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ORIGINAL ARTICLE

Diagnosis, differential diagnosis and misdiagnosis of Susac syndrome

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Abstract

Background and purpose: Susac syndrome (SuS) is an inflammatory condition of the brain, eye and ear. Diagnosis can be challenging, and misdiagnosis is common.

Methods: This is a retrospective review of the medical records of 32 adult patients from an Australasian cohort of SuS patients.

Results: An alternative diagnosis prior to SuS was made in 30 patients (94%) with seven patients receiving two or more diagnoses. The median time to diagnosis of SuS was 3 months (range 0.5–100 months). The commonest misdiagnoses were migraine in 10 patients (31%), cerebral vasculitis in six (19%), multiple sclerosis in five (16%) and stroke in five (16%). Twenty-two patients were treated for alternative diagnoses, 10 of whom had further clinical manifestations prior to SuS diagnosis. At presentation seven patients (22%) met criteria for definite SuS, 19 (59%) for probable SuS and six (19%) for possible SuS. Six patients (19%) presented

with brain–eye–ear involvement, 14 with brain–ear (44%), six with brain–eye (19%) and six (19%) with only brain involvement. In patients with the complete triad of symptoms the median delay to diagnosis was 3 months (range 1–9 months) compared to 5.25 months (range 0.5–100 months) for patients with encephalopathy and ocular symptoms at presentation.

Conclusions: Susac syndrome patients are frequently misdiagnosed at initial presentation, despite many having symptoms or radiological features that are red flags for the diagnosis. Delayed diagnosis can lead to patient morbidity. The varied ways in which SuS can present, and clinician failure to consider or recognize SuS, appear to be the main factors leading to misdiagnosis.

KEYWORDS
brain–eye–ear, migraine, multiple sclerosis, retinocochleocerebral vasculopathy, Susac syndrome

INTRODUCTION

Susac syndrome is a rare autoimmune mediated brain–eye–ear (BEE) syndrome affecting the small arterial vessels of the brain, inner ear and retina [1–3]. It is characterized by the clinical triad of encephalopathy, branch retinal artery occlusions (BRAOs) and sensorineural hearing loss (SNHL), usually affecting low- to mid-frequencies [4,5]. The annual incidence of Susac syndrome is estimated to be in the range 0.024–0.13 per 100,000 [6,7], with 60% of individuals aged between 21 and 35 years at the time of diagnosis and a reported male:female ratio of 1:3.5 [4].

The classic triad of features is present in only 13% of patients at onset, yet over 80% of patients eventually develop all symptoms [4]. Moreover, BEE organ involvement at onset may suggest other disorders [8], and a lack of awareness of clinical and radiological features and incomplete evaluation may lead to under-diagnosis, or critical delays in diagnosis, as well as morbidity from a delay in appropriate treatment [4,9–11]. Commonly reported misdiagnoses of Susac syndrome include multiple sclerosis, Ménière's disease, acute disseminated encephalomyelitis and cerebral vasculitis [12,13]. Whilst the median time to diagnosis for Susac syndrome in one study was 7 months from symptom onset [14], for some patients the diagnosis can take years [4,9–11,15]. Diagnostic delays or misdiagnosis may lead to recurrence or the development of new clinical symptoms [14].

To improve diagnosis, formal diagnostic criteria have been developed [16,17]. The 2017 European Susac Consortium (EuSaC) diagnostic criteria allow a diagnosis of *definite* Susac syndrome if there is evidence of all three BEE organs being affected, with *probable* Susac syndrome if only two BEE organs are involved and *possible* Susac syndrome if one BEE organ is affected (Table 1) [16]. Brain involvement is defined as at least one clinical finding consistent with encephalopathy together with characteristic magnetic resonance imaging (MRI) features of Susac syndrome. Ocular involvement is

TABLE 1 2017 EuSaC diagnostic criteria of Susac syndrome

1. Brain involvement	Both one or more symptoms (i) AND typical MRI findings (ii)
(i) Symptoms and clinical	New cognitive impairment and/or behavioural changes and/or new focal neurological symptoms and/or new headache
(ii) Imaging	Typical findings on cranial MRI; hyperintense, multifocal, round small lesions, at least one of them in the corpus callosum ('snowball') on T2 (or FLAIR) weighted sequences
2. Retinal involvement	One of either BRAOs or AWH on fluorescein angiography or characteristic signs of retinal branch ischaemia in fundoscopy or SD-OCT Clinical findings and symptoms not required
3. Vestibulocochlear	At least one symptom or clinical feature (i) supported by evaluations (ii)
(i) Symptoms and clinical	New tinnitus and/or hearing loss and/or peripheral vertigo
(ii) Examination of inner ear function	Hearing loss must be supported by an audiogram; vestibular vertigo must be supported by specific diagnostics
Definite	All three criteria met
Probable	Two of three criteria met
Possible	Only one of three criteria met

Abbreviations: AWH, arterial wall hyperfluorescence; BRAOs, branch retinal artery occlusions; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; SD-OCT, spectral domain optical coherence tomography.

defined as BRAOs or arterial wall hyperfluorescence by fundus fluorescein angiography (FFA) or characteristic signs of retinal branch ischaemia in funduscopy or spectral domain optical coherence tomography. Vestibulocochlear involvement is defined as new tinnitus and/or hearing loss and/or peripheral vertigo with classic findings on an audiogram of sensorineural hearing loss [16].

