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CASE REPORT

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Rare Case of Susac Syndrome

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ABSTRACT

Susac syndrome is a rare autoimmune disease affecting the precapillary arteries of the brain, eye and ears causing encephalopathy, branch retinal artery occlusion and sensorineural hearing loss. It is underdiagnosed as it rarely presents with the classic triad. Encephalopathy and branch retinal artery occlusion are curable if the treatment is started early, however the sensorineural hearing loss may be irreversible. The disease course may be monocyclic, polycyclic or chronic.

In this review present a case of Susac which was not diagnosed until late in the disease course. Even though the three criteria manifested clinically, the patient was successfully treated. We will also provide a clinical review on the disease based on our research from the literature.

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Case

A 33-year-old female presented with sudden onset of blindness in both eyes. Her past medical history is unremarkable, apart from being an ex-smoker, and a family history of massive pulmonary embolism in her mother at the age of fifty and protein C deficiency. Her father was diagnosed with heterozygous protein C deficiency, and her aunt was diagnosed with relapsing-remitting multiple sclerosis. Her uncle was diagnosed at the age of forty with acute demyelinating encephalopathy which was successfully completely treated with five days of methylprednisolone. She is not on any medication apart from the contraceptive pill. She is fully independent, works as a schoolteacher, and has two children.

The patient was admitted to the stroke unit, and was diagnosed with having suffered a small lacunar cortical infarct. Neurological examination showed homonymous hemianopia with macular sparing. The remainder of the neurological examination, including the cranial nerves and peripheral nervous system, did not show any abnormalities.

Diffusion-weighted magnetic resonance imaging showed restrictive small lesions in both occipital lobes, with hypo-intensity in the corresponding apparent diffusion coefficient, being consistent with stroke. The patient was noted to be confused and agitated, which was attributed as being due to delirium following stroke.

Due to the patient being admitted after the four-and-a-half-hour window, the patient was not offered thrombolysis. The patient was treated as per the stroke pathway, which included dual antiplatelet therapy for six weeks, followed by aspirin alone.

Five days of telemetry recording did not show any atrial fibrillation. Transthoracic and transoesophageal echocardiograms did not show any abnormalities such as a patent foramen ovale or septal atrial aneurysm. Carotid doppler did not show any functional or anatomical abnormalities. Pathology investigations did not show any abnormalities. These investigations included FBC, ESR, CRP, cANCA, pANCA, ANA, DNA, ACCP, complement, ACE, antiphospholipid screening, viral screening including EBV, CMV, HSV, herpes zoster, hepatitis screen, thrombophilia screen, serology for Lyme disease and syphilis, JAK-2 mutation screening, and COVID-19 testing. The patient made a complete recovery and was discharged from allied health, and was advised to have regular follow-up with her GP. The patient was deemed independent in her functioning.

Six months later, the patient presented to the Emergency Department (ED) with confusion and sudden onset of hearing loss. She was examined in the ED by the Neurology Advanced Trainee Registrar, who made the assessment that the patient was suffering from delirium and agitation. A limited neurological exam did not reveal any focal neurological signs. Her vital signs, including her oxygen saturation, were normal.

An urgent CT non-contrast was completely normal. The patient was sedated and had a lumbar puncture which showed lymphocytic pleocytosis (100 cells) and a mildly elevated protein level (0.8). Cerebrospinal fluid sugar (CSF) levels were 5 mmol (corresponding to 8 mmol in serum), opening pressure was normal [18]. Blood was taken for cultures and PCR for viral, bacterial, and tuberculosis screening, as well as cryptococci and listeriosis. The patient as started empirically on intravenous cephalosporin, vancomycin, rifampicin, vancomycin, dexamethasone, ampicillin and acyclovir.

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The patient improved after three days, after which all the mentioned investigations were returned as either negative or normal. Patient discharged home with a follow up appointment scheduled in the clinic. At this appointment, patient complained of her hearing loss and needing to sit closer to eh television to be able to hear. Subsequent Weber and Rinne testing by the Neurology Registrar suggested sensorineural deafness in both ears. The patient was then referred to an ENT clinic for audiometry.

A week later the patient was readmitted to hospital due to confusion and visual abnormalities. These visual abnormalities included reduced acuity, blurring, flashing nights, scintillation, and diplopia. Clinical examination was limited by the patient's confusion, however gross neurological examination did not show any focal neurology.

