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Rhomboencephalitis

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Abstract

Rhomboencephalitis – inflammation of the brainstem and cerebellum – has myriad clinical presentations including encephalopathy, cranial neuropathies, long tract signs and cerebellar dysfunction, and is associated with significant morbidity and mortality. There are a variety of potential underlying aetiologies which are variably responsive to treatment including infections, para-infectious syndromes, inflammatory disorders including autoimmune encephalitis and paraneoplastic syndromes.

This review provides an overview of the clinical presentation of rhomboencephalitis together with an outline of a practical approach to its investigation with the aim of facilitating prompt diagnosis and confirmation of the underlying cause with early instigation of appropriate management and optimisation of clinical outcome.

Introduction

The name rhombencephalon derives from the Greek for “rhombus” meaning diamond-shaped structure and “enkephalos” referring to the brain. It comprises both the metencephalon and myelencephalon of the hindbrain. The metencephalon includes the cerebellum, the pons with its adjacent fourth ventricle and cranial nerves V-VIII. The myelencephalon contains the medulla oblongata with its fourth ventricle counterpart along with the bulbar cranial nerves and a portion of the vestibulocochlear nerve (Figure 1).

Despite the rhombencephalon technically excluding the midbrain, the term rhomboencephalitis (also known as rhombencephalitis) is often used interchangeably with brainstem encephalitis and,

for practical purposes, we will include brainstem encephalitis in our discussion of rhomboencephalitis.

Aetiology

We searched MEDLINE (1946 – December 2019) and EMBASE (1974 – December 2019), with no limits to language, and identified all the documented causative agents of rhomboencephalitis. We used the primary search terms "rhomboencephalitis", "rhombencephalitis" and "brainstem encephalitis" including their synonyms, individually or in combination, to yield a search result of 1787 papers. These were then reviewed, and paediatric cases were excluded. The reported causes of rhomboencephalitis are summarised in Table 1 and the more common presentations are discussed below.

Table 1 - Causes of brainstem encephalitis

Infections	**Relative frequency in rhomboencephalitis**
Bacteria	
Listeria	**Common**
Tuberculosis	Uncommon
Borrelia burgdorferi	Uncommon
Mycoplasma	Uncommon
Haemophilus influenza	Rare
Pneumococcal	Rare
Melioidosis	Rare
Tuleraemia	Rare
Brucellosis	Rare
Coxiella burnetii	Rare
Nocardia	Rare
Viral	
Herpes simplex virus-1 and -2	**Common**
Enterovirus 71	Common in children, uncommon in adults
Epstein-Barr virus	Uncommon
Cytomegalovirus	Uncommon
Japanese Encephalitis	Common in children, uncommon in adults
Enterovirus D68	Uncommon
Coxsackie A16	Uncommon
SARS-CoV-2	Rare

Coxsackie B3	Rare
Varicella zoster virus	Rare
Human herpes virus-6	Rare
Adenovirus	Rare
Mumps	Rare
Hepatitis E	Rare
Rabies virus	Rare
Human parechovirus	Rare
West Nile virus	Rare
Eastern equine virus encephalitis	Rare
St Louis Encephalitis	Rare
Dengue Fever	Rare
Chandipura vesiculovirus	Rare
Fungal	
Aspergillus Flavus	Rare
Paracoccidiomycosis	Rare
Mucormycosis	Rare
Parasites	
Schistosomiasis	Rare
Cysticercosis	Rare
Toxoplasmosis	Rare
Inflammatory	
Neuro-Behçet's syndrome	**Common**
Systemic lupus erythematosus	Uncommon
Sjogren's syndrome	Rare
Relapsing polychondritis	Rare
Sarcoidosis	Rare
Paraneoplastic	
Intracellular antibody	
Anti-hu	Uncommon
Anti-ma2	Uncommon
Anti-amphiphysin	Uncommon
Anti-Ri	Uncommon
Anti-CV2/CRMP5	Uncommon
Anti-Tr	Uncommon
Anti-GAD65	Rare
Cell surface antibody	
Anti-MOG	**Common**
Anti-NMDA receptor encephalitis	Uncommon
Anti-IgLON5 receptor encephalitis	Uncommon
Anti-glycine receptor encephalitis	Uncommon
GABAb receptor encephalitis	Rare
Anti-DPPX receptor encephalitis	Rare
Voltage-gated calcium channel antibodies	Rare

