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Case Report

Characteristics of headache in relation to the manifestation of Susac syndrome

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ABSTRACT

Susac syndrome is characterized by a clinical triad of encephalopathy, branch retinal artery occlusion, and hearing loss. Due to the absence of the whole complex of the triad in the majority of cases at disease presentation, the syndrome often remains underdiagnosed and untreated. Headache is estimated to affect up to 80% of Susac syndrome patients, but the relevance of headache characteristics and profile is not yet clear. The proposed diagnostic criteria of the European Susac Consortium acknowledge headache as a possible brain manifestation if it is new, described as migrainous or oppressive, and precedes the other symptoms by not more than 6 months.

Herein, a case series of different migraine-like headache associations attributed to Susac syndrome is presented and discussed in relevance with previously published literature. Our patients experienced different presentations of migraine-like headache related with Susac syndrome: exacerbation and chronification of headache just before the manifestation of the first symptoms of Susac syndrome, the manifestation of headache during the first episode of the syndrome, and an increasing frequency of headache during the course of the disease. The diagnosis of Susac syndrome in all three cases was confirmed by typical clinical symptoms and findings in retinal fluorescein angiography, audiometry, and brain magnetic resonance imaging, based on the diagnostic criteria of the European Susac Consortium.

Based on the analysis of our presented cases, we conclude that headache attributed to Susac's syndrome is of migraine-like type but could be of different presentations in relation to the onset of the syndrome.

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1. Introduction

Susac syndrome (SuS) is a rare disorder that is thought to be caused by autoimmune-mediated occlusions of microvessels in the brain, retina, and the inner ear, and is characterized by a clinical triad consisting of encephalopathy, branch retinal artery occlusion (BRAO), and hearing loss [1]. Typical findings in patients with SuS include BRAO detected on retinal fluorescein angiography (FA), characteristic lesions (corpus callosum spokes, icicles, and snowballs on sagittal T2; black holes in central fiber seen on sagittal T1; capsule microinfarctions associated with white matter infarcts and leptomeningeal involvement) [2] on brain magnetic resonance imaging (MRI), and evidence of sensorineural hearing loss [3,4]. Due to multiple organ involvement and the absence of the classical clinical triad in the majority of cases at disease presentation, SuS often remains underdiagnosed, delaying the initiation of appropriate treatment [3,5]. The prevalence of SuS is unclear, and there were 304 cases of SuS reported worldwide [3]. Some authors estimated the prevalence rate of SuS at 0.14 cases per 100,000 population in the Central European population [6]. In Lithuania, the incidence rate of SuS is unclear because not a single case report has been published until now, and only solitary cases were diagnosed. Encephalopathy commonly is recognized as the initial manifestation of SuS and is associated with headache, psychiatric disorders (behavioral changes or cognitive impairment), and focal neurological symptoms [7]. Headache occurs in about 80% of the patients with SuS [3]. The proposed diagnostic criteria of the European Susac Consortium (EuSaC) acknowledge headache as a possible brain manifestation if it is new, described as migrainous or oppressive, and precedes the other symptoms by not more than 6 months [4]. Brain MRI, retinal FA, and audiometry are required tests for SuS diagnosis [3,8]. Due to the lack of randomized clinical trials, the treatment of SuS is symptomatic and based on clinical experience [3–5], but early immunosuppressive strategy is recommended [2]. It has been noticed that multiple sclerosis disease-modifying treatment is not effective and could deteriorate the neurological condition [9,10].

In this paper, we discuss three cases of patients who presented with different characteristics of headache associated with SuS.

2. Presentation of cases

2.1. *Case 1*

A 26-year-old woman with a history of rare migraine attacks from 15 years of age presented at the Emergency department when she experienced a sudden onset of an episode of diplopia that lasted for 30 min after 1 month of everyday migraine-like headache attacks (headache characteristics are described in Table 1; according to the ICHD-3 criteria). No specific treatment for headache was prescribed. Episodes of diplopia subsequently recurred several times during the period of a few days. Two weeks from the first episode of diplopia, the patient suddenly lost hearing in the left ear. Audiometry revealed left-sided sensorineural hearing disturbance. She was diagnosed with acute cochlear neuritis and was treated with glucocorticoids and hyperbaric oxygen therapy, which resulted in partial clinical improvement. One month later, the patient experienced an acute attack of somnolence, confusion/disorientation, vertigo, nausea, slurred speech, and hearing loss in the right ear, and was admitted to the Department of Neurology of our Hospital. Following an extensive diagnostic work-up, demyelinating disorders, vascular disorders, and chronic infections were ruled out, and the patient was diagnosed with SuS according to the diagnostic criteria of the EuSaC (all clinical presentations and diagnostic tests are shown in Table 2). The patient received treatment with high-dose glucocorticoids that was partly effective, and oral prednisolone was continued; headache attacks decreased, although sensorineural hearing loss in the right ear and slight ataxia remained. During the last 3 years of follow-up, no new bouts of SuS were suspected. Due to persistent deafness, the cochlear implantation in the right ear was performed. At this time, migraine attacks repeat 1–2 times a month, as it was before the manifestation of SuS.

