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Case report

Progressive sensorineural hearing loss many years preceding completion of Susac's syndrome triad: A case report

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ABSTRACT

Susac's syndrome (SuS) is a rare disorder with a clinical triad of encephalopathy, sensorineural hearing loss, and branch retinal artery occlusions. We report a 7-year-old girl who presented with chronic, progressive sensorineural hearing loss, who, years later, presented with encephalopathy and vision loss. Such prolonged period between symptoms is unusual and to our knowledge, this is the longest interval between onset of hearing loss and completion of the full triad in SuS. In addition, she had a protracted disease course, requiring multiple immune therapies for disease control.

1. Introduction

Susac's syndrome (SuS) is a rare disorder of unknown etiology, possibly an immune-mediated endotheliopathy and microangiopathy.[1] Classically, it is a clinical triad of encephalopathy, sensorineural hearing loss, and branch retinal artery occlusions (BRAOs).[1,2] SuS can be difficult to diagnose, as the full triad may not be present at symptom onset.[1] We report a case of a girl with progressive hearing loss, who, many years later, presented with the full triad of SuS.

2. Case presentation

A 7-year-old girl presented after failing a school screening audiogram. She had a normal birth and developmental history, and no prior trauma, surgery, otitis media, meningitis, or ototoxic drug exposure. She had no family history of hearing loss. Audiogram revealed left-sided sensorineural hearing loss, affecting low and middle frequencies (Fig. 1A). She was evaluated by an otolaryngologist, with note of normal tympanogram, otoscopic examination, and computerized tomography of her head and mastoids. Thereafter, she reported slowly progressive hearing loss bilaterally, and at 15-years-old, an audiogram identified right-sided sensorineural hearing loss (Fig. 1B). In addition, she reported intermittent dizziness and headache, which was diagnosed as a migraine variant without additional workup.

At 18-years-old, she presented to an Emergency Department with one week of vertigo and ataxia, followed by bilateral, painless vision blurriness, confusion, and worsened hearing. Brain magnetic resonance imaging (MRI) showed punctate areas of restricted diffusion (Fig. 2A and B), subcortical and periventricular hyperintense white matter signal abnormalities (Fig. 2C), and hyperintense white matter signal abnormalities in the corpus callosum (Fig. 2D and E, Arrows). Considerations at this time included demyelinating disorders such as multiple sclerosis (MS) and vasculitis.

Cerebrospinal fluid demonstrated a red blood cell count of 466 cells/μL, white blood cell count of 15 cells/μL (87% lymphocytes), protein of 278 mg/dL, and glucose of 60 mg/dL (serum glucose 88 mg/dL). Oligoclonal bands were not present and IgG index was normal. Infectious studies were negative including herpes simplex and varicella zoster virus, gram stain, and bacterial, fungal, and mycobacterial cultures. Serology showed elevated sedimentation rate (42 mm/h, normal < 25 mm/h) and C-reactive protein (0.7 mg/dL, normal < 0.5 mg/dL), and negative infectious (HIV, syphilis, tuberculosis) and autoimmune studies (ANA, anti-Ro/La, anti-dsDNA, antiphospholipid panel, ANCA panel, and normal complement levels). Brain MR angiography was normal; however, contrast-enhanced, high-resolution 3-dimension vessel wall MRI demonstrated linear foci of enhancement, compatible with abnormally enhancing small vessels. She underwent a brain biopsy, given concern for vasculitis and intravascular lymphoma, which did not show any abnormalities.

For her vision symptoms, she underwent dilated fundoscopic evaluation and fluorescein angiography, which showed multiple branch retinal artery occlusions (BRAOs) (Fig. 2F and G).

