REVIEW

Immune-mediated conditions affecting the brain, eye and ear (BEE syndromes)

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ABSTRACT

The triad of central nervous system symptoms, visual disturbance and hearing impairment is an oft-encountered clinical scenario. A number of immune-mediated diseases should be considered among the differential diagnoses including: Susac syndrome, Cogan syndrome or Vogt-Koyanagi-Harada disease; demyelinating conditions such as multiple sclerosis or neuromyelitis optica spectrum disorder; systemic diseases such as systemic lupus erythematosus, Sjögren syndrome or Behcet disease and granulomatous diseases such as sarcoidosis. In this article, we coin the term 'BEE syndromes' to draw attention to the various immune-mediated diseases that affect the brain, eye and ear. We present common disease manifestations and identify key clinical and investigation features.

INTRODUCTION

Visual or auditory symptoms in conjunction with symptoms attributable to central nervous system (CNS) involvement can be seen in several common and less common diseases. Prompt recognition of an underlying autoimmune basis to these conditions is important, as early diagnosis and treatment can prevent permanent disability.

Conditions such as Susac syndrome, Cogan syndrome and Vogt-Koyanagi-Harada (VKH) disease are rare, and some physicians will have greater familiarity with them than others. Each of these conditions may present incompletely at the outset, creating diagnostic uncertainty or treatment may delay their full phenotypic expression. Some diseases have specific patterns of involvement, and often there are diagnostic clues that can help the clinician toward the correct diagnosis, including characteristic callosal 'snowball' lesions in Susac syndrome or patchy multifocal areas of subretinal fluid accumulation in VKH.

In this article, we present the clinical and investigation findings of the major brain, eye and ear conditions with an immune or inflammatory pathogenesis, and coin the term brain, eye, ear syndromes or 'BEE syndromes', to draw attention to this group of disorders.

SUSAC SYNDROME

Epidemiology and demographics

Susac syndrome is characterised by the clinical triad of encephalopathy, branch retinal artery occlusions (BRAOs) and sensorineural hearing loss (SNHL).[1 2] Susac syndrome is rare with prevalence estimated at 0.14 per 100 000.[3] A male:female ratio of 1:3.5 has been reported with 60% of individuals aged 21–35 years.[2]

Presumed pathogenesis

Lesional pathology is of arteriolar endothelial cell hypertrophy resulting in microinfarction of the brain, retina and cochlea.[4] Sparse, perivascular, predominantly CD8+T cell infiltrates are seen within biopsied lesions without prototypic vasculitis.[4] Approximately 25% of patients have serum antiendothelial cell antibodies, but these are unlikely to be pathogenic as they occur non-specifically in other autoimmune conditions and brain histopathology does not show increased complement deposition at lesional sites which might be expected if Susac syndrome was an antibody-mediated disease.[4]

Clinical features and clues to diagnosis

The classic triad of features is present in 10%–15% of patients at onset, yet over 80% of patients eventually develop all symptoms, and it is the incompleteness of the triad which is a likely contributor to the high rates of misdiagnosis of Susac syndrome.[5] Headache is the most common presenting symptom. Encephalopathy is identified in 60% at presentation, while the remaining 40% have visual and/or auditory disturbance.[5]

Features of encephalopathy include; migraine-like headache which can be thunderclap in onset, potentially reflecting leptomeningeal vessel involvement; cognitive impairment; confusion and behavioural changes.[2]

Ophthalmological complaints include visual blurring, photopsia and visual field loss which may be transient and migrainous in nature, or persistent secondary to BRAOs. BRAOs may be asymptomatic depending on their extent and location.[2]

SNHL is common and can be acute or subacute, unilateral or bilateral, simultaneous or sequential in nature.[6] It can be both fluctuating and progressive, typically affecting low to mid frequencies and eventually progress to total loss, requiring cochlear implant.[6] Vertigo is occasionally reported though vestibular function test findings are non-specific.

Investigations

Brain MRI reveals characteristic callosal lesions (figure 1). 'Snowballs' are rounded, hyperintense

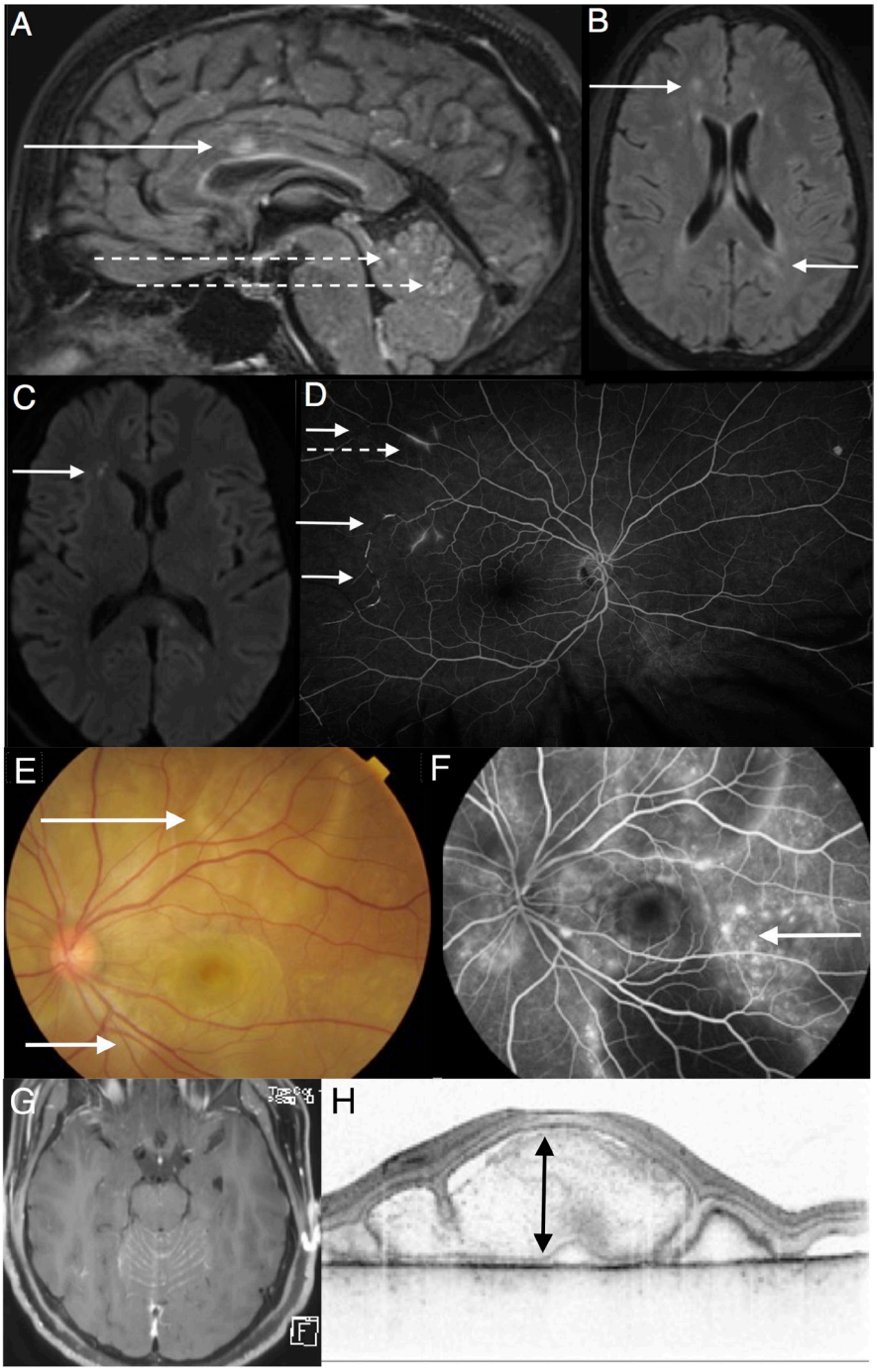

Figure 1 Susac syndrome and Vogt-Koyanagi-Harada disease. (A) Postgadolinium sagittal fluid attenuation inversion recovery (FLAIR) MRI of the brain in Susac syndrome demonstrating punctate hyperintensities within grey and subcortical white matter, and a classical 'snowball' lesion of the corpus callosum (solid arrow). A 'spoke' lesion is also faintly visible within the callosum adjacent to the genu. Irregular leptomeningeal enhancement is seen overlying the cerebral hemispheres and cerebellum (broken arrows), (B) axial FLAIR hyperintensities (arrows) in the subcortical white matter of both cerebral hemispheres, (C) axial diffusion weighted image shows foci of restriction (arrow) corresponding to some areas of T2 hyperintensity, (D) fluorescein angiogram in Susac syndrome reveals characteristic branch retinal artery occlusions (solid arrows) and long patches of arteriolar wall hyperfluoresence (broken arrow), (E) fundus photography revealing multiple subretinal serous detachments during acute phase of Vogt-Koyanagi-Harada disease secondary to subretinal effusions (arrows), (F) fundus fluorescein angiogram in Vogt-Koyanagi-Harada disease highlighting a characteristic 'starry sky' appearance (arrow) due to numerous hyperfluorescent pinpoint foci of leakage, which coincide with areas of choroiditis, are manifested at the level of the retinal pigment epithelium and result in accumulation of dye in the subretinal space, (G) postgadolinium axial T1 MRI of the brain in Vogt-Koyanagi-Harada disease demonstrating cerebellar leptomeningeal enhancement and (H) optical coherence tomography in Vogt-Koyanagi-Harada disease showing subretinal fluid accumulation (arrow).

