

Susac syndrome as an example of a rare vasculopathy

Magdalena Olszanecka-Glinianowicz¹, Antoni Hrycek²

¹ Division of Pathophysiology, Medical University of Silesia, Katowice, Poland

² Department of Internal, Autoimmune and Metabolic Diseases, Medical University of Silesia, Katowice, Poland

KEY WORDS

encephalopathy,
Susac syndrome,
vasculopathy

ABSTRACT

Susac syndrome is a rare vasculopathy affecting small vessels of the brain, the retina and the cochlea. The pathogenesis of this syndrome is unknown. It is characterized by a triad of clinical symptoms, i.e. encephalopathy, visual disorders and hearing disorders. The aim of this work was to review available data about the clinical course, diagnosis and treatment of Susac syndrome.

INTRODUCTION An immune system dysfunction leading to continuous production of pathogenic antibodies and formation of immune complexes underlies the development of systemic connective tissue diseases, formerly referred to as collagen tissue diseases. Genetic, environmental, infectious and endocrine factors, as well as the ageing process, contribute to the development of these diseases.¹

The incidence of systemic connective tissue diseases varies. In clinical practice, patients with rheumatoid arthritis and systemic lupus erythematosus (SLE) are most frequently encountered. It is noteworthy that relatively rare diseases from this group account for most diagnostic difficulties. Susac syndrome is among these rare vasculopathies, and is characterized by a triad of symptoms: encephalopathy, obliteration of branches of the retinal artery and hearing loss. Approximately 100 cases have been reported worldwide so far. It seems however that the actual incidence of Susac syndrome is higher, because it can be misdiagnosed, e.g. as multiple sclerosis, migraine, SLE, encephalitis, Ménière's disease, ischemic stroke of embolic etiology, aseptic meningitis, Lyme disease, Creutzfeldt-Jacob's disease, schizophrenia, etc.²⁻⁴ In addition, a differential diagnosis of Susac syndrome should include vasculitis associated with antiphospholipid syndrome or systemic lupus erythematosus, but also Wegener granulomatosis because hearing loss may be the first symptom of the disease.^{5,6}

The aim of this work was to review available data, and to present issues associated with clinical course, diagnosis and treatment of Susac syndrome.

History of Susac syndrome This syndrome was first diagnosed in 1974.^{2,7} Professor Susac, who consulted patients with the above-mentioned symptoms, initially thought that the lesions they had were a form of granulocytic vasculitis, however this disease was associated with vision disorders and hearing loss. Because these disorders affected only small precapillary arterioles, he termed them microangiopathy, probably caused by immune disorders. Professor Susac encountered further cases of this syndrome in 1986 and presented one of them during the Neuroophthalmic Symposium, when Dr William F. Hoyt was the first to use the term "Susac syndrome".³ Mass et al.⁸ proposed another term, i.e. RED-M (retinopathy, encephalopathy and deafness related to microangiopathy). Schwitter et al.⁹ to describe these disorders used the name SICRET (small infarcts of cochlea, retinal, and encephalic tissues), whereas Petty et al.¹⁰ described them as retinocochleocerebral vasculopathy.

Up to 1994 Susac syndrome was reported in 20 young women aged 21–41 years and therefore it seemed that it occurred only in this gender. Later it has been reported also in men. However, the majority of cases affect women, with a female to male ratio of 3:1. No age-related incidence of Susac syndrome has been observed. It has been

Correspondence to:

Magdalena Olszanecka-Glinianowicz,
MD, PhD, Katedra Patofizjologii,
Śląski Uniwersytet
Medyczny, ul. Medyków 18,
40-752 Katowice, Poland,
phone/fax: + 48-32-20-88-504,
e-mail: magols@esculap.pl

Received: April 1, 2008.

Revision accepted: May 14, 2008.

Conflict of interest: none declared.

Pol Arch Med Wewn. 2009;
119 (1-2): 80-83

Translated by Piotr Sawiec, MD
Copyright by Medycyna Praktyczna,
Kraków 2009

reported both in children (recently in a 9-year-old girl) and in the elderly aged 70 years.¹¹⁻¹³

Etiology and pathogenesis Factors contributing to the occurrence of the syndrome are unknown. Its pathogenesis has not been elucidated either. One of the hypotheses assumes that a viral infection (with an unknown pathogen) can be a cause of an autoimmune reaction leading to microvascular injury.

