Observational Study

Medicine®

OPEN

Susac syndrome: clinical characteristics, clinical classification, and long-term prognosis

Vicktoria Vishnevskia-Dai, MD[a,*], Joav Chapman, MD[b], Roee Sheinfeld, MD[b], Tal Sharon, MD[a], Ruth Huna-Baron, MD[a], Riri S. Manor, MD[c], Yehuda Shoenfeld, MD[d], Ofira Zloto, MD[a]

Abstract

Susac syndrome is a rare condition characterized by the clinical triad of central nervous system (CNS) dysfunction, sensorineural hearing impairment, and branch retinal artery occlusion (BRAO). The purpose of this study is to examine the demographics, clinical characteristics, treatment, and long-term prognosis of Susac syndrome. The data recorded for all Susac syndrome patients treated at the Sheba Medical Center between 1998 and 2014 included demographics, clinical signs at presentation and during the disease course, imaging findings, treatment, and prognosis.

Susac syndrome was diagnosed in 10 patients (age range 30–45 years). Only 2 patients presented with the full triad and 7 patients developed the full triad during mean follow-up period of 35 months. The average time to full triad was 7 months. Based on our observations at presentation, we divided the disease course into suspected, incomplete, and complete Susac syndrome. All 10 patients were treated at diagnosis with a pulse of high-dose intravenous methylprednisolone. There was improvement in visual acuity and visual field at the end of follow-up compared to baseline, but it was not statistically significant ($P=0.479$ and $P=0.053$, respectively). Five patients remained with neurological damage, and 5 patients had no improvement of their hearing loss at study closure. In conclusion, Susac syndrome is a rare condition that can mimic other disorders. The diagnosis is challenging because most patients do not initially present with the definitive triad. We suggest a clinical classification for the syndrome that may assist in early diagnosis.

Abbreviations: BRAO = branch retinal artery occlusion, CNS = central nervous system, FA = fluorescein angiography, MD = mean deviation, MRI = magnetic resonance imaging, VA = visual acuity.

Keywords: branch retinal artery occlusions, CNS dysfunction, sensorineural hearing impairment, Susac syndrome

1. Introduction

Susac syndrome is a rare condition that was first reported in 1973. It had been initially termed "small infarctions of cochlear, retinal, and encephalic tissues (SICRET)" syndrome[1,2] or "retinopathy, encephalopathy, and deafness microangiopathy (RED-M)" syndrome.[3] Susac et al[4] described it in 1979 and Hoyt named it "Susac's syndrome" in 1986.[5]

The syndrome is characterized by a clinical triad of encephalopathy, sensorineural hearing loss, and visual disturbance resulting from branch retinal artery occlusion (BRAO).[4] The encephalopathy is manifested by headache, motor deficiencies, sensor deficiencies, aphasia, cognitive impairment, and urinary insufficiency. The hearing loss is usually bilateral, and it can be associated with tinnitus and vertigo. The BRAO may be extensive or subtle and unilateral or bilateral. The specific etiology of the syndrome is unknown, however it is believed to be an autoimmune-mediated condition that causes micro infarcts due to endothelium-induced occlusion of the microvessels in the central nerve system (CNS), inner ear, and retina.[6,7] Although its prevalence is rare, Susac syndrome is an important differential diagnosis for several neurologic, psychiatric, ear, nose, and throat, and ophthalmologic conditions.[8] The diagnosis is difficult to establish since the full clinical triad rarely exists on the first presentation.[9]

A comprehensive search of the English literature yielded more than 100 case reports and a few case series of patients with Susac syndrome. All the published case series that include more than 2 patients were analyzed and they are listed in Table 1. Given that ocular and hearing involvements can be the first presentation of the condition, it is important for ophthalmologists and otolaryngologists to be aware of and recognize the syndrome.[7,9–12] The purpose of the present study is to examine the demographics, clinical characteristics, treatment, and long-term prognosis of patients with Susac syndrome that were treated in our center.

2. Methods

This is a retrospective consecutive case series of patients treated at a single referral center. The study was approved by the local institutional review board (IRB) of Sheba Medical Center.

Editor: Yung-Song Lin.

The authors have no conflicts of interest to disclose.

