Journal of Neurology
https://doi.org/10.1007/s00415-023-11936-3

REVIEW

Clinical characteristics and treatment approaches in patients with Susac syndrome: a scoping review of cases

Robin Stinissen[1] · Eldar Tukanov[1] · Martin Wyckmans[1] · Jeroen Kerstens[2] · Barbara Willekens[2,3,4]

Received: 19 May 2023 / Revised: 9 August 2023 / Accepted: 11 August 2023

Abstract

Background Susac syndrome (SuS) is a rare disease characterized by encephalopathy, hearing impairment and visual disturbances. Immunosuppressive treatments are used based on the hypothesis that an autoimmune endotheliopathy drives the disease. However, a solid evidence-based treatment approach is lacking. The aim of this review is to provide an overview of patient characteristics, disease course and treatment patterns related to successful outcome that have been reported in literature since 2013.

Methods Three reviewers conducted a systematic literature search in February 2022. The primary outcome was treatment used, derived from cases classified as probable or definite SuS, describing successful treatment outcome (i.e. no signs of disease activity for ≥ 1 month). Secondary outcomes were time-to-relapse and follow-up time. Published case reports and case series were included. Various clinical characteristics and treatment(s) were extracted and categorized into different phases of treatment.

Results A total of 810 records was identified. 120 articles met inclusion criteria and 161 cases were extracted. Of these, 151 cases were classified as probable or definite SuS and included in the final analysis. Number of combinations of treatments used per treatment phase were: 6 empirically, 35 after confirmed diagnosis, 43 for maintenance treatment, 22 after relapse, 18 during maintenance post-relapse. Median follow-up time was 12.3 months (0.5; 120) and median time to relapse was 4 months (1; 120).

Conclusion This scoping review summarizes treatment approaches in patients with SuS, highlighting variability. International efforts to collect clinical, imaging and treatment data from patients with SuS in registries are needed, in order to provide less biased and long-term follow-up information on treatment response, predictors of relapse and patient outcomes. This may lead to more evidence-based therapeutic approaches.

Keywords Autoimmune · Encephalopathy · Hearing loss · Retinal artery occlusion · Susac syndrome

Introduction

Susac syndrome (SuS) is a rare disease which was first described by Dr. John Susac in 1979 [1]. Epidemiological data are scarce with an estimated yearly incidence of 0.24/1,000,000 people in Austria [2]. It occurs most often in young women with a mean age at onset of 31.6 years (± 10.4, 8–65 years) and a male-to-female ratio of approximately 1:3.5 [3]. Patients can present with symptoms of encephalopathy, hearing impairment and/or visual disturbances [3, 4]. However, this clinical triad occurs in only 13% of patients at disease onset, complicating early diagnosis of definite SuS [5]. A diagnosis of probable SuS is made when two of the three organ systems (brain, eye, ear) are affected [5]. Ancillary investigations are used to demonstrate

Robin Stinissen, Eldar Tukanov, and Martin Wyckmans: first authors contributed equally.

✉ Barbara Willekens
barbara.willekens@uantwerpen.be

1 Faculty of Medicine and Health Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

2 Department of Neurology, Antwerp University Hospital, Drie Eikenstraat 655, 2650 Edegem, Belgium

3 Translational Neurosciences Research Group, Faculty of Medicine and Health Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

4 Laboratory of Experimental Hematology, Faculty of Medicine and Health Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

Published online: 05 September 2023

presence of sensorineural hearing loss (tone audiometry), branch retinal artery occlusions (fundoscopy or fluorescein angiography) and/or corpus callosum lesions [brain magnetic resonance imaging (MRI)], which are typical findings in SuS and may remain subclinical. The differential diagnosis of probable SuS at disease onset is broad and includes multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), central nervous system (CNS) vasculitis and infectious encephalitis [5, 6]. This makes a prompt diagnosis difficult, given the obscurity of this orphan disease.

The underlying pathophysiology has not been completely elucidated, but an important mechanism is $CD8^+$ T cell-mediated damage of the endothelium of the small vessels of the brain, inner ear, and retina [7]. Hence, SuS is regarded as an autoimmune endotheliopathy in which the autoantigen has not yet been found.

As the pathogenesis of SuS involves immune-mediated mechanisms, treatment consists of immunomodulators and immunosuppressants [4, 8]. While no randomized clinical trials have been conducted to date, treatment recommendations have been published in 2018, based on expert opinion and building on previous experiences in juvenile dermatomyositis, another $CD8^+$ T cell-mediated endotheliopathy [8]. Treatment options include methylprednisolone, intravenous immunoglobulins (IVIG), mycophenolate mofetil (MMF), rituximab (RTX) and cyclophosphamide (CYC) [4, 8]. However, it is unclear which treatments are used as acute and maintenance treatments, and for relapses in routine clinical practice.

In this scoping review, cases of SuS published between 2013 and 2022, in which successful treatment was reported, are summarized in order to provide an overview of patient characteristics, disease course and treatment options in relation to outcomes. The overarching research question was: "Which treatments have been successfully used in adult patients with SuS?". Additionally, we were interested in the clinical characteristics and disease course of these patients.

Methods

Search strategy

In February 2022 a literature search was conducted in Medline, Embase and Cochrane in accordance with the PRISMA-guidelines [9, 10]. The following search terms were used: 'susac', 'sicret', 'red-m', 'retinocochleocerebral vasculopathy' and 'small infarction of cochlear, retinal and encephalic tissue'. The search was expanded by identifying synonyms or closely related words. References of included articles were hand-searched to identify additional articles. The full search strategy can be found in Online Resource 1. Three reviewers (RS, ET and MW) independently assessed titles and abstracts according to in- and exclusion criteria, followed by screening of full-text articles. Each full-text article was assessed for eligibility by at least two of these reviewers. In case of discussion, a third reviewer was consulted.

Eligibility criteria

Articles published between 2013 and 2022 were considered, as the most recent systematic review on clinical characteristics of SuS was published in 2013 [3]. Language restrictions were set for English, French and Dutch. Inclusion criteria were: (1) diagnosis of SuS, either definite or probable, according to the 2016 proposed diagnostic criteria [5]; (2) patients were successfully treated for SuS (defined as no active disease for at least 1 month)*;* adult patients (18 years or older). Exclusion criteria were: (1) conference abstracts; (2) animal studies; (3) no diagnosis of SuS; (4) publication date before 2013 [3]; (5) no new cases or episodes; (6) no individual patient data reported; (7) no clear data on treatment and outcome.

Data extraction

A preliminary data set to extract from the included articles was agreed upon after discussion between researchers. This data set was piloted after random inclusion of five articles in the review. If a certain data point was not found in at least two out of five articles, researchers discussed and agreed upon removal of this data point. A summary of the preliminary data set can be found in Online Resource 2.

