eNeurologicalSci 10 (2018) 1–4

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Case report

Exquisite response to intravenous immunoglobulin in Susac syndrome during pregnancy

Enrique Gomez-Figueroa*,[1], Sofia Garcia-Trejo[1], Raul Anwar Garcia-Santos[1], Gerardo Quiñones-Pesqueira[1], Juan Manuel Calleja-Castillo[1]

Neurology Department, Instituto Nacional de Neurologia y Neurocirugia, Mexico City, Mexico

ARTICLE INFO

Keywords:
Susac syndrome
Neuroinflammation
Corpus callosum
Demyelinating disease
Vasculitis

ABSTRACT

Introduction: From its initial report on two female patients in 1979 by J.O. Susac, Susac syndrome (SuS) or SICRET (small infarctions of cochlear, retinal and encephalic tissue) has persisted as an elusive entity. To date the available evidence for its treatment is based on case reports and case series. The largest systematic review described only 304 reported cases since the 1970s. Here we presented the first reported case to our knowledge in Mexican population and the unusual presentation in a pregnant patient.

Case presentation: A 34-year-old Hispanic woman was brought to the ER in our hospital for apathy and behavioral changes. Upon arrival at the ER, her husband described a one-month history of behavioral changes with apathy, progressive abulia, visuospatial disorientation, and gait deterioration. The initial lab test shows no significance except by a positive qualitative hCG. An MRI was obtained and showed hyperintense periventricular white matter lesions in T2 and FLAIR sequences also involving bilateral basal ganglia and with predominant affection of the corpus callosum, in addition to infratentorial cerebellar lesions. After treatment with intravenous immunoglobulins a marked and prompt clinical and radiological improvement was observed.

Conclusion: SuS is still an elusive disease. To date, no definitive score or clinical feature can predict the outcome of the disease. The presentation during pregnancy is also rare and therefore the optimal treatment and the prognosis is unknown. We hope that this article will serve as a foundation for future research.

1. Introduction

From its initial report on two female patients in 1979 by J.O. Susac, Susac syndrome (SuS) or SICRET (small infarctions of cochlear, retinal and encephalic tissue) has persisted as an elusive entity. To date the available evidence for its treatment is based on case reports and case series. The largest systematic review described only 304 reported cases since the 1970s [1]. Here we presented the first reported case to our knowledge in Mexican population and the unusual presentation in a pregnant patient.

2. Clinical case

A 34-year-old Hispanic woman was brought to the ER in our hospital for apathy and behavioral changes. She had no prior neurological or systemic disease, no exposure to toxic or vascular risk factors, and had suffered a self-limiting (3-days duration) episode of incapacitating vertigo 6 months prior and an episode of right ear tinnitus (2 days of duration) 2 months before hospitalization without receiving any medical care.

Upon arrival at the ER, her husband described a one-month history of behavioral changes with apathy, progressive abulia, visuospatial disorientation, and gait deterioration. Initial exploration revealed a patient with auto-activation apathy, monotonous and dysprosodic speech and bilateral corticospinal involvement with hyperreflexia and Babinski's sign but no weakness.

The initial lab test shows no significance except by a positive qualitative hCG. The patient was unable to answer for any G/O history and her husband was also oblivious about it. An MRI was obtained and showed hyperintense periventricular white matter lesions in T2 and FLAIR sequences also involving bilateral basal ganglia and with predominant affection of the corpus callosum, in addition to infratentorial cerebellar lesions. Lesional restriction of diffusion but no contrast enhancement was observed. T1 weighted images showed hypointense lesions in the same topography (Fig. 1). Due to prominent pericallosal lesions with clinical findings of medial frontal syndrome and bilateral

* Corresponding author at: Instituto Nacional de Neurologia y Neurocirugia Manuel Velasco Suarez, Insurgentes Sur 3877, Tlalpan, Mexico city, Mexico.
E-mail address: enriquegfigueroa@comunidad.unam.mx (E. Gomez-Figueroa).
[1] These authors contributed equally to the manuscript.