An urgent diffusion weighted imaging-flair showed leptomeningeal enhancement. T2 and flair showed hyper-intense lesions in the splenium of the corpus callosum. An urgent CSF study showed increased protein (1 gram), lymphocytes [10] and no oligo-clonal bands. The patient returned a negative PCR for bacterial and viral infection. Fundal examination showed bilateral branch retinal vein occlusion. Retinal fluorescent angiogram showed leakage and arterial wall hyper-fluorescence.

A diagnosis of Susac syndrome was made based on the triad of encephalopathy, branch retinal artery occlusion and bilateral sensorineural deafness. Callosal lesions are one of the core features of Susac syndrome. The patient was treated with methyl prednisolone for five, followed by 1mg/mg oral steroids for 4 weeks with gradual tapering. The patient improved and was discharged home.

She was later readmitted again with ataxia and confusion. A repeat MRI showed black holes in the selenium of the corpus callosum in T1 images, and new lesions in T2 and flair images. CSF examination was unremarkable. The diagnosis was then refined to polycyclic Susac syndrome. The patient retreated with intravenous immunoglobulin and pulsed methyl prednisolone, followed by oral prednisolone with very slow tapering and introduction of azathioprine as a steroid sparing agent. The patient was discharged to a rehabilitation facility where she made a good recovery, apart from residual deafness which was treated with a cochlear implant.

Susac syndrome

Susac syndrome is an uncommon autoimmune microvasculitis affecting the retina, inner ears and the brain [1]. Clinical manifestations include visual disturbance, encephalopathy and sensorineural deafness [2]. The course of the disease may be monosymptomatic with complete recovery, polysymptomatic, or chronic. Failure to diagnose and treat the disease early will result in fixed neurological deficits, particularly inner ear deafness [3]. It is uncommon of the disease to present initially with the full triad of encephalopathy, branch retinal artery occlusion, and sensorineural deafness. This leads to underdiagnosis and failure to receive the appropriate treatment in a timely manner [4]. Thirty per cent of the patients have anti-endothelial cell antibodies. These are neither specific nor sensitive, as they are found in other autoimmune conditions such as systemic lupus erythematous, dermatomyositis, and Sjogren syndrome.

Disease was described by John O. Susac in 1997. Focal lesions within the central part of the corpus callosum are a characteristic finding, however the absence of callosal lesions do not rule out the diagnosis.

Although most of the brain lesions in Susac syndrome are within the supratentorial region, infratentorial lesions are not uncommon in the cerebellum and peduncles [5]. Diffusion Tensor imaging showed severe reduction of the integrity of the deep fibres and reduction of the fractional anisotropy which cannot be detected with the conventional MRI [6,7]. 7-Tesla (T) MRI field strength can identify multiple sclerosis lesions (such callosal lesions with centrally located veins and hypointense perilesional ring), which is a major differential diagnosis of Susac syndrome [8].

Branch retinal artery occlusion is very specific for Susac syndrome. Most patients present with scotoma, however some patients may be asymptomatic. If the lesion is small and in the periphery of the eye, it may be easily missed. Retinal fluorescein angiography is the standard of care. The arterial wall shows a failure of filling and hyper-fluorescence to gas plaques and leakage of lipids. Hyper-fluorescence of the arterial walls can occur away from the areas of occlusion [8]. Optical Coherence Tomography (OCT) is playing a major role as a non-invasive, optical interferometric technique which uses low-coherence near-infrared light to generate cross-sectional images of different layers of the retina. The inner retinal nerve fibre layer is the layer most commonly affected in Susac syndrome. OCT can play a major role in excluding other mimics of Susac syndrome.

Headache is the most common manifestation of encephalopathy [7,8]. New focal neurologic findings including personality changes, psychosis, agitation and seizures can occur and other diagnoses such as limbic encephalitis must be ruled out. Visual field defects and scotoma due to branch retinal artery occlusion are very specific when complemented with gas plaques and hyper-fluorescence seen on fluorescein angiography.

Sensorineural deafness of low and middle frequencies is a characteristic feature of Susac syndrome. Tinnitus and peripheral vertigo may also occur. CSF often shows higher protein compared with demyelinating diseases such as multiple sclerosis and acute demyelinating encephalopathy.

The triad of encephalopathy, branch retinal artery occlusion and sensorineural deafness is diagnostic of Susac syndrome, however the complete triad is only seen in 17% of patients. Ruling out mimics and differential diagnoses is of paramount importance so patients may be treated early, thus preventing any residual neurological deficits.

Mimics

Multiple sclerosis

7–Telsa (T) MRI field strength can identify lesions typical of multiple sclerosis, such as callosal lesions, centrally-located veins and hypointense perilesional rings. Deafness and branch retinal artery occlusion are not common in multiple sclerosis. Retinal disease typically manifests as optic neuritis and a relative afferent pupillary defect [9]. Oligoclonal band frequently occur and persist in 90% of the patients, including an IGG index.

