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Susac syndrome: a case report and PET imaging findings

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Abstract

We describe the case of a twenty year old woman with subacute encephalopathy, who subsequently developed hearing loss and ophtalmopathy. The clinical triad and typical findings on magnetic resonance imaging and cerebrospinal fluid analysis led to the diagnosis of Susac syndrome. Brain positron emission tomography showed abnormalities which are comparable with other types of central nervous system vasculitis, and distinct from those found in multiple sclerosis.

Key words: Susac syndrome; vasculopathy; PET scan; multiple sclerosis; acute disseminated encephalomyelitis.

Introduction

Susac syndrome (SS) is a rare vasculopathy of uncertain etiology, which is clinically characterized by the triad of encephalopathy, visual and auditory loss. Correct diagnosis of SS is complicated by the fact that most patients present with an incomplete clinical triad. SS can mimic several diseases, including demyelinating diseases, connective tissue disease, infection, neoplasia, procoagulant states, and cerebrovascular disease. Exhaustive diagnostic studies should be performed to exclude these entities. The differential diagnosis with acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) is particularly difficult.

Case report

A 20 year old woman was admitted in February 2007 with progressive cognitive decline, personality changes and diminished attention span. General physical examination was normal. An electroencephalogram (EEG) showed non-specific diffuse slowing. Magnetic resonance imaging (MRI) of the brain showed multiple small lesions in supra- and infratentorial regions, some of which were located in the deep gray matter and the central corpus callosum (Fig. 1a). Lesions were hyperintense on T2 and FLAIR weighted images (Fig. 1b), some were hyperintense on diffusion weighted images and there was no contrast enhancement. Analysis of cerebrospinal fluid (CSF) showed elevated protein (218 mg/dl, cutoff: 24-49 mg/dl) and a lymphocytic pleocytosis (49 cells/mm3 - 87% lymfocytes), with normal lactate, glucose, and an absence of oligoclonal bands on protein electrophoresis. An extensive workup was performed to exclude infectious causes (syphilis, Lyme's disease, Whipple's disease, Human Immunodeficiency Virus, cytomegalovirus, Epstein-Barr virus, Herpes Simplex virus, Mycoplasma), autoimmune disease (anti nuclear antibodies, rheumatoid factor, c-reactive protein, C3 and C4 complement levels, angiotensin converting enzyme, serum protein electrophoresis, anti-thyroglobulines and anti-microsome antibodies, and a classical angiography to exclude central nervous system angiitis), coagulation disorders (anti-phospholipid antibodies, proteine C and S deficiency, homocystein, antithrombine, APC resistance, DNA analysis of the Factor V gene and the prothrombine gene) and prion disease (protein 14-3-3 in CSF). Brain fluoro-deoxy-glucose positron emission tomography (FDG-PET) was performed at this stage, and showed marked hypometabolism in the right frontal, parietal and temporal lobes (Fig. 2a). The patient showed spontaneous partial recovery and was discharged with a tentative diagnosis of ADEM.

Four months later, she developed subacute hearing loss. Audiometry revealed a sensorineural hearing deficit in the low and mid frequencies. Although the patient had no visual complaints, retinal fluorescein angiography was performed and showed multiple sites of dye leakage (Fig. 3a). The development of the typical clinical triad of encephalopathy, hearing loss and retinal abnormalities, taken together with the findings of of MRI and CSF analysis confirmed

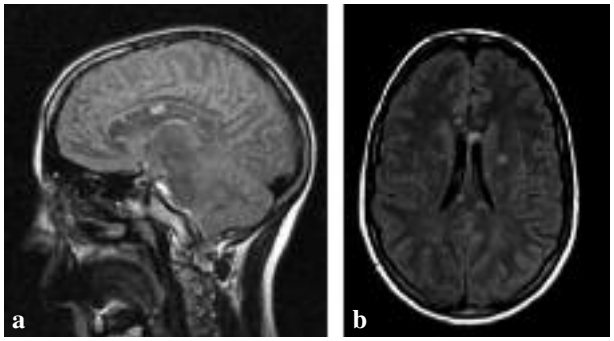

FIG. 1. — a) Sagital FLAIR MR image showing hyperintense lesions in the corpus callosum; b) Axial FLAIR MR image showing multiple hyperintense lesions in the periventricular white matter and a hyperintense lesion in the corpus callosum.

the diagnosis of SS. The patient was treated with intravenous methylprednisolone (1 g daily for 3 days), followed by 60 mg prednisolone daily for 6 months, followed by progressieve tapering. Treatment with intravenous immunoglobulines (IVIG) was initiated at a dose of 2 g/kg monthly for six months. The patient showed marked improvement of cognitive function with normalization of EEG, PET (Fig. 2b), decreased number of lesions on MRI and fluoroscein angiography. After tapering steroid treatment, the patient developed visual symptoms and fluoroscein angiography showed new sites of dye leakage (Fig. 3b). Treatment with intravenous methylprednisolone was repeated (1 g daily for 3 days) and adjunctive treatment with cyclophosphamide was initiated (1 g monthly) for 6 months, followed by azathioprine (3×50 mg/day). This resulted in the recovery of visual function.

