Anecdotal Response to Amphotericin in a Patient with Probable Susac Syndrome: Implications in the Pathogenesis

Um Caso de Provável Síndrome de Susac com Resposta Anedótica à Anfotericina: Implicações na Patogénese

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ABSTRACT

Susac syndrome is a rare, probably immune-mediated endotheliopathy presenting with encephalopathy, sensorineural hearing loss and retinal arterial occlusions. A 33-year-old female with Susac syndrome was worsening despite high-dose steroids so a brain biopsy was performed which suggested a possible fungal infection. Treatment with amphotericin B resulted in prompt reversal of symptoms and radiological findings, and no further symptoms occurred during 8 years of follow-up. A diagnosis of fungal infection was not confirmed. The etiology of Susac syndrome is unknown and this anecdotal observation suggests that an infectious agent susceptible to amphotericin might have caused or triggered Susac syndrome in this patient.

Keywords: Amphotericin B; Meningoencephalitis; Susac Syndrome

RESUMO

A síndrome de Susac é uma endoteliopatia rara, provavelmente imunomediada de encefalopatia, surdez neurosensorial e oclusões de ramos arteriais da retina. Apresenta-se o caso de uma mulher de 33 anos com o diagnóstico de síndrome de Susac que agravou sob terapêutica imunossupressora, pelo que se decidiu pela realização de uma biópsia cerebral, que levantou a suspeita de uma possível infecção fúngica. O tratamento com anfotericina B resultou numa recuperação clínica e imagiológica rápida e não se verificou recorrência de sintomas num período de seguimento de oito anos. O diagnóstico de meningoencefalite fúngica não foi confirmado. A etiologia da síndrome de Susac é desconhecida. A observação fortuita da resposta terapêutica deste caso sugere que um agente infeccioso suscetível à anfotericina B possa ter causado ou desencadeado esta síndrome, nesta doente.

Palavras-chave: Anfotericina B; Meningoencefalite; Síndrome de Susac

INTRODUCTION

Susac syndrome is a microangiopathy of uncertain pathogenesis causing small infarcts in the brain, cochlea and retina leading to the clinical triad of subacute encephalopathy, sensorineural hearing loss and branch retinal artery occlusions, although these features may not present simultaneously.1 It was proposed as an immune-mediated endotheliopathy2 that may possibly be self-limited,3 even if most cases show a fluctuant course.4 Sequela are frequent, often mild, but cases of severe encephalopathy and resistance to treatment occur5–5 with dramatic outcomes. The usual treatment options include immunosuppression3 and antiplatelet agents or anticoagulation.4 We report the case of a patient with refractory Susac syndrome who was treated with amphotericin and had an outstanding recovery. We discuss the similarities of Susac syndrome with fungal meningoencephalitis and speculate about a potential role of an infectious agent as a trigger or in the pathogenesis.

CASE REPORT

A 33-year-old female developed a flu-like illness followed by persistent headache, cognitive decline with self-limited episodes of urinary incontinence and gait instability. One month later she developed encephalopathy, showing persistent gait apraxia, marked psychomotor slowness and frontal release signs. Initial diagnostic hypothesis included acute disseminated encephalomyelitis and meningoencephalitis. Initial blood routines were normal, and the protein level in the cerebrospinal fluid (CSF) was 85 mg/dL. Initial empiric treatment with ceftriaxone (2 g/d, 2 weeks) and a short course of methilprednisone (1 g/d, 5 days) were started on admission, with clinical improvement. Electroencephalography showed bilateral asymmetrical frontal slowing. The neuroaxis magnetic resonence imaging (MRI) depicted typical lesions of Susac syndrome (Figs. 1 A, B, C) and the ophthalmological evaluation revealed a temporal arterial retinal branch infarct, confirmed by angiography. The audiogram and the auditory evoked potential test were normal, therefore this clinical presentation was compatible with the diagnosis of probable Susac syndrome.1

Normal laboratory testing included inflammatory markers, full panel of systemic auto-antibodies, angiotensin converting enzyme (ACE), lysozyme, serologies for
CASO CLÍNICO