The classical clinical triad was considered present at diagnosis when symptoms in all three cardinal organ systems (brain, inner ear, retina) had manifested between disease onset and diagnosis. A subclinical triad was considered present when disease activity in all three organ systems could be demonstrated by the results of ancillary investigations without having a symptomatic triad [for example presence of branch retinal artery occlusion (BRAO) on fluorescein angiography without visual symptoms]. Follow-up time was measured from hospital discharge after the last episode till the end of follow-up. Remission was defined as a stable situation with no new symptoms or new abnormalities on ancillary investigations suggesting disease activity for at least 1 month. Relapse was defined by the researchers as new inflammatory disease activity (either clinical or subclinical) after a stable disease course of at least a month.

Treatments were categorized as follows: misdiagnosis treatment; empiric treatment; treatment after confirmed diagnosis; maintenance treatment; relapse-related; post-relapse maintenance (Fig. 1). Combinations of treatment per phase were extracted for each case individually.

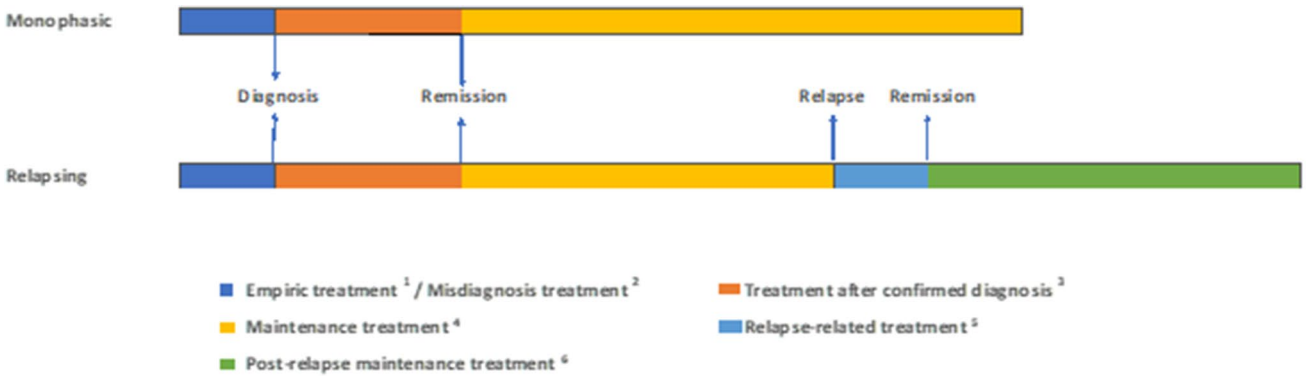


Fig. 1 Potential disease course in Susac syndrome, with variable treatment phases. (1) Empiric treatment is defined as treatment started before a diagnosis of SuS was established. (2) Misdiagnosis treatment is defined as treatment given when a diagnosis other than SuS was established. (3) Treatment after confirmed diagnosis is a treatment given in the acute phase whereby the diagnosis of SuS is established. (4) Maintenance treatment is defined as the treatment continued after at least one consecutive month of stable disease course. Relapse-related treatment is defined as all treatments that are given in the acute phase of any relapse in the patient's disease course. (6) Post-relapse maintenance treatment is defined as treatment continued after at least one consecutive month of stable disease course since the last known relapse in that patient

Methodological quality assessment

The risk of bias was analyzed with five out of eight proposed qualitative close ended questions [11]. Detailed information on how the assessment was carried out can be found in Online Resource 3.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 28. Demographic data were analyzed with descriptive statistics. A two-tailed Mann–Whitney U test was performed to compare the follow-up time in patients with and without relapse. Narrative synthesis and figures were used to describe the treatment sequences. A survival analysis was performed to determine the time interval between diagnosis and first relapse of patients with SuS and visualized by a Kaplan–Meier curve.

Results

Article selection

The search yielded a total of 810 results (Fig. 2, PRISMA flowchart). Finally, 120 articles, with a diagnosis of SuS were included. In the selected articles, 161 cases were reported. Of these, 10 possible SuS [5] cases were excluded, leaving a total of 151 cases with a diagnosis of probable or definite SuS [5], reported in 115 articles. All references and extracted individual patient level data, can be found in Online Resource 4.

Patient characteristics

Using proposed diagnostic criteria by Kleffner et al., of 161 cases, 6.2% (n = 10) were classified as possible SuS and were excluded from further analysis. 39.8% (n = 64) met criteria for probable SuS and 54% (n = 87) were categorized as definite SuS. All following analyses were performed on the 151 probable and definite cases A table summarizing patient characteristics can be found in Online Resource 5 (See also online reference list (online resource 8) of all included cases).

Patient demographics

For the 151 cases, the median age at diagnosis was 31 years (18; 67). The most common age groups at diagnosis were 18–24 years (29.1%) and 30–34 years (19.2%) (Online Resource 6).

Male to female ratio was approximately 1:2, with 61.6% female patients (n = 93) and 37.7% male patients (n = 57). One case reported no information on sex [12]. Ethnicity or race and family history could not be retrieved from most case-reports and is therefore not reported.

Diagnosis and misdiagnosis

In total, 82.8% of the cases (n = 125) reported time between symptom onset and SuS diagnosis. Out of these, 34.4% of patients (n = 52) were diagnosed within the first month after onset, with 15.2% (n = 23) of patients diagnosed within the first week after onset. Median time from onset of symptoms to diagnosis was 8 weeks (0; 679). 7.9% (n = 12) of patients did not receive the diagnosis of SuS until 1 year or more

