Susac Syndrome: A Rare Cause of a Confusional State

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Susac syndrome is a rare microangiopathic neurological syndrome that was firstly described by J.O. Susac in 1979. The classical clinical triad includes encephalopathy, branch retinal artery occlusion (BRAO), and hearing loss [1]. Encephalopathy has a myriad of presentations, including cognitive impairment, neuropsychiatric disturbances, sensorimotor disturbances, cerebellar dysfunction, and urine and bowel excretory dysfunction [1]. Clinically, visual symptoms can present as blurred vision, photopsia, scotomas, and sometimes monocular amaurosis fugax [2]. Moreover, Susac syndrome can present with sensorineural hearing loss and tinnitus, which occurs as result of cochlear involvement [1]. The etiology of Susac syndrome still remains elusive, yet an autoimmune etiology has been suggested. [3]. Histopathological findings also support infarct development in micro-vessels of the brain, cochlea, and retina, thus accounting for the clinical symptoms [2]. Susac syndrome has a greater tendency to affect women than men by a 3:1 ratio, with a higher preponderance in women between 20–40 years of age [1]. Susac syndrome, which is a rare disease entity, has been shown to have a yearly incidence of 0.024/100,000 [3].

In this case report, we present the challenges faced by medical professionals in establishing the disease diagnosis. The purpose of this report is to increase the awareness of clinical presentation and management of this rare disease to prevent delayed diagnosis and therefore a poor outcome.

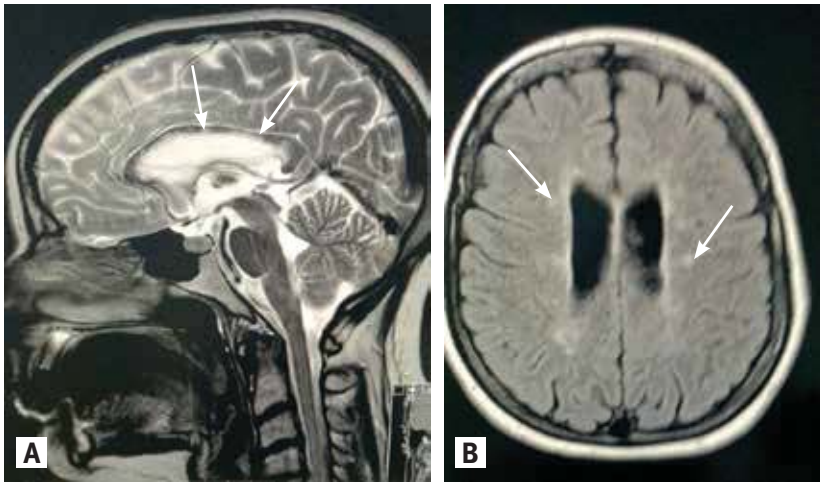
PATIENT DESCRIPTION

A 41 year old single woman presented to the hospital with a new onset of an acute confusional state and incapacitating weakening of her lower limbs, complaints that were previously unfamiliar to the patient or her family. These symptoms started less than a day before her presentation. A thorough medical history did not reveal any potential origin to her acute confusional status such as history of trauma, drug intoxication, or other causes

On her physical examination, vital signs were within the normal range. Systematic physical examination did not uncover any abnormal findings. A thorough neurologic examination was performed. On screening for cognition disturbance, the Montreal Cognitive Assessment (MoCA) score was found to be 20/30, with impairment in several components including visuospatial/executive function, attention, and delayed recall skills. Her MoCA score translated to moderate cognitive impairment. Kernig's sign, Brudzinski's sign, and nuchal rigidity were negative. Cranial nerve evaluation revealed a relative afferent pupillary defect noted in her right eye along with bilateral hearing loss. Other cranial nerves were intact. Due to her acute status and decreased cooperation, her neurological motor and sensory examination was limited and unreliable. However, the patient showed a symmetrically significant decrease in motor power in her lower limbs (2+/5), with diminished reflexes in the knees and ankles. Her sensory function was challenging to assess, but symmetrical response to pain was elicited. Her upper limb motor function was intact. Moreover, there were no reported complaints of urinary or stool incontinence. Cerebellar function was hard to assess due to her leg weakness and decreased cooperation.

