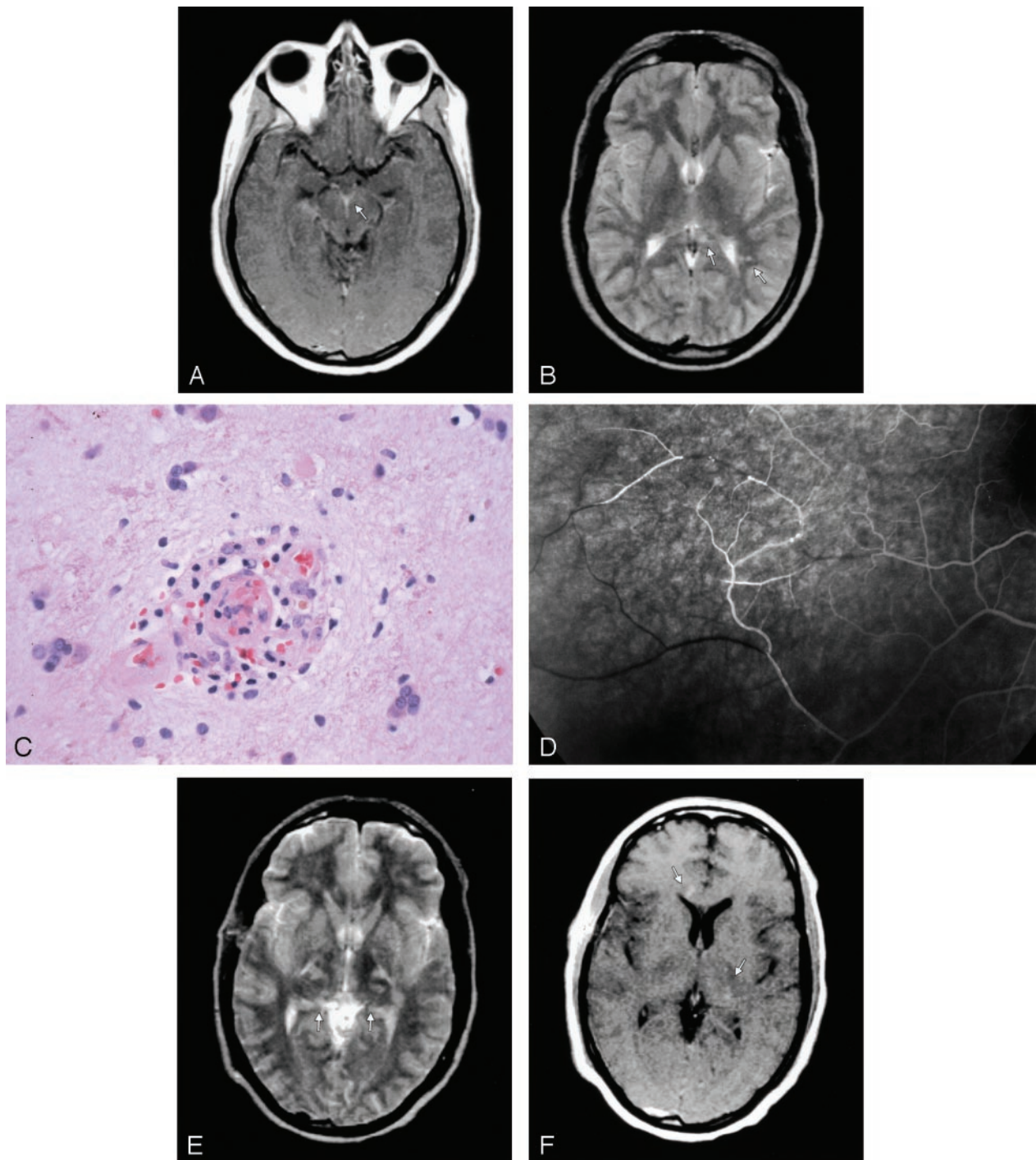


FIG 2. Case 2.

A, Axial T1-weighted postcontrast MR image shows leptomeningeal enhancement in the interpeduncular area.

B, Axial T2-weighted MR image shows hyperintense lesions in the corpus callosum and periventricular white matter.