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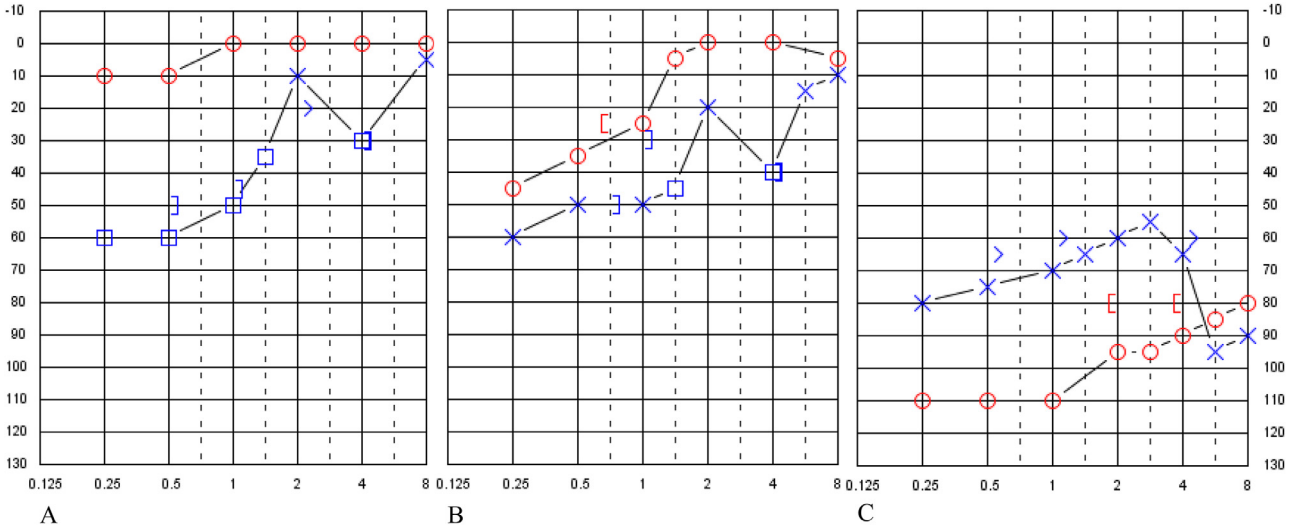

	Air conduction threshold		Bone conduction threshold	
	Right ear	Left ear	Right ear	Left ear
Unmasked	◯	X	<	>
Masked	△	□	⊏	⊐

Fig. 1. Audiogram (*see attachment*) Audiograms over a span of 11 years show progressive sensorineural hearing loss bilaterally, initially affecting low and middle frequencies in the left ear (A), later involving the right ear (B), and progressing to include all frequencies bilaterally (C).