The presence of antiphospholipid antibodies, factor V Leiden mutation and protein S deficiency have been observed.^{10,14-16}

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, and changes can be observed in small blood vessels in muscle tissue biopsies, which suggests a systemic character of the disease, with a predisposition towards a triad characteristic of this syndrome.¹²

Some authors assume that Susac syndrome results from the vasoconstrictive syndrome. However this hypothesis seems rather unlikely. 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.¹⁴⁻¹⁶

Symptoms and clinical course As already mentioned, Susac syndrome is characterized by a triad of symptoms. Besides, at the onset of the disease the majority of patients do not develop a full triad, that may manifest itself later, e.g. after several weeks or even years, which in the initial phase significantly hinders making the ultimate diagnosis. Neuropsychiatric disorders are observed in 75% of cases in the initial phase of the disease. During this time hearing and vision disorders are observed only in 10% of patients.^{14,16}

Encephalopathy in Susac syndrome can follow a diverse course and can manifest itself in severe headaches, sometimes migraine-like, as well as in personality changes, confusion, memory impairment and psychiatric disorders. Due to serious psychiatric disorders, sometimes with productive symptoms, some patients with Susac syndrome can be referred to psychiatric departments. However, the accompanying multifocal neurological symptoms usually make it possible to distinguish this syndrome from true psychiatric diseases. In some cases, the only possibility to arrive at an appropriate diagnosis is magnetic resonance imaging (MRI) of the central nervous system, which can visualize ischemic lesions of the corpus callosum, the amygdaloid body, basal ganglia, the hypothalamus and meninges.^{7,15,17,18}

Cranial nerves in Susac syndrome are not affected, and deafness is the result of cochlear injury. On the other hand, vertigo results from injury of semicircular canals. Imaging investigations have so far failed to visualize microinfarcts

in these structures, and therefore the cause of their injury remains unknown.¹⁹

The occlusion of the retinal artery branches is most difficult to diagnose, because vision disorders, i.e. reduced vision acuity and restriction of a vision field, can be mild, and thus less absorbing to the patient than other symptoms. Besides, these disorders rarely occur in the initial phase and develop with longer duration of the disease.^{17,20}

The course of Susac syndrome can be active, variable and self-limiting. The active form of the disease varies in duration, most frequently ranges within several months, and after resolution leaves various cognitive and functional defects. Some patients recover with persisting mild symptoms and signs. Other patients develop deep cognitive deficits, gait disorders and deafness. However, serious vision injury is not observed in the majority of cases. The remission duration varies and ranges from several months to 10–20 years.¹⁶

Additional investigations Detailed laboratory tests fail to demonstrate typical abnormalities characteristic of connective tissue diseases, clotting disorders and infectious diseases are observed.

There are no high protein levels in cerebrospinal fluid, sometimes with moderate pleocytosis, and usually with accompanying lymphocytosis. Occasionally elevated immunoglobulin G levels with increased synthesis of these antibodies and oligoclonal bands can lead to the misdiagnosis of multiple sclerosis.¹⁰ The changes in the electroencephalogram recording are also non-specific.⁴ The results of the cerebral arteriography are nearly always normal, because the involvement of precapillary arterioles (<100 µm) can not be visualised in this test. On the other hand, fluorescein angiography, very useful in the diagnosis of Susac syndrome, frequently reveals an occlusion in arterial branches of the retina, as well as pathognomonic multifocal fluorescence in arterial branches.^{20,21}

Loss of hearing in an audiometric test is usually observed within low and middle frequencies. Vestibular dysfunction is evaluated with a caloric test.^{19,22,23}

Magnetic resonance imaging of the central nervous system is becoming a very useful technique in the diagnosis of Susac syndrome. Ischemic lesions in the central nervous system characteristic of Susac syndrome are located in:

- 1 corpus callosum (central fibers with sparing of peripheral fibers)
- 2 amygdaloid body (almost always)
- 3 basal ganglia and the hypothalamus (70%)
- 4 meninges (33%).