C, Histopathologic examination shows areas of capillary hyaline thrombi with perivascular inflammatory cells (hematoxylin and eosin stain; magnification $\times 400$).

D, Retinal fluorescein angiography shows peripheral retinal arteriolar branch occlusions in the left eye.

E, Axial T2-weighted MR image shows bilateral hyperintense lesions in the thalamus and posterior arm of the internal capsule.

F, Axial T1-weighted postcontrast MR imaging shows enhancing lesions in the corpus callosum and the posterior arm of the internal capsule.

et al named this condition “retinocochleocerebral vasculopathy” (7).

In the literature, most cases of Susac syndrome occur in young, healthy women, aged 18–40 years. No

familial case has been reported (8). Our four cases comprise two women and two men in the age range of 23–40 years. Diagnoses were made between 1996 and 2001. The disease is rare, with fewer than 100 total

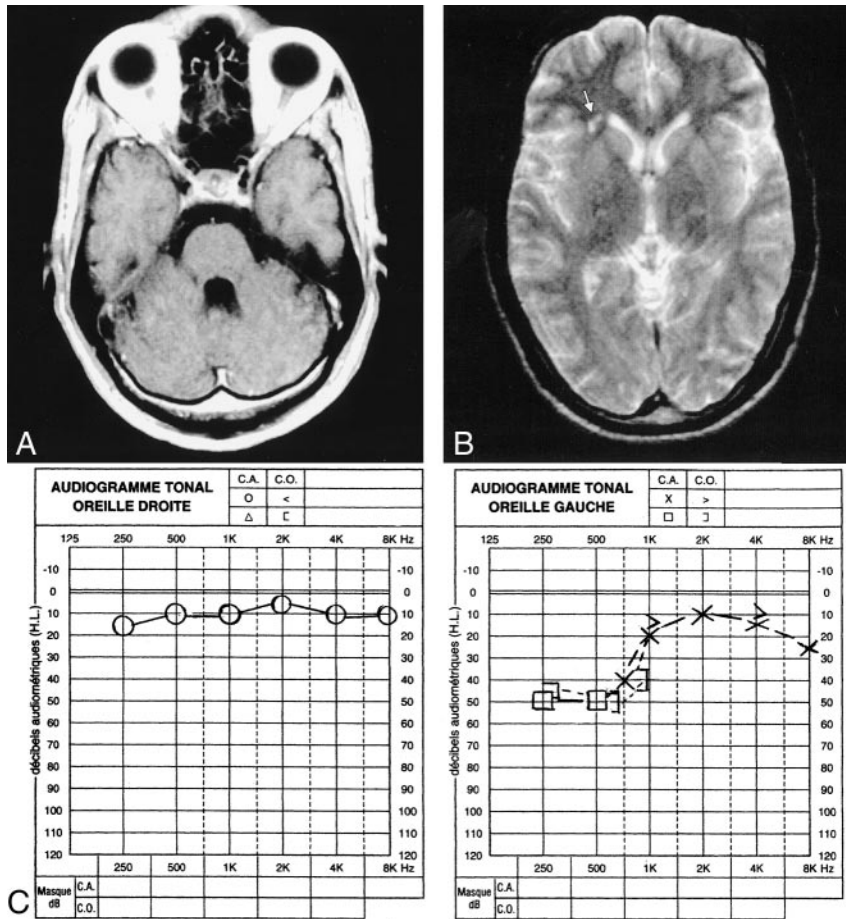


FIG 3. Case 3.
 A, Axial T1-weighted postcontrast MR image shows numerous foci of enhancement in the cerebellum.
 B, Axial T2-weighted MR image shows small, hyperintense lesions in the right periventricular frontal white matter.
 C, Audiogram shows moderate to severe sensorineural hearing loss on the left ear.

cases reported, and is frequently misdiagnosed as multiple sclerosis, migraine, lupus erythematosus, encephalitis, Ménière disease, thromboembolic stroke, and even schizophrenia (7, 9). Its frequency is certainly underestimated (8–10). The disease usually has an active fluctuating monophasic self-limited course, lasting from months to years, with varying functional outcomes and residual disabilities. Patients infrequently have a stuttering or progressive course, as noted in one of our cases. A recent case was reported of recurrence after an 18-year remission (9).