After two weeks there was clinical worsening and elevation of CSF protein levels (up to 164 mg/dL), and thus 1 mg/kg/day prednisone was started. However, the encephalopathy progressed with drowsiness, confusion, apathy, amnesia and inability to perform simple mental tasks. There was weekly elevation of CSF protein levels (reaching 232 mg/dL 7 weeks later) with all other CSF parameters remaining normal, including glucose level, cell content and seven negative fungal cultures. Considering the possibility of the alternative diagnosis of central nervous system vasculitis, angiography and biopsy were undertaken — brain angiography revealed mild tortuosity of the pericallosal artery; the callosal biopsy showed glial tissue, scarce inflammatory infiltrate and round subependymal structures, suggestive of *corpora amylacea* bodies. Samples were sent for electronic microscopy (from paraffin) to exclude dimorphic fungus, which was later not confirmed. Brain tissue culture was not performed.

Due to the possibility of a dimorphic fungus, amphotericin B (1 mg/kg, 8 g total) was started during the 8th week and prednisone was tapered in the following two weeks while waiting for the electronic microscopy result. Clinical improvement was noted after 48 hours, and full clinical recovery occurred at the 12th week when MRI showed marked reduction of the number and size of the brain lesions and resolution of the leptomeningeal enhancement. The patient was discharged during the 16th week, and returned to her normal life without limitations and has been followed up yearly since then. She remains well after eight years of follow-up, having had a successful pregnancy two years ago.

DISCUSSION

This young healthy female presented with subacute onset encephalopathy after a flu-like illness in which the MRI showed typical brain lesions of Susac syndrome,2,6 high protein content in CSF and an asymptomatic arterial retinal branch infarct, without auditory involvement — the most frequent inaugural symptoms7 fulfilling the proposed diagnostic criteria for probable Susac syndrome.1 Although an initial response to steroids was observed, it was followed by persistent clinical decline unrelated to complications.
of steroid therapy, and that has been described by Susac et al., and usually implies escalation to aggressive immunosuppression. An angiography and biopsy were undertaken to evaluate the possibility of primary angiitis of the central nervous system although the MRI had not shown hemorrhagic lesions. Angiography revealed very mild focal callosal abnormalities and histological analysis casted doubts about the possibility of a dimorphic fungus, as there were no signs of vessel wall damage. Considering the catastrophic clinical worsening, amphotericin was started, steroids were tapered and a fast and dramatic clinical and radiological improvement ensued, and this argued against a possible spontaneous remission or a delayed steroid effect. Electron microscopy confirmed the presence of corpora amylacea-like bodies, described by Susac et al. and these were associated with antifungal antibodies. Corpora amylacea are glycoproteinaceous structures that are found in aged, normal human brains, but also in several diseases, in particular neurodegenerative or infectious/inflammatory conditions. Recent evidence suggests that these structures are part of an organized physiological cleaning process in the central nervous system, serving as ‘waste containers’. Brain tissue cultures were not done, which is the major limitation against being able to establish a definitive diagnosis. The yield of a positive fungal culture in fungal meningoencephalitis is lower than 50%, even with repeated CSF sampling as was done, so it often remains a presumptive diagnosis — nevertheless, there was never pleocytosis in 7 repeated CSF analysis. All the clinical and para-clinical data of this case supported the diagnosis of Susac syndrome, except for the anecdotal response to amphotericin. This fortuitous observation leads to speculation — could this have been a fungal encephalomeningitis? Or could a fungal (or other amphotericin responsive) agent might have triggered an immune response simulating a Susac-like syndrome in our patient? Or even less likely, could Susac syndrome have been caused by an amphotericin-responsive agent? Or could Susac syndrome have responded to amphotericin due to an unknown mechanism?

The etiology of Susac syndrome is unknown, although the finding of anti-endothelial cell antibodies (AECA) in some patients suggests an immunological humoral inflammation of the microvascular endothelium. A study of AECA in a large clinical sample of patients with Susac syndrome did not find an association of high-titer IgG1 and IgM AECA with clinical data, response to treatment nor outcome, so we did not find an association of high-titer IgG1 and IgM AECA with the finding of anti-endothelial cell antibodies (AECA) in our patient. However, the average symptom duration described before remission in Susac syndrome is two years and often residual symptoms persist. In our case, the complete and fast inversion of the clinical worsening tendency that persisted for eight weeks despite adequate treatment had a close temporal relationship of days with the change in treatment course, casting doubts of it being an occasional coincidental finding. Our long completely symptom free follow-up period of eight years favors either a monophasic infectious illness or a monophasic Susac syndrome; the occurrence of an uncomplicated pregnancy without relapses in our patient argues against Susac syndrome.