Anti-aquaporin-4 antibodies (AQP-4, NMO)	Rare
Others	
Bickerstaff's brainstem encephalitis	**Common**
Acute disseminated encephalomyelitis	Uncommon
Immune checkpoint inhibitor-induced (e.g. pembrolizumab and nivolumab)	Uncommon
Vogt-Koyanagi-Harada	Rare
Kikuchi-Fujimoto disease	Rare
Anti-SRP antibodies	Association in 2 cases found
DPPX = dipeptidyl-peptidase–like protein 6, GABA = Gamma aminobutyric acid, GAD = glutamic acid decarboxylase, IgLON5 = immunoglobulin-like cell adhesion molecule 5, MOG = myelin oligodendrocyte glycoprotein, NMDA = N-methyl-D-aspartate, NMO = neuromyelitis optica, SRP = signal recognition particle	

Infections

Infectious rhomboencephalitides are typically bacterial or viral. Although more frequently reported in immunocompromised individuals, they may also occur in the immunocompetent.

Bacterial

Listeria rhomboencephalitis

The most common cause of rhomboencephalitis is infection with the Gram-positive bacteria *Listeria monocytogenes.* Public Health England recorded 135 cases of listeriosis in the UK in 2017. The bacterium is present in soil and vegetation and 1-5% of the population are asymptomatic carriers. Outbreaks have been associated with contamination of unpasteurised cheeses or milks, cured meats, pâtés, smoked fish, cooked shellfish and, rarely, pre-packed salads, particularly if mixed with meat. Brainstem infection is thought to occur due to retrograde axonal translocation *via* the cranial nerves innervating the oropharynx. It can also occur opportunistically in skull base erosion typically associated with cocaine abuse.[1]

Although listeriosis can affect the immunocompetent, it typically presents in the elderly, immunocompromised or pregnant population, manifesting as meningitis or meningoencephalitis. The risk appears to be particularly high with infliximab (anti-tumour necrosis factor-α); first year risk estimated at 4.3-15.5 cases per 100,000.[2] The source of infection may be from contaminated food consumption or chronic faecal carriage, although the predilection for the complication to occur early in treatment, may favour re-emergence of latent disease and patients on anti-TNF-α blockers should be advised to take additional precautions with food hygiene e.g. avoidance of raw or undercooked eggs, pate, meat and poultry as well as unpasteurised dairy products or soft and blue cheeses

Rhomboencephalitis occurs in approximately 9% CNS listeria infections (Figure 2) and can occur in immunocompetent individuals. Of particular note for neurologists, cases have also been reported in association with disease modifying treatment for multiple sclerosis.[3 4] Traditionally, it begins with a biphasic 'flu-like illness followed, over a period of days, by the emergence of encephalopathy and brainstem signs. Magnetic resonance imaging (MRI) of the brain may demonstrate multifocal abscesses e.g. T2-hyperintensities or ring-enhancing lesions on post-contrast T1-sequences found in the thalamus, pons, medulla and cerebellar peduncles (Figure 2).[5] Diagnosis is confirmed by culture of the organism from blood or cerebrospinal fluid (CSF) although CSF polymerase chain reaction (PCR) has greater sensitivity. There are limited data to support brain biopsy in cases of diagnostic uncertainty.