2.2. *Case 2*

A 40-year-old woman with no past history of headache first presented at the Department of Neurology of our Hospital 1 year before due to an intensive headache attack that was followed by diplopia and vertigo of approximately 20 min in duration. Headache mostly affected the upper part of her head bilaterally, was of pulsating quality, and was associated with nausea and intensive tinnitus. Intensive headache lasted less than an hour, and then slowly diminished. The diagnosis of probable migraine with an aura was made. After the manifestation of the first headache episode, the patient started experiencing severe attacks of bifrontal headache 2–3 times a month lasting from 2 to 12 h and accompanied by nausea, photophobia and phonophobia, and avoidance of physical activity (the characteristics of the headache are described in Table 1 according to the ICHD-3 criteria). These headache attacks were alleviated with analgesics. Two months later, the patient experienced an episode of hemiparesis and hemihypesthesia accompanied by vertigo and balance disturbance. Due to suspected multiple sclerosis, the patient was treated with high doses of glucocorticoids, which resulted in clinical improvement; for maintenance, oral steroids were prescribed, and headache attacks decreased. Her migraine-like headache attacks repeated frequently for several months, and then gradually disappeared. A year later, such symptoms as balance impairment, hearing difficulty (mostly affecting the right ear), and diplopia appeared, and hypoesthesia and hemiparesis recurred. The patient was hospitalized in our department for further investigations for the second time. MS, vascular disorders, and chronic infections were ruled out, and the patient was diagnosed with SuS according to the diagnostic criteria of the EuSaC (Table 2). High doses of intravenous glucocorticoids were prescribed, which resulted in a significant clinical improvement, and immunosuppressive treatment was started subsequently. Currently, the patient has no complaints of headache.

Table 1 – Characteristics of headache in the presented clinical cases according to the International Classification of Headache Disorders [11].

Headache characteristics	Case report 1	Case report 2	Case report 3
Age at the onset, years	15	40	14
Episode duration, h	>4	>2	>4
Pulsating quality	Yes	Yes	Yes
Pain intensity	Moderate/severe	Severe/Very severe	Moderate/severe
Aggravation by routine physical activity	Yes	Yes	Yes
Nausea and/or vomiting	Yes	Yes	Yes
Photophobia and phonophobia	No	Yes	No
Aura symptoms	No	No	No
Headache in relation to SuS	Exacerbation and chronification before the first SuS episode	Initial symptom	Increased frequency after the SuS manifestation

Table 2 – Clinical manifestations and diagnostic tests of our presented cases.

Manifestation	Case 1	Case 2	Case 3
CNS			
Encephalopathy			
Cognitive impairment	Yes	Yes	Yes
Confusion	Yes	Yes	Yes
Behavioral changes	Yes	Yes	Yes
Ataxia	Yes	Yes	Yes
Vertigo	Yes	Yes	Yes
Sensory disturbance	No	Yes	No
Paresis	No	Yes	Yes
Visual disturbance	Yes	Yes	Yes
Tinnitus	Yes	Yes	No
Hearing loss	Yes	Yes	Yes
Oligoclonal bands	Positive	Negative	Negative
Visual evoked potentials	Normal	Normal	Normal
Fluorescence angiography	Absence of perfusion duo to BRAO in the inferior temporal artery branches; segmental leakage of the vascular wall and arterial wall hyperfluorescence near the site of the obstruction.	The diameter of arteries between the eyes is different because of narrowing in some places; this could suggest a previous occlusion	Progressing occlusion of peripheral temporal arteries throughout the artery length, suggesting BRAO
MRI lesions (Fig. 1)	Small multifocal lesions in the supratentorial white matter (deep and subcortical) including the left side of the genu of corpus callosum; not enhancing c/m	Multifocal lesions in the supratentorial white matter (deep and subcortical) including the corpus callosum (mostly in the body and the splenium); some of them vacuolated; not enhancing c/m	Diffuse, slightly hyperintense lesions in deep white matter; no lesions in the corpus callosum.
	No lesions visible on spinal MRI	No lesions visible on spinal MRI	No lesions visible on spinal MRI
Audiometry	Sensorineural hearing loss in the right ear	Sensorineural hearing loss in the right ear	Sensorineural hearing loss in both ears