Discussion

SS is a rare clinical entity presenting with the typical triad of encephalopathy, hearing loss and visual disturbances. It occurs most frequently in women between the ages of 20 and 30. It was first described by John O. Susac in 1979 in two young women suffering from encephalopathy, multifocal branch retinal artery occlusions and sensorineural

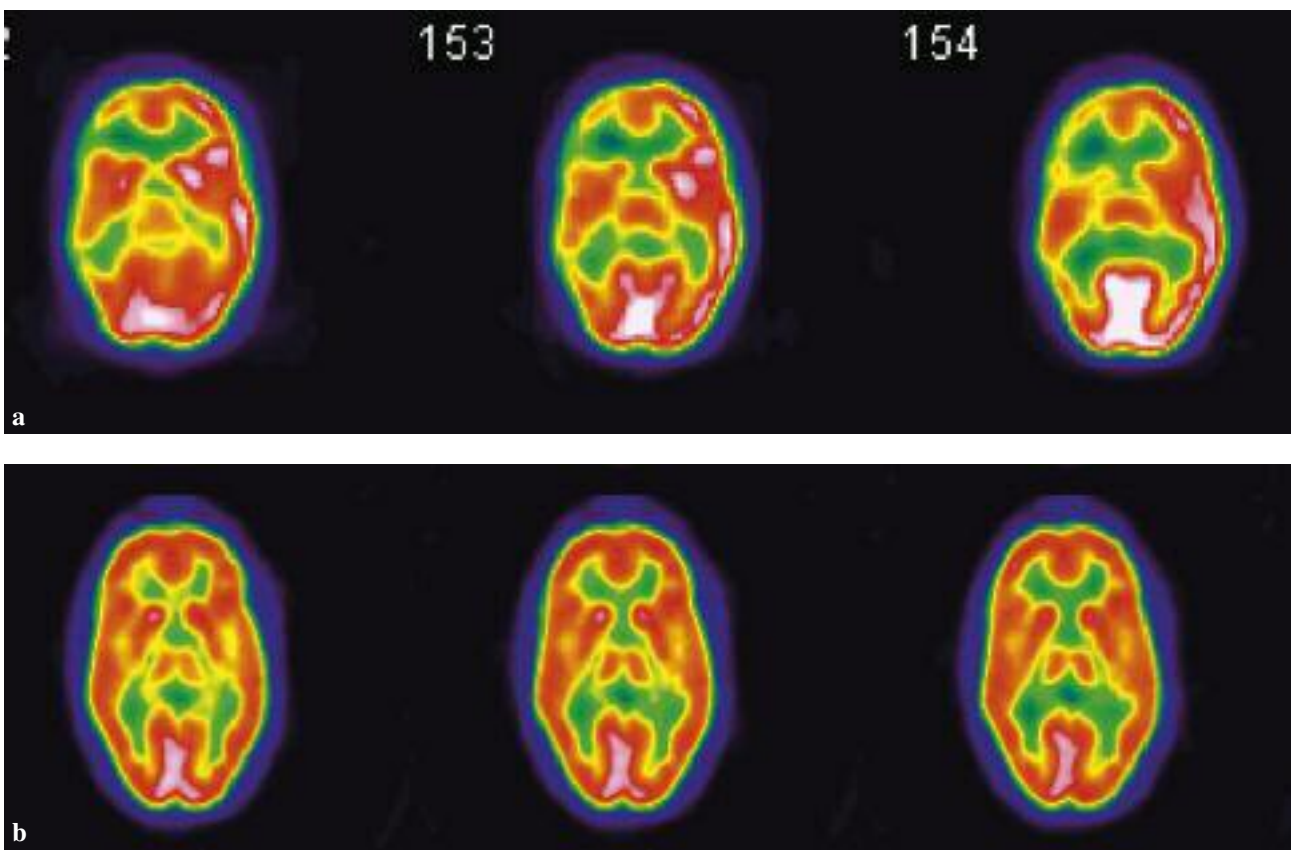

FIG. 2. — a) Brain PET scan shows right frontal, parietal and temporal hypometabolism; b) Normalization after treatment with IVIG (2 g/kg monthly) and prednisolone (60 mg daily) for 6 months.