The importance of early recognition and initiation of appropriate treatment is highlighted by mortality rates; 100% for untreated listeria rhomboencephalitis, falling to 76% with suboptimal antimicrobials and 40% with targeted therapy e.g. intravenous amoxicillin or ampicillin 2g every four hours ± gentamicin or co-trimoxazole. Abscess formation may necessitate longer duration of treatment and development of hydrocephalus or intraventricular haemorrhage, which occur in 10-

15% and 5% cases respectively, necessitate consideration of neurosurgical intervention.[6] Intraventricular antibiotics may also be considered if there is poor response to standard therapy.[6]

Tuberculosis

CNS involvement occurs in approximately 10% patients with tuberculosis (TB), and approximately 5% of these have brainstem disease. Caseating granulomata can mimic bacterial abscesses and tumour necrosis on neuroimaging, although core T2-hypointensity with vivid peripheral contrast enhancement on MRI representing gliosis and monocyte invasion are suggestive.[7]

TB diagnosis is confirmed through detection of acid-fast bacilli e.g. in respiratory samples, early morning urine or biopsy of tuberculoma. CSF culture and staining have sensitivities of <20%, although this increases with repeated sampling. Larger CSF volumes may also increase the diagnostic yield. CSF adenosine deaminase (ADA), a marker of cell-mediated immunity, has reported sensitivities and specificities between 44-100% and 71-100% respectively.[7] Given the significant morbidity and mortality, treatment for CNS involvement should be initiated if the clinical findings and investigation results are consistent with the diagnosis even if a rapid diagnostic test has returned negative results.[8]

NICE recommends CNS TB treatment that includes rifampicin, isoniazid (with pyridoxine), pyrazinamide and ethambutol for 2 months, followed by 10 months of rifampicin and isoniazid (with pyridoxine).[8] High dose corticosteroids are recommended with initiation of treatment with subsequent taper over 4-8 weeks. Neurosurgical management is typically reserved for complications such as hydrocephalus, reducing mass effect due to tuberculomas and abscess drainage.

Neuroborreliosis

Lyme disease has protean CNS manifestations including lymphocytic meningitis, cranial neuropathies or a painful radiculitis 4-6 weeks after tick exposure. An index of clinical suspicion is required

because only half of patients with neuroborreliosis report a rash consistent with erythema migrans and one quarter recall a tick bite. Serology (serum and CSF if rhomboencephalitis suspected) is recommended with input from a reference laboratory for extended immunoblotting if results are positive or equivocal. Interval serological testing e.g. at 4 weeks can also be performed if tests are non-corroborative and there is ongoing clinical suspicion. CSF lymphocytosis is present in virtually all cases. Parenchymal brain changes are rare in neuroborreliosis but there are reports of pontine and cerebellar peduncle involvement. Treatment of Lyme disease affecting the CNS is with 4g total intravenous ceftriaxone daily for 21 days, whilst observing for a Jarisch-Herxheimer reaction which can occur 1-12 hours following initiation of therapy.

Viral

Herpes Simplex Virus-1 and Herpes Simplex Virus-2 (HSV-1 and HSV-2)

HSV encephalitis (HSVE) is the commonest form of sporadic encephalitis and neurological involvement typically causes temporal lobe, insular cortex, orbital frontal lobe and angular gyrus inflammation with sparing of the basal ganglia and lobar white matter. More rarely, it can lead to rhomboencephalitis and, when this does occur, 80% are attributable to the HSV-1 subtype.[9] Retrograde spread is thought to occur from the cisternal portion of the trigeminal ganglion into the brainstem and the radiological presentation may mimic an underlying neoplasm. Those with rhomboencephalitis may have isolated brainstem MRI changes although approximately 50% have concomitant supratentorial lesions,[10] and the diagnosis is usually confirmed on CSF PCR. Treatment is with intravenous acyclovir (10mg/kg three times per day) for a minimum of two weeks and current UK guidelines recommend repeat CSF analysis to confirm HSV PCR negative prior to discontinuation of therapy.[11]

SARS-CoV-2

Coronavirus disease-2019 (COVID-19) is caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is known that SARS-CoV-2 can gain access to the CNS,[12] and related viruses are thought to enter the brain *via* the olfactory bulb with spread to the thalamus and brainstem. Indeed, it has been postulated that brainstem involvement may contribute to respiratory failure in some patients with COVID-19.[13] However, at the time of writing, only two cases of rhomboencephalitis have been described in association with COVID-19. One had MRI findings consistent with rhomboencephalitis but normal CSF and improved rapidly with supportive therapy.[14] The second was thought most likely to be in keeping with a post-infectious syndrome having presented with a brainstem syndrome including hyperekplexia, and normal MRI and CSF and was treated with corticosteroids with rapid improvement.[15]

Other infectious causes

Multiple additional viral infections have been reported to cause rhomboencephalitis although these are more likely to occur in children.