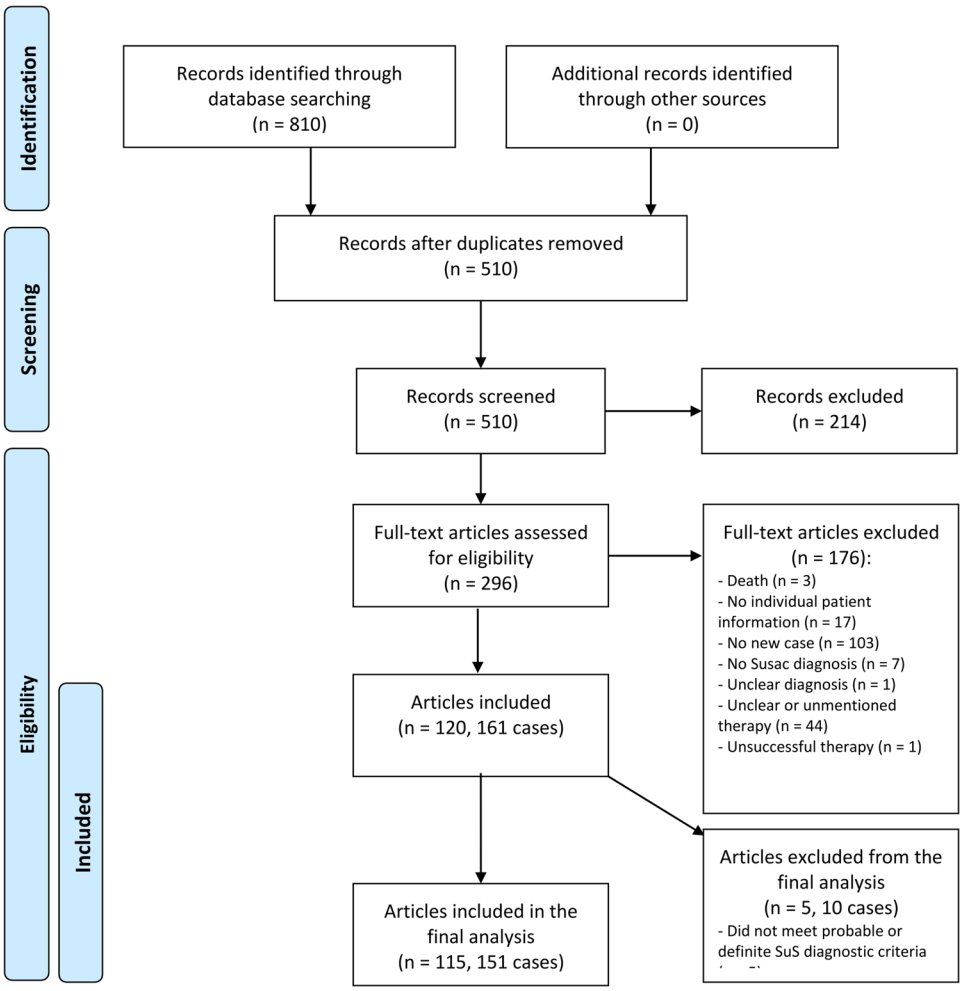


Fig. 2 PRISMA flowchart for the selection of eligible case reports

after onset because of earlier misdiagnosis (n = 7) and slow progression with incomplete triad (n = 5).

Forty-four (44) patients received a total of 52 misdiagnoses. The most common misdiagnoses were ADEM (n = 12), MS (n = 10), other vasculitides (n = 8), viral encephalitis (n = 4), migraine (n = 3) and vertigo (n = 2). Other misdiagnoses that were mentioned once can be found in Online Resource 2 and details in Online Resource 4.

Symptoms, clinical triad and subclinical triad

88.1% (n = 133) of patients had CNS symptoms, 67.5% (n = 102) reported visual disturbances and 78.1% (n = 118) reported symptoms of vestibulocochlear involvement. Ancillary investigations showed CNS involvement in 98% (147/151), retinal involvement in 98% (148/151) and vestibulocochlear involvement in 92.5% (123/133) of patients. Headache, another frequent complaint, was present in 66.9% (101/151) of patients. Of the 64 patients with probable SuS, 48 cases (75%) did not fulfill vestibulocochlear criteria, six cases (12.5%) did not meet ocular criteria and 12 cases (25%) lacked CNS involvement. The clinical triad of encephalopathy, vestibulocochlear symptoms and visual disturbances was present at diagnosis in 47.7% of patients (72/151). A subclinical triad was attained in 69.6% of patients (55/79) without a clinical triad. (Online Resource 5).

Ancillary investigations

Diagnostic investigations that were carried out can be found in Table 1.

Fundus examination (fundoscopy and/or retinal fluo-angiography) was performed in 150 cases. In these cases, the following ophthalmological findings were reported: BRAO in 92% (n = 138), arteriolar wall hyperfluorescence (AWH) in 40% (n = 60), arteriolar sheathing in 1.3% (n = 2) and Gass plaques in 5.3% (n = 8). Brain MRI was performed in all 151 cases. Callosal lesions were found in 91.4% (n = 138). Contrast-enhancing lesions were present in 73.9% cases (65/88) where contrast was administered. Cerebrospinal fluid analysis was reported in 76.2% cases (n = 115). In 67% (77/115) oligoclonal band (OCB) analysis was reported. In 93.5%

Table 1 Diagnostic investigations carried out in each patient

	EYE Fundoscopy and/or retinal fluo angiogram	BRAIN Brain MRI	EAR Tone audiometry/auditory or vestibular evoked myogenic responses/caloric testing
Performed	99.3% (150)	100.0% (151)	88.1% (133)
Not reported	0.7% (1)	0	11.9% (18)
Positive	98.0% (147)	98.0% (148)	92.5% (123)
Negative	2.0% (3)	2.6% (4)	7.5% (10)
Unclear	2 n = 1 not reported (case 125 [13],), n = 1 inconclusive due to abulia (case 151, [14])	0	18 n = 18 lack of information: n = 14 hearing loss but no test reported, n = 4 vestibulo-cochlear involvement not discussed

(72/77) OCB were absent. Of note, three out of five patients in whom OCB were detected, were initially misdiagnosed. Two of them had a misdiagnosis of MS [15, 16], the other one [17] was believed to have an acute cochlear neuritis after first assessment. Detailed description of CSF analysis can be found in Online Resource 5.

Brain biopsy

Brain biopsy was performed in nine cases. Most commonly, T-cell infiltrates ($CD3^+$, $CD4^+$ or $CD8^+$), foci of myelin loss and nonspecific perivascular inflammation were found. Biopsied blood vessels showed perivascular lymphocytic cuffing, lymphocytic infiltration, and perivascular inflammation. Detailed description of all cases with brain biopsy can be found in Online Resource 7.

Disease course

Follow-up time was mentioned in 62.3% of cases (n = 94), with a median follow-up time of 12.3 months (0.5; 120). In the cases where follow-up time was mentioned, patients with a relapse (n = 21) had a median follow-up time of 36 months (7.5; 102), while patients without a relapse (n = 72) had a median follow-up of 12 months (0.5; 120). The Mann–Whitney U test showed a significant difference between the follow-up time in patients with relapse and without relapse ($p < 0.001$).

Relapses were reported in 36 cases. The time interval between diagnosis and first relapse was described in 30 cases. Median time to relapse was 4 months (1; 120) with a mean time to relapse of 13 months. 83.3% of patients with at least one relapse, had their first relapse within 2 years from diagnosis. (Fig. 3).

Treatment

An overview of all treatments used in various phases of the disease is presented in Table 2. Full details of the other treatments are available in Online Resource 5. This category includes all reported treatments, including antiplatelets and anticoagulants, empiric antibiotic and antiviral treatments, supplements, hormonal treatments used and symptomatic treatments.

One case report did not mention the treatment course after confirmed diagnosis as only the first relapse was described [18]. Out of 36 relapsing cases, relapse-related treatment and post-relapse maintenance treatment were described in 31 (86.1%) cases.

Combinations of treatment used in individual cases are summarized in Fig. 4. Six combinations were used during the empiric treatment phase and 35 combinations after probable or definite SuS diagnosis was confirmed. When remission was reached 43 different treatment combinations were used as maintenance treatment. Relapse-related treatment included 22 different combinations while 18 treatment combinations were used as post-relapse maintenance treatment.