Despite recognition that misdiagnosis occurs frequently, the differential diagnoses and the determinants of diagnostic delay or failure have not yet been studied systematically. Here the diagnostic experience of adult patients from an Australasian Susac syndrome cohort is retrospectively reviewed to better understand the diagnosis and misdiagnosis of Susac syndrome.

MATERIALS AND METHODS

Patients with definite or probable Susac syndrome according to the EuSaC diagnostic criteria [16] were identified by investigators in the Neuroimmunology Clinic at Concord Hospital and the Brain and Mind Centre, University of Sydney, Australia. Medical records were reviewed retrospectively in September 2020 for clinical, laboratory, electrodiagnostic, radiological and pathological information. The study was approved by the Sydney Local Health District Human Research Ethics Committee with a waiver of patient consent (HREC/16/CRGH/293).

Time to diagnosis was defined as the time from initial onset of symptoms leading to presentation to a medical practitioner that were attributable to Susac syndrome. Organ involvement at presentation was defined as symptomatic complaints, clinical signs and/or objective investigation findings used for the diagnosis of Susac syndrome (MRI, audiology assessment, ophthalmic assessment). An alternative diagnosis was defined as a diagnosis mentioned in the clinical record by the managing practitioner prior to the diagnosis of Susac syndrome. An initial diagnosis was defined as the first diagnosis mentioned in the clinical record. A 'neuro-immunologist' refers to a neurologist who has undergone a neuro-immunology fellowship, undertaken a PhD in a neuro-immunological condition or who was working in a dedicated neuro-immunological clinic.

Categorical data were expressed as the proportion of the total number of patients. Continuous data were calculated as mean, median, minimum and maximum. Correlations were calculated after rank transformation using the Spearman rank method. p values <0.05 were considered significant.

RESULTS

Thirty-two patients (17 female) with a final diagnosis of definite or probable Susac syndrome between 2011 and 2020 were identified (Table 2). Six patients (19%) presented with BEE involvement, 20 (63%) with two organs involved (14 brain–ear, six brain–eye) and six (19%) with only brain involvement. Headache was the most common initial symptom occurring in 27 (84%) patients. Other common presenting symptoms were encephalopathy in 20 patients (63%), visual disturbance in 12 (38%), vertigo in nine (28%), hearing loss in seven (22%), sensory disturbance in five (16%), tinnitus in four (13%) and ataxia in three (9%) patients. One patient had weakness, and another presented with a seizure.

All patients underwent MRI of the brain at the time of presentation. At presentation six patients (19%) underwent audiological assessment and five patients (16%) underwent ophthalmological assessment with FFA. Ten patients (31%) had a cerebrospinal fluid (CSF) assessment performed at initial presentation, six (19%) had an electroencephalogram and four (13%) underwent a brain biopsy.

Ultimately, after a diagnosis of Susac syndrome was confirmed, 30 (94%) patients had undergone FFA, which was abnormal in 29 patients including BRAOs being identified in 28 patients and branch retinal vascular abnormalities consistent with Susac syndrome in one other patient. Thirty-one patients (97%) underwent audiology assessment, which was abnormal in 27 patients. CSF analysis was collected and analysed in 28 (88%) patients; the mean protein was elevated at 1.77 g/l (range 0.26–3.68 g/l), and 14 of 28 patients had >6 white cells (range 0–20). No patient had CSF-restricted oligoclonal bands. Four patients (13%) underwent a brain and meningeal biopsy with histopathological features consistent with Susac syndrome.

Alternative diagnoses

Thirty patients (94%) were initially diagnosed with an alternative diagnosis prior to Susac syndrome including seven patients (23%) with two or more diagnoses (Table 3). The commonest misdiagnoses were migraine in 10 patients (31%), primary cerebral vasculitis in six patients (19%), multiple sclerosis in five patients (16%) and stroke in five patients (16%). Viral encephalitis was presumed, or at least considered, in four patients (13%), all of whom were commenced on anti-viral therapy. At the time of the alternative diagnosis, seven patients (22%) met the criteria for definite Susac syndrome, 19 (56%) for probable and six (19%) for possible Susac syndrome. Three of the 19 patients (16%) with probable Susac syndrome developed further symptoms and subsequently would have met the criteria for definite Susac syndrome but were misdiagnosed prior to the final diagnosis of Susac syndrome.

At initial presentation up to 26 of the 32 patients (81%) in this series would have met criteria for probable or definite Susac syndrome if complete ophthalmological and audiological assessments were performed.

Diagnostic delay

The median time to diagnosis of Susac syndrome was 3 months (range 0.5–38 months). Twenty-one patients (66%) were diagnosed with Susac syndrome within 6 months of presentation and diagnosis was delayed by over 12 months in eight patients (25%).