https://doi.org/10.1016/j.ensci.2017.12.004
Received 30 November 2017; Accepted 20 December 2017
Available online 22 December 2017

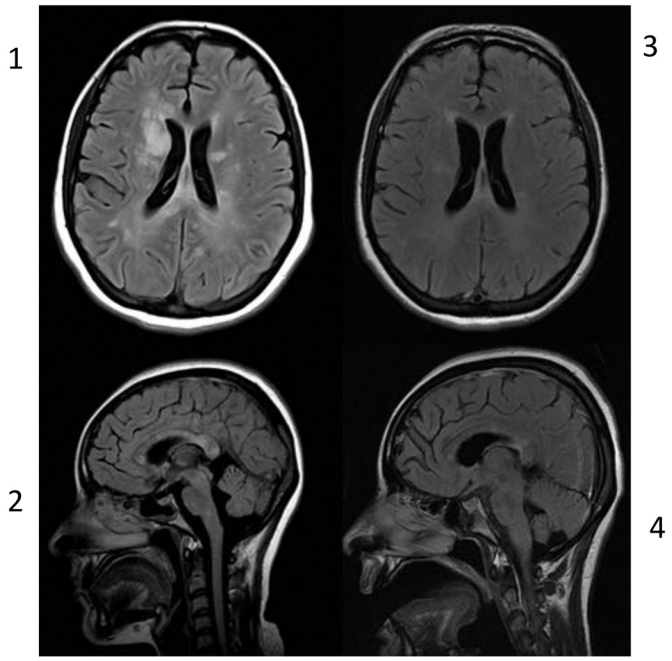

Fig. 1. MRI FLAIR sequence. Part 1 and 2 Pretreatment images shows hyperintense lesions with predominantly pericallosal involvement in the subependymal striatons and the *snowball* lesions. Part 3 and 4 shows IgIV post treatment changes with almost complete disappearance of the previous lesions.

corticospinal involvement of monophasic subacute evolution, primary vs secondary demyelinating disease was suspected. A lumbar puncture was performed resulting and CSF values showed proteins of 77 mg/dl, glucose of 52 mg/dl (serum glucose of 89 mg/dl), and no cells. Anti-AQP4 antibodies and oligoclonal bands were absent in CSF. A comprehensive workup for viral encephalitis and atypical infectious-disease result negative and cultures for fungi and bacteria. Also given the impossibility to further image studies as a complete CT and PET, a workup for paraneoplastic neurologic antibodies was obtained that was also negative Complete rheumatologic workup was negative except for 1: 2560 antinuclear antibodies in a speckled staining fine pattern without any systemic clinical correlate. Obstetric evaluation showed a normal development 15 weeks GA fetus.

Upon admission, 5 pulses of methylprednisolone were administered without obvious clinical improvement. Immunomodulatory treatment was escalated to intravenous immunoglobulin (IVIg) at 0.4 g/kg/day for 5 days. After treatment with IVIg, neuropsychiatric symptoms of medial frontal syndrome remitted, and the patient could cooperate for further study. Ophthalmologic assessment revealed retinal vasculitis corroborated by fluorangiography (FA) (Supplementary Fig. 1). Audiometric testing showed bilateral sensorineural hearing loss. A new MRI showed prior lesions to be smaller or absent, and the patient showed clinical improvement confirmed by neuropsychological testing. Once the diagnosis of SuS was established. The husband decided not to continue further with the pregnancy and a therapeutic abortion was performed, the patient was discharged for further treatment with oral steroids and CCF.

3. Discussion and conclusion

Here we discuss an atypical patient with the unusual diagnosis of Susac syndrome in a Mexican woman who was also in the first trimester of pregnancy. The anatomical basis of the clinical diagnosis as a subacute and evolving frontal syndrome in a young woman guide or workup to focus in autoimmune disorders, demyelinating disorders and structural lesions. The MRI allows to focus on the overview of predominantly callosal disease.