Pregnancy

Pregnancy and SuS has been reviewed recently [19]. Thirteen patients were pregnant during their disease course. Two patients were diagnosed postpartum. The mean age was 28.8 years (19; 40). An elective caesarean section was performed in one case and therapeutic abortion was opted for in two cases [20–22]. Following treatments were administered during pregnancy: corticosteroids (61.5%; 8/13), IVIG (30.8%; 4/13), plasma exchange (7.7%; 1/13) and CYC (7.7%; 1/13). Treatment options given after pregnancy were corticosteroids (69.2%; 9/13), AZA (30.8%; 4/13), IVIG (23.1%; 3/13), MMF (23.1%; 3/13), CYC (23.1%; 3/13), MTX (7.7%; 1/13) and RTX (7.7%; 1/13).

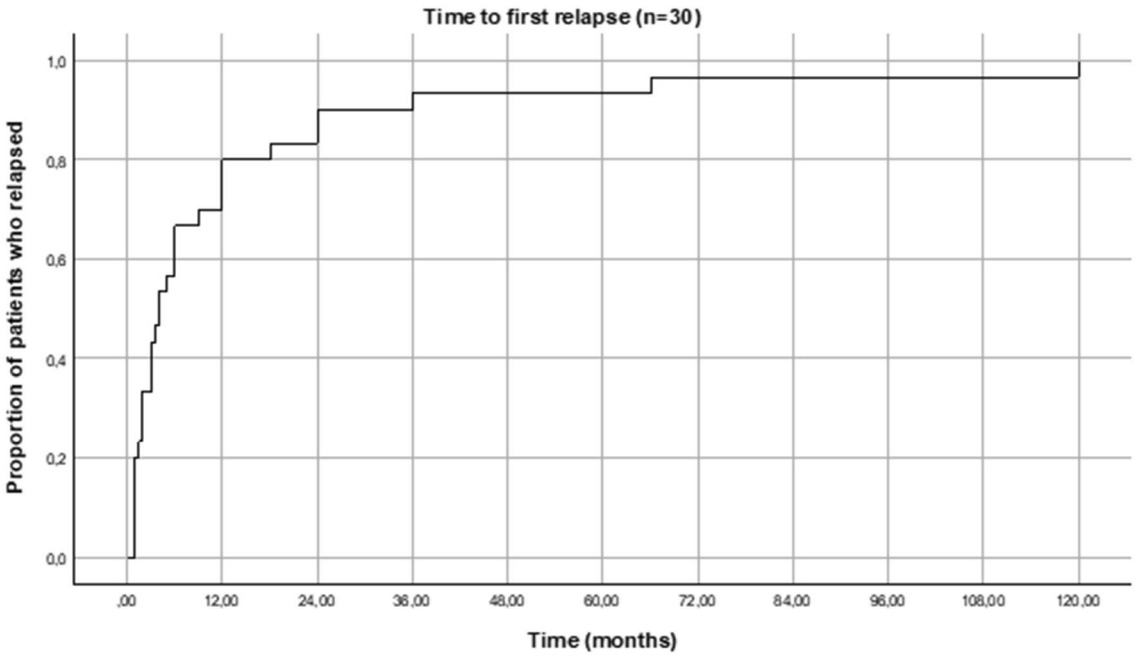


Fig. 3 Kaplan–Meier curve of time interval between diagnosis and first relapse. The x-axis shows time in months and the Y-axis shows the proportion of patients who relapsed

Table 2 Treatment options used in different phases of the disease

	Empiric treatment (n = 30; 19.9%)	Treatment after confirmed diagnosis (n = 150; 99.3%)	Maintenance treatment (n = 128; 84.8%)	Relapse related treatment (n = 31; 20.5%)	Post-relapse maintenance treatment (n = 31, 20.5%)
IV CS	21 (70.0%)	121 (80.7%)	2 (1.6%)	25 (80.6%)	2 (6.5%)
PO CS	16 (53.3%)	107 (71.3%)	105 (82.0%)	22 (71.0%)	18 (58.1%)
IVIG	3 (10.0%)	61 (40.7%)	39 (30.5%)	15 (48.4%)	6 (19.4%)
MFT	0	22 (14.7%)	27 (21.1%)	12 (38.7%)	13 (41.9%)
RTX	0	12 (8.0%)	9 (7.0%)	11 (35.5%)	4 (12.9%)
CYC	1 (3.3%)	40 (26.7%)	36 (28.1%)	14 (45.2%)	8 (25.8%)
MTX	0	1 (0.7%)	6 (4.7%)	0	1 (3.2%)
INX	0	1 (0.7%)	0	5 (16.1%)	4 (12.9%)
CYSP	0	2 (1.3%)	1 (0.8%)	1 (3.2%)	0
AZA	0	16 (10.7%)	23 (18.0%)	6 (19.4%)	2 (6.5%)
Other	15 (50.0%) A*	76 (50.7%) B*	54 (42.2%) C*	16 (51.6%) D*	6 (19.4%) E*

*A** antiplatelet drugs (10%; 3/30), anticoagulants (3.3%; 1/30), antiviral drugs (6.7%; 2/30), antibiotics (10%, 3/30), hyperbaric oxygen therapy (3.3%; 1/30), *B** antiplatelet drugs (%; 37/76), anticoagulants (10.3%, 8/76), antibiotics (2.6%, 2/76), antivital drugs (1.3%; 1/76), PLEX (10.5%; 8/76), TAC (1.3%; 1/76), *C** antiplatelet drugs (63%; 34/54), anticoagulants (3.7%; 2/54), PLEX (1.9%; 1/54) [30], TAC (1.9%; 1/54) [44], *D** antiplatelet drugs (25%; 4/16), antiviral drugs (18.8%; 3/16), PLEX (31.25%; 5/16), autologous hematopoietic stem cell transplantation (6.25%; 1/16) [45], tocilizumab (6.25%; 1/16) [29], *E** antiplatelet drugs (3.2%, 1/31), antiviral drugs (3.2%; 1/31), PLEX (3.2%; 1/31) [46], TAC (3.2%; 1/31) [20], subcutaneous IgG (3.2%; 1/31), *IV CS* IV corticosteroids, *PO CS* oral corticosteroids, *IVIG* Intravenous immunoglobulins, *MFT* mycophenolate mofetil, *RTX* Rituximab, *CYSP* cyclosporine, *MTX* methotrexate, *INX* Infliximab, *CYC* cyclophosphamide, *AZA* azathioprine, *PLEX* plasma exchange, *TAC* tacrolimus, *cART* combination antiretroviral therapy, *GnRHa* gonadotropin-releasing hormone agonist

Assessment of methodological quality

The results of the risk of bias assessment are shown in Fig. 5, with more details in Online Resource 3 [11]. Overall, 47 articles were judged as high quality (40.9%), 55 articles as moderate quality (47.8%) and 13 as low quality (11.3%).

