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Review

Susac's syndrome — Pathogenesis, clinical variants and treatment approaches

Antonio Greco [a], Armando De Virgilio [a,*], Andrea Gallo [b], Massimo Fusconi [a], Rosaria Turchetta [c], Mario Tombolini [a], Maria Ida Rizzo [a], Marco de Vincentiis [a]

[a] Department Organs of Sense, ENT Section, University of Rome "La Sapienza", Viale del Policlinico 155, 00100 Roma, Italy
[b] Department of Medico-Surgical Sciences and Biotechnologies, Otorhinolaryngology Section, University of Rome "La Sapienza", Corso della Repubblica 79, 04100 Latina, LT, Italy
[c] Department Organs of Sense, Audiology Section, University of Rome "La Sapienza", Viale del Policlinico 155, 00100 Roma, Italy

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ABSTRACT

Susac's syndrome is a rare disease that is characterised by the clinical triad of encephalopathy, branch retinal artery occlusion, and sensorineural hearing loss. It was first described as a distinctive syndrome by Susac in 1979. There have been 304 reported individual patients with Susac's syndrome.
Etiopathogenesis is not clear, although it is now thought that it is an immune-mediated endotheliopathy that affects the microvasculature of the brain, retina, and inner ear.
Antiendothelial cell antibodies (AECAs) play an important role in mediating the endothelial cell injury with consequent deposition of thrombotic material in the lumen of the small vessel.
In biopsies of the brain, microinfarcts with atrophy of the white and grey matter could be detected. These microinfarcts are caused by a microangiopathic process with arteriolar wall proliferation, lymphocytic infiltration and basal lamina thickening.
At clinical onset, the most common manifestation was central nervous system symptoms, followed by visual symptoms and hearing disturbances.
Diagnosis is based on Magnetic Resonance Imaging (MRI), retinal fluorescein angiography, and audiometry; these are considered crucial tests to enable diagnosis. Antiendothelial cell antibodies (AECAs) are also of diagnostic relevance.
Based on the hypothesis of being an autoimmune disease, treatment has to be immunosuppressive. In addition, anticoagulation measures, antiplatelet agents and antivasospastic agents should be considered.
The majority of patients did not initially present with the complete triad of symptoms. An appropriate approach would be to perform a search for absent components of the triad if the clinical presentation is suggestive of Susac's syndrome. Improved understanding of the presentation of Susac's syndrome will prevent misdiagnosis and ensure that patients receive the best possible care.

Contents

* Corresponding author at: Department Organs of Sense, ENT Section, University of Rome "La Sapienza", Viale del Policlinico 155, 00100 Roma, Italy. Tel.: +39 380 3408909; fax: +39 06 49976803.
E-mail addresses: antonio.greco@uniroma1.it (A. Greco), armando.devirgilio@gmail.com (A. De Virgilio), andrea.gallo@uniroma1.it (A. Gallo), massimo.fusconi@uniroma1.it (M. Fusconi), rosaria.turchetta@uniroma1.it (R. Turchetta), mario.tombolini@yahoo.com (M. Tombolini), mariaidarizzo@gmail.com (M.I. Rizzo), marco.devincentiis@uniroma1.it (M. de Vincentiis).

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1. Introduction

Susac's syndrome is a rare disease that is characterised by the clinical triad of encephalopathy, branch retinal artery occlusion, and sensorineural hearing loss [1].

SS was first described as a distinctive syndrome by Susac in 1979; it was designated as Susac's syndrome by Hoyt in 1986 [2]. Other acronyms and names include SICRET, or small infarcts of cochlear, retinal, and encephalic tissue [3]; RED-M, microangiopathy with retinopathy, encephalopathy, and deafness [4]; and retinocochleocerebral vasculopathy [5].

Since the first descriptions of Susac's syndrome in the 1970s, numerous reports of single patients with this disorder, as well as small case series, have been published. Given the lack of systematic data on Susac's syndrome, our current knowledge concerning this disorder largely depends on anecdotal data.

Dörr et al. reported 304 individual patients with Susac's syndrome [6].