Enterovirus-71 (EV71) is the second most common infective cause of rhomboencephalitis overall, but predominantly affects those <5 years of age.[16] Outbreaks have tended to occur in the Asia-Pacific region, with transmission *via* airborne droplets or faeco-oral route. It is a recognised cause of hand foot and mouth disease but, in severe cases, can cause an acute, polio-like, flaccid paralysis, aseptic meningoencephalitis and rhomboencephalitis. In adults, neurological complications are uncommon.

Other infectious aetiologies include Japanese encephalitis (JE), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In the unvaccinated, JE tends to affect young adults and children exposed to

animals including pigs which carry the virus transmitted from the Culex mosquito around the Pacific rim, eastern and southern Asia. Patients with JE have been reported to have transient parkinsonian features with 'dull, flat, mask-like facies with unblinking eyes', although tremor is not commonly reported and hypophonia may be marked. MRI-brain characteristically shows high T2 signal within the thalamus, brainstem and basal ganglia and is thereby distinct from the typical appearances of HSV encephalitis.[17]

EBV encephalitis predominantly affects children, although cases in adults are well-recognised.[18] EBV encephalitis may affect the temporal lobes, masquerading as HSVE, but can also damage the diencephalon or, less frequently, cause rhomboencephalitis. Features suggesting infection with EBV include cervical lymphadenopathy, hepatosplenomegaly and transaminitis.

CMV encephalitis should be suspected in immunodeficient patients with an EBV-like constellation of symptoms, transaminitis, diarrhoea, retinitis, pneumonia or painful ulcers in the oesophagus or intestine. It can lead to direct damage of the brainstem through CMV inclusions and microglial nodules.[19] Importantly, both EBV and CMV can lead to perivascular lymphocytic infiltration with oedema and glial nodules due to Bickerstaff's brainstem encephalitis (BBE).

Para-infectious

Bickerstaff's brainstem encephalitis

Typically, BBE is a monophasic, post-infectious syndrome involving a triad of ophthalmoplegia, ataxia, and depressed level of consciousness. Electroencephalogram (EEG) abnormalities are common and, although MRI brain is usually normal, it can show scattered T2 hyperintensities in the brainstem and basal ganglia with limited enhancement and mild diffusion restriction.[20] In contrast to Miller-Fisher syndrome (MFS) and Guillain-Barre syndrome (GBS), BBE is associated with

hyperreflexia. However, peripheral motor axonal neuropathy and detection of anti-GQ1b antibodies have been reported in approximately two-thirds of patients with BBE. Intravenous immunoglobulin (IVIg) and/or plasma exchange may be considered in an attempt to expedite recovery although, overall, the prognosis is relatively favourable; a retrospective analysis of 62 cases reported 66% complete remission at 6 months.[21]

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a rare inflammatory disorder of the CNS causing destruction of myelin and cerebral white matter. Although more common in children, ADEM is well-recognised in adults. Patients may present 1-3 weeks after a viral prodromal illness or vaccination and symptoms can include a combination of fever, ataxia, confusion, seizures and/or coma. Characteristically, ADEM is a monophasic illness which progresses over days before reaching a plateau although relapse is reported in a minority of patients and a rare, fulminant form, known as acute haemorrhagic leukoencephalitis (AHLE) (Figure 3), is also recognised.[22]

The pathophysiology of ADEM is not fully understood but cell-mediated or antibody cross-reaction with myelin autoantigens are thought to occur in response to an environmental trigger or increased CNS vascular permeability due to inflammation post-vaccination or infection. Putative causative organisms include several viruses directly linked to rhomboencephalitis such as EBV, CMV, HSV, Human Herpes Virus 6 (HHV-6).

Typical MRI findings in ADEM include fleeting multi-focal asymmetrical white matter T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities with ‘open-ring’ contrast enhancement but no central restriction on diffusion-weighted imaging.[23] This has been said to have a ‘grass-fire appearance’ with relatively less mass effect than might be expected given the lesion size.