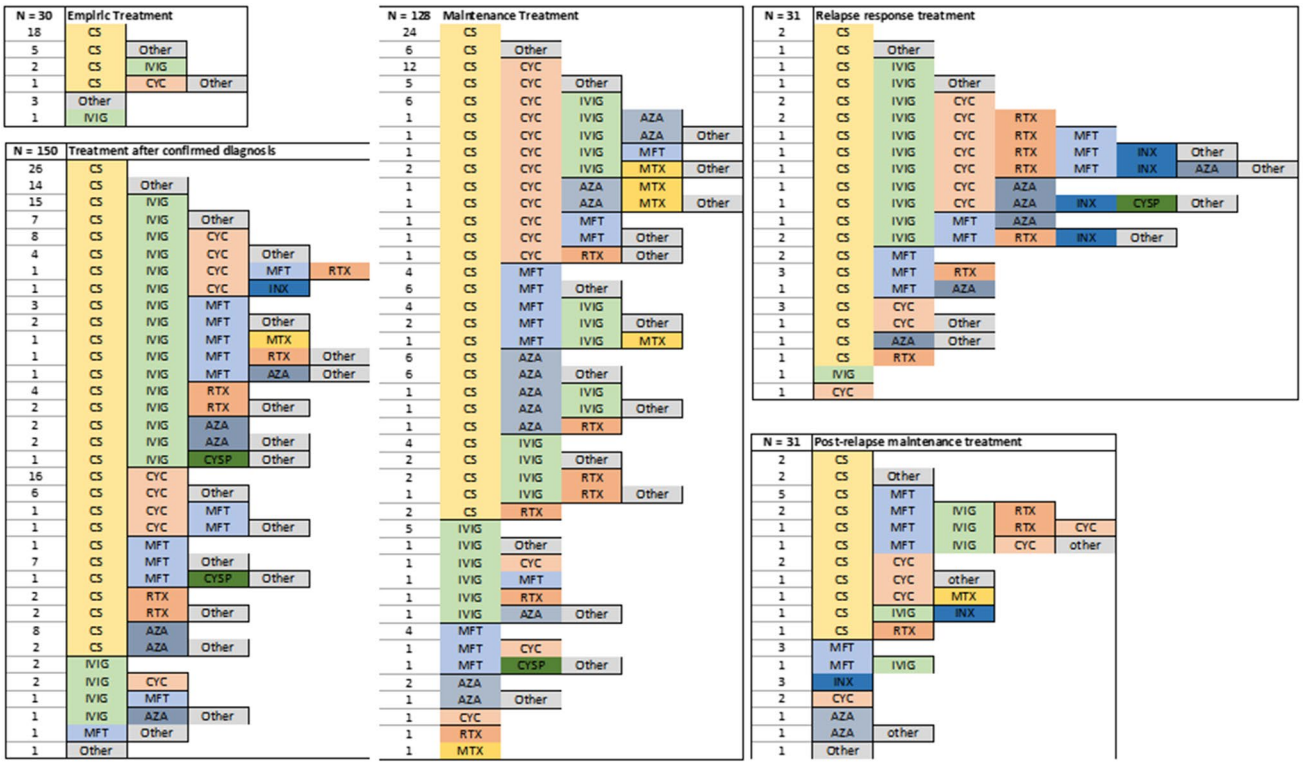
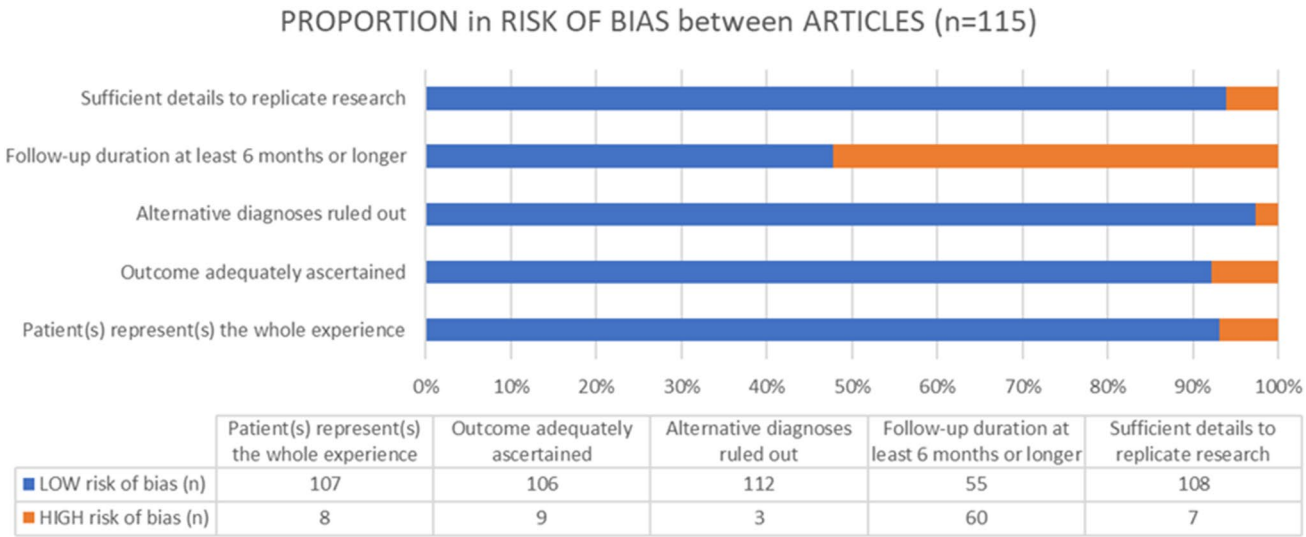


Fig. 4 Treatment combinations per individual case for each treatment phase. *CS* corticosteroids, *IVIG* intravenous immunoglobulins, *MFT* mycophenolate mofetil, *RTX* rituximab, *CYSP* cyclosporine, *MTX* methotrexate, *INX* infliximab, *CYC* cyclophosphamide, *AZA* azathioprine, *PLEX* plasma exchange, *TAC* tacrolimus



	Patient(s) represent(s) the whole experience	Outcome adequately ascertained	Alternative diagnoses ruled out	Follow-up duration at least 6 months or longer	Sufficient details to replicate research
LOW risk of bias (n)	107	106	112	55	108
HIGH risk of bias (n)	8	9	3	60	7

Fig. 5 Risk of bias assessment of included articles

Discussion

In this scoping review on clinical characteristics and treatment patterns of 151 recent individual SuS cases published in the past decade, several new insights are obtained compared to previously reported syntheses.

In a previous review, patients with the complete clinical triad at presentation accounted for 13% of cases [3]. In this scoping review, 47.7% of patients (n = 72) developed the

clinical triad in the time period between onset of symptoms and diagnosis of SuS. The proportion of patients who presented with the complete clinical triad could not be extracted reliably from the case reports due to variable and unclear reporting of development of symptoms over time.