TABLE 2 Patient demographics at presentation

	Patients ($n = 32$) (%)
Gender (female)	17 (53%)
Age, mean (range)	37 years (21–61 years)
Organ involvement at presentation	
Brain, ear and eye	6 (19%)
Brain and ear	14 (44%)
Brain and eye	6 (19%)
Brain only	6 (19%)
Presenting symptoms	
Headache	27 (84%)
Encephalopathy	20 (63%)
Visual disturbance	12 (38%)
Vertigo	9 (28%)
Hearing loss	7 (22%)
Sensory disturbance	5 (16%)
Tinnitus	4 (13%)
Ataxia	3 (9%)
Seizure	1 (3%)
Motor disturbance	1 (3%)

Presenting symptoms and delay to diagnosis

Time to diagnosis was dependent on clinical involvement at presentation and review (Figure 1). In the six patients with the complete triad of symptoms at presentation the median delay to diagnosis was 3 months (range 1–9 months). In the six patients with encephalopathy and ocular symptoms at presentation the median delay to diagnosis was 10 months (range 0.5–100 months). In the 14 patients with encephalopathy and vestibulocochlear symptoms at presentation the median delay to diagnosis was 3 months (range 1–38 months). In the patients with only brain involvement at presentation the median delay to diagnosis was 2.5 months (range 2–26 months).

Twenty-two (69%) patients were reviewed by a neuro-immunologist prior to the diagnosis of Susac syndrome of whom seven (22%) patients were first assessed by a neuro-immunologist. The time to Susac syndrome diagnosis was shorter in patients initially assessed by a neuro-immunologist than in those first assessed by other specialists which included general neurologists, neurologists with other subspecialty interests and ophthalmologists (2 months, range 0.5–8 vs. 3 months, range 0.75–38). Fifteen (47%) patients were referred to a neuro-immunologist for a second opinion prior to the diagnosis of Susac syndrome. The median time to referral and secondary review by a neuro-immunologist was 2.5 months (range 0.5–92 months) after symptom onset and the median time from neuro-immunology review to diagnosis of Susac syndrome was 0.5 months (range 0.5–24 months).

The time taken to make a diagnosis of Susac syndrome was similar amongst patients who presented after 2015 (15 patients, median 3 months, range 0.5–38 months) and those who presented prior to 2015 (17 patients, median 3 months, range 0.75–100 months).

Factors leading to misdiagnosis

Factors that led to a misdiagnosis included insufficient investigation of patient symptoms or failure to screen BEE organs for asymptomatic involvement, which contributed to misdiagnosis in 23 patients, and radiologist or treating clinician being unaware of known diagnostic features such as classic MRI findings in 16 patients (50%).

All patients underwent an MRI brain with corpus callosum lesions specific for Susac syndrome identified on the initial scans in 25 patients (78%) (Table 4). Prior to an alternative diagnosis being made of the 20 patients who presented with auditory symptoms, only six (30%) patients underwent evaluation with audiogram or vestibular function testing and only five (42%) of the 12 patients who presented with visual symptoms underwent evaluation with FFA prior to an alternative diagnosis being made, one of which was incorrectly interpreted, leading to a 1-month delay in the diagnosis of Susac syndrome.

Treatment

Twenty-two patients (69%) (four definite, 14 probable, four possible) received treatment for their alternative diagnosis (Table 1). Treatment included intravenous or oral corticosteroids in 17 patients (53%), intravenous immunoglobulin in three (9%), plasma exchange in one (3%), migraine preventative medication in five (19%), aspirin in five (19%), anti-viral medication in four (13%), beta-interferon immunotherapy for multiple sclerosis in one (3%) and surgical closure of a patent foramen ovale in one patient (3%).

Clinical relapses or new symptoms developed prior to the diagnosis of Susac syndrome in 10 of the 22 patients (45%) who received treatment for an alternative diagnosis and three patients who had received no treatment for their alternative diagnosis. Amongst the 10 patients who received treatment, isolated visual impairment developed in two patients, isolated central nervous system (CNS) dysfunction in two patients, a combination of vestibulocochlear dysfunction plus CNS dysfunction in two patients, visual and CNS dysfunction in two patients and one patient each experienced vestibulocochlear plus visual loss or CNS, visual and vestibulocochlear manifestations. The one patient who received beta-interferon for multiple sclerosis had new, recurrent visual dysfunction prior to the diagnosis of Susac syndrome. All three patients who received no treatment developed encephalopathy requiring hospitalization; one of these patients also had new vestibulocochlear dysfunction.