Involvement of the thalami, brainstem (Figure 3) and cerebral cortex may aid radiological differentiation from MS.[23] Initial treatment for ADEM is with intravenous methylprednisolone 1g over 3-5 days followed by plasma exchange or IVIg (0.4g/kg/day for 5 days) in steroid refractory cases. Cyclophosphamide can also be considered in fulminant ADEM. Oral steroids should be tapered over 6 weeks and vaccinations avoided for 6 months following treatment. Decompressive hemicraniectomy may be life-saving when cerebral oedema is refractory to medical treatment.[24]

Paraneoplastic syndromes

Paraneoplastic antibodies have been well-documented to cause rhomboencephalitis and discovery of new cell surface autoantibodies and characterisation of their respective clinical phenotypes is a rapidly expanding field. Table 2 lists paraneoplastic antibodies reported to be associated with rhomboencephalitis, tumour associations and treatment options.

Table 2 – Paraneoplastic antibodies associated with rhomboencephalitis

Antigen Location	**Antibody**	**Oncological Association**	**Treatment**
Intracellular	Anti-Hu (ANNA-1)	Small-cell lung cancer	Cancer targeted therapy +/- immunosuppression*
	Anti-Ri (ANNA-2)	Breast, lung	Cancer targeted therapy +/- immunosuppression
	Anti-Ma2	Testicular germ cell tumour	Cancer targeted therapy +/- immunosuppression
	Less common paraneoplastic anti-neuronal antibodies: anti-Yo, Anti-Tr, anti-amphiphysin,	*Breast, gynaecological, small-cell lung cancer and Hodgkin's lymphoma (anti-Yo); Hodgkin's lymphoma (anti-Tr); breast and small-cell lung cancer (anti-amphiphysin);*	*Cancer targeted therapy +/- immunosuppression*
Cell Surface	Anti-NMDA	Ovarian teratoma	Immunosuppression +/- cancer targeted therapy
	Anti-IgLON5	None currently	Immunosuppression
	Anti-glycine receptor	Breast, thymoma, Hodgkin's lymphoma	Immunosuppression +/- cancer targeted therapy
	Less common: anti-DPPX	*Lymphoma*	*Immunosuppression +/- cancer targeted therapy*

*Immunosuppression is usually with high dose steroids and either intravenous immunoglobulin (IVIg) or plasma exchange first line followed by rituximab or cyclophosphamide. ANNA = anti-neuronal nuclear antibody, DPPX = dipeptidyl-peptidase–like protein 6, IgLON5 = immunoglobulin-like cell adhesion molecule 5, NMDA = N-methyl-D-aspartate

Cell surface antibodies

Anti-NMDA receptor encephalitis

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common autoimmune cell surface-mediated encephalitis. It is characterised by a combination of dysautonomia, seizures, movement disorders and psychiatric symptoms. It is often associated with malignancy, particularly ovarian teratomas, but has also been described following HSV and varicella zoster virus encephalitis.[25 26]

Anti-NMDAR encephalitis has been associated rarely with rhomboencephalitis in adults although this appears to be a more frequent manifestation in the paediatric population. Despite the marked clinical features, brain MRI can frequently be normal and is recognised as a clinical-radiological paradox. However, T2 hyperintensities in the brainstem, mesial temporal lobes and posterior periventricular white matter with cranial nerve enhancement have been reported.[27] Paired serum and CSF antibody testing is recommended.

First-line treatment for NMDAR encephalitis is high dose steroids followed by IVIg or plasma exchange and escalation to cyclophosphamide or rituximab and/or introduction of a steroid-sparing agent as required. There may be clinical uncertainty whilst waiting for antibody test results but there is emerging evidence to support use of IVIg in some forms of encephalitis. Indeed, the question of whether there may be a role for prophylactic immunosuppression in HSVE patients to prevent development of secondary NMDAR antibodies has been raised,[26] and a UK-based, double-blinded randomised trial is currently underway to determine whether IVIg improves outcomes in children with infective or immune-mediated encephalitis (IgNiTE; ISRCTN15791925).