lesions in the central fibres between the ventricular surface and superior aspect of the callosum on T2/fluid attenuation inversion recovery (FLAIR) sequences.[7] T2/FLAIR sequences may also reveal callosal 'spoke' and 'icicle' lesions.[7–9] On T1 sequences, 'punched out' central callosal holes are seen, which differ in location and morphology from the callosal lesions of multiple sclerosis (MS).[7–10] Other MRI findings include multiple punctate lesions throughout the deep and peripheral white matter,

cerebellum, cerebellar peduncles, brainstem and thalamus.[7] The grey matter is involved in 70% of patients. Leptomeningeal enhancement is seen in around 33% of patients with Susac syndrome but not in MS.[7] Acute lesions in Susac syndrome are often markedly hyperintense on diffusion-weighted images with matched alteration of apparent diffusion coefficient (ADC) maps consistent with restricted diffusion. In comparison, acute MS lesions only occasionally exhibit true restricted diffusion.[10] Susac syndrome should always be considered in patients with diffusion-restricted lesions in more than one vascular territory, as this appearance is not always due to microembolic infarction or CNS vasculitis.

If an MRI raises the possibility of Susac syndrome then fundus fluorescein angiography (FFA) should be performed as this often shows typical features of multiple BRAOs, retinal ischaemia, arteriolar wall hyperfluorescence and fluorescein leakage (figure 1). Retinal yellow-white deposits seen proximal to sites of occlusion, known as Gass plaques, reflect underlying endothelial dysfunction.[11] Ocular examination without FFA can miss features of Susac syndrome, particularly if the relevant arteriolar changes occur more peripherally in the retina. Optical coherence tomography (OCT) has been documented to show focal thinning of the retinal nerve fibre layer (RNFL) and macular volume change, reflecting retinal microvascular ischaemia.

Typically, audiology shows low to mid frequency SNHL, more commonly bilateral than unilateral, while in severe cases, there can be pantonal loss.

CSF examination often demonstrates a markedly elevated protein (mean of 1.6 g/L) with a normal cell count or mild lymphocytic pleocytosis, and absent oligoclonal bands (OCBs).[2]

VKH DISEASE

Epidemiology and demographics

VKH is a rare systemic granulomatous autoimmune disease targeting melanocyte containing tissues, including the eye (uvea, retina), CNS (leptomeninges), inner ear and skin. The classic presentation of VKH involves bilateral granulomatous panuveitis, vitiligo, poliosis and SNHL. Diagnostic criteria published in 2001, allow for a diagnosis of 'incomplete' or 'probable' disease when some extraocular manifestations are delayed or absent.[12]

Presumed pathogenesis

VKH is a T-cell mediated disease directed against melanocyte-specific antigens including tyrosinase family proteins.[12] The disease may be triggered by an infectious agent, with molecular mimicry responsible for the misdirected immune response against melanocyte antigens. A genetically determined susceptibility is suggested by an increased prevalence in Asian, Middle Eastern, Hispanic and Native American populations.[13] Furthermore several human leucocyte antigen (HLA) genotypes have increased frequency among affected individuals (eg, HLA-DRB1*0405).[13]

Clinical features and clues to diagnosis

VKH is classically a three-stage disease. Stage one is a prodromal meningoencephalitic phase characterised by non-specific neurological symptoms including headache, meningismus, vestibular symptoms and occasionally cranial neuropathies.[14] SNHL loss may occur and is generally mild and symmetrical in nature preferentially affecting higher frequencies. During the prodrome, 70% develop blurred vision within 1–2 days.

Stage two reflects intraocular and auditory inflammation, characterised by acute, bilateral panuveitis, optic disc oedema, and bilateral serous retinal detachments (figure 1). Vision loss can be profound early in the disease often accompanied by SNHL and tinnitus. The presence of bilateral posterior uveitis with exudative retinal detachments is highly suggestive of VKH.[15 16] After a month the exudative retinal detachments generally resolve and depigmentation of the choroid may give the classic 'sunset glow', and perilimbal vitiligo called Sugiura sign may develop. Clusters of epithelioid cells known as Dalen-Fuchs nodules may be seen in the inferior retina.

The final convalescent stage results in integumentary changes including vitiligo, alopecia and poliosis. Many patients later develop chronic, recurrent granulomatous intraocular inflammation, having an increased risk of blindness due to cataract, glaucoma, subretinal fibrosis and neovascular membrane formation.[14]

Investigations

Orbital MRI typically shows choroidal thickening with scleral sparing and retinal detachment.[15] Scattered periventricular T2 hyperintensities, pachymeningeal and/or diffuse leptomeningeal enhancement may be seen on MRI brain. Brainstem and cerebellar peduncle T2/FLAIR lesions and spinal cord T2 hyperintensities can occur.

Comprehensive ophthalmic examination and OCT are vital for diagnosis and monitoring of VKH. Classic findings include subretinal membranous structures, high retinal detachment (>450 um), hyper-reflective dots and retinal pigment epithelial folds.[16]

FFA shows typical multifocal hyperfluorescent dots with accumulation of dye in the subretinal space, referred to as a 'starry sky' appearance.[16] Indocyananine green angiography, can be used to monitor evolution of the choroidal inflammation and therapeutic response.[16] Ocular b-scan ultrasound shows diffuse thickening of the posterior choroid.

Audiometry commonly shows bilateral low-grade hearing loss particularly affecting high frequencies.[17] Videonystagmography may reveal nystagmus, even in asymptomatic patients.

Cerebrospinal fluid (CSF) examination is rarely required for the diagnosis of VKH, yet it typically reveals pleocytosis especially in the early stages of the disease.

COGAN SYNDROME

Epidemiology and demographics

Cogan syndrome is an autoimmune disease primarily affecting the eye and audiovestibular apparatus. Young Caucasian adults are most commonly affected, with a median age of onset of 25 years and no sex differences. The first cases described shared common symptoms of non-syphilitic interstitial keratitis, vertigo, tinnitus and deafness,[18] however, the clinical spectrum has widened to include other ocular inflammatory manifestations or variable audiovestibular symptoms. The majority of patients have additional symptoms suggestive of systemic vasculitis.

Presumed pathogenesis

Identification of antibodies directed against an immunodominant peptide, connexin 26, expressed on the sensory epithelia of the inner ear and on endothelial cells, supports an underlying autoimmune pathogenesis.[19]

Clinical features and clues to diagnosis

Neurological symptoms are common; with headache most frequently described.[20] Meningitis, encephalitis, psychosis,

coma, seizures, myelopathy, neuropathy and cerebral infarction may also occur.[20]

Interstitial keratitis presents as ocular pain, erythema, photophobia and blurred vision. Faint scattered corneal opacities are seen, often with little to no associated vascularisation. By comparison, the lesions of congenital syphilis have deep stromal vascularisation. Scleritis, episcleritis, iritis, conjunctivitis and retinal vasculitis are also reported.[20] Poorly controlled ocular inflammation can cause permanent visual loss from neovascularisation and corneal scarring.

Acute hearing loss is the most common initial symptom with audiovestibular and ocular symptoms usually presenting within weeks of symptom onset.[20] Abrupt unilateral or bilateral simultaneous or sequential SNHL preferentially affecting middle and high frequencies associated with tinnitus, vertigo, nausea and vomiting is frequently encountered due to endolymphatic hydrops, fibrosis and new bone formation in the ear. SNHL does not fluctuate and can eventually become total, necessitating cochlear implantation. Severe bilateral vestibular dysfunction produces oscillopsia and ataxia.