Involved healthcare practitioners

Specialists other than neurologists reviewed 11 patients (34%) with Susac syndrome before the initial diagnosis was made. Seven patients (22%) were reviewed by ophthalmologists, three patients (9%) by audiologists, and an otolaryngologist, immunologist, rheumatologist, dermatologist and infectious disease specialist each reviewed

TABLE 3 Diagnostic information

Patient	Symptoms at review	Delay (months)	Alternative diagnosis	Diagnostic criteria at presentation	Treated	Treatment
1	Hearing loss, encephalopathy	3	ADEM	Probable	Y	IVMP, PO steroids
2	Ataxia, vomiting and headache	3	Vasculitis	Probable	Y	IVIG, IVMP, PO steroids
3	Sensory disturbance, encephalopathy, visual loss	4	TIA, Hashimoto encephalitis, vasculitis	Definite	Y	IVIG, IVMP
4	Encephalopathy, headache	2	Viral encephalitis, neurosarcoidosis, CNS lymphoma	Possible	Y	Ganciclovir, IVMP
5	Headache, vertigo, unilateral hearing loss, tinnitus	28	MS	Probable	Y	PO steroids, interferon beta
6	Encephalopathy, headache, deafness	18	Histoplasmosis	Probable	Y	PO steroids, antifungals
7	Visual disturbance, headache	3	Migraine	Probable	N	
8	Headache, quadrantanopia visual loss	0.75	Migraine	Probable	Y	Migraine preventers
9	Unilateral hearing loss, tinnitus, paraesthesia, headache, vertigo, patchy vision loss, photopsia	3	Migraine, vasculitis	Definite	Y	IVMP, PO steroids, azathioprine
10	Encephalopathy, ataxia	2	Viral encephalitis, vasculitis	Probable	Y	Acyclovir, IVMP, PO steroids
11	Encephalopathy, drowsiness, dysarthria, lower limb weakness	3	Auto-immune encephalitis	Possible	Y	IVIG, IVMP, PLEX
12	Encephalopathy, vertigo, headache, blurred vision	13	ADEM	Probable	N	
13	Encephalopathy, vertigo, headache, hearing loss	19	BPPV, MS	Probable	Y	IVMP
14	Headache	3.5	MS, vasculitis	Probable	Y	IVMP, aspirin, PO steroids, migraine preventers
15	Headache, scotomatous vision loss	36	Migraine	Probable	Y	Migraine preventers
16	Dizziness, nausea, headache, encephalopathy	0.75	BPPV	Probable	N	
17	Headache, encephalopathy, vertigo	2	MS	Possible	Y	IVMP
18	Headache, encephalopathy, visual loss	100	Migraine	Probable	Y	Migraine preventers
19	Headache, encephalopathy, tinnitus, vertigo, hearing loss	1.25	Migraine, cocaine vasculopathy	Definite	N	
20	Vertigo, encephalopathy, hearing loss	38	Migraine, strokes	Probable	Y	Aspirin, apixaban, PFO closure

(Continues)

TABLE 3 (Continued)

Patient	Symptoms at review	Delay (months)	Alternative diagnosis	Diagnostic criteria at presentation	Treated	Treatment
21	Sensory disturbance, vision loss	0.5	Strokes	Probable	N	
22	Headache, visual loss, tinnitus	2		Definite		
23	Headache, encephalopathy	26	Migraine	Possible	N	
24	Encephalopathy, headache, sensory disturbance	3	Migraine	Probable	N	
25	Headache, encephalopathy	2	Viral encephalitis	Definite	Y	Acyclovir
26	Seizure, headache, encephalopathy	7	Migraine, epilepsy	Possible	Y	Migraine preventers, aspirin, levetiracetam
27	Headache, vertigo	5	Strokes	Probable	Y	Aspirin
28	Encephalopathy, headache, visual disturbance, vertigo	1	Viral encephalitis	Probable	Y	Acyclovir
29	Headache, visual symptoms, encephalopathy, sensory symptoms	1	Strokes	Definite	Y	Aspirin
30	Headache, visual symptoms	7	IIH	Probable	N	
31	Headache, visual symptoms, encephalopathy, hearing loss	1		Definite	N	
32	Headache, vertigo, ataxia, encephalopathy	2	Stroke	Probable	Y	Aspirin

Abbreviations: ADEM, acute disseminated encephalomyelitis; BPPV, benign paroxysmal positional vertigo; CNS, central nervous system; IIH, idiopathic intracranial hypertension; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MS, multiple sclerosis; PFO, patent foramen ovale; PLEX, plasma exchange; PO, per oral; TIA, transient ischaemic attack.