In the population without a clinical triad (n = 79), 69.6% of patients (n = 55) showed diagnostic findings compatible with a subclinical triad. Additionally, the definition of CNS involvement in SuS did not include headache in a previous review [3], but new headache has been included in the proposed diagnostic criteria by Kleffner et al. [5]. In this review, in 66.9% of patients headache was reported as a symptom that could be related to CNS involvement. Pathophysiology of headache in SuS remains poorly understood, but is likely associated to leptomeningeal inflammation, that is more easily detected with 3D FLAIR MRI [23, 24]. A better knowledge of specific headache characteristics, as prodrome, or symptom of disease activity could help to improve early diagnosis and aid in treatment decisions. However, more research is needed to better understand these characteristics in relation to other symptoms and outcomes.

We found that symptoms of CNS involvement were most common at presentation while symptoms of visual or vestibulocochlear involvement were reported less often. At the same time, these patients might have involvement of other organ systems that may only be detected with additional hearing, vestibular or vision tests. Indeed, several articles reported patients whose condition was too severe to clearly communicate hearing impairment or visual disturbances to healthcare providers or to cooperate during examinations. Keeping in mind that 58.4% of patients were diagnosed at least 1 month after symptom onset and that 29.1% of patients were initially misdiagnosed, early bed-side screening for hearing or vision loss could lead to an earlier diagnosis and potentially a less severe disease course when treatment is started earlier rather than later. A fundoscopy, fluoangiography and audiogram should be obtained promptly if available and possible as soon as SuS is considered in the differential diagnosis. In this review, six case reports describing patients with a diagnosis of possible SuS were excluded due to unclarity in one or more diagnostic findings, while 24 cases were classified as probable SuS due to unclarity in reported diagnostic findings, but might have been given a definite diagnosis if reporting had been more detailed. These findings underscore the importance of performing detailed diagnostic investigations of the BEE (Brain–Eye–Ear) systems in order to make a correct diagnosis. Other diagnostic findings, such as high levels of CSF protein, absence of CSF OCB (which was the case in the majority of patients in whom analysis of CSF OCB was reported) and more recent imaging techniques such as contrast-enhanced black-blood imaging [25] have potential to be of added value in the diagnosis of SuS, but should be investigated further.

A common misconception in many case reports seems to be that a diagnosis of SuS requires a complete triad, which seemed a contributing factor to initial misdiagnosis in almost 1 out of 3 SuS patients. However, a diagnosis of probable SuS can be made once at least two out of three organ systems are affected and in our opinion one should not wait to start treatment until the triad is complete. Education in the diagnosis of rare diseases such as SuS may be very relevant to avoid misdiagnosis or late diagnosis.

Corticosteroids and IVIG were the most frequently used first-line, empirical treatments. Antiplatelet drugs, antibiotics and antiviral drugswere used to cover a broad number of other conditions that were considered in the differential diagnosis including vasculitis, bacterial meningitis, and viral encephalitis. After confirmed diagnosis of SuS, corticosteroids and IVIG remained the most frequently used treatments. Corticosteroids and/or IVIG were sufficient as treatment in 29.3% (44/150) of cases leading to disease remission without additional treatment. Of the patients that reached remission using only corticosteroids and/or IVIG, 11 patients had a relapse. The occurrence of relapses in the group that only received corticosteroids and/or IVIG was comparable to the whole patient population (11/44; 25%). Breakthrough disease was seen in 16.6% (25/151) of cases, requiring additional immunosuppressive treatment. RTX, CYC and PLEX were reported more often as additional immunosuppressive treatment than in the initial diagnostic phase. INX was used for relapsing disease in a minority of cases (16.1%; 5/31) and this approach was successful in all of them. In several case reports, authors suggested that INX could be considered in refractory cases when other options have been unsuccessful. The first successful use of INX in a patient with SuS was described more than 10 years ago [26], but more research on the use of TNF-α inhibitors in SuS is needed [26–29]. TAC has been suggested as treatment for severe cases in combination with MMF [8]. However, in this review, TAC was prescribed in a minority of patients (1.3%, 2/151). In one case of SuS associated with the use of pembrolizumab, TAC and MMF were initiated as maintenance treatments [30]. In the other case, a patient was prescribed TAC and oral corticosteroids after a relapse [20]. No specific argumentation was given for the preference to initiate TAC. One might assume that the experience of the treating physician with the use of certain immunosuppressants may play a role, besides the local (un)availability and/or reimbursement status of certain medications as well as the experience with TAC in the treatment of immune checkpoint inhibitor-related adverse events.

Many different combinations of treatment were used in the treatment phases. The large variation in treatment choices justifies the need for a dedicated, international, Susac registry, in which clinical characteristics, results of

MRI, fluoangiograms and audiograms, treatments, outcomes, pregnancies and long-term follow-up are recorded. This would inform the set-up of future studies and aid in creation of more evidence-based guidelines based on clinical data rather than on expert-opinion.

It has been suggested to distinguish monocyclic, polycyclic or chronic continuous disease courses [3]. However, the 2-year cut-off that has been suggested previously is not evidence based and the classification of disease course may be incorrect when follow-up time is limited or patients do not have check-ups for subclinical disease activity [3, 31]. This has also been noted in people with multiple sclerosis, where subclinical disease activity on MRI is a lot more frequent than clinical relapses [32]. Categorizing case reports in these three groups of disease course requires ample follow-up time. Previous recommendations suggested at least 2 years follow-up time, which was not reached in most cases included in our review [3]. Only 39.4% (37/94) of the cases reported a follow-up time of 2 years or longer. Not only does this distort the demographic data considering these categories of disease course, the number of relapses and breakthrough disease may remain underreported. In the 94 cases where follow-up time could be defined (62.3%; 94/151), a significant shift ($p < 0.001$) towards longer follow-up time was found in patients with relapse compared to patients without relapse. A similar analysis has been performed by others who showed a significantly longer follow-up time in polycyclic patients [33]. This suggests that relapses might be missed in practice by loss to follow-up and is an argument that advocates for long follow-up time.

Patients who suffered a relapse require regular and multidisciplinary follow-up, with a current recommendation being at least 2 years [31]. An argument can be made that follow-up of 2 years is not based on empiric evidence but only on expert opinion and is too short to establish the patient's disease course. The analysis of 30 cases in this review provides additional evidence. As five patients (16.6%) relapsed after 2 years, the risk of relapse beyond 2 years of disease history remains very relevant. One case was reported with a relapse occurring after a period of remission of 10 years [34]. Hence, long-term follow-up is advisable in all patients with SuS. International registries are needed to gather prospective real-world data on SuS patients with long-term follow up to assess relapse frequency in the short and long term. This will enable us to better characterize the disease course and investigate prognostic factors, which are important to inform clinical care.