Immunoglobulin-like cell adhesion molecule 5 (IgLON5) receptor encephalitis

IgLON5 receptor is a neuronal cell adhesion protein of uncertain physiological function. Antibodies against IgLON5 trigger deposition of tau in the hypothalamus and tegmentum and are associated with HLA-DRB1*1001 and HLA-DQB1*0501. IgLON5 receptor encephalitis was first described in 2014 as a disorder of sleep, brainstem and hypothalamic function, movement (particularly chorea), cognition and a progressive supranuclear palsy-like syndrome. Typically, brainstem involvement causes bulbar dysfunction manifesting as dysphagia, sialorrhea, stridor or acute respiratory insufficiency. A retrospective analysis of 22 patients with anti-IgLON5 antibodies reported 81.8% had normal/non-specific brain MRI changes with mild brainstem and hippocampal atrophy in 13.7% and 4.5% respectively.[28] CSF was unremarkable with 50% showing only a mildly raised protein. Outcome was poor; 59% died of respiratory complications.

Anti-IgLON5 disease should be considered in rhomboencephalitis presenting on the background of sleep disorder, chorea, bulbar dysfunction or central hypoventilation. Early treatment with immunotherapy may prevent life-threatening acute respiratory failure and/or avoid further unnecessary investigations.[29]

Progressive encephalomyelitis with rigidity and myoclonus (PERM)

PERM is characterised by painful spasms, autonomic dysfunction, hyperekplexia, brainstem myoclonus and breathing problems;[30] it has been labelled 'stiff-person syndrome-plus' given the additional brainstem abnormalities. It has only recently been associated with anti-glycine receptor (anti-GlyR) antibodies and the clinical phenotype in the largest retrospective cohort of 52 patients included hyperekplexia, stiffness/spasms/rigidity, oculomotor disturbance and facial/bulbar motor involvement. This was followed by seizures, encephalopathy and cognitive defects. Respiratory failure occurred in 27%.[30] Brain MRI findings were relatively non-specific although a minority demonstrated bilateral temporal lobe hyperintensities. Continuous motor activity may be seen on

electromyography (EMG) and 6/29 showed spontaneous or stimulus-induced activity. CSF pleocytosis is typical and unmatched oligoclonal bands may be present.

Anti-GlyR antibodies should be requested in the serum and CSF in patients with suspected stiff-person syndrome and evidence of brainstem dysfunction. CSF antibody testing can be helpful when serum anti-GlyR antibodies are low (<1:20 dilution) and discussion with specialist neuro-immunology laboratories is encouraged. PERM has been associated infrequently with other antibodies including anti-DPPX (dipeptidyl-peptidase–like protein 6), anti-amphiphysin, and anti-GAD65 (glutamic acid decarboxylase-65) antibodies.[31]

Intracellular antibodies

Anti-Hu (anti-neuronal nuclear antibodies-1; ANNA-1) antibody is most commonly associated with small cell carcinoma which targets the cell nucleus. In 15% of patients it occurs secondary to an extra-thoracic malignancy. In the context of rhomboencephalitis, it preferentially affects the medulla causing dysphagia, dysarthria and central hypoventilation. In contrast, anti-Ma2 paraneoplastic syndrome typically affects the mesencephalon causing a vertical gaze palsy and being associated with T2-hyperintensities in the superior colliculi or periaqueductal grey region.[32] These features, particularly if accompanied by malignancy or risk factors including smoking, should raise the possibility of a paraneoplastic syndrome (PNS) rhomboencephalitis. Importantly, the PNS commonly precedes other clinical manifestations of malignancy, and if a cancer is not initially detected, ongoing screening is required for a minimum of 5 years.

CSF interrogation in PNS may yield a mild pleocytosis, but extended immunoblotting screens are usually required to search for all additional or atypical anti-neuronal antibodies in both serum and CSF. Of the three most common neuronal antibodies linked to rhomboencephalitis (anti-Hu, anti-Ri and anti-Ma2), anti-Ma2 has the most favourable prognosis following combination immunotherapy and tumour removal but prognosis is generally poor.