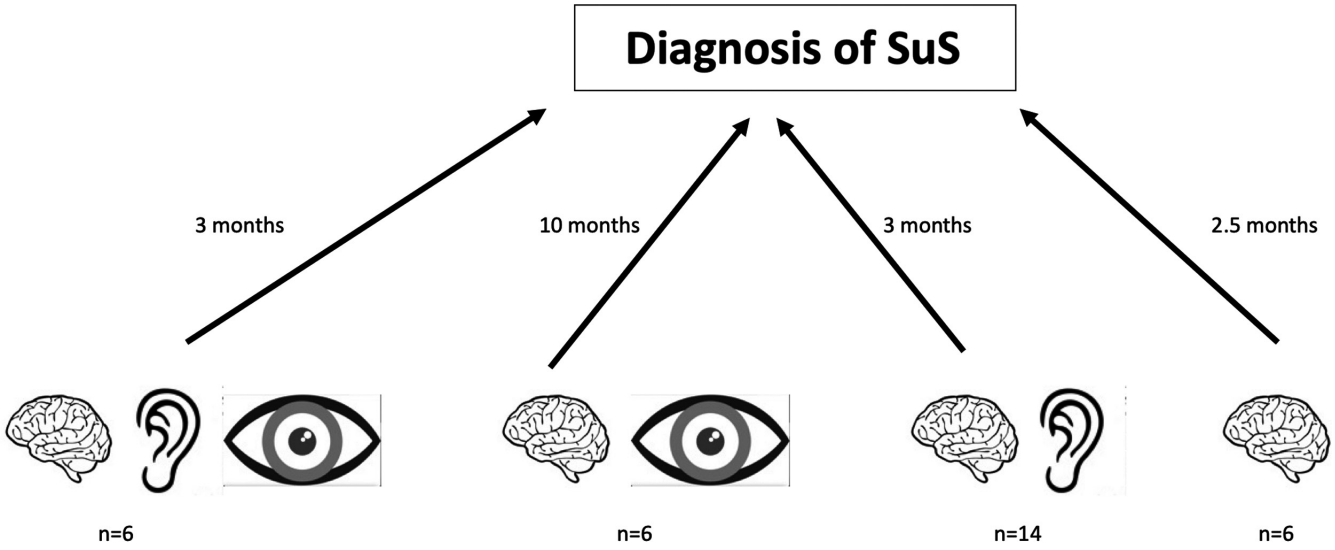

FIGURE 1 Median time to the diagnosis of Susac syndrome based on symptoms at presentation

TABLE 4 Magnetic resonance imaging (MRI) abnormalities on initial MRI brain

Abnormality	Number	%
Initial MRI abnormal	30	94
T2 hyperintensities	29	91
Corpus callosum involvement	25	78
Leptomeningeal enhancement	14	44
Diffusion restriction	18	56
Diffusion restriction in multiple vascular territories	13	41
Ischaemia	2	6

one patient (3%). Patients saw a median of two healthcare specialists (1–4) prior to their initial diagnosis.

Self-initiated search for diagnosis

Two patients performed a self-initiated search for their diagnosis and sought out referral to specialty neuro-immunology clinics for review of possible Susac syndrome.

DISCUSSION

This study systematically reports the diagnostic experience in Susac syndrome, and the association between various clinical presentations and diagnostic delay. Our results indicate that a diagnostic evaluation requiring the involvement of several healthcare professionals is associated with a substantial increase in diagnostic delay, that patients presenting with visual symptoms or vestibulocochlear symptoms are associated with greater diagnostic delay (Figure 1) and that there is an under-appreciation of the specific clinical features and imaging findings in Susac syndrome which may contribute to diagnostic delay.

The first specialist healthcare professionals, other than general practitioners, that Susac syndrome patients in our study typically encountered were neurologists, with only a minority of patients being reviewed by other clinicians. The seven patients who were initially reviewed by a clinician with expertise in neuro-immunology had the shortest time to diagnosis of Susac syndrome. However, the referral of patients directly to an expert centre is dependent on patient location and accessibility to neuro-immunology services. Direct referral to a neuro-immunologist was associated with a substantially shorter diagnostic delay even if the referral diagnosis was unclear. Once patients were reviewed by a neuro-immunologist they were more likely to undergo complete evaluation for audiological and ophthalmic involvement which aided the diagnosis of Susac syndrome with a median time to diagnosis of 0.5 months.

The differential diagnosis for Susac syndrome includes common and rare neuro-inflammatory conditions, especially multiple sclerosis, genetic conditions such as adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, and miscellaneous conditions including microembolic stroke and Ménière's disease (Table 5). Our study found that migraine, cerebrovascular diseases such as cerebral vasculitis, multiple sclerosis and stroke were the commonest misdiagnoses. Our study also adds further differential diagnoses to this list including histoplasmosis, viral encephalitis, Hashimoto's encephalitis and CNS lymphoma.

The median diagnostic delay of 3 months in this series was slightly less than that reported in a retrospective review of cases in the literature (7 months) [4]. The shorter time to diagnosis in our series may be due to clinical deterioration in some patients and referral to sub-specialist neuro-immunology clinics. Furthermore, the ability to assess the delay in comparison to the types of presentations is unique to our study. The diagnosis of Susac syndrome was similar amongst patients who presented

TABLE 5 Differential diagnoses of Susac syndrome

Neuro-immunological	Genetic	Infectious	Other
Multiple sclerosis	CADASIL	Histoplasmosis	Micro-embolic infarction
ADEM	MELAS	CJD	Cocaine-induced encephalopathy
CNS vasculitis	ALSP	Viral encephalitis	Migraine with aura
Cerebral SLE	RVCL-S	Tuberculosis	Cerebral amyloid angiopathy
Cerebral APLS		Neurosyphilis	Ménière's disease
Neurosarcoidosis		HIV	CNS lymphoma
Neuro-Behçet's disease			Marchiafava–Bignami disease
Cogan syndrome			Psychosis
Autoimmune encephalitis			

Abbreviations: ADEM, acute disseminated encephalomyelitis; ALSP, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; APLS, antiphospholipid syndrome; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CJD, Creutzfeldt–Jakob disease; CNS, central nervous system; HIV, human immunodeficiency virus; MELAS, myopathy, encephalopathy, lactate acidosis and stroke-like episodes; RVCL-S, retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; SLE, systemic lupus erythematosus.

before and after 2015 indicating that recognition of Susac syndrome as a diagnosis has not substantially improved over the last 10 years.