[a] Goldschleger Eye Institute, [b] Department of Neurology, Sagol Neuroscience Center, Tel Hashomer, [c] Department of Ophthalmology, Sheba Medical Center, Tel Hshomer, [d] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, are affiliated to the Sackler faculty of medicine Tel Aviv University, Israel.

[*] Correspondence: Vicktoria Vishnevskia-Dai, Goldschleger Eye Institute; Department of Ophthalmology, Sheba Medical Center, Tel Hshomer, Tel Aviv University, Israel. 52621, Israel (e-mail: vivida65@gmail.com).

Medicine (2016) 95:43(e5223)

Received: 4 November 2015 / Received in final form: 1 October 2016 / Accepted: 4 October 2016

http://dx.doi.org/10.1097/MD.0000000000005223

Table 1

Case series of Susac syndrome.

Author	Year	Number of cases	Initial clinical presentation	% of patients with full triad at presentation	% of patients with full triad at the end of follow-up	Final outcome
Jarius et al[15]	2014	25	Encephalopathy (72%) Hearing loss (20%) Visual disturbances (24%)	0	80	Neurological deficits (64%) Auditory deficits (84%) Visual deficits (75%)
Mateen et al[17]	2012	29	Encephalopathy (90%) Hearing loss (83%) Visual disturbances (83%)	55	Not reported	Not reported
Hung do et al[30]	2004	4	Encephalopathy (100%) Hearing loss (100%) Visual disturbances (100%)	100	No change	Neurological deficits (50%) Visual deficits (25%)
Snyers et al[31]	2006	4	Encephalopathy (75%) Hearing loss (100%) Visual disturbances (100%)	75	No change	Neurological deficits (25%)

2.1. Patients

All patients diagnosed as having Susac syndrome and treated at a tertiary medical center (Sheba Medical Center, Tel Hashomer, Israel) between 1998 and 2014 were included.

Data on the following parameters were retrieved from the medical database and analyzed: patient demographics (gender and age at diagnosis), medical history and medications, presence of neurological diseases, ear, nose, and throat history and ocular history, neurological, hearing and ocular signs and symptoms at presentation, magnetic resonance imaging (MRI) findings at presentation, auditory evaluation and fluorescein angiography (FA) findings at presentation, visual acuity (VA), visual field (VF; Humphrey 24-2 SITA-standard), treatment modality, response to treatment, and long-term prognosis. The major outcome measurements were disease recurrence rates and complications, and the minor outcome measurements were VA and VF. The mean duration of follow-up was 35 months.

2.2. Statistical analysis

Snellen VA was converted to log MAR values. The mean deviation (MD) on the VF test was analyzed in numeric values. Distributions for different categories parameters were measured and matched pair analyses (small sample size) for log MAR and MD at presentation and at the end of follow-up were carried out. The overall significance level was set to an alpha of 0.05. Statistical analyses were performed using JMP Statistical Discovery Software 7.0 (SAS Institute, Cary, NC).

3. Results

The series was composed of 10 patients (4 males, 6 females) whose mean age at presentation was 38 ± 10.99 years (range 30–45 years). The medical history of all patients was negative for neurological diseases and auditory deficits. Two patients had a positive ocular history (glaucoma and Duane syndrome). Two female cases presented during the postpartum period of their pregnancies (around 2 months after the delivery of their infants).

3.1. Clinical characteristics at presentation

Only 2 (20%) patients initially presented with the full triad of Susac syndrome. Seven patients subsequently developed the full triad during the follow-up period, and the average time to full triad was 7 months. All male patients in the series developed the full triad. The most common manifestation at presentation in decreasing order was CNS involvement (80%), ocular involvement (50%), and auditory involvement (30%). All 10 patients had CNS and ocular involvement. Table 2 summarizes the signs

Table 2

Clinical presentation, treatment, and prognosis in 10 Susac syndrome patients.