In rare cases, SuS can have an extremely severe course and lead to death, despite treatment. Three articles, excluded during our search, have reported the death of patients with SuS during their disease course. In these cases, the therapy was either insufficient to control the disease activity or lead to fatal complications. The first case, a 24-year-old woman with a subclinical triad, was treated empirically with intravenous and oral corticosteroids, IVIG and PLEX [35]. She rapidly developed a coma and intubation was necessary. While MMF and CYC were added once the diagnosis of SuS was confirmed, palliative care was opted for and the patient died shortly afterwards. The second case, a 24-year-old woman without a subclinical triad, was treated empirically with corticosteroids (unclear whether intravenous or oral), IVIG, acyclovir and PLEX [36]. CYC was added after confirmed diagnosis of SuS. The patient ultimately died due to neurological compromise. These cases are a reminder that SuS may be a very severe and potentially fatal condition that requires prompt and aggressive treatment. A third case reports the death of a 58-year-old man due to a urinary tract infection and pneumonia with subsequent bacteremia [37]. The immunomodulatory and immunosuppressive medications used to treat SuS likely predisposed this patient to surinfection and these factors likely played a role in this case fatality.

Recent insights in the pathophysiology of SuS have placed an emphasis on the role of $CD8^+$ T-cells [7, 38]. Given this T-cell mediated pathophysiology, natalizumab (NAT) was considered as a potentially interesting treatment option in patients with SuS. NAT is an α4-integrin monoclonal antibody mainly used for treatment of MS [39]. NAT has not been mentioned previously in treatment recommendations [8] and no cases were found in the search where NAT was prescribed as treatment. A small-scale study of four patients has shown beneficial results in patients with relapsing SuS, but was excluded during our full-text screening due to lack of individual patient information that could be extracted [7]. Although further studies are needed, the current evidence is insufficient to recommend NAT over currently used therapies. Besides, the risk of progressive multifocal leukoencephalopathy in John Cunningham virus positive MS patients treated with NAT, likely precludes the use of NATbeyond 2 years and additional caution is warranted due to additional immunosuppression with corticosteroids and potentially other immunosuppressive drugs or carry-over effects. Nevertheless, the mode of action of NAT, may teach the scientific community relevant lessons on pathophysiology of SuS.

In this respect, a misdiagnosis of MS in SuS patients may lead to inappropriate treatment that couldresult in exacerbation of the disease course due to either insufficient disease control or a possible harmful effect of treatment. Indeed, an exacerbation of SuS has been mentioned in two patients that were misdiagnosed with and treated for MS. Of note and in contrast to the potential beneficial effects of NAT in four patients with SuS, one case report described a remarkable disease exacerbation after treatment with NAT in a patient with presumed SuS [40]. This patient was initially diagnosed with MS and received monthly 1000 mg methylprednisolone

IV-pulse treatment for several months, followed by maintenance treatment with NAT. However, in a reply to this case report, doubt on the diagnosis of SuS was cast [41]. Another case described a 20-year-old woman with a visual field defect in the lower temporal quadrant who was diagnosed with MS [42]. Interferon beta-1a was started but discontinued after 7 weeks due to a presumed prothrombotic effect. The patient was switched to glatiramer acetate. However, after 2 weeks, neurological worsening was observed. A diagnosis of SuS was made based on new-onset BRAO, symptoms of hearing loss and characteristic brain lesions on MRI. The patient's neurological state improved with a combination of corticosteroids, IVIG and AZA. SuS should be in the differential diagnosis of MS, especially when atypical visual symptoms, hearing loss or encephalopathy are important clinical manifestations.

Finally, SuS can manifest during or after pregnancy and there is a female predominance in the gender ratio. Treating patients for SuS during pregnancy can be challenging, as both the condition of the mother and the unborn child must be considered. Corticosteroids, acetylsalicylic acid, AZA, CYSP, TAC, TNF-α inhibitors, RTX and NAT require caution and specific guidelines when used during pregnancy. MMF, MTX and CYC are contra-indicated due to teratogenicity. These restrictions and considerations are further discussed in a recent review [19].

Limitations

Certain limitations must be considered to properly interpret the results of this scoping review.

Firstly, data were extracted from published case reports. This makes the review prone to publication bias, as some existing cases with negative treatment outcomes or different presentations might not be published. For example, median time from onset of symptoms to diagnosis is 8 weeks, which is notably low. This may be caused by publication bias to cases with a quick diagnosis and effective treatment, while less classic presentations with delayed and less effective treatment remain unpublished. The information that can be extracted from published cases is limited when compared to patient records, as authors must communicate their cases in a brief and concise manner. Remission of SuS while treated with a combination of immunosuppressants does not sufficiently prove that this approach is effective, as remission may occur spontaneously. Furthermore, the follow-up time was variable with a median follow-up time of 12 months, which is relatively short. This means that important information on long-term disease course is not available.

Although expert opinion-based recommendations to estimate disease severity exist, there are no currently used algorithms to score SuS severity in a consistent manner [8]. Disease severity was also not reported in this review due to lack of information. As a result, treatment combinations could not be compared based on disease severity.

Secondly, treatment in these cases has been categorized in different sequences to make analysis of collected data possible. Decisions on the categorization process and treatment sequences were made jointly by all authors before the literature review started. However, this categorization makes it more difficult to follow which treatments were carried over between treatment sequences in an individual patient.

Thirdly, this review only included cases that went into remission after treatment as the aim of this review was to highlight effective treatment options and the regimen in which they were administered. This means that patients who received certain treatments but did not reach remission were not included. Important to note, however, is that we have discussed five excluded cases with unsuccessful treatment or death, in order to give a brief description of these cases and possible reasons for not reaching remission.

Finally, we used a cut-off period of 1 month to define a clinical remission for the purposes of data-analysis. While this might be considered a very short period, we decided upon this cut-off period based on the descriptions and limited follow-up time described in the case reports. Also, in MS, a relapse is commonly defined in the same way [43]. This definition remains open to discussion but is important when interpreting the results of this review. Consensus-based definitions to describe the disease course in SuS are lacking but are essential for the scientific community to allow more uniform reporting in registries and observational studies in order to compare outcomes between patient groups.

Conclusion

SuS is an immune-mediated endotheliopathy for which no definitions of the disease course, nor evidence-based treatment guidelines exist. In this review, we provide an overview of clinical characteristics and treatment patterns of 151 SuS cases, published in the past decade. The lack of a definitions to describe the disease course should be addressed in the near future. The variability in treatment patterns underscores the need for a prospective international dedicated SuS registry to optimize diagnosis and management of people affected by SuS.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-11936-3.

Funding The authors did not receive support from any organization for the submitted work.

Declarations

Conflicts of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical standards The manuscript does not contain clinical studies or patient data. This manuscript only contains patient information from published cases.