Differential diagnosis of corpus callosum lesions includes demyelinating, non-demyelinating inflammatory lesions, and transient splenial lesions. Demyelinating lesions include MS, neuromyelitis optica and ADEM, all of which were discarded in this patient based on the respective criteria for each one. Non-demyelinating inflammatory lesions include SuS and CNS vasculitis [2]. It is particularly important to differentiate SuS from MS. In SuS, lesions of the corpus callosum are typically centrally located, while the lesions in MS and ADEM involve the undersurface at the septal interface, in MS, these lesions are often extended around the venules of the brain, resulting in a finger-like appearance ("Dawson fingers"), while lesions appear circular in SuS. Typically, these callosal lesions involve the central fibers and spare the periphery [3] MRI reveals widespread abnormalities of the corpus callosum, manifested as small central holes, particularly in the splenium. Linear defects of the corpus callosum can also be detected, the so-called "spokes", representing microinfarctions of obliquely radiating axons [4]. The localization of the lesions is probably explained by the angioarchitecture of the corpus callosum. The inflammation and occlusion of the small precapillary arterioles with a diameter under 100 μm result in infarction of the central portion, but not the undersurface of the corpus callosum [4]. Subsequent documented involvement of retinal vasculitis and vestibulocochlear damage established the diagnosis in our patient.

SuS is currently considered a vasculitis with predominantly endothelial affection of autoimmune origin probably mediated by endothelial cell antibodies (AECA), with subsequent response by complement with C4d deposits, "mummification" phenomena, and endothelial necrosis [5]. Nevertheless, a study showed that in fact only 30% of patients with definite SuS have AECA, suggesting that AECA represent a secondary phenomenon in an etiologically heterogeneous syndrome, with a pathogenesis still far from fully understood [6]. Respecting the other autoantibodies and considering the high titers of ANA in our patients we found that antinuclear autoantibodies have been described in patients with SuS, but do not occur more often than in healthy controls [6].

Diagnosis of SuS is predominantly clinical and based on the evidence of the originally described triad with encephalic, retinal and vestibulocochlear affection. The clinical features include encephalopathy that is characterized by headache that may be migrainous or oppressive. Headache often occurs up to six months before the onset of the other symptoms. It is probably due to an affection of the leptomeningeal vessels. The other symptoms of encephalopathy have a stroke-like or subacute onset, with neuropsychological deficits, bladder disturbance, long tract signs, focal neurological signs, seizures, and often disturbance of consciousness [1]. The hearing loss can be a dramatic and severely disabilitating feature of Susac syndrome. It often occurs overnight and may affect both ears. A loss of the low or middle frequencies is typical, but loss of high frequencies can also occur. The severe hearing loss is often accompanied by vertigo and a roaring tinnitus. The hearing loss is caused by occlusion of the cochlear precapillary arterioles and those of the semicircular canal. Hearing loss is often irreversible and may require cochlear implants or hearing devices for a whole life [7]. Typical findings in patients with SuS include branch retinal artery occlusions (BRAO) detectable on retinal fluorescein angiography, the occlusions may affect the periphery and may not lead to clinical symptoms, but they can also affect the larger branches resulting in visual field deficits. Many patients complain about blurred vision or photopsia [7]. MRI, retinal fluorescein angiography, and audiometry are considered crucial tests to enable diagnosis.

In 2016, specific diagnostic criteria based on a cohort of 32 patients was proposed: Definitive SuS requires involvement of these 3 systems [8]. Being a rare disease, the clinical course and prognosis is largely unknown. Based on empirical stratification [9] the course can be monocyclic, polycyclic and chronic–continuous with a cutoff parameter of 2 years separating the monocyclic course from the other forms.

Many treatment approaches for SuS have been described in case

Table 1
Comparison of data of the different reported cases of Susac syndrome with onset in pregnancy.