2.3. *Case 3*

A 55-year-old woman with a history of migraine-like headache attacks from 14 years of age was admitted to our department for the revision of the diagnosis and the suspicion of SuS. After comprehensive clinical and diagnostic tests, the diagnosis of SuS was confirmed (Table 2).

The anamnesis data showed that at 15 years of age, she suddenly lost hearing, which was immediately followed by an increase in the frequency of headache attacks to 5–6 times/month (the characteristics of the headache are described in Table 1, according to the ICHD-3 criteria [11]). Audiometry revealed bilateral sensorineural hearing disturbance, and thus bilateral cochlear neuritis was diagnosed at that time. Hearing loss persisted, and one year later, she received a right side cochlear implant, which she is still using.

At 47 years of age, she experienced an episode of confusion, disorientation, memory loss, speech disturbance, ataxia, and visual disturbances (short episodes of blurring and flashing) that lasted 4 h. This clinical episode was diagnosed as a transient ischemic attack. A few months later, brain MRI revealed similar to demyelinating lesions in the periventricular area and in the brainstem. The diagnosis of MS was suspected, and treatment with high doses of prednisolone was started, which resulted in clinical improvement. The patient received disease-modifying treatment, which was ineffective – the patient did not tolerate the treatment, and thus it was discontinued. Maintenance treatment with glucocorticoids

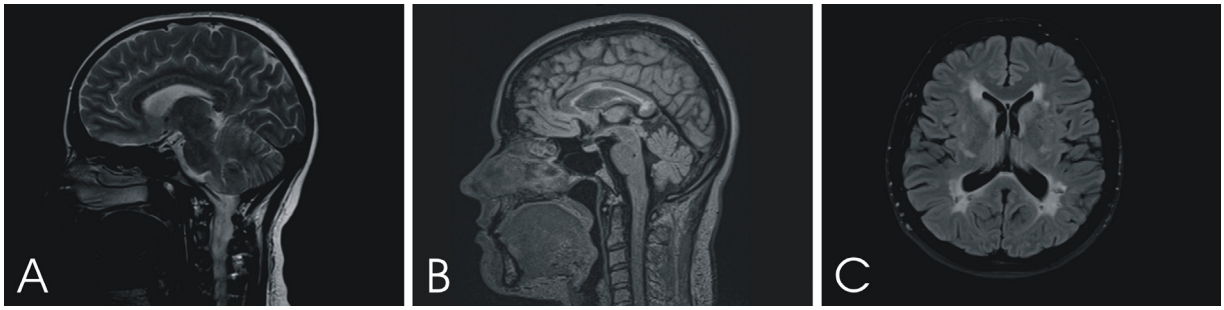

Fig. 1 – Magnetic resonance imaging of the brain. Sagittal T2 MRI of the brain shows lesions in corpus callosum, especially in the left side of the genu (A). Sagittal T2 FLAIR MRI of the brain shows corpus callosum lesions in the body and the splenium (B). Axial T2W FLAIR MRI of the brain shows multifocal white matter lesions (C).

was prescribed, and later on, the frequency of headache dropped to a few times per month. After 6 years, the patient again experienced vertigo, ataxia, and visual disturbance, and was hospitalized in our department. Brain MRI was repeated, and small white matter lesions including the corpus callosum were found (Fig. 1). The diagnosis was reviewed and, according to the diagnostic criteria of the EuSaC (Table 2), SuS with residual symptoms and migraine without aura was confirmed. No specific treatment for migraine was prescribed. At this time, headache occurs 1–2 times per month. During the last 1-year follow-up, no new bouts of SuS have occurred.

3. Discussion

We report three cases of SuS associated with headache. Our patients experienced different presentations of migraine-like headache in relation with the manifestation of SuS.

Headache is a common symptom of SuS, affecting up to 80% of SuS patients [3]. Although the proposed diagnostic criteria of the European Susac Consortium (EuSaC) acknowledge headache as a possible brain manifestation if it is new, described as migrainous or oppressive, and precedes the other symptoms by not more than 6 months [4], these headache characteristics are not yet approved as actual diagnostic criteria of the SuS.