Seventy per cent of patients have systemic involvement thought to be secondary to medium and large vessel vasculitis.[20]

Investigations

MRI abnormalities are rarely reported with T1-weighted imaging occasionally showing increased signal in the cochlear, vestibule and semicircular canals with abnormal contrast enhancement (figure 2), that likely correlates with disease activity.[21] Pachymeningeal enhancement, ischaemic infarcts and white matter lesions suggestive of cerebral vasculitis are described but also raise the possibility of Susac syndrome.

The key ophthalmological finding is a corneal infiltrate consistent with interstitial keratitis on slit-lamp examination.[20] Early corneal changes may resemble viral keratitis or chlamydial infection. Appropriate microbiological and serological testing is important to exclude infection, particularly syphilis.

Audiometry typically shows SNHL affecting the middle and high frequencies, unlike in Susac syndrome where low frequencies are preferentially affected.[20] Caloric vestibular responses are abnormal in almost all patients.

Even in asymptomatic patients, CSF analysis may show lymphocytosis and/or elevated protein.

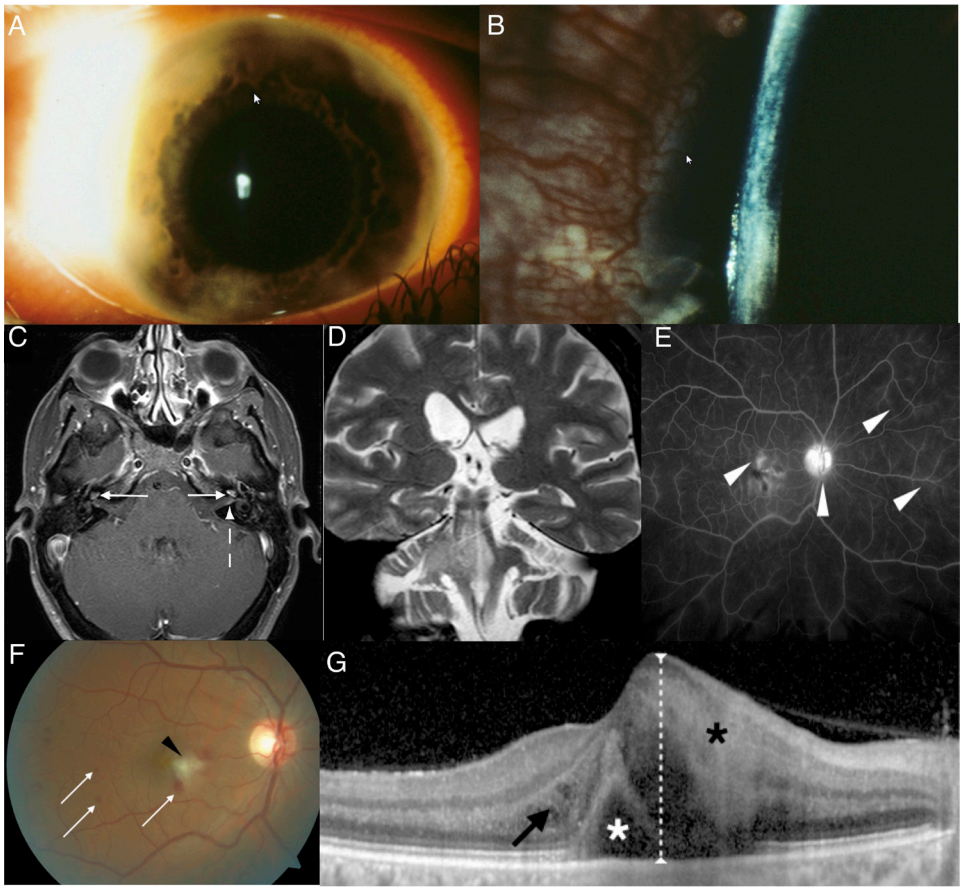

Figure 2 Cogan syndrome and Behcet disease. (A) Ocular photograph of a patient with Cogan syndrome, (B) slit lamp image of the same patient revealing interstitial keratitis, without the deep stromal vascularisation seen in congenital syphilis, (C) axial MRI T1 brain with contrast in Cogan syndrome revealing enhancement of the left cochlea (solid arrows) and internal auditory meatus / eighth nerve enhancement (broken arrow), (D) coronal T2 MRI sequence in Behcet disease showing brainstem and cerebellar atrophy plus high signal intensity in the right pons and medulla (solid arrow) extending into the right cerebellar peduncle (broken arrow). The lesion extends just across, the midline, (E) right eye late phase fluorescein angiography in Behcet disease revealing areas of retinal vasculature and optic nerve head leakage (white arrowheads), (F) retinal photograph of the right eye in Behcet disease revealing small haemorrhages (white arrows) and a focal ischaemic area looking whitish (black arrowhead), (G) optical coherence tomography scan of right eye in Behcet disease encompassing the fovea. The retinal thickness is increased due to extracellular oedema (black arrow), subretinal fluid accumulation (white asterisk) and intracellular oedema/intraretinal blood appearing hyper-reflective (black asterisk).

BEHCET DISEASE

Epidemiology and demographics

Behcet disease is an autoimmune systemic vasculitis characterised by the clinical triad of recurrent oral and genital ulceration and uveitis. Diagnosis is primarily based on clinical findings, together with supportive ancillary investigations. 10%–15% of patients experience neurological involvement, which is associated with significant morbidity and mortality.[22]

Onset is typically in the third decade of life without sex preponderance, with males generally having a more severe and aggressive course and higher rates of neurological manifestations.[22] Prevalence is increased from China through the Middle East to the Mediterranean, being highest in Turkey, with up to 420 per 100 000 population affected compared with 5.2 per 100 000 population in Western countries.[23] Though only present in 10%–12% of European patients, carriers of the HLA-B*51 haplotype have the greatest risk of developing Behcet disease.[22]

Presumed pathogenesis

Behcet disease appears to be driven by a dysregulated innate immune system in association with elevated levels of proinflammatory cytokines, such as tumour necrosis factor alpha. Histopathological studies typically show perivascular inflammation affecting vessels of all sizes.

Clinical features and clues to diagnosis

Neurological involvement includes cognitive dysfunction, encephalopathy, psychosis and seizures.[22] Both parenchymal and vascular structures may be involved. Most patients suffer parenchymal disease characterised by a subacute meningoencephalitis involving the brainstem, mesodiencephalic structures, cerebral hemispheres or spinal cord. Isolated meningitis has also been described.

Cerebral venous sinus thrombosis causing increased intracranial pressure is the most common neurovascular manifestation. Other complications include intracranial and extracranial aneurysms, dissection and ischaemic stroke.[22]

The majority of patients experience uveitis or occlusive retinal vasculitis (figure 2). Transient hypopyon associated with bilateral anterior uveitis is highly suggestive of Bechet's disease, as are branch retinal vein occlusions with vasculitis. Recurrent attacks of ocular inflammation can result in permanent visual loss, with retinal necrosis and neovascularisation. Optic neuropathy has also been reported.[22]

SNHL occurs in 20%–30%, is often mild, bilateral and preferentially affects high frequencies, but rarely it is severe and acute in onset. SNHL is frequently accompanied by vertigo and nystagmus due to central vestibular inflammation.

Mucocutaneous involvement is the most common manifestation with painful oral and genital aphthous ulceration identified in most when carefully sought. Skin manifestations include erythema nodosum, acneiform lesions, papulopustulosis, leukocytoclastic vasculitis and pyoderma gangrenosum. Systemic involvement occurs in 50% of cases including arterial and venous thrombosis, myocarditis, valvular heart disease, gastrointestinal symptoms and musculoskeletal complaints.[22]

Investigations

Patients with parenchymal disease frequently demonstrate MRI T2/FLAIR hyperintense lesions throughout the cerebral hemispheres excluding periventricular regions (unlike MS), with a predilection for the upper brainstem extending into the thalamus and basal ganglia (figure 2).[24] The radiological changes are often less marked than in MS for the same degree of disability, suggesting more destructive lesions. Acute lesions often enhance with gadolinium and microhaemorrhages can sometimes be seen within lesions. We would argue that any inflammatory brainstem lesion should alert the clinician to the possibility of Behcet disease. Spinal lesions can be longitudinally extensive spanning multiple vertebral segments, mimicking neuromyelitis optica spectrum disorder (NMOSD). The presence of isolated brainstem atrophy is a useful discriminator from other neuroinflammatory conditions.[25]

A positive pathergy test, present in around 30% of patients, has long been considered pathognomonic. Erythrocyte sedimentation rate (ESR) is often elevated during attacks and can be useful in monitoring disease activity. HLA-B*51 haplotype is supportive.