Case	Signs at presentation	Treatment (in addition to IV methylprednisolone and oral prednisone)	Outcome at last follow-up visit	VA RE	VF RE (MD)	VA LE	VF LE (MD)
1	Neurological and ocular signs	Oral cyclophosphamide + intravenous immunoglobulin	Residual neurological damage + hearing loss	NC	NC	NC	NC
2	Neurological signs		Residual neurological damage	I	D	NC	D
3	Neurological signs		Residual neurological damage + hearing loss	D	I	NC	D
4	Neurological signs		None	NC	I	NC	I
5	Ocular signs		Residual hearing loss	I	I	D	D
6	Neurological and ocular signs	Intravenous immunoglobulin		I	I	D	I
7	Hearing signs		Residual hearing loss	NC		NC	
8	Neurological and ocular and hearing signs	Oral cyclophosphamide + intravenous immunoglobulin	Residual neurological damage + hearing loss	NC		NC	
9	Neurological and ocular and hearing signs	Oral cyclophosphamide + intravenous immunoglobulin	Residual neurological damage	NC	I	NC	D
10	Neurological signs		None	NC	I	NC	I

D = declined, I = improved, LE = left eye, MD = mean deviation, NC = no change, RE = right eye, VA = visual acuity, VF = visual field.

Table 3

Clinical manifestations during the disease of Susac syndrome patients.

Auditory signs		Ocular signs			Neurological signs				
Hearing loss	Diplopia	Decrease visual field	Blurred vision	Urinary dysfunction	Aphasia	Gait abnormality	Cognitive impairment	Headache	Number
V	V				V	V		V	1
	V		V				V		2
V			V		V	V	V		3
		V				V	V	V	4
V		V		V	V	V		V	5
		V					V		6
V			V	V				V	7
V			V	V				V	8
V		V				V	V	V	9
V		V			V	V			10
70	20	50	40	30	40	60	50	60	%

at presentation of each patient. Table 3 displays the development of neurological and ophthalmic symptoms during the follow-up period for each patient, and Table 4 displays those developments for all patients.

All patients underwent MRI scans of the head (with and without gadolinium 1.5 or 3 T), audiometric testing and retinal FA. The MRI scans demonstrated corpus callosum and periventricular lesions in all cases (Fig. 1). Two patients had a low frequency sensorineural hearing loss.

3.2. Neurological characteristics

Eight patients (80%) had neurological manifestations at presentation, and all patients developed neurological deficits over time. Six patients (60%) developed gait abnormality and 6 patients (60%) developed headache. Five patients (50%) developed cognitive impairment, 4 patients (40%) developed aphasia, and 3 patients (30%) developed urinary dysfunction. Five patients (50%) had persistent neurological damage at the end of follow-up (Tables 2 and 3).

3.3. Ocular characteristics

BRAO was observed in all cases during the disease course. The occlusion was located in the superotemporal artery in 10 cases (Fig. 2A) and in the infratemporal artery in 3 cases.

Both eyes were involved in 3 cases, and only the right eye was involved in 7 cases. There was more than one occlusion in 6 cases. The Average occlusion number was: 1.6. The mean log MAR at presentation was 0.149 ± 0.21 (range 0.00–0.69) for the right eye and 0.062 ± 0.143 (range 0.03–0.15) for the left eye. The visual field defects included an altitudinal defect (n = 3), a central scotoma (n = 3), and a paracentral scotoma (n = 7). The mean MD at presentation was -12.49 ± 6.95 (range -25.53 to -4.74) for the right eye and -10.01 ± 5.59 (range -15.08 to -4.93) for the left eye.

Table 4

Manifestations at presentation and during the disease course.

Symptoms	Manifestation at presentation (% of total cases)	Manifestation during disease course (% of total cases)
Complete triad	2 (20)	7 (70)
CNS involvement	8 (80)	10 (100)
Ocular involvement	5 (50)	10 (100)
Auditory involvement	3 (30)	7 (70)

CNS = central nervous system.

3.4. Treatment

All patients were treated at diagnosis with a pulse of high-dose intravenous methylprednisolone (1000 mg) followed by slow tapering of oral prednisone. Shortly following the acute event, 3 patients were additionally treated with daily oral cyclophosphamide (2.5–3 mg/kg), and 4 patients with intravenous immunoglobulin (0.4 g/kg body weight/day monthly). The treatments for each patient are summarized in Table 2. They were all treated with long-term prophylactic antithrombotic and anticoagulation medications: 7 patients received concomitant treatment with antithrombotic and anticoagulation treatment, 2 patients received only antithrombotic treatment and 1 patient received only anticoagulation treatment.