On laboratory investigations, a significant abnormality in blood count and coagulation profile were not revealed: hemoglobin levels were 12.8 g/dl, leukocyte count was 10,400/µl, platelet levels were 335,000/µl. Immunologic markers including anti-neutrophil cytoplasmic antibody (C/P ANCA), antinuclear antibody (ANA), anti-double stranded DNA, anti-Ro, anti-La, anti-centromere, anti-phospholipid antibodies, rheumatic factor, and complement C3 and C4 were all in the normal range. Screening for cytomegalovirus; hepatitis A, B, and C virus; Epstein-Barr virus, *Toxoplasma gondii*, Brucella, and Mycoplasma were all negative. Thromboembolic events were ruled out after a normal transesophageal echo-cardiogram and cervical duplex scan. The cerebrospinal fluid showed only elevated proteins of 95 mg/dl, with four mononuclear cells, normal glucose levels of 60 mg/dl, and an opening pressure of 17 mmH_2O. Cultured fluid did not show any organismal growth. Moreover, an oligoclonal bands scan was negative. Electroencephalogram studies did not show any signs of epileptic activity. On brain magnetic resonance imaging (MRI), periventricular and mid-callosal lesions were noted with a characteristic snowball appearance [Figure 1].

Figure 1. [A] MRI of the patient's brain, sagittal T2 weighted sequence, showing multiple 'snowball' lesions (arrows) in the central part of the corpus callosum **[B]** An axial view of the patient's brain using fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) showing high signal lesions (arrows) in the periventricular region



While reviewing her past medical records, it was noted that 10 years before her current admission she was hospitalized four times over the period of 2 years in the ophthalmologic department with visual disturbances that were diagnosed as recurrent episodes BRAO without underling rheumatologic, vasculitic, and embolic etiologies. Two years prior to her current admission, the patient presented to the hospital with complaints of sudden hearing loss. Audiometry showed bilateral sensorineural hearing loss mainly to lower frequency.

COMMENT

Susac syndrome is a rare disease that presents with a classical triad of encephalopathy, visual deficits, and hearing impairment. In the literature, only 13% of cases had the clinical triad at presentation [1]. Other cases showed a 2 year latency until the completion of a Susac triad [2]. According to clinical presentation, Vishnevskia-Dai and colleagues [4] proposed a classification system that divided the patients to three groups: suspected, incomplete, and complete Susac syndrome. Suspected cases had risk factors including female gender, age between 20–40 years, and presence of characteristic MRI findings. Incomplete Susac syndrome is defined in a patient with two of three abnormalities forming the triad [4]. Finally, complete Susac syndrome is present in patients with three characteristic clinical manifestation [4].

The challenging step in the diagnosis of Susac syndrome is the myriad of differential diagnoses of the presenting symptoms, for example, neurodegenerative disease processes such as multiple sclerosis and acute disseminated encephalomyelitis as well as collagen vascular diseases. In addition, autoimmune diseases such as systemic lupus erythematosus, sarcoidosis, Sjögren syndrome, and Behçet disease can present with such symptoms. Moreover, neurological diseases such as stoke, prion disease, and central nervous disease lymphoma could possibly present in a similar manner.

Imaging modalities, including MRI, have been shown to prompt disease diagnosis. Lesions in the mid-portion of the corpus callosum with a snowball appearance are characteristic for the disease and their absence should question the aforementioned diagnosis. Furthermore, string of pearls micro-infarcts in the internal capsule constitute an additional radiographic finding [2]. Although findings on cerebrospinal fluid analysis are non-specific, an elevation of protein levels with an occasional positive oligoclonal bands scan can be documented. Similar findings are expected in other disease entities including, for example, multiple sclerosis [1]. The gold standard for ophthalmological evaluation includes retinal fluorescein angiography, which can show abnormalities in leaking patterns [5].

Guidelines for the treatment are still elusive. Treatment with immunosuppressive medications remains the mainstay of management due to the possible role of the autoimmune process in disease etiopathogenesis [5]. Cyclophosphamide, intravenous immunoglobulin, and rituximab are used in otherwise resistant cases [5].