Cases	1	2	3	4	5	6	7	8
Published by	Gordon1991[8]	McFayden1987[9]	Hua2014[10]	Ionnides2013[11]	Engelholm2013[12]	Antulov2014[13]	Feresiadou2014[14]	Our case
Origin	US	Canada	US	Australia	Germany	Croatia	Sweden	Mexico
Age	28	31	25	28	32	21	35	34
Gestational age at onset (weeks)	28	No specified	14	13	32	35	37	15
Previous medical history	None	None	None	Epilepsy from a perinatal ischaemic event	None	None	Apparent similar clinical picture at 12 yo, treated with steroids	None
System of onset	Eye	Eye	Auditory	Neurologic	Neurologic	Neurologic	Auditory	Auditory
Neurologic symptoms	Unilateral weakness, dysarthria and apathy	Ataxia and dysarthria	Amnestic syndrome, Gait disorder, Bilateral severe weakness	Bilateral severe weakness and dysarthria	Encephalopathic syndrome and Unilateral weakness	Bilateral severe weakness and progressive cognitive affection	None	Cognitive affection (frontal medial syndrome) and bilateral weakness
Ophthalmologic symptoms	Visual field deficit	Visual field deficit	Loss of visual acuity	Loss of visual acuity	Visual field deficit	None	Loss of visual acuity and visual field deficit	Loss of visual acuity
Auditory symptoms	Bilateral neurosensorial hearing loss	Bilateral tinnitus and neurosensorial hearing loss	Tinnutus	Right neurosensorial hearing loss	Neurosensorial hearing loss	Left neurosensorial hearing loss	Tinnitus and left neurosensorial hearing loss	Tinnitus and bilateral neurosensorial hearing loss
Additional or atypical affection	None	None	Cervical cord involvement	None	Livedo racemosa	None	None	None
Time until fully triad (months)	1	2	6	4	1.5	Not completed	Not completed	6
MRI findings								
Deep grey matter	No	Not done	Yes	Yes	Yes	Yes	No	Yes
White matter	Callosal and periventricular	Not done	Callosal and periventricular lesions	Callosal	Callosal and periventricular lesions	Callosal and periventricular lesions	No	Callosal
Posterior fossa involvement	No	Not done	Yes	No, but also reported meningeal enhancement	Yes	Yes	No	No
Gadolinium enhancement	No reported	Not done	Yes	No reported	Yes	No reported	No	Yes
CSF findings								
Proteins mg/dl	No reported	252	95	2000	1800	1009	No performed	77
Cells (Mono)	No reported	0	6	9	No reported	No reported	No performed	0
Treatment								
Initial treatment	Heparin	None	IVMP × 5	IVMP × 3	IVMP × 5	IGIV × 5	IVMP × 5	IVMP × 5
Response	Partial		Partial	No response	Partial	Complete response	Partial	No response
2nd line treatment	None	None	Oral prednisone	PLEX and IVIg	Oral prednisone	None	None	IgIV
Chronic treatment	Warfarin	Oral prednisone	MMF	MMF	MMF + MTX	AZA	Oral prednisone	CCF
Response	Almost complete recovery	Partial remission	Partial remission	No response	Almost complete recovery	Almost complete recovery	Almost complete recovery	Partial remission
Prognosis								
Follow up (years)	0.2	4	1.5	3.5	1	0.2	3	0.5
Sequels	Visual deficit	Mild hearing loss	Cognitive deficit with visuospatial and word recall	No specified	Mild cognitive deficit	Subtle weakness	Mild left hearing loss	Cognitive deficit
Course of disease		Monocyclic	Monocyclic	Chronic continuous	Probably Monocyclic	Probably Monocyclic	Monocyclic	Probably Monocyclic
Final pregnancy state	Healthy product	Healthy product	Healthy product	Therapeutic abortion at 15 weeks GA	Healthy product	Healthy product	Healthy product	Therapeutic abortion at 17 weeks GA

reports and series, but rigorous analysis of these therapies is limited by inconsistent and often incomplete reports. In the acute period, treatment with steroids, IVIg, plasma exchange, and even rituximab has been reported with predominantly successful response [10]. Antithrombotic agents and nimodipine have also been used, aiming to maintain blood flow and prevent vasospasm [7]. Optimal chronic management and duration of treatment is unknown, yet the decision to withdraw treatment must incorporate surveillance brain MRI and FA findings in addition to clinical symptoms and signs.