3.5. Treatment outcome and prognosis

The mean follow-up time was 35 ± 25.58 months (range 16–53 months). During this time, 4 patients developed recurrent disease with new complaints (2 neurological and 2 ocular). There were also new findings on the MRI in 2 patients, and 2 patients had 1 additional episode of BRAO. Five patients (50%) were left with residual neurological damage at the end of the study: 5 had

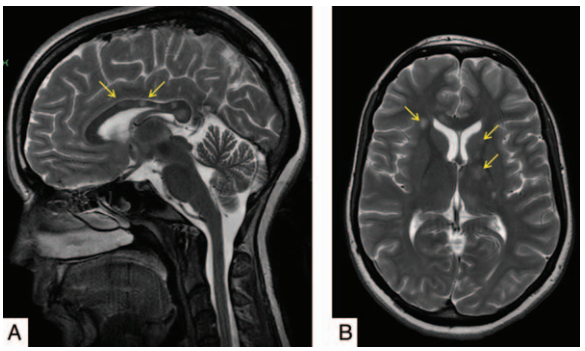

Figure 1. MRI scans of patient number 3. (A) Corpus callosum lesions (arrows). (B) Periventricular lesions (arrows).

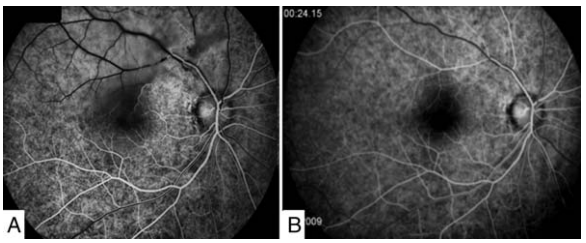

Figure 2. Retinal fluorescein angiography of patient number 3. (A) Occlusion of the superior temporal artery at the beginning of follow-up. (B) The occluded artery is still visible at the end of follow-up.

cognitive impairment, 1 had motor deficiency and 1 had sensory deficiency. Five patients (50%) had no improvement in their hearing deficit. The outcome of each patient is summarized in Table 2.

The mean VA log MAR at the end of follow-up was 0.071 ± 0.141 (range 0.00–0.47) in the right eye and 0.164 ± 0.31 (range 0.00–1) in the left eye. The mean MD on the VF defect study at the end of follow-up was -9.11 ± 7.94 (range -22.61 to $-4.3.62$) in the right eye and -10.26 ± 6.60 (range -18.85 to -1.44) in the left eye. There was improvement in VA in both eyes at the end of the study but it did not reach a level of significance ($P = 0.247$ and $P = 0.284$ for the right and left eyes, respectively, matched pairs). There was a significant improvement in the VF of the right eye at the end of follow-up ($P = 0.01$ matched pairs). There was no significant improvement in the VF of the left eye at the end of follow-up ($P = 0.807$ matched pairs). The occluded artery was identified on FA in all eyes with no recanalization at the end of the follow-up (Fig. 2B).

4. Discussion

Susac syndrome is a rare and underdiagnosed condition whose etiology is unknown.[1,2] Several authors have speculated that the pathophysiology of Susac syndrome is that of an immune-mediated endotheliopathy.[13–15] Autoimmune diseases are usually more prevalent in females, and Susac syndrome was similarly found in previous studies to be more common in females, with a male/female ratio of 1:3.5.[9] In our current series, the male/female ratio was 1:1.5. The syndrome was manifested as a full triad on presentation only in males, a finding that may indicate that although it is more prevalent in females, it is more severe in males.[16] Also interesting was the finding that the syndrome presented during the postpartum period of 2 of our female patients. There are 11 published cases documenting the occurrence of the syndrome in the context of pregnancy.[17–28] We therefore speculate that pregnancy might be a risk factor for disease flare-up.

Susac syndrome is characterized by a triad of symptoms, but only 2 of our patients had the full triad at first presentation and a full triad was reached within an average of 7 months in 7 others. This finding is in accordance with the reports of the largest meta-analysis published by Dorr et al[9] who found that only 13% of patients presented with the clinical triad at disease onset. The facts that the triad is not full at presentation and that the clinical symptoms can mimic other more common disorders make the diagnosis of the syndrome even that more challenging.