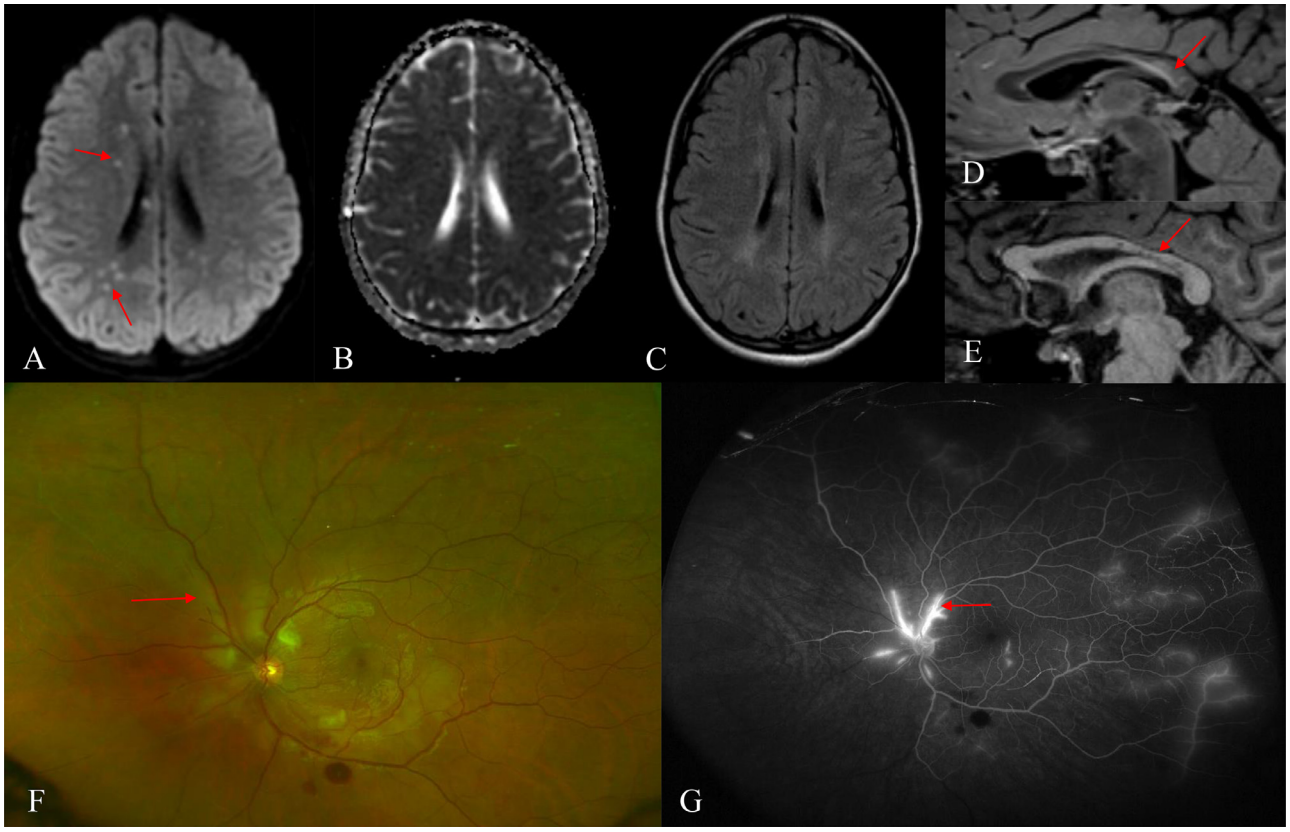

Fig. 2. Brain MRI, fundoscopy, and retinal fluorescein angiogram *(see attachment)* (A, B) Axial DWI and ADC sequences show punctate areas of restricted diffusion (Arrow). (C) Axial FLAIR sequence shows subcortical and periventricular hyperintense white matter signal abnormalities. (D) Sagittal FLAIR sequence shows corpus callosal hyperintense white matter signal abnormalities (Arrow). (E) Sagittal T1 sequence shows punctate hypointense lesions in the corpus callosum (Arrow). (F) Fundus photograph of the left eye demonstrates retinal whitening adjacent to the optic disc and along the inferotemporal arcade, with scattered cotton wool spots and intraretinal hemorrhages. There are numerous sections of retinal arterial sheathing (Arrow), seen most prominently nasal to the disc. (G) Late phase fluorescein angiogram of the left eye shows prominent hyperfluorescence of arterial segments coming off of the optic disc (Arrow), with distal nonperfusion. There are patches of peripheral retinal nonperfusion as well, with adjacent vessel leakage.

Table 1
Comparison of Susac's syndrome and Multiple sclerosis.

	Susac's syndrome	Multiple sclerosis
Demographics	Young, female	Young, female
Clinical features	Encephalopathy, headache, hearing loss	Optic neuritis, myelitis, focal neurologic symptoms
MRI findings	Punctate white matter hyperintense lesions, centrally located corpus callosal lesions, leptomeningeal enhancement	Ovoid white matter hyperintense lesions, peripherally located corpus callosal lesions, spinal cord lesions
CSF findings	Elevated protein and pleocytosis	CSF-specific oligoclonal bands and elevated IgG index
Ophthalmologic findings	BRAO	Optic neuritis

Audiometry showed worsened sensorineural hearing loss bilaterally, affecting all frequencies, more severe in the low to mid frequencies (Fig. 1C).

She was diagnosed with SuS, and received 5 days of high-dose intravenous steroids followed by a prednisone taper, with marked improvement. However, she had recurrence of her neurologic symptoms, as well as additional BRAOs. Maintenance immune therapy was started due to her refractory disease course. She has been tried on various combinations of azathioprine, mycophenolate mofetil, intravenous immunoglobulin (IVIg), prednisone, cyclophosphamide, and rituximab. Currently, at 3-year follow up since diagnosis, she is on low-dose prednisone, monthly IVIg, mycophenolate mofetil, and rituximab every 4–6 months with adequate disease control.