All our patients experienced migraine-like headache that was of severe intensity and was responsive to analgesics (the characteristics of the headache are shown in Table 1). In the first two cases, the manifestation of SuS started with visual symptoms in relation with headache, which later were followed by other SuS symptoms. In the diagnostics of SuS, especially in its manifestation, it can be difficult to tell apart a migrainous visual aura from visual symptoms relating to branch retinal artery inflammation.

With regards to the clinical course of SuS in relation to headache, our patients experienced three types of migraine-like headache: (1) exacerbation and chronification of migraine-like headache one month before the manifestation of SuS; (2) migraine-like headache preceded the manifestation of other SuS symptoms; (3) migraine-like headache increased in frequency after SuS (clinical presentations are shown in Table 3). According to literature [3,4,7], headache is a common symptom during the initial manifestation of SuS, but there is a lack of information about the associations, intensity, quality and profile of SuS-related headache in relation with the course of SuS.

SuS is a rare disorder that affects the brain, ears, and eyes. It often remains undiagnosed due to multiple system involvement imitating other disorders, which prolongs time to diagnosis. In all of our patients, MS was suspected at first. However, it is important to distinguish SuS from MS. Focal neurologic symptoms and signs are not helpful for the differential diagnosis because both conditions can affect any area of the central nervous system and cause similar symptoms [3,12]. Hearing loss, vertigo, and tinnitus could also be found in MS, but they are not permanent. Bilateral hearing loss and tinnitus are not common for MS, thus leading to the diagnosis of SuS or other diagnoses [12]. Visual symptoms due to optic neuritis are common in MS, but changes in fluorescein angiography are more common in SuS [8]. Optic coherence tomography could also be helpful in distinguishing SuS from MS [13–15]. Together with headache, encephalopathy (cognitive impairment, confusion, and disorientation) is considered to be one of the most frequent manifestation of SuS [3]. At the onset or during the course of the disease, all our patients experienced episodes of confusion, disorientation, and behavioral changes, which were mistakenly attributed to panic or transient ischemic attacks. Headache and the symptoms of encephalopathy are very rare in MS and could be helpful in differential diagnosis [12,16].

Table 3 – Clinical presentation of the presented SuS cases.

Symptoms	Case 1	Case 2	Case 3
CNS involvement	During the course of the disease	At the onset of the disease	During the course of the disease
Eye involvement	During the course of the disease	During the course of the disease	During the course of the disease
Ear involvement	At the disease onset	During the course of the disease	At the onset of the disease
Headache	Exacerbation and chronification before the onset of the disease	Initial symptom at the onset of the disease	Increased frequency after the onset of the disease

The pathophysiology of SuS is not clear, but so far it has been thought to be immune-mediated endotheliopathy [17]. It was suggested that anti-endothelial antibodies cause endothelial changes leading to occlusions in small microvessels and thus to small infarcts in the brain, retina, and cochlea [5]. Headache is most likely the result of leptomeningeal vessel damage [17]. Endothelial changes are typical for anti-endothelial antibody-mediated injury [5]. However, recently, based on 3 patients' experience and the results of brain biopsy, Hardy et al. suggested a T-cell-mediated inflammatory contribution to lesion pathogenesis of SuS [18]. Brain biopsy sampling revealed T-cell inflammation in small- and medium-sized vessels [18]. It is difficult to distinguish whether humoral immunity or cellular mechanisms play a role in disease pathogenesis. For the evaluation of anti-endothelial antibodies and their role in SuS pathogenesis, further serological studies are required [19]. More histopathological studies need to be performed to clarify the cellular mechanism, considering disease duration, lesion location, and treatment [18].

The proposed diagnostic criteria of the EuSaC acknowledge headache as a possible brain manifestation if it is new, described as migrainous or oppressive, and precedes the other symptoms by not more than 6 months [4]. The three cases presented in our paper have shown that there can be different presentations of migraine-like headache in relation to the manifestation of SuS.

This statement needs further analysis of more patients with SuS focusing on the relationship of headache with the manifestation and the course of the disease in order to improve the understanding of the characteristics of headache in relation to the syndrome.

4. Conclusions

Based on the results of our analysis, we conclude that migraine-like headache as a symptom of SuS could have different presentations in relation to the manifestation of SuS: exacerbation and chronification of headache just before the manifestation of the first symptoms of SuS, the manifestation of migraine-like headache during the first episode of the syndrome, and an increasing frequency of headache during the course of the disease.