References

1. Susac JO, Hardman JM, Selhorst JB (1979) Microangiopathy of the brain and retina. Neurology 29(3):313–316
2. Seifert-Held T et al (2017) Susac's syndrome: clinical course and epidemiology in a Central European population. Int J Neurosci 127(9):776–780
3. Dörr J et al (2013) Characteristics of Susac syndrome: a review of all reported cases. Nat Rev Neurol 9(6):307–316
4. Marrodan M, Fiol MP, Correale J (2022) Susac syndrome: challenges in the diagnosis and treatment. Brain 145(3):858–871
5. Kleffner I et al (2016) Diagnostic criteria for Susac syndrome. J Neurol Neurosurg Psychiatry 87(12):1287–1295
6. Triplett JD et al (2022) Diagnosis, differential diagnosis and misdiagnosis of Susac syndrome. Eur J Neurol 29(6):1771–1781
7. Gross CC et al (2019) CD8(+) T cell-mediated endotheliopathy is a targetable mechanism of neuro-inflammation in Susac syndrome. Nat Commun 10(1):5779
8. Rennebohm RM et al (2020) Guidelines for treatment of Susac syndrome—an update. Int J Stroke 15(5):484–494
9. Tricco AC et al (2018) PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 169(7):467–473
10. Page MJ et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71
11. Murad MH et al (2018) Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 23(2):60–63
12. Fonderska P et al (2022) Susac's syndrome diagnostic difficulties—the neurological point of view. Neurol Neurochir Pol 56(2):141–147
13. Marrodan M et al (2019) Video head impulse test contributes to Susac syndrome diagnosis. J Neurol 266(8):2070–2072
14. Reedy MB et al (2021) Successful Treatment of incomplete Susac syndrome with simultaneous corticosteroids and plasmapheresis followed by rituximab. Case Rep Neurol Med 2021:5591559
15. Qiu J et al (2020) Pregnancy without relapse following treated Susac syndrome. Mult Scler Relat Disord 45:102357
16. Mansukhani SA et al (2021) Sea fan frond neovascularization: a unique finding in a patient with Susac syndrome. J Neuroophthalmol 41(2):e160–e162
17. Obelienienė D et al (2017) Characteristics of headache in relation to the manifestation of Susac syndrome. Medicina (Kaunas) 53(6):420–425
18. Reynolds GL, Talbot K, Sharma SM (2017) Fundus fluorescein angiography in Susac's syndrome. Pract Neurol 17(6):472–473
19. Willekens B, Kleffner I (2021) Susac syndrome and pregnancy: a review of published cases and considerations for patient management. Ther Adv Neurol Disord 14:1756286420981352
20. Ramos-Ruperto L et al (2020) Susac syndrome and pregnancy: a relationship to clarify. About two cases and review of the literature. J Matern Fetal Neonatal Med 35:1–6
21. Ioannides ZA et al (2013) Susac syndrome and multifocal motor neuropathy first manifesting in pregnancy. Aust N Z J Obstet Gynaecol 53(3):314–317
22. Gomez-Figueroa E et al (2018) Exquisite response to intravenous immunoglobulin in Susac syndrome during pregnancy. eNeurol Sci 10:1–4
23. Dawe JA, Green AL (2021) Headache in Susac's syndrome. Curr Pain Headache Rep 25(4):25
24. Engisch R et al (2016) Susac's syndrome: leptomeningeal enhancement on 3D FLAIR MRI. Mult Scler 22(7):972–974
25. Baskin J et al (2020) Black blood MRI: endotheliopathy of Susac syndrome unmasked. Neurol Sci 42:325
26. Hardy TA et al (2011) Tumour necrosis factor (TNF) inhibitor therapy in Susac's syndrome. J Neurol Sci 302(1–2):126–128
27. Buelens T et al (2020) Evaluation of tumor necrosis factor inhibitor therapy in Susac syndrome. Retina 40(3):581–590
28. Fernando SL et al (2020) The successful use of infliximab in a relapsing case of Susac's syndrome. Case Rep Neurol Med 2020:9317232
29. Demuth S et al (2022) Good therapeutic response to infliximab in a case of Susac syndrome refractory to immunotherapies including tocilizumab. J Neurol 269(6):3347–3350
30. De Groot M et al (2020) Susac's syndrome as an immune-related adverse event after pembrolizumab: a case report. J Neurol 267(1):282–284
31. Rennebohm RM, Egan RA, Susac JO (2008) Treatment of Susac's syndrome. Curr Treat Options Neurol 10(1):67–74
32. Reich DS, Lucchinetti CF, Calabresi PA (2018) Multiple sclerosis. N Engl J Med 378(2):169–180
33. Vodopivec I, Prasad S (2017) Short follow-up bias confounds estimates of the "typical" clinical course of Susac syndrome. J Neuroophthalmol 37(2):149–153
34. Capiluppi E et al (2018) Aggressive immunosuppression in Susac's syndrome: 10 years of follow-up. Neurol Sci 39(10):1807–1809
35. Agamanolis DP et al (2019) Neuropathological findings in Susac syndrome: an autopsy report. J Neuropathol Exp Neurol 78(6):515–519
36. Shields RA et al (2018) A fatal case of Susac syndrome: The importance of ophthalmic examination in confirming the diagnosis. Am J Ophthalmol Case Rep 12:18–20
37. Liu Y et al (2022) Sudden onset hearing loss as initial presentation of Susac syndrome: a rare case report and brief review. Neurol Sci 43(1):683–686
38. Wiendl H et al (2021) Fundamental mechanistic insights from rare but paradigmatic neuroimmunological diseases. Nat Rev Neurol 17(7):433–447
39. Derfuss T et al (2013) Natalizumab therapy for multiple sclerosis. Semin Neurol 33(1):26–36
40. Zhovtis Ryerson L et al (2015) Incomplete Susac syndrome exacerbated after natalizumab. Neurol Neuroimmunol Neuroinflamm 2(5):e151
41. Ryerson LZ, Kister I, Snuderl M, Magro C, Bielekova B (2015) Incomplete Susac syndrome exacerbated after natalizumab. Neurol Neuroimmunol Neuroinflamm 2(5):e151. https://doi.org/10.1212/NXI.0000000000000151
42. Roskal-Wałek J et al (2021) Manifestation of Susac syndrome during interferon beta-1a and glatiramer acetate treatment for misdiagnosed multiple sclerosis: a case report. BMC Ophthalmol 21(1):352
43. Thompson AJ et al (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17(2):162–173
44. Campbell P, Kaski D, Saifee TA (2019) Susac syndrome presenting with acute hemibody paraesthesia. JRSM Cardiovasc Dis 8:2048004019844687
45. Ruizde Morales JG et al (2020) Autologous hematopoietic stem cell transplantation for Susac syndrome. Ann Intern Med 173(4):315–317

46. Staelens C et al (2016) Is Susac syndrome associated with bipolar disorder? Clin Neurol Neurosurg 149:64–67