Elevated CSF protein and leucocytosis indicate CNS parenchymal involvement, and is usually normal in patients with isolated CNS non-parenchymal vascular disease. OCBs are typically negative.[22]

NEUROSARCOIDOSIS

Epidemiology and demographics

Sarcoidosis is a chronic idiopathic inflammatory multisystem disorder, commonly affecting the lungs and intrathoracic lymph nodes. Significant racial and geographical heterogeneity exists, with the highest prevalence reported in Northern Europe and the USA.[26] Annual incidence is estimated at 10 to 20 per 100 000 people. The mean age of presentation is 43 years, with women more frequently affected. Neurosarcoidosis symptomatically affects 5%–15% of patients, although may be found in up to 25% of autopsies,[26] and can be misdiagnosed as MS.

Presumed pathogenesis

Sarcoidosis is characterised by infiltrating clusters of non-caseating granulomas consisting of multinucleated giant cells surrounded by lymphocytes (predominantly CD4 T-cells), mast and plasma cells in addition to epithelioid cells.[27] Encephalomeningeal infiltration results from disseminated nodules or plaques, which have a predilection for the basal meninges and may cause meningeal arachnoid inflammation. Granulomatous infiltration, a source of angiotensin-converting enzyme (ACE) production, may also be associated with lymphocytic necrotising vasculitis and cytokine release, through an enhanced T-helper 1 response.

Clinical features and clues to diagnosis

Various central and peripheral nervous system (PNS) manifestations may arise, including neuropathy, myopathy, aseptic meningitis, myelopathy and cerebral or cerebellar sequelae.[26] CNS parenchymal or meningeal involvement may present with seizures, or focal deficits in addition to nuchal rigidity, fevers and headaches.[27] Cranial neuropathies are the most frequent neurological presentation, occurring in over 50% of patients, with the facial nerve most commonly involved. Sarcoidosis, like other granulomatous diseases, is often associated with pituitary or hypothalamic infiltration, and the presence of such findings should raise the suspicion of this diagnosis.

Ocular manifestations are reported in up to 25%–60% of patients and include conjunctivitis, uveitis, retinal vasculitis and optic neuropathy.[28] The anterior uveitis has typical granulomatous or 'mutton fat' keratitic precipitates. Interstitial keratitis rarely occurs. The classic fundus finding of periphlebitis with a 'candle wax-dripping' appearance is highly suggestive of sarcoid. Orbital inflammation typically involves the lacrimal glands,

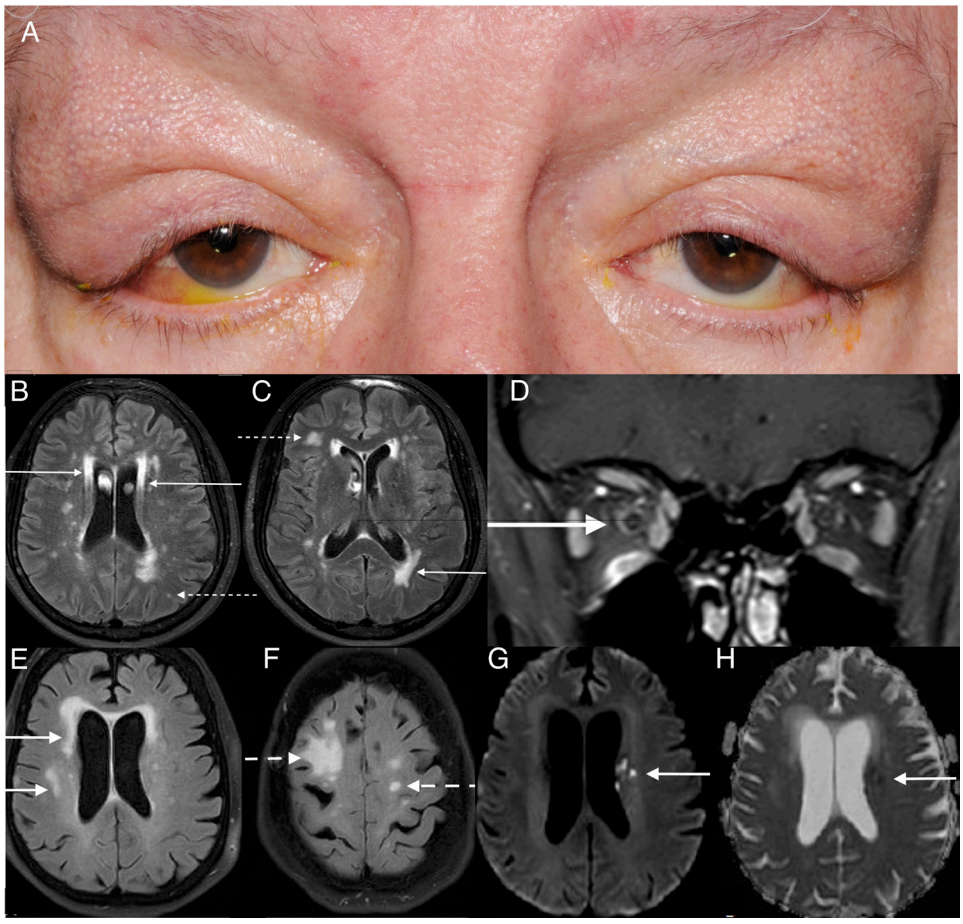

Figure 3 Sarcoidosis and Sjogren syndrome. (A) Photograph of a patient with sarcoidosis revealing painless superolateral swelling secondary to lacrimal gland inflammation, (B,C) axial fluid attenuation inversion recovery (FLAIR) sequences in neurosarcoidosis showing diffuse periventricular (white arrows and deep white matter hyperintensities throughout both cerebral hemispheres (broken arrows), (D) coronal T1 post contrast MRI sequence in neurosarcoidosis showing enhancement of the right optic nerve sheath complex (arrow), (E, F) axial FLAIR MRI of the brain in Sjogren syndrome revealing periventricular (white arrows) and subcortical white (broken arrows) matter hyperintensities, (G) axial DWI and (H) apparent diffusion coefficient map in Sjogren syndrome shows foci of restricted diffusion in the left periventricular white matter (white arrows) consistent with acute infarction.

presenting with superolateral painless swelling. Optic neuropathy is subacute and commonly causes central visual field loss. Optic nerve involvement can involve the chiasm, and needs to be differentiated from NMOSD.

Lower cranial nerve manifestations include vertigo, SNHL, dysarthria or dysphagia. Mild to severe, unilateral or bilateral SNHL can occur and may require cochlear implant. Mild to severe unilateral or bilateral vestibular dysfunction may accompany SNHL.[29]

Investigations

The presence of non-caseating granulomas on histological analysis in addition to clinical and radiological features confirm the diagnosis. MRI with gadolinium can show characteristic nodular thickening of the basilar meninges[26] and vestibulocochlear nerves.[29] Parenchymal lesions can manifest as multiple, small, non-enhancing periventricular or subcortical T2-hyperintense white matter lesions, similar to those observed in MS, but without a 'Dawson's fingers' appearance (figure 3).[26] In many cases, the parenchymal pathology of neurosarcoidosis appears to extend inward from the meninges, known as 'the outside in sign'. In spinal lesions, extension inward from the posterior cord meninges can lead to the 'trident sign' differentiating it from NMOSD,[30] which has a pattern of ring enhancement.[31] Cranial or peripheral nerve involvement can be demonstrated by thickened, enhancing nerves. Active lesions appear moderately hypermetabolic on ^{18}F-FDG positron emission tomography (PET), making PET useful in determining the extent of disease activity, identifying biopsy sites and monitoring treatment response.

Numerous serum and CSF biomarkers have been evaluated in sarcoidosis, but none are diagnostic. Elevated serum calcium, ESR and soluble interleukin-2 receptor can suggest sarcoidosis. Raised serum ACE levels are seen in 23.5% of patients,[26] but substantial elevations are rare in isolated neurosarcoidosis. Supportive CSF features include pleocytosis, an elevated protein, raised immunoglobulin G indices, elevated ACE, increased CD4/CD8 T-cell ratio and presence of OCBs.

Conjunctival biopsy, though rarely performed shows histological evidence of sarcoid in up to 54% of cases, even when ocular lesions are absent.