Acute demyelinating encephalopathy

Acute demyelinating encephalopathy is a monophasic polysymptomatic disease usually occurring in young people with a history of recent infection or vaccinations. It is usually self-limiting, and patients recover with no residual neurologic defects [10].

CADASIL syndrome

CADASIL syndrome (cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy) is a syndrome which mainly affects young people with a family history due to a NOTCH3 mutation. Parietal lobes are most affected. Occipital lobes are less commonly affected.

MELAS syndrome

MELAS syndrome (comprised of a mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) is caused by a mutation in mitochondrial DNA POLG1. The syndrome is most common in children. It commonly manifests with seizures, leading to intellectual disability.

Systemic Lupus Erythematous (SLE)

SLE is a multisystem disease which may affect the skin, kidney, joints, brain (causing seizures), and blood (causing anaemia and cytopenia). SLE may cause branch retinal occlusion due to an associated antiphospholipid syndrome or peripheral neuropathy.

Sarcoidosis

Sarcoidosis may affect the lung, cranial nerves, brain, and heart. Heart involvement may include conduction blocks and restrictive cardiomyopathy. Serum ACE levels may be elevated; however, this is non-specific. PET scan is used for diagnosis, and confirmation is made via biopsy.

Lymphoma

As well as the lymph nodes, lymphoma may affect the brain, cause organomegaly, and lead to blood abnormalities such as haemolytic anaemia and cytopenia. Brain disease is steroid responsive; however, steroids should be stopped prior to biopsy. Flow cytometry is diagnostic.

Cerebral angiitis

Cerebral angiitis can cause encephalopathy and seizures. Cerebral angiography and brain biopsy are essential for the diagnosis.

Cogan syndrome

Cogan syndrome is an autoimmune vasculitis causing interstitial keratitis (non-syphilitic). Audio vestibular symptoms such as vertigo, tinnitus and gradual hearing loss may occur. Other organs may also be affected. Aortitis, aortic incompetence, stroke, and other vasculitides such as polyarteritis nodosa, Wegener's granulomatosis, Giant Cell Arteritis, and Takayasu disease may also occur.

Treatment

Susac syndrome is a pauci-immune CD8-mediated disease characterised by ischaemic occlusive epsiodes causing microvascular endotheliopathy and basement membranopathy. It affects the brain, retina and inner ear. It initially manifests as a microvasculopathy. Less than 17% of patients will present with the classic triad, leading to underdiagnosis. Failure to diagnose and treat the condition results in permanent disability.

There are no randomised controlled trials or perspective treatment studies of Susac syndrome. We reviewed 25 cases of confirmed Susac diagnoses based on the presence of the triad, either on presentation or later in the course of the illness.

It appears there are no clear guidelines regarding the treatment of Susac syndrome. The best treatment appears to be pulsed methylprednisolone 1g for 5 days, followed by oral prednisolone 1mg/kg with very gradual tapering. Rapid tapering should be avoided as it precipitates flare-ups. If patients do not respond to methylprednisolone, IV immunoglobulin has been used previously with success. Alternatively, plasmapheresis has been used, complemented with monthly IV immunoglobulin. Whilst patients are on low-dose oral prednisolone, a steroid sparing agent should be started. This is particularly important if the patient has developed side-effects of the steroids.

Some patients were started on rituximab 1000mg for two weeks, with regular CD20 and CD19 monitoring to assess the effectiveness of the treatment. Some patients fail to respond to methylprednisolone, and are treated with pulsed cyclophosphamide 10-15mg/kg (to a maximum of 1200mg), with a repeat dose in the second week. Following this, cyclophosphamide is replaced with mycophenolate or azathioprine to maintain remission. Patient are also usually started on aspirin to prevent microvascular complications [10-13].

Susac vasculopathy in the internal ear is usually irreversible and may require a cochlear implant. Retinal branch artery occlusion is reversible if treated early. Patients who develop neovascularisation should be treated laser photocoagulation. Encephalopathy is fully responsive to treatment. We are not aware whether growth factor inhibitors have been used to treat neovascularization in Susac syndrome.

In summary

Susac syndrome is a rare autoimmune occlusive microvascular endotheliopathy. It may affect the brain, inner ear, and the retina. It is usually underdiagnosed or misdiagnosed, and has several differential diagnoses to be excluded before a diagnosis is made. Timely diagnosis and treatment are essential to avoid permanent disability.

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