The etiology and pathogenesis of this microangiopathy remains unknown: no procoagulant state or definite connective tissue disease has been consistently documented. Theories of an immune-based mechanism that might be triggered by previous infection have been proposed (2, 7, 8, 9). Vasospastic arteriolar occlusions or microembolizations seem unlikely (7, 8, 9). The distribution of arteriolar disease affecting brain, eye, and ear is also an enigma. Analogous, blood-brain barrier and common embryologic origin may act as a possible substratum for multiple infarcts tissue specificity (8). Some patients, however, have constitutional symptoms and microvascular changes on muscle biopsy, which suggests a possible systemic disease with predilection for the triad of symptoms of Susac syndrome either because microvascular occlusions in the brain, retina, and cochlea

produce more striking symptoms than elsewhere or because of selective vulnerability of these organs (9).

Susac syndrome can mimic several diseases. The differential diagnosis includes any disorder that can produce multifocal neurologic symptoms, visual impairment, hearing loss, or any combination of these and is therefore very large: demyelinating disease, connective tissue disease, infection, neoplasm, procoagulant state, and ischemic disease of different etiologies (7). Exhaustive diagnostic studies are performed to exclude other entities. There is no entirely specific feature of Susac syndrome (8). Characteristic findings on brain MR images, ophthalmologic examination, and audiogram should facilitate the diagnosis. A high index of suspicion must be present because a high percentage of patients—as many as 97%—do not have the clinical triad at the time of onset of symptoms (7). The triad may become complete after a delay of weeks to more than 2 years, and partial forms of the syndrome have been reported, making the diagnosis more difficult. Encephalopathic symptoms may also obscure initial visual or auditory complaints as was noted with two of our patients. Neuropsychiatric disturbance may be seen in 75% of cases; in only 10% of cases is the illness revealed by cochlear or ophthalmologic symptoms (2). Only one of our patients presented initially with the classic triad. Early recognition and appropriate therapy of this syndrome