Our case provided a challenging diagnostic problem, most notably due to the aberrant pattern of symptom presentation. The patient underwent rigorous investigations for a possible cause for encephalopathy, which failed to provide any clue to a possible trigger to her presentation. Coupled with her recurrent episodes of BRAO 10 years ago and with her sensorineural hearing loss, the diagnosis of Susac syndrome became more plausible. To our knowledge, there were no documented cases in the literature that showed such latency between symptom presentation. As a result, we were compelled to be more prudent in diagnosing this condition.

In light of our diagnosis, we started the patient on pulse methylprednisolone with intravenous immunoglobulin. At a 2 week follow-up, our patient showed slow progress in her cognitive status but demonstrated noticeable improvement in her motor responses, while still requiring assistance with walking.

Due to possible atypical presentations, diagnostic uncertainty could render multiple cases undiagnosed. This case report emphasizes the importance of high clinical index of suspicion in disease diagnosis. This report adds to the data published in the literature displaying existing variations in the disease presentation. Furthermore, the natural history of Susac syndrome, as well as the variants in its presentation, remain ambiguous; therefore, more reports are needed to elucidate these points.

Because many of the patients diagnosed with Susac syndrome have residual deficits, it is questionable whether our treatment modalities are effective. Furthermore, it remains questionable whether earlier treatment before triad development could have prevented further clinical deterioration as well as complete triad formation.

Conclusions

In conclusion, Susac syndrome diagnosis remains challenging to physicians due to the variations in presentations, chronicity of symptom development, and the lack of definitive diagnostic criteria. Susac syndrome should be kept in mind as a cause of confusional state, mainly in those with unclear etiology and for young females.

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Capsule

Recurrent and functional regulatory mutations in breast cancer

Genomic analysis of tumors has led to the identification of hundreds of cancer genes on the basis of the presence of mutations in protein-coding regions. By contrast, much less is known about cancer-causing mutations in non-coding region. Rheibay and colleagues performed deep sequencing in 360 primary breast cancers and develop computational methods to identify significantly mutated promoters. Clear signals are found in the promoters of three genes. *FOXA1*, a known driver of hormone-receptor positive breast cancer, harbors a mutational hotspot in its promoter leading to overexpression through increased E2F binding. *RMRP* and *NEAT1*, two non-coding RNA genes, carry mutations that affect protein binding to their promoters and alter expression levels. This study shows that promoter regions harbor recurrent mutations in cancer with functional consequences and that the mutations occur at similar frequencies as in coding regions. Power analyses indicate that more such regions remain to be discovered through deep sequencing of adequately sized cohorts of patients.

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Eitan Israeli

Capsule

Cervical neoplasia in systemic lupus erythematosus

The aim of this study was to examine the risk of cervical neoplasia in women with systemic lupus erythematosus (SLE), overall and with respect to treatment, compared with women from the general population. By linking national Swedish registers, Wadstrom and colleagues assembled a cohort including women with SLE (n=4976) and matched general population comparators (n=29,703). Two subcohorts of treated SLE patients were defined on the basis of treatment with antimalarials (n=1942) and other immunosuppressants, azathioprine (AZA), cyclophosphamide (CYC), cyclosporine, methotrexate (MTX), mycophenolate mofetil (MMF) or rituximab (n=2175). The main outcome was defined as a first cervical neoplasia (dysplasia or cancer) during follow-up. Secondary outcomes were first cervical intraepithelial neoplasia (CIN) 1; first CIN grades 23; and first invasive cervical cancer during follow-up. Cox regression models estimated relative risks adjusted for age, level of education, healthcare utilization, number of children, marital status, family history of cervical cancer and prior cervical screening. Based on 121 events of cervical neoplasia during 23,136 person-years among SLE patients, there was an increased risk of any cervical neoplasia compared with the general population (hazard ratio [HR] = 2.12). The risk of CIN 1 (HR = 2.33), CIN 23 (HR = 1.95), but not invasive cervical cancer (HR = 1.64), was increased in women with SLE. The subcohort treated with other immunosuppressants was at highest risk of cervical neoplasia.

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"A word as to the education of the heart. We don't believe that this can be imparted through books; it can only be imparted through the loving touch of the teacher"

Cesar Chavez, (1927–1993), American civil rights leaders, farm worker, labor leader