We suggest that further analysis of SuS cases should focus more on the characteristics of headache in relation to the manifestation of SuS as well as other symptoms of this syndrome.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from the patients for publication of this article and accompanying images.

Authors' contributions

The individual contributions of the authors to the manuscript are equal.

REFERENCES

[1] Susac JO, Hardman JM, Selhorst JB. Microangiopathy of the brain and retina. Neurology 1979;29(March (3)):313–6.

[2] Marrodan M, Correale J, Alessandro L, Amaya M, Fracaro ME, Köhler AA, et al. Susac Syndrome: a differential diagnosis of white matter lesions. Multiple Scler Relat Disord 2017;15(April):42–6.

[3] Dörr J, Krautwald S, Paul F, Dörr J, Krautwald S, Wildemann B, et al. Characteristics of Susac syndrome: a review of all reported cases. Nat Publ Group 2013;9(10):307–31682.

[4] Kleffner I, Dörr J, Ringelstein M, Gross CC, Böckenfeld Y, Schwindt W, et al. Diagnostic criteria for Susac syndrome. J Neurol Neurosurg Psychiatry 2016;87(12):1287–95.

[5] García-Carrasco M, Mendoza-Pinto C, Cervera R. Diagnosis and classification of Susac syndrome. Autoimmun Rev 2014;13(4–5):347–50.

[6] Seifert-Held T, Langner-Wegscheider BJ, Komposch M, Simschitz P, Franta C, Teuchner B, et al. Susac's syndrome: clinical course and epidemiology in a Central European population. Int J Neurosci 2016;7454(March 2017):1–5.

[7] Kowacs F, Ferreira Gomes M, Pigozzo T, Rodrigues Palmeira AL, Muratt Carpenedo C, Castro Ribeiro M. Migraine-like headache as presentation symptom in Susac syndrome. Headache 2016;56(10):1667–9.

[8] Egan RA, Hills WL, Susac JO. Gass plaques and fluorescein leakage in Susac Syndrome. J Neurol Sci 2010;299(1–2):97–100.

[9] Algahtani H, Shirah B, Amin M, Altarazi E, Almarzouki H. Susac syndrome misdiagnosed as multiple sclerosis with exacerbation by interferon beta therapy. Neuroradiol J 2017. 197140091771226.

[10] Ryerson LZ, Kister I, Snuderl M, Magro C, Bielekova B. Incomplete Susac syndrome exacerbated after natalizumab. Neurol Neuroimmunol NeuroInflamm 2015;2(5):1–3.

[11] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629–808.

[12] Buzzard KA, Reddel SW, Yiannikas C, Sean Riminton D, Barnett MH, Hardy TA. Distinguishing Susac's syndrome from multiple sclerosis. J Neurol 2014;262(7):1613–21.

[13] Brandt AU, Oberwahrenbrock T, Costello F, Fielden M, Gertz K, Kleffner I, et al. Retinal lesion evolution in Susac syndrome. Retina 2016;36(2):366–74.

[14] Brandt AU, Zimmermann H, Kaufhold F, Promesberger J, Schippling S, Finis D, et al. Patterns of retinal damage facilitate differential diagnosis between Susac syndrome and MS. PLoS ONE 2012;7(6).

[15] Ringelstein M, Albrecht P, Kleffner I, Bühn B, Harmel J, Müller AK, et al. Retinal pathology in Susac syndrome detected by spectral-domain optical coherence tomography. Neurology 2015;85(7):610–8.

[16] Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. Lancet 2016;6736(16):292–302.

[17] Greco A, De Virgilio A, Gallo A, Fusconi M, Turchetta R, Tombolini M, et al. Susac's syndrome – pathogenesis, clinical variants and treatment approaches. Autoimmun Rev 2014;13(8):814–21.

[18] Hardy TA, O'Brien B, Gerbis N, Barnet MH, Reddel SW, Brewer J, et al. Brain histopathology in three cases of Susac's syndrome: implications for lesion pathogenesis and treatment. J Neurol Neurosurg Psychiatry 2015;86:582–4.

[19] Jarius S, Kleffner I, Dörr JM, Sastre-Garriga J, Illes Z, Eggenberger E, et al. Clinical, paraclinical and serological findings in Susac syndrome: an international multicenter study. J Neuroinflamm 2014;11:1–11.