Based on our observations and on information derived from the reported literature (case reports, reviews and meta-analysis), we propose a classification of Susac syndrome according to the clinical presentation: suspected, incomplete, and complete (Table 5). Suspected Susac syndrome will refer to a patient without known risk factors for arteriosclerosis or coagulopathy with one manifestation from the triad (BRAO/hearing problem/neurological symptom) and one of the following risk factors: female between 20 and 40 years of age, female within 1 year of pregnancy, and presence of characteristic corpus callosum or periventricular lesions on MRI. Incomplete Susac syndrome will be defined as a patient with 2 manifestations of the triad, and complete Susac syndrome will be defined when all 3 symptoms are present (Table 4).

Table 5

Proposed classification of Susac syndrome.

Classification	Definition
Suspected Susac syndrome	No known risk factors for arteriosclerosis or coagulopathy, one manifestation from the triad and one of the following risk factors: (1) Female between 20 and 40 years of age with no other risk factors for occlusive arterial disease (2) Female within 1 year of pregnancy (3) Presence of characteristic MRI lesions in the corpus callosum or periventricular
Incomplete Susac syndrome	Two manifestations of the triad
Complete Susac syndrome	Three manifestations of the triad

MRI = magnetic resonance imaging.

The clinical classification of the patient can change during the course of the disease when other clinical manifestations emerge. Noteworthy, patients that fall into the categories of suspected Susac syndrome and incomplete Susac syndrome may fulfill the criteria of other diagnoses as well. The range of the differential diagnosis is wide, and it includes demyelinating diseases (e.g., multiple sclerosis, acute disseminated encephalomyelitis), autoimmune diseases (e.g., lupus erythematosus, neuro-Behçet disease) and vascular occlusion (such as from an embolus or atherosclerosis). Furthermore, the diagnosis of Susac syndrome should be included in the differential diagnosis and if the likelihood is considered as being high, treatment with antiinflammatory and antithrombotic drugs should be considered. The findings on MRI imaging can mimic other neurological disorders, such as multiple sclerosis. However, when lesions of the corpus callosum are observed, as seen in all of our cases, the suspicion of Susac syndrome should be high, especially when there are coexisting auditory or BRAO problems.

To date, there are no therapeutic guidelines for Susac syndrome. The current reported treatment strategy is based on clinical experience, case reports, and small case series. Our patients received intensive antiinflammatory and antithrombotic treatment, but 6 of them nevertheless have irreversible damage to the neurological, auditory, and/or ocular systems. Similar findings have been reported by others.[18,29] These results emphasize the need for multicenter prospective trails to evaluate treatment strategies and long-term outcome. Several studies have suggested that early diagnosis may lead to better prognosis in those young patients.[6,9] We believe that diagnosis could be arrived at earlier by applying our proposed classification system.

The limitations of the study include its small size and retrospective nature. Both are caused by the rarity of the syndrome.

In summary, this retrospective case series examined the characteristics of Susac syndrome and the patients' long-term outcomes. Our observations should raise the awareness to the importance of early and correct diagnosis of Susac syndrome in

those young patients. We propose a clinical classification that may help physicians to diagnose the syndrome early in its course. Future multicenter prospective studies are needed for better understanding of the syndrome, validation of the proposed classification, and effective planning of treatment strategy.

References

[1] Schwitter J, Agosti R, Ott P, et al. Small infarctions of cochlear, retinal, and encephalic tissue in young women. Stroke 1992;23:903–7.

[2] Mala L, Bazard MC, Berrod JP, et al. Small retinal, cochlear, and cerebral infarctions in the young patient, "SICRET" syndrome of Susac syndrome [French]. J Fr Ophtalmol 1998;21:375–80.

[3] Nicolle MW, McLachlan RS. Microangiopathy with retinopathy, encephalopathy, and deafness (RED-M) and systemic features. Semin Arthritis Rheum 1991;21:123–8.

[4] Susac JO, Hardman JM, Selhorst JB. Microangiopathy of the brain and retina. Neurology 1979;29:313–6.

[5] Susac JO. Susac's syndrome: the triad of microangiopathy of the brain and retina with hearing loss in young women. Neurology 1994;44: 591–3.

[6] Magro CM, Poe JC, Lubow M, et al. Susac syndrome: an organ-specific autoimmune endotheliopathy syndrome associated with anti-endothelial cell antibodies. Am J Clin Pathol 2011;136:903–12.