3. Discussion

SuS is difficult to diagnose, as it is rare, requiring a high index of suspicion, and the full triad may not be present at symptom onset. (Dörr et al., 2013) SuS has a female predominance and typical age at presentation is 16–40 years old. (Dörr et al., 2013) There have been various proposed diagnostic criteria over the years, with the most recent criteria from the European Susac Consortium in 2016. (Kleffner et al., 2016) For a definite diagnosis, involvement of the brain, retina, and vestibulocochlear system must be found. Brain involvement must include both clinical symptomatology and characteristic brain MRI findings including corpus callosum involvement. (Kleffner et al., 2016) Retinal involvement can be assessed with fundus examination, as well as fluorescein angiography, which demonstrates retinal arterial wall hyperfluorescence and BRAO. (Kleffner et al., 2016) Vestibulocochlear involvement requires both clinical symptoms (new tinnitus, hearing loss, or vertigo) and evaluation of inner ear function with audiogram, caloric testing, or vestibular evoked potentials. (Kleffner et al., 2016)

SuS may be misdiagnosed as MS, and subsequently, MS disease modifying therapies may be initiated. Besides the inherent risk profile of some of these agents, there are case reports of SuS exacerbation after initiation of MS treatment. (Algahtani et al., 2018) Differentiating SuS from MS may be difficult, especially if the full triad of SuS has not yet manifested. There are, however, a number of important distinguishing clinical features (Table 1). One key feature is encephalopathy at presentation, which is common in SuS but rare in MS. (Dörr et al., 2013; Buzzard et al., 2015) Distinguishing paraclinical findings include punctate white matter lesions in SuS versus ovoid ones in MS; central corpus callosal involvement in SuS versus peripheral in MS; findings of meningeal enhancement in SuS that is not seen in MS; and elevated protein in SuS with typically a lack of CSF specific oligoclonal bands. (Buzzard et al., 2015)

The clinical course of SuS is varied. Rennebohm et al. proposed stratification into three major clinical courses: monocyclic, polycyclic, and chronic-continuous. (Rennebohm and Susac, 2007) The majority of patients follow a relapsing course rather than the chronic-continuous type, with average duration of active phase being 21 months and average of 2.4 relapses experienced per patient; (Dörr et al., 2013; Jarius et al., 2014) however, there may be bias due to the short duration of follow up in reported cases of SuS. (Vodopivec and Prasad, 2017) Due to the rarity of the condition, there are no prospective studies on the best treatment intervention(s) for these patients. However, retrospective reviews and case reports support the use of various immune therapies, including IVIg, plasmapheresis, steroids, mycophenolate mofetil, cyclophosphamide, azathioprine, and rituximab. (Mateen et al., 2012) Though many patients respond to immune therapy with stability or improvements in their symptoms, some follow a protracted, progressive course of the disease and require aggressive treatment.

Our case demonstrates the presence of progressive sensorineural hearing loss over many years preceding the presentation of the full triad of SuS. To our knowledge, this is the longest interval between onset of hearing loss and completion of the full triad in SuS. According to a review by Dörr et al., the average time between presentation and completion of the triad is 21 weeks, with only 13% presenting with the full triad at onset. (Dörr et al., 2013) Initial presentation with ear involvement was noted in 37% of individuals. (Dörr et al., 2013) SuS is an important entity to consider in otherwise undiagnosed sensorineural hearing loss, especially if it is progressive and additional neurologic and/or ophthalmologic symptoms manifest. There is a paucity of clinical course and outcome data in SuS; however, we demonstrate in this case that SuS can be a progressive, treatment-refractory condition, requiring early-diagnosis and initiation/maintenance of immune therapies. (Rennebohm and Susac, 2007; Mateen et al., 2012) Further studies to identify prodromal, subclinical manifestations of SuS may be helpful in providing further insights into the disease pathophysiology and clinical course.

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Declaration of Competing Interest

Yujie Wang and Bryn Burkholder have reports no disclosures. Scott Newsome - Attended Scientific Advisory Boards: Biogen, Genentech, Celgene, EMD Serono; Advisor: Gerson Lehrman Group; Clinical Adjudication Committee Member for medDay Pharmaceuticals clinical trial. Grant/Research Funding (paid directly to Institution): Biogen, Genentech, Department of Defense, National MS Society, Patient Centered Outcomes Research Institute.

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