SJÖGREN SYNDROME

Epidemiology and demographics

Sjögren syndrome (SS) is a chronic autoimmune disorder, characterised by periductal lymphocytic infiltration of the exocrine glands, resulting in loss of secretory function.[32] Primary SS (pSS) occurs in isolation, while secondary SS is associated with other autoimmune

diseases. Females are affected 10 times more frequently than males, with onset commonly during the fourth and fifth decades of life. Prevalence of pSS varies from 0.1% to 3.0%.[33] Extraglandular features include PNS and CNS involvement. Reports of CNS involvement vary between 0.3% and 48%, primarily due to a lack of clear diagnostic criteria, and may precede pSS diagnosis.[34]

Presumed pathogenesis

Immune-mediated small vessel vasculopathy is the most common abnormality on histopathological analysis of brain tissue, with true vasculitis less common. An immune-mediated mechanism is supported by intrathecal activation of the terminal complement pathway and intrathecal synthesis of IgG in patients with active CNS involvement.[35] The deposition of autoantibodies and autoreactive T-cells in the stria vascularis of the basal turn of the cochlea is the likely cause of high frequency hearing loss.[36]

Clinical features and clues to diagnosis

CNS involvement is characterised by cognitive deficits, aseptic meningoencephalitis, or an MS or stroke-like syndrome of focal and multi-focal deficits. Headache, typically migrainous without aura, occurs in up to 35%. Focal CNS manifestations include motor, sensory and cerebellar deficits, aphasia, dysarthria, seizures and movement disorders. Transverse myelitis is a rare but well-described complication. CNS involvement is associated with PNS manifestations in up to 63% of cases.[37]

Keratoconjunctivitis sicca is nearly universal, with patients describing chronic persistent and troublesome eye symptoms. Coexistent xerostomia is also suggestive. Isolated optic neuritis is often binocular and characterised by frequent relapses.[38]

Otological symptoms can manifest as otalgia, tinnitus, external ear canal dryness, hearing loss and vertigo. SNHL is reported in up to 78% of pSS using conventional pure tone audiometry.

Investigations

MRI abnormalities are common and T2/FLAIR hyperintensities in the subcortical and periventricular white matter (figure 3) are detected in up to 80% of patients with focal neurological dysfunction.[39] White matter abnormalities are usually less pronounced in pSS than in MS and rarely involve the basal ganglia or the cerebral cortex. The appearance is often that of microangiopathic white matter disease.

Schirmer test or use of ocular surface dye may aid in diagnosis. Anti-Sjögren's syndrome-related antigen A and anti-Sjögren's-syndrome-related antigen B antibodies are the hallmark antibodies in SS, and are associated with earlier disease onset and extraglandular manifestations.[40] Elevated CSF protein and lymphocytosis is characteristic of aseptic meningitis.

SYSTEMIC LUPUS ERYTHEMATOSUS

Epidemiology and demographics

SLE is a chronic systemic autoimmune disease, more common among females, with prevalence highest in the USA, Caribbean and Brazil.[41] Neuropsychiatric SLE (NPSLE) manifestations are reported in up to 80% of adults with SLE.[42] SLE is separately associated with NMOSD and aquaporin-4 (AQP4) antibodies and antiphospholipid syndrome (APS).

Presumed pathogenesis

In NPSLE, lymphocyte entry into the CNS is hypothesised to result from blood–brain-barrier breakdown and proinflammatory cytokine mediated upregulation of adhesion molecules on vascular endothelial cells, including intercellular adhesion molecule-1.[43] A microvasculopathy, suspected to arise from complement activation, is the most common histological brain finding.

Clinical features and clues to diagnosis

CNS manifestations include aseptic meningitis, headache, seizures, cerebrovascular disease and demyelination.

Around a third of patients have ocular involvement,[44] with worsening ocular disease often indicating underlying systemic disease activity. Keratoconjunctivitis sicca affects ~30% of patients, but sight-threatening peripheral ulcerative keratitis can also occur.[44] Scleral involvement is rare although it can occur with uveitis.[44]

Lupus retinopathy, an immune-complex vasculopathy, occurs in around 10% of patients, but with improved systematic management, the prevalence appears to be decreasing. Less common retinal manifestations include pseudoretinitis pigmentosa, choroidopathy with serous retinal detachments and frosted-branch angiitis-like vasculopathy. Unilateral or bilateral ischaemic optic neuropathies and inflammatory optic neuritis are also reported.

SNHL is present in up to 30% of cases and may affect any or all frequencies, be unilateral or bilateral, and acute or chronic in nature. It reflects loss of outer hair cells, type 1 vestibular hair cells and stria vascularis shrinkage.

Investigations

The majority (40%–80%) of MRI abnormalities in NPSLE are small focal lesions in the periventricular and subcortical white matter. Cortical atrophy, ventricular dilation, diffuse white matter hyperintensities and gross infarctions can be seen (figure 4).

High titre antinuclear antibody levels carry a high sensitivity but low specificity for SLE, while double stranded DNA is highly specific for SLE, with rising levels suggesting active disease. Anti-Sm antibodies are specific for SLE but, only present in 30% of patients. Low complement levels, a positive direct Coombs' test and the presence of antiphospholipid antibodies, aid in the diagnosis.

ANTIPHOSPHOLIPID SYNDROME

Epidemiology and demographics

APS is defined by the association of thrombotic events and high titres of APLA, namely anticardiolipin IgG and IgM, lupus anticoagulant and beta-2-glycoprotein-1 antibodies. APLA prevalence ranges between 1% and 5% yet only a minority develop APS. The prevalence of APS is estimated to be 40–50 cases per 100 000 persons.[45]

Presumed pathogenesis

APS can occur in isolation or be associated with other autoimmune diseases, most commonly SLE. The prothrombotic APLA cause activation of the coagulation cascade, platelet aggregation, altered fibrinolysis and endothelial activation.

Clinical features and clues to diagnosis

Neurological involvement in APS is common, with stroke and transient ischaemic attack the most often encountered. APLA are detected in 5.9% of cerebral venous sinus thrombosis cases.[46]

Chronic headache or episodic migraines are common, and seizures are seen in up to 8.8% of patients, with most related to SLE. Chorea is a rare, yet characteristic, manifestation while dementia, cognitive deficits, psychiatric disorders and transverse myelitis are also encountered.

Ocular involvement occurs in up to 88% of patients.[47] Complaints include monocular or binocular visual blurring, amaurosis fugax, transient scotoma and visual field defects.[47] The

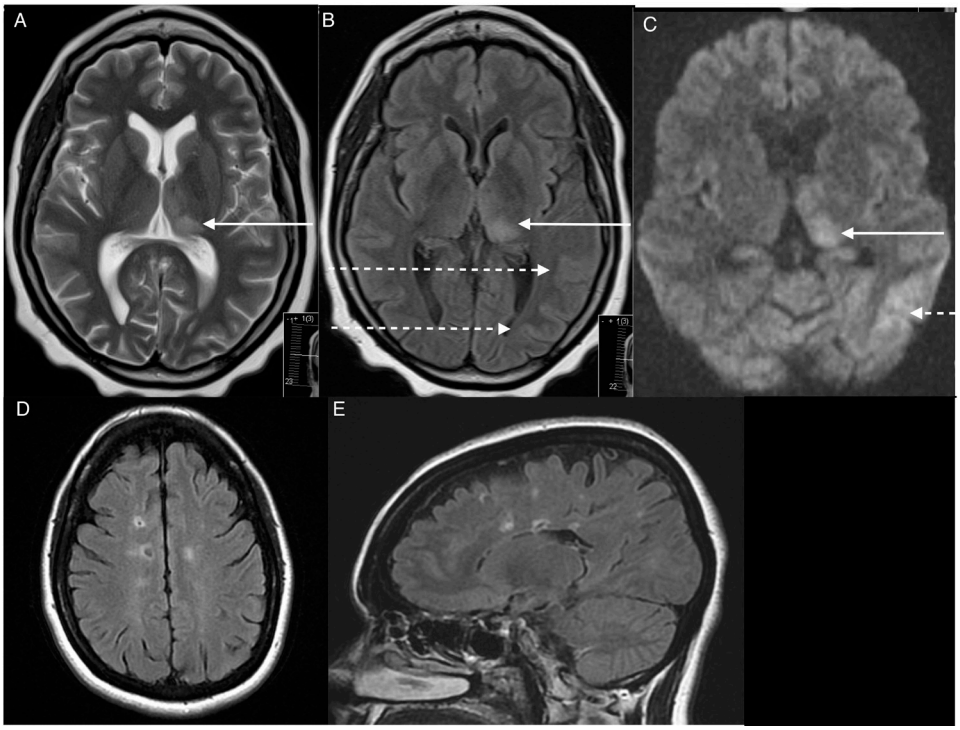

Figure 4 Systemic lupus erythematosus and antiphospholipid syndrome. (A) Axial T2 MRI and (B) axial fluid attenuation inversion recovery (FLAIR) MRI of the brain in systemic lupus erythematosus revealing hyperintensity involving the left thalamus (arrow) consistent with a subacute infarct, with subtle signal change also involving the gyri of the left occipital lobe (broken arrow), (C) axial DWI sequence in systemic lupus erythematosus shows resolving restricted diffusion in the left thalamus (solid arrows) and in the left occipital lobe (broken arrows), (D) MRI brain axial and (E) sagittal FLAIR sequence in cerebral antiphospholipid syndrome showing multiple punctate areas of FLAIR signal in the subcortical and periventricular white matter consistent with chronic small vessel disease and microinfarction.

presence of eyelid telangiectasia, erythema and purpura can aid in diagnosis.