[7] Brandt AU, Zimmermann H, Kaufhold F, et al. Patterns of retinal damage facilitate differential diagnosis between Susac syndrome and MS. PLoS ONE 2012;7:e38741.

[8] Dorr J, Radbruch H, Bock M, et al. Encephalopathy, visual disturbance and hearing loss-recognizing the symptoms of Susac syndrome. Nat Rev Neurol 2009;5:683–8.

[9] Dorr J, Krautwald S, Wildemann B, et al. Characteristics of Susac syndrome: a review of all reported cases. Nat Rev Neurol 2013;9:307–16.

[10] Boukouvala S, Jacob S, Lane M, et al. Detection of branch retinal artery occlusions in Susac's syndrome. BMC Res Notes 2014;7:56.

[11] Yildirim Y, Kar T, Kaya A. Progression of retinal artery occlusion from one eye to the other seems to be a characteristic finding in Susac syndrome. Arq Bras Oftalmol 2013;76:391.

[12] Seamone ME, Fielden M. A case of isolated Susac occlusive retinal vasculitis. J Neuroophthalmol 2013;33:260–2.

[13] Saw VP, Canty PA, Green CM, et al. Susac syndrome: microangiopathy of the retina, cochlea and brain. Clin Exp Ophthalmol 2000;28:373–81.

[14] Rennebohm RM, Susac JO. Treatment of Susac's syndrome. J Neurol Sci 2007;257:215–20.

[15] Jarius S, Kleffner I, Dorr JM, et al. Clinical, paraclinical and serological findings in Susac syndrome: an international multicenter study. J Neuroinflammation 2014;11:46.

[16] Greco A, De Virgilio A, Gallo A, et al. Susac's syndrome—pathogenesis, clinical variants and treatment approaches. Autoimmun Rev 2014; 13:814–21.

[17] Mateen FJ, Zubkov AY, Muralidharan R, et al. Susac syndrome: clinical characteristics and treatment in 29 new cases. Eur J Neurol 2012; 19:800–11.

[18] Aubart-Cohen F, Klein I, Alexandra JF, et al. Long-term outcome in Susac syndrome. Medicine (Baltimore) 2007;86:93–102.

[19] Coppeto JR, Currie JN, Monteiro ML, et al. A syndrome of arterial-occlusive retinopathy and encephalopathy. Am J Ophthalmol 1984; 98:189–202.

[20] MacFadyen DJ, Schneider RJ, Chisholm IA. A syndrome of brain, inner ear and retinal microangiopathy. Can J Neurol Sci 1987;14:315–8.

[21] Gordon DL, Hayreh SS, Adams HPJr. Microangiopathy of the brain, retina, and ear: improvement without immunosuppressive therapy. Stroke 1991;22:933–7.

[22] Petty GW, Engel AG, Younge BR, et al. Retinocochleocerebral vasculopathy. Medicine (Baltimore) 1998;77:12–40.

[23] Cador-Rousseau B, Cazalets C, Decaux O, et al. Susac's syndrome in post-partum [French]. Rev Med Interne 2002;23:667–8.

[24] Grinspan ZM, Willey JZ, Tullman MJ, et al. Clinical reasoning: a 28-year-old pregnant woman with encephalopathy. Neurology 2009;73: e74–9.

[25] Pawate S, Agarwal A, Moses H, et al. The spectrum of Susac's syndrome. Neurol Sci 2009;30:59–64.

[26] Finis D, Stammen J, Gonnermann J. Retinal arteritis in pregnancy [German]. Ophthalmologe 2011;108:676–82.

[27] Hardy TA, Garsia RJ, Halmagyi GM, et al. Tumour necrosis factor (TNF) inhibitor therapy in Susac's syndrome. J Neurol Sci 2011;302:126–8.

[28] Deane KD, Tyler KN, Johnson DW, et al. Susac syndrome and pregnancy: disease management. J Clin Rheumatol 2011;17:83–8.

[29] Papo T, Biousse V, Lehoang P, et al. Susac syndrome. Medicine (Baltimore) 1998;77:3–11.

[30] Do TH, Fisch C, Evoy F. Susac syndrome: report of four cases and review of the literature. American journal of neuroradiology 2004;25: 382–8.

[31] Snyers B, Boschi A, De Potter P, Duprez T, Sindic C. Susac syndrome in four male patients. Retina 2006;26:1049–55.