The finding in this series that headache was the most common presenting symptom occurring in 78% (25/32) is similar to other studies which report its presence in over 60% of patients at disease onset [4]. Headache in Susac syndrome can be indistinguishable from migraine which explains why migraine was a common initial diagnosis in our study and why patients with headache and visual disturbance had a longer time to diagnosis than other presentations. It is argued that Susac syndrome should be considered in any patient with new onset migraine with visual symptoms and an MRI brain showing white matter lesions involving the corpus callosum, or if associated with diffusion-weighted imaging change and/or gadolinium enhancement. It is advocated that these patients also have an ocular review and audiology specifically to exclude Susac syndrome or another BEE syndrome.

Previous reports suggest that 40% of patients have auditory and/or visual disturbance at presentation [18]. In this series 63% (20/32) had vestibulocochlear disturbance and 38% (12/32) visual disturbance at presentation. Patients with visual disturbance at presentation had a longer delay in time to diagnosis than those with vestibulocochlear presentations (5.25 vs. 3 months). Vestibulocochlear symptoms were common at presentation yet were only fully investigated with quantitative neuro-otology testing at presentation in 30% of patients (6/20). SNHL in Susac syndrome can be acute or subacute, unilateral or bilateral, simultaneous or sequential in nature, and typically affects low- to mid-frequencies [19,20]. A potential diagnostic dilemma is the commonly encountered overlap of vestibular migraine and Ménière's disease, particularly in young females, which also presents with headache, vertigo and fluctuating hearing loss [21]. It is suggested that, in addition to MRI of the internal acoustic canals to exclude a retrocochlear lesion in any patient who presents with headache, vertigo and documented low- to mid-frequency asymmetric SNHL, a full MRI of the brain should also be obtained concurrently with a view to excluding Susac syndrome. Visual symptoms were investigated with FFA in only 42% (5/12) of patients at presentation. Furthermore, one of the five patients who underwent FFA had the FFA inaccurately reported at the time of presentation, leading to a 1-month delay in diagnosis.

Eventually, when patients underwent audiology testing or FFA, the FFA was abnormal in 29 patients, including BRAOs being identified in 28 patients and microangiopathic abnormalities consistent with Susac syndrome in one patient. Audiology assessment was abnormal in 27 of 31 patients. The asymptomatic or mildly symptomatic and non-disabling complaints of BRAOs and vestibulocochlear abnormalities highlight the importance of a thorough initial diagnostic evaluation at the onset of encephalopathy with MRI features suggestive of Susac syndrome or encephalopathy accompanied by acute visual or auditory disturbances.

Our study also highlights the importance of accurate appreciation of MRI brain findings in patients with suspected Susac syndrome. The importance of a radiologist identifying and reporting lesions compatible with Susac syndrome is essential to the diagnosis, and accordingly failure of a radiologist to raise Susac syndrome as a diagnostic possibility can lead to meaningful diagnostic delays. MRI of the brain may reveal characteristic callosal lesions [22–25], which were identified in 78% (25/32) of patients on their initial MRI. These include 'snowball' lesions (Figure 2) which are rounded, hyperintense lesions in the central fibres between the ventricular surface and superior aspect of the corpus callosum on T2/fluid attenuated