Surface disorders such as conjunctivitis sicca are common and conjunctival findings include vascular tortuosity, microaneurysms and telangiectasias. Glaucomatous changes are occasionally seen. Corneal findings include punctate epithelial keratopathy and filamentary keratopathy. Retinal manifestations are predominantly vascular occlusive, rather than inflammatory in nature, including BRAOs and choroidal infarctions. Non-arteritic and arteritic ischaemic optic neuropathies are also reported.

Acute unilateral SNHL is well documented with labyrinthine circulation thrombosis, the presumed mechanism of injury.

Investigations

The spectrum of imaging findings in APS is largely the consequence of multiple arterial or venous thromboses. MRI brain may show cortical and subcortical infarctions, lacunar lesions or diffuse white matter lesions with cerebral atrophy (figure 4).[48]

Diagnosis of APS relies on the detection of APLA confirmed on two separate occasions, at least 12 weeks apart.

MULTIPLE SCLEROSIS

Epidemiology and demographics

MS is a chronic, immune-mediated, demyelinating disorder of the CNS with an estimated global prevalence of 2·3 million people, with females 2.3–3.5 times more likely to be affected.[49]

Presumed pathogenesis

The characteristic pathological feature of relapsing MS is the presence of focal plaques of demyelination in the CNS white matter, accompanied by variable degrees of inflammation and gliosis, with partial preservation of axons.

Clinical features and clues to diagnosis

Paraesthesia, weakness, ataxia and pain are common, and depend on the location of demyelinating plaques.

Optic neuritis affects more than 50% of patients with MS and is characterised by subacute visual loss and pain with eye movement. The vision loss is rarely severe, and acuity of count fingers or worse should raise suspicion of an alternate diagnosis such as sarcoid optic neuropathy or NMOSD. Disc oedema occurs in 1/3 of cases and disc haemorrhage or a macular star are rare; and so the presence of either should raise suspicions of another cause for an optic neuritis.

Efferent visual abnormalities affect up to 25% of patients. Internuclear ophthalmoplegia or a sixth nerve palsy in a young patient, must raise suspicion for MS.

Ocular inflammation is often under-recognised in MS, particularly pars planitis (intermediate uveitis), with uveitis is 10 times more common than in the general population.[50]

Sudden unilateral hearing loss, a presumed consequence of demyelinating lesions involving the intra-axial portion of the cochlear nerve, is described in approximately 4% of patients but is rarely the presenting feature.[51] Sequential bilateral hearing loss, vertigo and central hyperacusis with phonophobia and an acute central vestibular syndrome are also described.

Investigations

MRI typically shows multifocal T2-hyperintense white matter lesions characteristically in the periventricular, cortical,

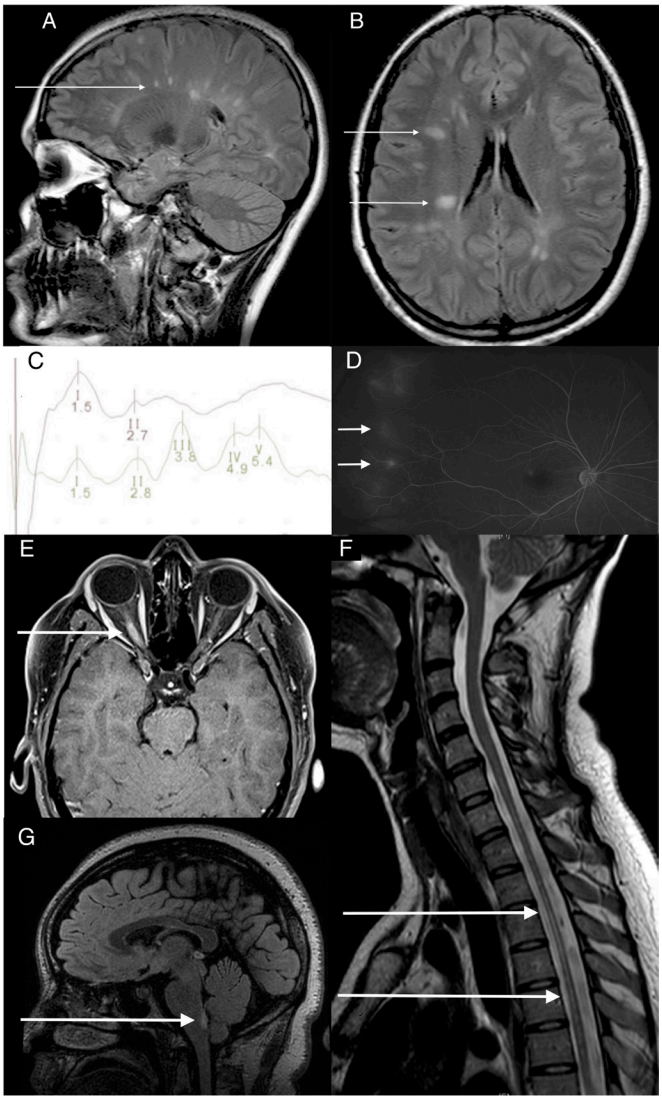

Figure 5 Multiple sclerosis and neuromyelitis optica spectrum disorder. (A) MRI brain sagittal fluid attenuation inversion recovery (FLAIR) sequence in multiple sclerosis revealing perivenular white matter lesions (arrow) radiating perpendicular to the ventricular surface, (B) MRI brain axial FLAIR in multiple sclerosis revealing ovoid periventricular lesions (arrows), (C) brainstem auditory evoked potentials in multiple sclerosis. showing abnormality in left ear responses with absence of wave III–V, consistent with pontine pathology, (D) left eye late phase fluorescein angiography in multiple sclerosis revealing areas of peripheral retinal vasculitis and leakage (arrows), (E) axial FLAIR MRI brain in neuromyelitis optica spectrum disorder demonstrating long-segment right optic nerve oedema (arrow) (F), sagittal T2 MRI spine in neuromyelitis optica spectrum disorder demonstrating a long segment of hyperintensity over multiple vertebral levels (arrows) and (G) sagittal FLAIR in neuromyelitis optica spectrum disorder showing hyperintensity in the dorsal midbrain at the area postrema (arrow).

juxtacortical, infratentorial and pericallosal regions, and in the optic nerves and spinal cord (figure 5).[51] Lesions are typically small (<1 cm diameter) and ovoid with homogeneous signal on T2-weighted sequences. Acute lesions often enhance with gadolinium.

Visual-evoked potentials (VEP) can provide supportive evidence of MS. VEP after optic neuritis show p100 latency delay with relative amplitude preservation. While reduced VEP amplitude and RNFL thinning are frequent findings following optic neuritis in MS, NMOSD-associated optic nerve pathology is usually more severe and has a greater impact on measures of axonal density. Prolonged or absent I–V interpeak latency in brainstem auditory evoked potentials is the most common abnormality in MS-associated deafness.

Detection of CSF-restricted OCBs occurs in up to 90% of patients with MS. OCBs are not specific for MS, however, and therefore require careful interpretation.

NEUROMYELITIS OPTICA SPECTRUM DISORDER

Epidemiology and demographics

NMOSD accounts for 1%–4% of demyelinating disease in Caucasians but between 20% and 48% in South East Asians.[52 53] The average age of onset is 40 years with females constituting 70%–90% of affected individuals.[54]

Presumed pathogenesis

NMOSD typically involves inflammation of optic nerves, spinal cord and periventricular sites where there is high AQP4 expression, including astrocyte foot processes.[55] Cell-based assays detect antibodies against AQP4 (AQP4-IgG) in approximately 75% of cases,[56] with antibody binding leading to complement activation.