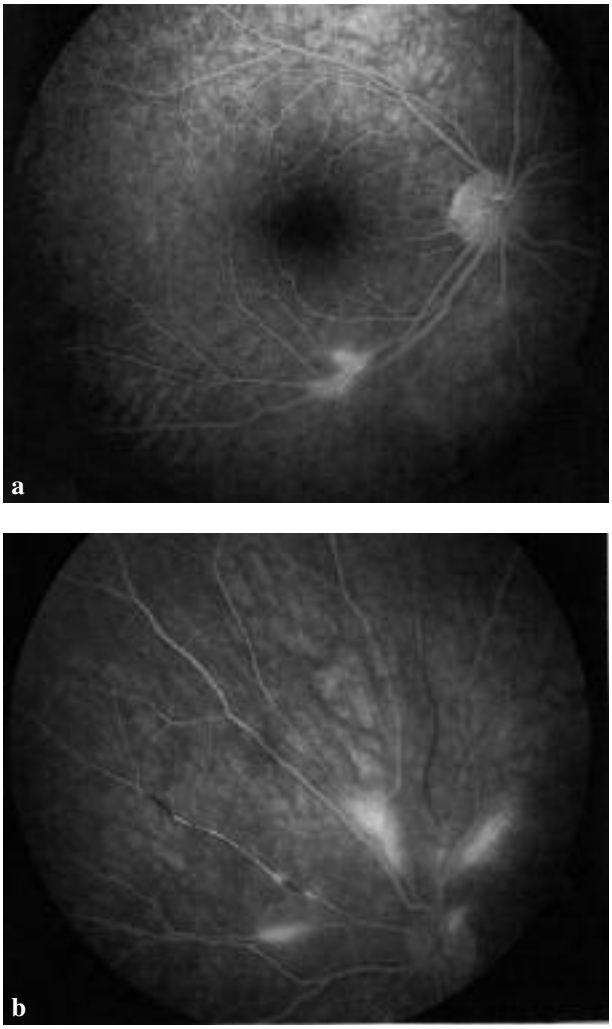

FIG. 3. — a) Retinal fluorescein angiogram shows an inflamed right retinal arteriole with a leaking arteriolar wall; b) Retinal fluorescein angiogram during relapse, with multiple sites of dye leakage.

hearing loss (Susac *et al.*, 1979). Approximatively one hundred cases have been reported in the medical literature to date.

The etiology and pathogenesis of SS remain incompletely understood, but are assumed to be auto-immune. Pathological examinations in patients with SS have revealed a vasculitis of precapillary arterioles. High titers of circulating anti-endothelial cell antibodies have been detected in the serum of patients with SS. It has been suggested that these antibodies may play a role in mediating endothelial cell injury as found in dermatomyositis (Rennebohm *et al.*, 2007). Preceding hepatitis C infection (Chawla *et al.*, 2007) and smallpox-vaccination (Landa *et al.*, 2006) have been described, but previous immunisation is not a common finding in SS. The triad of cerebral, retinal and cochlear symptoms also occurs in other diseases, such as Cogan's syndrome (Albayram *et al.*, 2001) and Vogt-Koyanagi-Harada syndrome (Read *et al.*, 2001). This may indicate a common antigenic susceptibility of these organ systems, which share a common embryological origin.

Disease course can vary widely. Monocyclic, polycyclic and chronic continuous forms have been described. The monocyclic form usually has a fluctuating course over 1-2 years. The polycyclic form presents with episodes of remission and exacerbation, which usually persist for more than 2 years. Patients with the chronic continuous form have a continuous disease activity, which often lasts for many years. Anecdotal evidence suggests that patients presenting with severe encephalopathy are more likely to have a monocyclic form than patients with initital auditory and/or visual symptoms (Rennebohm *et al.*, 2007). Although earlier reports suggested a spontaneous resolution after a 2-4 year disease course, evidence has accumulated in favour of a more longstanding disease, with retinal arteriolar involvement that may occur as a late relapse (Aubart-Cohen *et al.*, 2007).

Encephalopathy may be acute or subacute, with cognitive decline and psychiatric features, often preceded by headaches which closely resemble migraine. Ataxia, seizures, and corticospinal tract dysfunction have rarely been described (Susac, 1994). Visual complaints may consist of scintillating scotoma or segmental viual loss. Sometimes these are subclinical due to encephalopathy or peripheral localization of the lesions. Fluorescein angiography is the preferred test for ophthalmologic investigation, which may show arteriolar occlusion or leakage of dye (O'Halloran *et al.*, 1998). Hearing loss is often acute, can be uni- or bilateral and is sometimes accompanied by tinnitus, nausea and vertigo. Audiometry typically shows loss in the low and mid-frequencies, which are generally attributed to lesions in the apex of the cochlea (Papo *et al.*, 1998; Petty *et al.*, 1998).