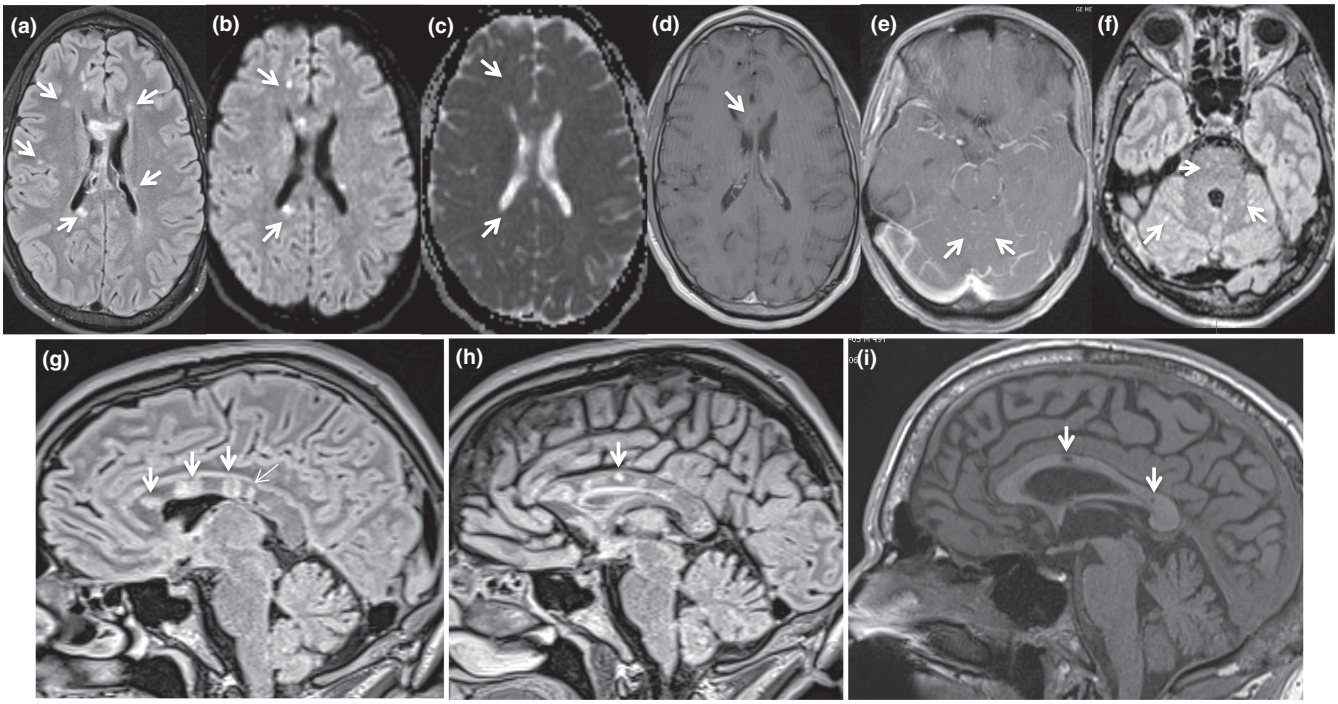

FIGURE 2 Characteristic MRI findings from patients with Susac syndrome. (a) Axial fluid attenuation inversion recovery (FLAIR) sequence shows typical punctate hyperintensities throughout the white matter (arrows). (b), (c) Axial diffusion-weighted imaging and apparent diffusion coefficient sequence showing punctate areas of restricted diffusion (arrow) corresponding to two of the FLAIR lesions (arrows). (d) Axial T1 post-gadolinium sequence showing partial enhancement of a corpus callosum lesion (arrow). (e) Axial T1 post-gadolinium sequence showing multiple areas of punctate enhancement of the cerebellar meninges (arrows). (f) FLAIR sequence showing further punctate lesions in the brainstem and cerebellum (arrows). (g) Sagittal FLAIR sequence showing three 'snowball' lesions in the corpus callosum (thick arrows) and a thinner 'spoke' lesion traversing the callosum (thin arrow) with (h) an 'icicle' lesion arising from the roof of the callosum (arrow). (i) Sagittal T1 sequence showing typical 'punched out holes' in the corpus callosum (arrows)

inversion recovery (FLAIR) sequences [22]. Callosal 'spoke' and 'icicle' lesions are also commonly identified on T2/FLAIR sequences [23,24]. 'Punched out' central callosal holes are seen on T1 sequences and differ in location and morphology from the callosal lesions of multiple sclerosis which tend to occur at the under-surface of the callosum [22–25].

An important MRI differentiator from multiple sclerosis is leptomeningeal enhancement which was seen in 44% of this cohort (on post-gadolinium T1 or FLAIR sequences) but which is not seen in multiple sclerosis. In our series, leptomeningeal enhancement was seen in one of the three cases previously diagnosed as multiple sclerosis. A recent study has suggested that up to 100% of patients with Susac syndrome demonstrate leptomeningeal enhancement on post-gadolinium FLAIR sequences [26]. Cerebrovascular inflammation and enhancement can also be seen using a 'black blood' MRI sequence [27]. Acute lesions in Susac syndrome are often markedly hyperintense on diffusion-weighted images with matched alteration of apparent diffusion coefficient maps consistent with restricted diffusion, whilst in comparison acute multiple sclerosis lesions only occasionally exhibit true restricted diffusion [25]. In our series, 18 patients showed restricted diffusion on their initial MRI and in 13 of these patients the lesions crossed vascular territories. This highlights that Susac syndrome should always be considered in patients with diffusion-restricted lesions in more than one vascular territory.

Cerebrospinal fluid examination was performed in 28 patients and protein was markedly elevated at 1.77 g/l. This is in keeping with previously reported CSF findings in Susac syndrome revealing a mean protein of 1.6 g/l [4] and may be an important early diagnostic clue to Susac syndrome. The CSF findings are again different from those found in multiple sclerosis where a cellular CSF is uncommon, CSF protein is usually normal or mildly elevated and oligoclonal bands are frequent; and also different from viral encephalitides where the CSF is usually highly cellular.

Incorrect alternative diagnoses may result in treatment with inappropriate medications including beta-interferon for multiple sclerosis, placing patients at risk of harm from adverse effects. Beta-interferon has previously been reported to be associated with worsening of ocular manifestations in Susac syndrome [28,29], and although it was not associated with abrupt clinical deterioration our patient did re-present with visual disturbance after it was commenced. One patient also underwent a closure of a patent foramen ovale during the work up to their eventual diagnosis of Susac syndrome due to the MRI brain appearance of multiple small ischaemic infarcts which were thought to be due to microembolic disease. Although no patient who received intravenous immunoglobulin or plasma exchange suffered significant side effects from these therapies they were exposed to unnecessary procedures. Brain biopsy was performed in four patients contributing to morbidity and placing

these patients at risk of procedure-related complications. A brain biopsy should not be required routinely for the diagnosis of Susac syndrome.