Clinical features and clues to diagnosis

Core clinical characteristics include optic neuritis, acute myelitis, area postrema syndrome, brainstem syndromes, diencephalic syndromes or a symptomatic cerebral syndrome with NMOSD-typical MRI lesions.[57]

Optic neuritis in NMOSD is usually more severe and more often bilateral than in MS. Approximately one-half of patients with NMOSD present with isolated optic neuritis and 20% with bilateral optic neuritis.[54]

Sudden unilateral and bilateral hearing loss secondary to cochlear nuclei lesions are reported, and may be accompanied by tinnitus and vertigo.

Investigations

MRI tends to reveal longer optic nerve segment involvement in optic neuritis compared with MS, often extending from the intraorbital portion to involve the chiasm and even optic tracts.[58] Small subcortical white matter T2-hyperintensities are the most common lesion seen in the brain, while circumventricular lesions, extending from ventricular ependyma, are highly characteristic of NMOSD. Focal T2-hyperintense lesions of the dorsal brainstem are considered typical of NMOSD, with involvement of the area postrema particularly suggestive. In patients with transverse myelitis, MRI of the spine classically shows longitudinal involvement of ≥3 vertebral segments of the spinal cord (figure 5).[57]

OCT reveals more severe peripapillary RNFL loss following optic neuritis in NMOSD than MS, with atrophy more prominent in the superior and inferior quadrants in NMOSD vs temporal quadrant atrophy in MS.

A CSF pleocytosis is present in around 50% of samples, however CSF-restricted OCBs are absent in the majority.

DISCUSSION

The spectrum of immune-related and inflammatory-related syndromes that affect the brain, eye and ear can collectively be referred to as BEE syndromes (table 1). The presence of a characteristic manifestation in one BEE organ should prompt

Table 1 Distinguishing features of the inflammatory BEE syndromes

	Characteristic clinical features		
Disease	**Brain**	**Eye**	**Ear**
Susac syndrome	Encephalopathy, headache occasionally resembling migraines, cognitive impairment, confusion, behavioural changes. MRI—callosal lesions including 'snowballs' and 'spoke' or 'icicle' lesions on T2/FLAIR sequences, 'punched out' central callosal holes on T1 sequences. CSF increased protein with normal lymphocyte count or slight lymphocytosis.	Visual blurring, field defects, photopsia Branch retinal artery occlusions, arteriolar wall hyperfluorescence and Gass plaques may only be visible on FFA. Focal thinning of retinal nerve fibre layer and macular volume change on OCT.	Acute or subacute, unilateral or bilateral, simultaneous or sequential SNHL typically affecting low to mid frequencies. Hearing loss may be either fluctuating or progressive and eventually can be total.
VKH	Prodromal meningoencephalitic phase characterised by non-specific neurological symptoms including headache, meningism, vertigo and occasionally cranial neuropathies and focal neurological signs.	Granulomatous panuveitis, exudative retinal detachments, subretinal effusions leading to orange-red 'sunset glow' fundus, iris nodules, focal pigment atrophy of the iris.	Mild symmetrical SNHL preferentially affecting high frequencies.
Cogan syndrome	Headache, focal neurological syndromes, meningitis, encephalitis, psychosis, seizures, myelopathy, oscillopsia	Interstitial keratitis, photophobia, scleritis, iritis, conjunctivitis, retinal vasculitis	Abrupt unilateral or bilateral simultaneous or sequential SNHL preferentially affecting middle and high frequencies. Can eventually be total needing cochlear implant. Recurrent acute unilateral vestibular dysfunction producing vertigo attacks which eventually become severe. Bilateral loss produces oscillopsia and ataxia.
Behcet disease	Encephalopathy, cognitive dysfunction, psychosis, seizures, subacute meningoencephalitis, cerebral venous sinus thrombosis, focal neurological deficits. MRI - T2/FLAIR hyperintense lesions throughout the cerebral hemispheres, excluding periventricular regions, with a predilection for the upper brainstem, thalamus and basal ganglia	Anterior, posterior or panuveitis, hypopyon, retinal vasculitis, optic neuropathy, conjunctival ulceration	Mild SNHL occurring in 20%–30%, often bilateral preferentially affecting high frequencies, Rarely it is acute and severe Vertigo and nystagmus secondary to unilateral central vestibular inflammation.
Sarcoidosis	Cranial neuropathies, meningoencephalitis MRI—diverse presentations; parenchymal lesions manifest as multiple small, non-enhancing periventricular or subcortical T2-hyperintense white matter lesions, similar to those observed in MS, but without Dawson's fingers MRI with gadolinium can show typical nodular basilar meningeal thickening and leptomeningeal enhancement.	Anterior uveitis with typical granulomatous or 'mutton fat' keratitic precipitates, periphlebitis with a 'candle wax-dripping' appearance. Orbital inflammation involving the lacrimal glands, causing superolateral painless swelling. Optic neuritis often involving the chiasm. Optic neuropathy with central field loss.	Mild to severe, unilateral or bilateral SNHL can occur, requiring cochlear implant in severe cases. Vestibular dysfunction may be mild to severe and unilateral or bilateral.
Sjogren syndrome	Aseptic meningoencephailitis, headache, focal neurological deficits. MRI—evidence of T2/FLAIR hyperintensities typically involving the subcortical and periventricular white matter, rarely involving basal ganglia or cerebral cortex Anti-SSA and anti-SSB antibodies.	Keratoconjunctivitis sicca nearly universal, optic neuritis and neuropathies.	SNHL in majority preferentially affecting high frequencies accompanied by vertigo and ear canal dryness.
SLE	Encephalopathy, aseptic meningitis, headache, seizures, cerebrovascular disease, demyelination	Sicca, corneal erosion, ulcerative keratitis, scleritis, uveitis, retinopathy, frosted angiitis	SNHL may affect any or all frequencies, be unilateral or bilateral, and acute or chronic in nature.
APS	Stroke and transient ischaemic attack, cerebral venous sinus thrombosis, epileptic seizures, headache, chorea (rare), dementia, cognitive deficits, psychiatric disorders, MS-like disease, transverse myelitis Presence of APLA	Monocular or binocular visual blurring, amaurosis fugax, transient scotoma and other visual field defects, non-arteritic and arteritic ischaemic optic neuropathy	Acute unilateral SNHL
MS	Most often relapsing remitting neurological symptoms involving brain and spinal cord. MRI—evidence of T2/FLAIR hyperintensities typically involving the periventricular, cortical, juxtacortical, infratentorial regions and short segments of the spinal cord. Positive CSF-restricted oligoclonal bands.	Relapsing remitting optic neuritis, anterior uveitis, pars planitis (intermediate uveitis). Preferential temporal quadrant atrophy on OCT.	Occasional sudden unilateral hearing loss, which may be temperature dependent and can rarely progress to sequential bilateral hearing loss. Vertigo, central hyperacusis, phonophobia.
NMOSD	Focal inflammation—diencephalic, cerebral, area postrema, brainstem and longitudinally extensive myelitis ≥3 vertebral segments in length. AQP4 IgG positive in 80%, MOG IgG positive in 20% of patients with AQP4 seronegative.	Bilateral or sequential optic neuritis, often involving the chiasm. Preferential superior and inferior quadrant atrophy on OCT with greater degree of RNFL thinning than in MS.	Sudden, unilateral or bilateral hearing loss with lesions of the cochlear nuclei; can be accompanied by vestibulopathy consisting of tinnitus and vertigo.

APLA, antiphospholipid antibodies; APS, antiphospholipid syndrome; AQP4, aquaporin-4; BEE, brain, eye and ear syndromes; CSF, cerebrospinal fluid; FFA, fundus fluorescein angiography; FLAIR, fluid attenuation inversion recovery; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; SLE, systemic lupus erythematosus; SNHL, sensorineural hearing loss; SSA, anti-Sjögren's syndrome-related antigen A; SSB, anti-Sjögren's syndrome-related antigen B; VKH, Vogt-Koyanagi-Harada syndrome.