We have managed to find 7 cases previously reported in the literature in English and in Spanish of cases that have started with Susac syndrome during pregnancy [11–17] (Table 1). Unfortunately, the behavior of the disease is heterogeneous. Dr. Aubert-Cohen et al. have also managed to report the behavior of the disease before and after pregnancy in 4 patients. Obviously, the low frequency of the disease does not allow obtaining any statistically significant result. But we hope that this article will serve as a foundation for future research.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2017.12.004.

Contributions

Dr. Calleja-Castillo was in charge of the diagnosis, treatment care and follow up of the patient and supervised the elaboration of the manuscript. Dr. Gomez-Figueroa prepared the draft. All authors were part of the patient care team and approved the final submitted version.

Written consent to publish was obtained from the patient.

Conflict of interest

All authors declare no competing interests or external funding.

References

[1] J. Dörr, S. Krautwald, B. Wildemann, et al., Characteristics of Susac syndrome: a review of all reported cases, Nat. Rev. Neurol. 9 (2013) 307–316.
[2] N. Gaig, S.W. Reddel, D.H. Miller, et al., The corpus callosum in the diagnosis of multiple sclerosis and other CNS demyelinating and inflammatory diseases, J. Neurol. Neurosurg. Psychiatry 0 (2015) 1–9.
[3] I. Kleffner, M. Deppe, S. Mohammadi, Neuroimaging in Susac's syndrome: focus on DTI, J. Neurol. Sci. 299 (2010) 92–96.
[4] I. Kleffner, et al., A brief review of Susac syndrome, J. Neurol. Sci. 322 (2012) 35–40.
[5] J.O. Susac, et al., Susac's syndrome: 1975–2005 microangiopathy/autoimmune endotheliopathy, J. Neurol. Sci. 257 (1) (2007) 270–272.
[6] Jarius et al., Clinical, paraclinical and serological finding in Susac syndrome: an international multicenter study, J. Neuroinflammation 11 (2014) 46.
[7] V. Vishnevskia-dai, J. Chapman, R. Sheinfeld, Susac syndrome: clinical characteristics, clinical classification, and long-term prognosis, Medicine (Baltimore) 95 (2016) e5223.
[8] I. Kleffner, J. Dörr, M. Ringelstein, et al., Diagnostic criteria for susac syndrome, Neurol. Neurosurg. Psychiatry 87 (2016) 1287–1295.
[9] R.M. Rennebohm, R.A. Egan, J.O. Susac, Treatment of Susac's syndrome, Curr. Treat. Options Neurol. 10 (2008) 67–74.
[10] I. Vodovipec, S. Prasad, Treatment of Susac syndrome, Curr. Treat. Options Neurol. 18 (2016) 3–8.
[11] D.L. Gordon, S.S. Hayreh, H.P. Adams Jr., Microangiopathy of the brain, retina, and ear: improvement without immunosuppressive therapy, Stroke 22 (1991) 933–937.
[12] D.J. MacFadyen, R.J. Schneider, I.A. Chisholm, A syndrome of brain, inner ear and retinal microangiopathy, Can. J. Neurol. Sci. 14 (1987) 315–318.
[13] Hua, L.H. et al. A case of Susac syndrome with cervical spinal cord involvement on MRI. J. Neurol. Sci., 337, 1, 228–231.
[14] Z.A. Ioannides, C. Airey, N. Fagermo, et al., Susac syndrome and multifocal motor neuropathy first manifesting in pregnancy, Aust. N. Z. J. Obstet. Gynaecol. 53 (2013) 314–317.
[15] M. Maik Engeholm, B. Leo-Kottler, H. Rempp, et al., Encephalopathic Susac's syndrome associated with livedo racemosa in a young woman before the completion of family planning, BMC Neurol. 13 (185) (2013).
[16] R. Antulov, I. Holjar-Erlic, O. Perkovic, et al., Susac's syndrome during pregnancy—the first Croatian case, J. Neurol. Sci. 341 (1–2) (2014) 162–164.
[17] A. Feresiadou, U. Eriksson, H.-C. Larsen, et al., Recurrence of Susac syndrome following 23 years of remission, Case Rep. Neurol. 6 (2014) 171–175.