Neuroinflammatory causes

Neuro-Behçet's syndrome

Although diagnostic criteria are available, the diagnosis of Behçet's disease can be challenging (Table 3). Careful questioning regarding recurrent oro-genital ulceration and symptoms of iritis or erythema nodosum are necessary. Pathergy testing and HLA-B51 allele screening may be required. Retinal angiography is also recommended to look for retinal vasculopathy which is easily overlooked on routine ophthalmological examination.

Manifestations of neuro-Behçet's can be divided into a CNS inflammatory parenchymal disease with predilection for the corticospinal, spinothalamic and posterior column tracts and a non-parenchymal vascular form which typically presents as dural venous sinus thrombosis.

Radiologically, neuro-Behçet's favours the brainstem although may sometimes affect the diencephalon but the mechanism behind this predilection is unclear.[33] Acutely, T2- and FLAIR-weighted hyperintensities with corresponding hypo-/isointensities on T1 sequences predominate with patchy T1-gadolinium enhancement (Figure 5). A longitudinal myelitis-like, inflammatory lesion can be seen extending to the brainstem giving a distinct appearance known as the 'bagel sign' due to venous engorgement and/or acute blood products. Occasionally, brainstem and subcortical lesions may mimic multiple sclerosis.[33]

Table 3: International Study Group for Behçet's Disease Classification criteria. A definite diagnosis requires recurrent oral ulceration with at least two of the other findings in the absence of other clinical explanations.	
Finding	**Definition**
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or reliably described by the patient which recurred at least three times over a twelve-month period
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or reliably described by the patient
Eye lesions	Anterior or posterior uveitis or cells in the vitreous body on slit-lamp examination, or retinal vasculitis detected by an ophthalmologist
Skin lesions	Erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules not related to glucocorticoid treatment or adolescence
Positive pathergy test	Interpreted as positive by the physician at 24-48 hours

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder. 'Neurolupus' has myriad clinical manifestations including seizures, myelopathy, strokes, aseptic meningitis, psychosis and unexpected movement disorders including myoclonus and parkinsonism.[34] A prospective study of 7 patients with SLE-induced rhomboencephalitis reported headache, vertigo and reduced level of consciousness as the most common clinical features.[35] Microvasculopathy leads to ischaemia, antibody-mediated cell injury and cytokine-induced blood brain barrier permeability allowing leukocyte translocation and inflammation.

Radiologically, CNS lupus typically causes subcortical and periventricular white matter changes on MRI with diffuse T2 and FLAIR hyperintensities within the deep white matter, brainstem and

cerebellum.[35] Brainstem involvement is rare in SLE, although concomitant periventricular lesions necessitate consideration of the diagnosis.

Other demyelinating conditions

A number of demyelinating conditions may be associated with inflammatory brainstem lesions such as ADEM (discussed previously), multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) including anti-myelin oligodendrocyte (MOG) and anti-aquaporin-4 (AQP4) antibodies.

An area postrema syndrome may occur with clinical features such as intractable hiccups, nausea and vomiting which may appear in isolation or together with optic neuritis and myelitis to suggest neuromyelitis optica (NMO). NMO typically favours the dorsal region of the medulla and pons surrounding the fourth ventricle. Additional clues suggesting anti-MOG disease include an ADEM-like presentation, bilateral optic nerve involvement, cortical encephalitis and/or the presence of 'fluffy' brainstem appearances (30%).[36] Serological testing confirms the diagnosis with no current evidence for improved sensitivity with CSF testing suggesting predominantly extrathecal production.

Mimics

An awareness of the radiological mimics of rhomboencephalitis is important (Table 4 and Figure 6). The most common differential diagnosis is a primary intracerebral malignancy, particularly glioma. Additional investigations may therefore include CSF cytology and flow cytometry (assuming safe to proceed with lumbar puncture) and MR spectroscopy which may demonstrate raised choline/NAA (n-acetylaspartate) ratio suggestive of malignancy.