Table 2 Significant investigation findings which may lead to diagnosis

Investigation technique	Investigatory finding	Suggested diagnosis
MRI brain	T2/FLAIR callosal hyperintensities 'snowball', 'icicle' or 'spoke' like in nature.	Susac syndrome
	T2/FLAIR hyperintensities with predilection for inflammatory lesions of upper brainstem or thalamus, hemi-brain stem atrophy in chronic cases.	Behcet disease
	Nodular meningeal thickening and enhancement, involvement of pituitary and hypothalamus, 'outside-in' lesions.	Sarcoidosis
	Stroke, cerebral venous sinus thromboses.	APS
	T2/FLAIR hyperintensities located in periventricular, cortical, juxtacortical, infratentorial and pericallosal regions.	Multiple Sclerosis
	T2 hyperintensities affecting dorsal brainstem, especially area postrema; circumventricular lesions, extending from ventricular ependyma.	NMOSD
MRI Orbits	Optic nerve enhancement with 'outside in' enhancement—may involve the chiasm.	Sarcoidosis
	Typically, short T2-hyperintense lesions involving optic nerve.	Multiple Sclerosis
	T2 signal change and oedema in optic nerve(s), often longitudinally extensive and involving the chiasm.	NMOSD
Ophthalmic examination	Branch retinal artery occlusions, arteriolar wall hyperfluorescence	Susac syndrome
	Granulomatous panuveitis, 'sunset glow' fundus, exudative retinal detachments	VKH
	Interstitial keratitis, retinal vasculitis	Cogan syndrome
	Anterior, posterior and panuveitis, retinal vasculitis	Behcet syndrome
	Granulomatous keratitic precipitates, anterior uveitis, periphlebitis	Sarcoidosis
	Keratoconjunctivitis sicca	Sjogren sydnrome
	Frosted angiitis, ulcerative keratitis	SLE
	Branch retinal artery occlusion, non-arteritic and arteritic ischaemic optic neuropathy, eyelid telangiectasia	APS
OCT	Focal atrophy of retinal nerve fibre layer and macular volume	Susac syndrome
	Preferential temporal quadrant atrophy	MS
	Preferential superior and inferior quadrant atrophy	NMOSD
FFA	Branch retinal artery occlusions, arteriolar wall hyperfluorescence and Gass plaques	Susac
	Frosted angiitis	SLE
	Branch retinal artery occlusions	APS
Audiometry	Low to mid frequency loss	Susac syndrome
	Symmetrical high frequency loss	VKH
	Mid to high frequency loss	Cogan
	High frequency loss in majority	Sjogren syndrome
	Pantonal or any frequency impairment	SLE
	Acute unilateral pantonal impairment	APS
CSF	Elevated protein with, normal WCC count	Susac
	Elevated CSF protein and lymphocytosis	Sjogren syndrome
	CSF-restricted OCBs seen in majority	MS
Serology	Elevated ESR and HLA-B*51 haplotype	Behcet syndrome
	SSA and SSB antibodies commonly identified	Sjogren
	Elevated ACE, ESR and calcium	Sarcoidosis
	Elevated dsDNA and anti-Sm antibodies highly specific. Elevated ANA highly sensitive, low specificity. Hypocomplementaemia, positive direct Coombs test and APLA presence suggestive of SLE.	SLE
	Positive APLA on two separate occasions separated by 12 weeks.	APLS
	Positive serum AQP4 antibodies in over 75% of cases; MOG antibodies.	NMOSD

ACE, angiotensin-converting enzyme; ANA, anti nuclear antibodies; APLA, antiphospholipid antibodies; APS, antiphospholipid Syndrome; AQP4, aquaporin-4; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; FFA, fundus fluorescein angiography; FLAIR, fluid attenuation inversion recovery; HLA, human leucocyte antigen; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; OCBs, oligoclonal bands; OCT, optical coherence tomography; SLE, systemic lupus erythematosus; SSA, anti-Sjögren's syndrome-related antigen A; SSB, anti-Sjögren's syndrome-related antigen B; VKH, Vogt-Koyanagi-Harada syndrome; WCC, white cell count; anti-Sm, anti Smith antibody; dsDNA, double stranded DNA.

consideration of involvement of the other BEE organs, and is important for the purposes of differential diagnosis and investigation.

The work-up and diagnosis of patients presenting with auditory, visual and neurological symptoms can be challenging although certain investigation findings are highly diagnostic (table 2). We advocate an MRI of the brain with volumetric FLAIR, T1 with and without gadolinium, T2, DWI, ADC and SWI sequences, in patients with BEE symptoms. Sagittal or volumetric FLAIR images are particularly helpful as they provide the best views of the corpus callosum where morphology and lesion distribution can help to distinguish between Susac syndrome, MS and NMOSD.[8] Orbital volumetric fat suppressed T1 post-gadolinium sequences are excellent for assessing subtle enhancement of the optic nerves.

A thorough ophthalmological examination including dilated fundus examination and careful slit lamp biomicroscopic examination of the anterior and posterior segment are recommended in patients suspected of having a BEE syndrome. In many cases, adjunctive FFA is indicated to investigate the retinal vasculature. OCT is also useful to show subretinal fluid, retinal thinning and RNFL changes. While this may not be diagnostic acutely, the pattern of changes over time may help with diagnosis.

A close temporal association between hearing loss and new brain and eye symptoms is an important red flag for neuroimmunological disease, and ideally should prompt involvement of experienced subspecialists from across relevant disciplines. An audiogram demonstrating low frequency SNHL can be a particularly important clue to Susac syndrome.[4] Neurophysiological testing including VEP, in some cases mfVEP and mfERG, plus BEAP, lumbar puncture and various serological investigations including a serum vasculitis screen, ACE, AQP4 IgG and myelin oligodendrocyte glycoprotein (MOG) IgG can also be valuable in establishing the correct diagnosis in the appropriate clinical context.

Other inflammatory disorders in which BEE symptoms can occur include acute disseminated encephalomyelitis, MOG antibody-associated demyelination, ANCA-associated vasculitides, relapsing polychondritis, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids and retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations.[59] NMOSD associated with MOG antibodies has been more recently recognised as having an overlapping clinical phenotype with AQP4-associated disease, but MOG-associated optic neuritis is even more frequently bilateral, generally associated with optic disc swelling and rapidly steroid responsive,[58] though functional outcomes can still be poor. Chronic relapsing inflammatory optic neuropathy is increasingly being recognised as a clinical phenotype associated with MOG antibodies. Rare cases of MOG-associated disease are associated with hearing loss or vertigo.

Patients can present with BEE symptoms due to more than one pathological process. A common scenario is a patient with migrainous visual disturbance and headache, non-specific white matter lesions (NSWML) on MR imaging, and high frequency hearing loss and tinnitus due to occupational noise exposure or congenital hearing loss. NSWMLs are a major cause of MS misdiagnosis,[60] and the clinician needs to be particularly vigilant about misattributing them to a sinister disease process, particularly in older patients who frequently have microangiopathic disease and unrelated hearing impairment or ocular disease, as immunotherapies carry the potential for serious adverse events.

A full discussion of every potential cause of BEE symptoms is beyond the scope of this review but infections such as syphilis, tuberculosis with pachymeningitis, herpes virus infections, enteroviral infections (especially with hearing loss), HIV; malignancies such as lymphoma and infiltrating base of skull neoplasms and genetic and mitochondrial diseases all need to be considered (table 3). Idiopathic intracranial hypertension is another syndrome in which patients can present with BEE symptoms of headache, tinnitus, visual field loss and papilloedema due to raised intracranial pressure.

In conclusion, the range of neuroinflammatory BEE syndromes is varied and reaching a diagnosis can be challenging. Correct diagnosis, however, is important to allow targeted immune treatments and to limit or prevent disability.

Table 3 Non-inflammatory causes of BEE syndromes

Infectious	Syphilis
	Tuberculosis with pachymeningitis
	HIV
	Enteroviral infections
	Herpes virus infections
	Lyme disease
Malignant	Lymphoma
	Infiltrating base of skull neoplasms (eg, nasal squamous cell carcinoma)
	Carcinomatous meningitis
Genetic	Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations due to three prime repair exonuclease 1 (TREX1) mutations
	Autosomal dominant optic neuropathy and sensorineural hearing loss—wolframin (WFS1), optic atrophy-1 gene (OPA1) gene
	Autosomal recessive—Usher syndrome
	X-linked inheritance—Mohr-Tranebjaerg syndrome
Mitochondrial	Harding's syndrome—Leber's hereditary optic neuropathy (LHON) plus MRI lesions and clinical consistent with MS
Other	Syndromes of raised intracranial pressure for example, IIH
	Migraine with aura

HIV, human immunodeficiency virus; IIH, idiopathic intracranial hypertension; MRI, magnetic resonance imaging; MS, multiple sclerosis.

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