EEG may show non-specific diffuse slowing or frontal intermittent rythmic delta activity (Woolridge *et al.*, 2006). Cerebral angiography is typically normal, because the involved precapillary arterioles are beyond the resolution of angiography (< 100 μm). Factor VIII and von Willebrand factor antigen levels may be elevated, possibly due to endothelial damage (Susac *et al.*, 2007). MRI shows a distinctive pattern of supratentorial white matter lesions that always involve the corpus callosum. Based on the microvascular blood supply, callosal lesions in SS typi-

cally involve the central fibers of the corpus callosum. This can be helpful in distinguishing SS from demyelinating diseases, where lesions are usually located on the undersurface of the callosum at the septal interface (Gean-Marton *et al.*, 1991). SS lesions in the corpus callosum are typically small (3-7 mm), but some are larger and are referred to as snowball lesions because of their typical appearance. Another diagnostic aid are lesions of the deep gray matter, which occur in 70% of SS cases but are rare in MS. Posterior fossa lesions occur frequently. Contrast enhancement (Susac *et al.*, 2003) and hyperintense lesions on diffusion-weighted images (DWI) (White *et al.*, 2004) have been described. While DWI lesions with decreased apparent diffusion coefficient are uncommon in patients with MS, such lesions have been observed in the acute stage of SS (White *et al.*, 2004). It should be noted that MRI findings in SS may be consistent with the Barkhof criteria which are used for the diagnosis of MS. CSF analysis typically shows very high protein content with lymphocytic pleocytosis, oligoclonal bands can occur but are rare (Susac *et al.*, 2007). This very high protein content is unusual for MS.

In our case, PET scan of the brain showed marked lateralized hypometabolism. To our knowledge, this is the first time that such lateralisation has been reported in SS. Pathological alterations on PET imaging have been described in different types of CNS vasculitis, such as neuro-lupus and neuro-Behçet. In neuro-lupus, PET may be more sensitive than MRI in detecting early changes in brain imaging. The most common finding appears to be hypometabolism in the parieto-occipital region, which may resolve with successful treatment (Peterson *et al.*, 2005). Comparable alterations have been reported in neuro-Behçet (Mineura *et al.*, 1989). In MS, hypometabolism tends to be more widespread, with inclusion of subcortical nuclei, white matter and infratentorial structures, while large or active lesions may be hypermetabolic (Padma *et al.*, 2005). The PET findings in our patient are comparable to those observed in CNS vasculitis, and different from MS-related abnormalities. In a recent report, diffusion tensor imaging (DTI) was performed in four cases of SS and revealed extensive damage in otherwise normal appearing white matter, particularly in the corpus callosum and prefrontal areas (Kleffner *et al.*, 2008). The extent of DTI abnormalities, which most probably reflect damage to fiber integrity, correlated much better with the severity of the encephalopathy than those on conventional MRI. In our case, the hypometabolism on PET was also more wide-spread than on conventional MRI, suggesting that it may reflect a similar disruption of connectivity as DTI. Further studies comparing PET and DTI in SS are needed to confirm this.

Correct diagnosis of SS is complicated by the fact that most patients present with an incomplete clinical triad. SS can mimic several diseases, including demyelinating diseases, connective tissue disease, infection, neoplasia, procoagulant states, and cerebrovascular disease. Exhaustive diagnostic studies should be performed to exclude these entities. Complementary tests that may fascilitate the diagnosis of SS include MRI, CSF analysis, as well as the aforementioned ophthalmologic and auditory tests. The differential diagnosis with ADEM and MS is particularly difficult. The initial diagnosis in our patient was ADEM. However, the absence of oligoclonal bands, the presence of high CSF protein level (Susac *et al.*, 2007) as well as the presence of lesions in the deep gray matter and the central part of the corpus callosum (Susac *et al.*, 2003) are both atypical findings in demyelinating diseases, and could have pointed towards another diagnosis.

Treatment of SS remains largely based on anecdotal evidence. A recent article proposes different treatment schemes based on the supposed pathophysiological resemblance to dermatomyositis (Rennebohm *et al.*, 2007). A combination of corticosteroids, IVIG and cyclophosphamide seems most helpful. Our patient was initially treated with corticosteroids and IVIG, which resulted in a marked improvement of the cognitive symptoms. Visual symptoms prompted us to install treatment with cyclophosphamide (6 months) followed by azathioprine. Since then, the patient has remained stable for the past 7 months.

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