Interestingly, no close relationship has been observed between the severity of encephalopathy and the intensity of lesions detectable in MRI. It should be noted that the resolution of clinical symptoms of encephalopathy is

followed by the disappearance of typical lesions in the white matter, but an evident atrophy remains. Small microinfarcts of the cerebral cortex are not visible in magnetic resonance imaging,²⁴⁻²⁶ but their presence there can be conceived, because they have been observed in biopsy specimens. In addition to the cerebral cortex, they have also been revealed in the white matter and meninges. Moreover, it should be noticed that mild perivascular inflammatory lesions have been observed as well.¹⁵

Therapy It should be stated that no currently accepted therapeutic algorithm of Susac syndrome is available. In some patients monotherapy is effective using glucocorticosteroids, cyclophosphamide and immunoglobulins. In other patients concurrent use of these agents in various combinations has good outcomes. Positive effects of plasmapheresis and hyperbaric oxygen have also been reported.^{7,10,14,15,17,21,27,28}

The prospective 6-year follow-up of 9 patients with Susac syndrome demonstrated that glucocorticosteroids were effective in the treatment of encephalopathy, however dose reduction resulted in the resolution of symptoms. Glucocorticosteroid therapy did not result in hearing improvement and did not prevent further occlusions of retinal artery branches. On the other hand, anticoagulants yielded a positive result preventing relapses of encephalopathy and renal vessel occlusion.²⁹ Fox et al.³⁰ reported a significant hearing improvement and reduced lesions in the central nervous system visible in the MRI shortly after intravenous administration of γ -globulin and methylprednisolone.

Investigators studying Susac syndrome^{31,32} state that the treatment of this syndrome should be initiated immediately after establishing the diagnosis in order to avoid mental dementia, deafness and blindness. Initially, the treatment should be given intravenously, and followed by a long-term oral therapy. In some patients, disease remission is obtained by using high doses of intravenous glucocorticosteroids. However, additional therapy in the form of intravenous immunoglobulins, mycophenolate mofetil or cyclophosphamide becomes sometimes necessary. There are also suggestions that treatment of this syndrome may involve monoclonal antibodies used while treating malignant lymphomas, which selectively bind with the CD20 antigen present in maturing lymphocytes B (rituximab).

In conclusion, the following facts should be noted:

- 1 Susac syndrome is a rarely diagnosed disease, which may partially result from diagnostic difficulties, as mentioned above
- 2 Susac syndrome should be included in differential diagnosis in cases of unexplained encephalopathy
- 3 MRI of the central nervous system is the most useful diagnostic technique to confirm the diagnosis of Susac syndrome.