2. Epidemiology

The majority of reports have been from North America and Europe and, in most cases, have concerned white individuals. The incidence of Susac's syndrome is higher in females than in males. The male:female ratio is 1:3.5. As autoimmunity is generally more common in females than in males, female predominance in Susac's syndrome is in line with the putative autoimmune aetiology of this disease [7–9].

The first clinical manifestations were reported in patients between 16 and 40 years of age with an extended age range of 7 to 72 years [2].

Notably, eleven cases of Susac's syndrome have occurred in the context of pregnancy: seven during pregnancy [5,10–16] and four in the postpartum period [17,18].

3. Aetiopathogenesis

Susac's syndrome is an infrequent disorder, the pathophysiology of which is not entirely clear, although it is now thought that it is most likely an immune-mediated endotheliopathy that affects the microvasculature of the brain, retina, and inner ear [19,20]. The pathogenesis of Susac's syndrome remains unclear; immune mechanisms, vasospastic phenomena, coagulopathy and viral infection have all been implicated [21,22], but they remain unproven [5,23].

Infection prior to the first onset of the disease was reported in 19 cases [24–33], suggesting that an infectious trigger of the disease is unlikely.

Magro identified similar pathological changes in dermatomyositis [34,35]. The pathology of SS most closely resembles that observed in dermatomyositis, in which there is microinfarction of muscle and skin instead of the brain, retina and inner ear.

Anti-endothelial cell antibodies (AECAs) in SS have also recently been documented by Jarius et al. [8] and Magro et al. [7].

Previous studies have demonstrated that an intracellular antigen can evoke a strong autoantibody response and that autoreactive IgG antibodies reacting with intracellular antigens are associated with the generation of autoimmunity. Another possibility is that the intracellular antigen generating the antibody response may relocalise to the surface via apoptosis and, hence, become susceptible to circulating antibodies [36,37].

The exact nature of the protein eliciting the antibody response is not known. Investigators in other studies showing AECAs directed at a 50-kDa protein have speculated with respect to targets. Potential targeted antigens suggested in other studies focusing on AECAs include cytoskeletal proteins (β-actin, α-tubulin, and vimentin), glycolytic enzymes (glucose-3-phosphate-dehydrogenase and α-enolase), and the prolyl-4-hydroxylase β subunit, a member of the disulfide isomerase family [38,39]. The concept of antibodies with endothelial cell specificity was first introduced in the context of autoimmune disease, including scleroderma and Behçet disease.

There are clinical studies that establish a link between the presence of AECAs in serum samples and the severity of disease activity in various autoimmune states [40].

The biopsy findings are those of a microangiopathy characterised by endothelial cell necrosis. These histomorphologic features are the accepted and defining pathology for other syndromes associated with AECAs [40–42]. Further evidence supporting a humorally mediated basis for the microangiopathy was the intense deposition of C4d in more than 50% of the capillaries in the brain biopsy. C4d deposition in the microvasculature is the diagnostic hallmark of antibody-mediated microvascular injury syndromes [43].

We believe that antiendothelial cell antibodies play an important role in mediating the endothelial cell injury with consequent deposition of thrombotic material in the lumen of small vessels with consequent occlusion (Fig. 1).

It still has not been explained why, in the majority of patients, the pathologic process is restricted to blood vessels in the brain, eyes and ears. However, some patients develop systemic symptoms. Relationships have also been observed between development of symptoms, pregnancy and hormonal therapy, which suggests a contribution of sex hormones to the pathogenesis of this syndrome [44,45]. Susac's syndrome has also been suggested to represent an autoimmune endotheliopathy similar to the catastrophic antiphospholipid syndrome [22]. It is hypothesised that antiphospholipid and/or anti-endothelial cell antibodies may play a role in mediating the endothelial cell injury in Susac's syndrome because they have been reported in patients with this condition [46].

4. Sintomatology

The finding that only 13% of patients with available data had the characteristic clinical triad of Susac's syndrome at disease onset is of high clinical importance. The assumption that presence of the triad is