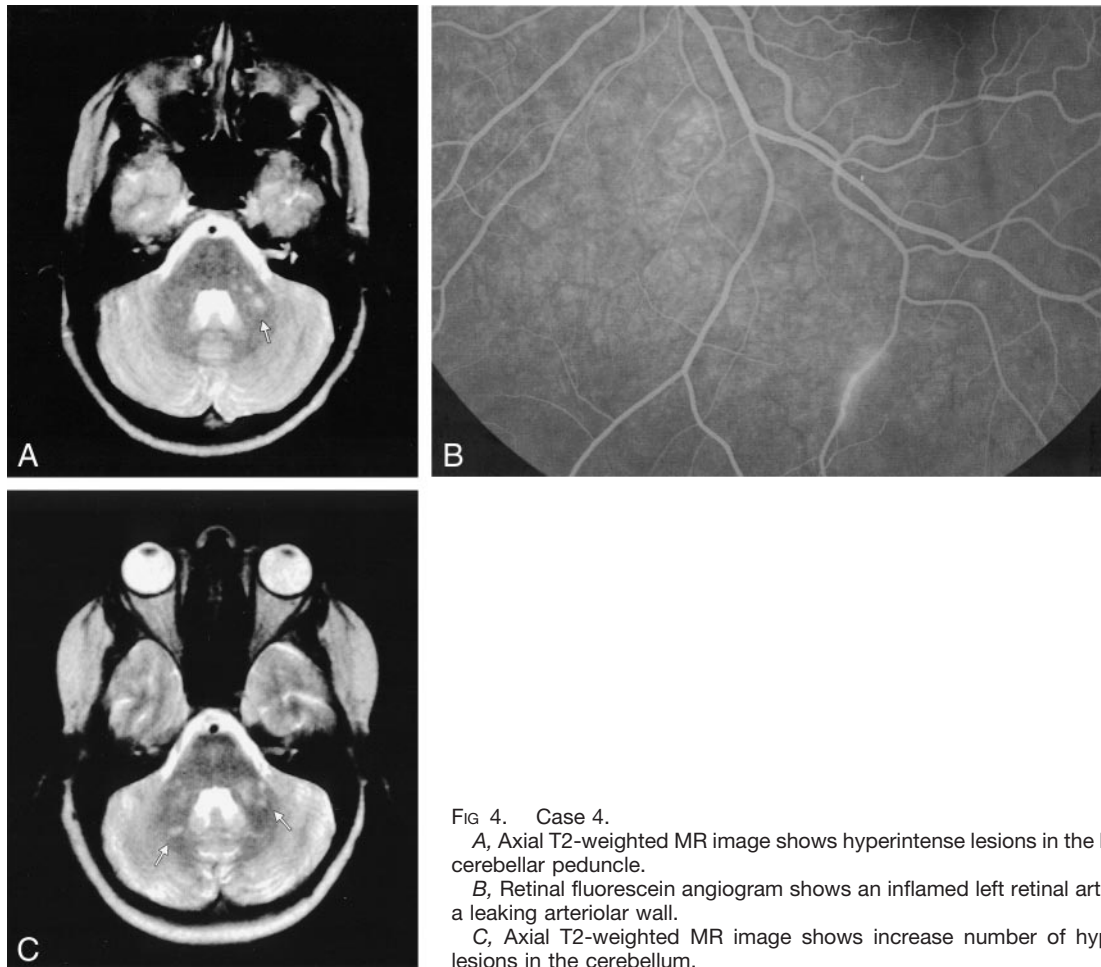


FIG 4. Case 4.

A, Axial T2-weighted MR image shows hyperintense lesions in the left middle cerebellar peduncle.

B, Retinal fluorescein angiogram shows an inflamed left retinal arteriole with a leaking arteriolar wall.

C, Axial T2-weighted MR image shows increase number of hyperintense lesions in the cerebellum.

may reduce the permanent sequelae seen with this disease (2–10).

MR is the neuroimaging technique of choice. Findings include multiple small foci of high T2 signal intensity and contrast enhancement throughout both gray and white matter in the cerebrum and infratentorial structures (7, 10). The lesions are seen in the corpus callosum (genu, body, and splenium), centrum semiovale, internal capsule, periventricular white matter, brain stem, cerebellum, cerebral and cerebellar peduncles, basal ganglia, and thalamus (3, 8–11). Our cases show similar imaging findings. Contrast-enhanced studies should be used; lesions that are acute or subacute often enhance during attacks (8, 10). In three of our patients, there were punctuate foci of enhancement after contrast medium administration; the fourth patient had no enhanced study. In addition, one of our patients had leptomeningeal enhancement before the appearance of most T2 hyperintense lesions. This nonspecific finding has not been described in the literature; it might be associated with Susac syndrome, because CSF is often abnormal with mild pleocytosis and increased protein level (7). In addition, this patient had signs of meningeal irritation on admission before lumbar puncture.

To this day, there has been no report of signal intensity or enhancement abnormalities in the co-

chlea, but neither has been sought. In future imaging of patients with suspicion of Susac syndrome, high-resolution additional study of the inner ear might show abnormalities and contribute to the diagnosis and comprehension of this syndrome. Brain CT and angiography findings used mostly to exclude other diseases are usually normal. Brain atrophy may be seen in late stages of the illness in some cases (7, 10). There was some correlation between imaging findings and neurologic status in our patients: disappearance or decrease of lesions at MR imaging followed resolution of clinical symptoms, and increase of lesions was often shown during new attacks, although in one case imaging findings were unchanged. In the literature, MR imaging abnormalities have been shown in partial forms of Susac syndrome with no neurologic symptoms (7).

The encephalopathy may be acute or subacute and is frequently seen with psychiatric features of personality change and bizarre behavior. It may be preceded by headache, often with migrainous features as a prominent symptom seen initially in more than half of the patients. Common manifestations of brain involvement are impaired cognition and memory, ataxia, dysarthria, vertigo, and corticospinal tract dysfunction. Multifocal or diffuse neurologic symptoms and signs may progress during the active phase of the illness (3, 8).