ACKNOWLEDGMENTS

The authors would like to acknowledge significant contribution to clinical discussion and daily clinical support from the medical team in Hospital da Luz, especially Paulo Martins Campos (Ophthalmology) who studied the ophthalmological manifestations, Manuel Cunha e Sá (Neurosurgery) who performed the brain biopsy and also to José Ferro for helpful input on differential diagnosis.

We also like to acknowledge the helpful input that Jan Markus Dörr made to the discussion of this report. This case report was awarded the 2nd António Flores award, for poster presentations, at the Portuguese Neurological Society Congress in 2009.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients’ data publication.

PATIENT CONSENT

Obtained.

CONFLICTS OF INTEREST

All authors report no conflict of interest.

FUNDING SOURCES

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Hemoperitoneu Espontâneo na Gravidez

Spontaneous Hemoperitoneum in Pregnancy

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https://doi.org/10.20344/amp.11169

RESUMO

A endometriose é uma doença benigna, crônica e estrogênio-dependente. Pensa-se que a gravidez tenha um efeito positivo na endometriose através da inibição da ovulação, contudo tem surgido evidência da associação da endometriose não só com infertilidade, mas também com complicações obstétricas. Descreve-se o caso de uma grávida de 34 semanas, com antecedentes clínicos e ecográficos sugestivos de endometriose, admitida por dor abdominal súbita e intensa. Durante a cesariana emergente, realizada por bradicardia sustentada, constatou-se a presença de um volumoso hemoperitoneum e focos hemorrágicos na parede uterina posterior. Apesar de raro, o hemoperitoneu espontâneo é uma complicação possível na gravidez, sobretudo em mulheres com antecedentes de endometriose. Dadas as complicações materno-fetais associadas, uma rápida suspeição diagnóstica e intervenção são fundamentais.

Palavras-chave: Complicações na Gravidez; Endometriose; Gravidez; Hemoperitoneu

ABSTRACT

Endometriosis is a benign, estrogen-dependent chronic disorder. Pregnancy is considered to have a positive effect on endometriosis due to blockage of ovulation; however, evidence is emerging on the role of endometriosis not only in infertility but also in poor pregnancy outcomes. We present the case of a pregnant woman admitted for sudden and severe abdominal pain at 34 weeks gestation. Her previous medical history included endometriosis suspected by clinical symptoms and ultrasound. During cesarean section, performed by sustained fetal bradycardia, a large volume hemoperitoneum and multiple hemorrhagic foci in the posterior uterine wall were detected. Although rare, spontaneous hemoperitoneum may occur in pregnancy, especially in women with endometriosis. Thus, a prompt suspicion and expedite intervention are needed to improve maternal and fetal outcomes.

Keywords: Endometriosis; Hemoperitoneum; Pregnancy; Pregnancy Complications

INTRODUÇÃO

A endometriose define-se pela presença de tecido endometrial fora do útero, mais frequentemente na pelve, afetando cerca de 10% das mulheres em idade reprodutiva.1 Clínicamente pode associar-se a dor pélvica, dismenorreia grave, dispareunia e infertilidade, ou ser assintomática e descoberta de forma acidental intra-operatoriamente.2

É historicamente aceite que a gravidez tem um efeito positivo na endometriose e nos seus sintomas devido ao estado anovulatório, que previne a hemorragia nos implantes, e às alterações metabólicas, hormonais, imunológicas e angiogênicas que caracterizam a gravidez.2 Contudo, têm sido reportadas complicações obstétricas associadas à endometriose, como o hemoperitoneu espontâneo (HE) que apesar de raro pode pôr em risco a vida materna e feto.3,4

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5. Recebido: 05 de novembro de 2018 – 15 de março de 2019 | Copyright © Ordem dos Médicos 2019

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