REFERENCES

- 1 Beeson P. Age and sex associations of 40 autoimmune diseases. *Am J Med.* 1994; 96: 457-462.
- 2 Susac JO, Hardmann JM, Selhorst IB. Microangiopathy of the brain and retina. *Neurology.* 1979; 29: 313-316.
- 3 Ayache D, Plouin GI, Bakouche P, et al. Microangiopathy of the inner ear, retina, and brain (Susac syndrome): report of a case. *Arch Otolaryngol Head Neck Surg.* 2000; 126: 82-84.
- 4 Szilasiova J, Klimova E. Susac syndrome: retinocochleocerebral vasculopathy. *Croatian Med J.* 2004; 45: 338-343.
- 5 Cieřlik P, Hrycek A, Kluciński P. Vasculopathy and vasculitis in systemic lupus erythematosus. *Pol Arch Med Wewn.* 2008; 118: 57-63.
- 6 Dębski MG, Źyćńska K, Czarkowski M, et al. [Progressive hearing loss as the leading sign of Wegener's granulomatosis]. *Pol Arch Med Wewn.* 2007; 117: 266-269. Polish.
- 7 Susac JO. Susac's syndrome: the triad of microangiopathy of the brain and retina with hearing loss in young women. *Neurology.* 1994; 44: 591-593.
- 8 Mass M, Bourdette D, Bernstein W, et al. Retinopathy, encephalopathy, deafness associated microangiopathy (the RED M syndrome): three new cases. *Neurology.* 1988; 38 (Suppl): 215.
- 9 Schwitter J, Agosti R, Ott P, et al. Small infarctions of cochlear, retinal, and encephalic tissue in young women. *Stroke.* 1992; 23: 903-907.
- 10 Petty GW, Engel AG, Younger BR, et al. Retinocochleocerebral vasculopathy. *Medicine (Baltimore)* 1998; 77: 12-40.
- 11 Do TH, Fisch CH, Evoy F. Susac Syndrome: Report of four cases and review of the literature. *Am J Neuroradiol.* 2004; 25: 382-388.
- 12 Saliba M, Pelosse B, Momtchilova M, et al. Susac syndrome and ocular manifestation in a 14-year-old girl. *J Fr Ophtalmol.* 2007; 30: 1017-1022.
- 13 Eluvathingal Muttikkal TJ, Vattoth S, Keluth Chavan VN. Susac syndrome in a young child. *Pediatr Radiol.* 2007; 37: 710-713.
- 14 Ayache D, Plouin GI, Bakouche P, et al. Microangiopathy of the inner ear, retina, and brain (Susac syndrome): report of a case. *Arch Otolaryngol Head Neck Surg.* 2000; 126: 82-84.
- 15 Papo T, Biousse V, Lehoang P, et al. Susac syndrome. *Medicine (Baltimore)* 1998; 77: 3-11.
- 16 Petty GW, Matteson EL, Younger BR, et al. Recurrence of Susac syndrome (retinocochleocerebral vasculopathy) after remission of 18 years. *Mayo Clin Proc.* 2001; 76: 958-960.
- 17 O'Halloran HS, Pearson PA, Lee WB, et al. Microangiopathy of the brain, retina, and cochlea (Susac syndrome): a report of five cases and a review of the literature. *Ophthalmology.* 1998; 105: 1038-1044.
- 18 Susac JO. Susac's syndrome. *Am J Neuroradiol.* 2004; 25: 351-352.
- 19 Cubillana Herrero JD, Soler Valcarcel A, Albaladejo Devis I, et al. Susac syndrome as a cause of sensorineural hearing loss. *Acta Otorrinolaringol Esp.* 2002; 53: 379-383.
- 20 Egan RA, Nguyen TH, Gass DM, Jot al. Retinal arterial wall plaques in Susac syndrome. *Am J Ophthalmol.* 2003; 135: 483-486.
- 21 Martinet N, Fardeau C, Adam R, et al. Fluorescein and indocyanine green angiographies in Susac syndrome. *Retina.* 2007; 27: 1238-1242.
- 22 Monteiro ML, Swanson RA, Coppeto JR, et al. A microangiopathic syndrome of encephalopathy, hearing loss, and retinal arteriolar occlusions. *Neurology.* 1985; 35: 1113-1121.
- 23 Bateman ND, Johnson LJ, Gibbin KP. Susac's syndrome: a rare cause of fluctuating sensorineural hearing loss. *J Laryngol Otol.* 1997; 111: 1072-1074.
- 24 Susac JO, Murtagh FR, Egan RA, et al. MRI findings in Susac's syndrome. *Neurology.* 2003; 61: 1783-1787.
- 25 Xu MS, Tan CB, Umapathi T, et al. Susac syndrome: serial diffusion-weighted MR imaging. *Magn Reson Imaging.* 2004; 22: 1295-1298.
- 26 White ML, Zhang Y, Smoker WR. Evolution of lesions in Susac syndrome at serial MR imaging with diffusion-weighted imaging and apparent diffusion coefficient values. *AJNR Am J Neuroradiol.* 2004; 25: 706-713.
- 27 Nicolle MW, McLachlan RS. Microangiopathy with retinopathy, encephalopathy, and deafness (RED-M) and systemic features. *Semin Arthritis Rheum.* 1991; 21: 123-128.
- 28 Rennebohm RM, Lubow M, Rusin J, et al. Aggressive immunosuppressive treatment of Susac's syndrome in an adolescent: using treatment of dermatomyositis as a model. *Pediatr Rheumatol Online J.* 2008; 29: 3.
- 29 Aubart-Cohen F, Klein I, Alexandre JF, et al. Long-term outcome in Susac syndrome. *Medicine (Baltimore)* 2007; 86: 93-102.
- 30 Fox RJ, Costello F, Judkins AR, et al. Treatment of Susac syndrome with gamma globulin and corticosteroids. *Neurol Sci.* 2006; 251: 17-22.
- 31 Rennebohm RM, Egan RA, Susac JO. Treatment of Susac's syndrome. *Curr Treat Options Neurol.* 2008;10: 67-74.
- 32 Rennebohm R, Susac JO. Treatment of Susac's syndrome. *J Neurol Sci.* 2007; 257: 215-220.