The retinopathy is characterized by multiple peripheral retinal arteriolar branch occlusions that can be seen on ophthalmoscopic examination or retinal fluorescein angiography. The occlusions may be quite extensive or may be very subtle (3, 10). Segmental loss of vision in one or both eyes and visual scintillating scotoma are typical visual complaints. Some patients do not complain of visual deficit, despite the typical arteriolar occlusive process. This may be due to either encephalopathy or the retinal infarct being too small or too peripheral (5, 7, 8). Occlusions at the posterior pole cause profound visual loss, whereas more peripheral lesions might be associated with no subjective visual symptoms (10). Fundoscopy may show occlusion of the branches of the central retinal artery; the fundi are sometimes considered normal when the occlusions are confined to the small arterioles in the retinal periphery. Retinal fluorescein angiography is the best method for detecting the retinal arteriolar occlusions. It may also show leakage of dye. Arteriolar wall hyperfluorescence has been noted before the occurrence of retinal arteriolar occlusion, as in one of our patients. This can be taken as an indicator of active disease and hasten preventive treatment (10).

Hearing loss is often acute, unilateral or bilateral, asymmetrical, and associated with tinnitus, vertigo, nausea, vomiting, nystagmus, and unsteady gait (7, 8). Careful questioning may be necessary to obtain evidence of hearing loss, which may at times be obscured by the other neurologic symptoms (2, 7). As for retinopathy, sensorineural hearing loss may be asymptomatic and disclosed only by the audiogram (7). Audiometry demonstrates sensorineural hearing loss usually in the low- to mid-frequency ranges. Monteiro et al attribute this to infarction of the cochlear apex in the distribution of the small end arteries (7, 11). Bateman et al suggest that some loss is retrocochlear in nature (12). Vestibular dysfunction may be demonstrated by caloric testing. The progression of the hearing loss is variable during the active phase of the illness. Some patients experience rapid progression and deafness, whereas others have significant improvement of previously impaired cochlear function on one side and subsequent involvement contralaterally, as was noted with our cases.

Brain biopsy specimens show small infarcts about 500 μ in diameter in both cerebral cortex and white matter and minimal perivascular inflammatory changes (8). There is no fibrinoid necrosis, necrotizing vasculitis, or amyloid angiopathy (7, 8). Findings in our cases consisted of ischemic microlesions affecting the cerebral cortex. Resolution of some lesions at MR imaging implies that some abnormalities are due to inflammation or ischemia as opposed to irreversible infarcts (7).

Various treatments have already been used: corticosteroids, an immunosuppressive agent (Cyclophosphamide), antiplatelets, antithrombotic agents, intravenous immunoglobulins, plasmapheresis, and hyperbaric oxygen (2, 3, 5, 7, 8, 10, 11). The rarity of the disease, its clinical course, the tendency to improve spontaneously, the unknown pathogenesis, and the variety of therapies make it very difficult to eval-

uate the efficacy of the various treatments (7, 9). It appears that in patients in whom diagnosis and treatment are delayed, permanent morbidity is higher in terms of neurologic deficit, visual loss, and hearing loss. Rapid and early therapy should reduce sequelae of this disease (2, 10). In our cases, three patients had a good recovery following appropriate therapy. One patient had a poor outcome, with severe sequelae. The delay of diagnosis for this last patient was longer than that for the three others.

The radiologist should suspect Susac syndrome in any adult or young patient presenting with a subacute encephalopathy and proteinorachia (>1 g/L), which are not common in multiple sclerosis, with or without visual or auditory symptoms and high T2 lesions at brain MR imaging. These hyperintense T2 lesions are small, numerous, may enhance after contrast medium administration, and involve the white matter as in multiple sclerosis but also the gray matter (basal ganglia and thalamus), which is unusual with multiple sclerosis. The diagnosis is then confirmed by complete ophthalmologic evaluation with retinal fluorescein angiography demonstrating peripheral retinal arteriolar branch occlusions.

Conclusion

We presented four cases of Susac syndrome, an entity first described in the radiologic field. It is a rare, commonly underdiagnosed, disease that is characterized by brain, retina and inner ear involvement and usually found in healthy people of middle age, predominantly in women. Imaging, including brain MR imaging, retinal fluorescein angiography, and audiology study, with a high index of suspicion, is important for correct diagnosis, enabling early appropriate therapy to reduce permanent sequelae. MR imaging findings show multiple small foci of abnormally high T2 signal intensity and some T1 enhancing lesions that can mimic multiple sclerosis as well as other pathologic conditions.

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