Our study is limited by small numbers of patients and the retrospective data collection which meant that it could be difficult to be certain of the precise onset of symptoms such as headache or visual disturbance. In addition, clinicians often consider several potential diagnoses at once, or establish a provisional diagnosis, only coming to a firmer conclusion later in the diagnostic process. It is therefore possible that Susac syndrome was considered early in the diagnostic process by some clinicians but not made explicit in the patient record until other more common diagnoses had been excluded. Our data were collected at two specialty neuro-immunology clinics with a special interest in Susac syndrome. Nevertheless, most patients were assessed at other centres first and so our data would appear to be representative of real-world experience with the disease but a selection bias toward less typical cases cannot be excluded. Notably, our cohort had a relatively even male to female ratio which is different from the female preponderance reported in other studies.

Recommendations from this study to improve the diagnostic accuracy of Susac syndrome include (1) consideration of Susac syndrome in a patient presenting with a BEE symptom; (2) undertaking an MRI brain with contrast with new onset headaches accompanied by visual, auditory or cognitive disturbance; (3) improving recognition of the specific MRI findings suggestive of Susac syndrome including callosal 'snowball' lesions, callosal 'spoke' and callosal 'icicle' lesions on T2 FLAIR, central callosal holes on T1 sequences, multiterritorial areas of restricted diffusion in active cases and leptomeningeal enhancement (when present); (4) if investigations reveal characteristic features of Susac syndrome in one BEE organ, then other BEE organs should be tested, even if the patient is asymptomatic; and (5) the consideration for prompt referral to a sub-specialist neuro-immunology clinic if there is diagnostic uncertainty.

In conclusion, most patients with Susac syndrome are not diagnosed correctly at their initial presentation, with the commonest misdiagnosis being migraine. Patients are more promptly diagnosed with Susac syndrome if they present with clinical involvement of all three BEE organs or see a neuro-immunologist. The varied ways in which Susac syndrome can present, and clinician failure to consider or recognize key features of Susac syndrome, appear to be the main factors leading to misdiagnosis.

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CONFLICT OF INTEREST

The authors report no competing or conflicting interests.

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James Triplett: Conceptualization (equal); data curation (equal); formal analysis (lead); investigation (lead); methodology (equal); writing—original draft (equal); writing—review and editing (supporting). Jessica Qiu: Conceptualization (equal); data curation (supporting); investigation (supporting); writing—review and editing (supporting). Billy O'Brien: Conceptualization (supporting); investigation (supporting); methodology (supporting); writing—review and editing (supporting). Sumana Gopinath: Investigation (supporting); writing—review and editing (supporting). Benjamin Trewin: Investigation (supporting); methodology (supporting); writing—review and editing (supporting). Penelope J. Spring: Formal analysis (supporting); investigation (supporting); methodology (supporting); writing—review and editing (supporting). Mohamed Shaffi: Investigation (supporting); writing—review and editing (supporting). Jerome Ip: Investigation (supporting); methodology (supporting); writing—review and editing (supporting). Fiona Chan: Investigation (supporting); methodology (supporting); writing—review and editing (supporting). Luke Chen: Data curation (supporting); investigation (supporting); methodology (supporting); writing—original draft (supporting); writing—review and editing (supporting). Ian Wilson: Data curation (supporting); investigation (supporting); methodology (supporting); project administration (supporting); writing—original draft (supporting); writing—review and editing (supporting). Claire Muller: Data curation (supporting); methodology (supporting); writing—review and editing (supporting). Heidi Beadnall: Data curation (supporting); investigation (supporting); methodology (supporting); writing—original draft (supporting); writing—review and editing (supporting). Mike Boggild: Data curation (supporting); investigation (supporting); methodology (supporting); writing—original draft (supporting); writing—review and editing (supporting). Anneke van der Walt: Investigation (supporting); methodology (supporting); writing—original draft (supporting); writing—review and editing (supporting). Richard Roxburgh: Data curation (supporting); investigation (supporting); methodology (supporting); writing—original draft (supporting); writing—review and editing (supporting). Nabil Seery: Data curation (supporting); writing—review and editing (supporting). Tomas Kalincik: Investigation (supporting); methodology (supporting); project administration (supporting); writing—original draft (supporting); writing—review and editing (supporting). Michael Barnett: Data curation (supporting); investigation (supporting); methodology (supporting); writing—review and editing (supporting). John D.E. Parratt: Data curation (supporting); formal analysis (supporting); investigation (supporting); writing—review and editing (supporting). Stephen W. Reddel: Data curation (supporting); formal analysis (supporting); writing—review and editing (supporting). Ben Tsang: Data curation (supporting); methodology (supporting); writing—original draft (supporting); writing—review and editing (supporting). Todd A. Hardy: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); supervision (lead); writing—original draft (equal); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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