Table 4 – Rhomboencephalitis Mimics
Intra-axial neoplasms – primary intracerebral malignancy, CNS lymphomas, metastases
Tumefactive demyelination
Vascular: brainstem stroke, vasculopathies and advanced small vessel ischaemic changes
Central pontine myelinolysis or osmotic demyelination syndrome (ODS)
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)
Syringobulbia
Histiocytosis
Toxins – heroin-induced leukoencephalopathy, cocaine abuse, methylbromide, carbon monoxide poisoning or hyperammonaemia

Clinical approach

History

Key points to explore when taking a history of rhomboencephalitis include the following:

- A febrile illness may suggest infectious pathology (See Table 5)
- Enquiring about recreational drug use, particularly cocaine which can erode the surrounding skull base and sinuses creating a pathway from the nasal cavity to the brainstem
- Smoking history to assess the risk of PNS
- 'B' symptoms (fever, weight loss and night sweats) which could indicate an underlying lymphoma or TB
- A gynaecological history including post-menopausal bleeding/discharge, menstrual cycle changes, pelvic pain or bloating which may be associated with an underlying malignancy
- Outcomes of breast examinations/screening in females should be explored
- Males should be asked about testicular self-examination findings and investigated accordingly
- Sleep disorders such as obstructive sleep apnoea or parasomnias may suggest anti-IgLON5 disease
- Connective tissue disease symptoms should be probed including: mouth/genital ulcers, rash, arthralgias/myalgias, xerostomia/xerophthalmia, symptoms of iritis or serositis, Raynaud's and photosensitivity
- Discrete neurological relapses including features of myelitis or optic neuritis may suggest MS or NMOSD

Table 5 – Practical approach to history taking in infective rhomboencephalitis	
Specific Questions	**Infective Agent**
Have you consumed any unpasteurised cheeses or milks, cured meats, pâtés, smoked fish, cooked shellfish or non-supermarket ice creams recently?	***Listeria monocytogenes*** or ***brucellosis***
Are you taking any medications to suppress your immune system?	All but particularly **HHV-6** (human herpes virus-6) and ***Listeria monocytogenes***
Travel history: - Travel destination (including rural/urban) - Reason for traveling - Travel dates and time from returning to symptoms - Sexual history, including HIV risk factors and recreational drugs - Pre-travel vaccinations and prophylaxis - Animal contact (especially pigs, bats, dogs, cats) and mosquito/tick bites - Fresh water contact	- **Japanese encephalitis** (Pacific rim, eastern and southern Asia) - **Enterovirus-71** (Asian-Pacific countries) - **Scrub typhus** *(Southeast Asia, Indonesia, China, Japan, India, and northern Australia)* - **West Nile virus** *(Africa, the Middle East, Asia and Australia)* - **Rabies encephalitis** *(All continents except Antarctica)*
Any unwell contacts? Any children with viral infections including hand, foot and mouth?	**Enterovirus-71**
Any recent mouth or genital ulcers?	**HSV-1** and **HSV-2** *(note Behçet's or SLE can cause ulcers)*
Any recent sore throats or neck swelling?	**EBV** and **CMV**
Any diarrhoea, pain on swallowing (suggesting oesophageal ulcers), blurred or loss of night vision (suggesting retinitis), productive cough?	**CMV**

Examination

A complete systemic and neurological examination is required with attention paid to the following:

- Fever and lymphadenopathy may suggest infective causes such as EBV/CMV or an underlying malignancy/PNS
- Mouth/genital ulcers could suggest HSV, Behçet's or SLE
- Inspection of the nasal passage may reveal erosions suggesting portal of entry for infection
- Autonomic dysfunction (systolic blood pressure drop ≥20mmHg on standing, resting tachycardia, constipation and/or urinary retention) may suggest a cell surface-mediated PNS

- Movement disorders including orofacial dyskinesias, dystonias, chorea and stereotypies could suggest anti-NMDA receptor encephalitis or Japanese encephalitis.
- Breast examinations and testicular examinations should be carried out in females and males respectively to look for underlying malignancies
- Vertical gaze palsy may be associated with anti-Ma2 antibodies but, in combination with features of parkinsonism, could suggest anti-IgLON5 disease
- Hyperekplexia in response to auditory or tactile stimulation with rigidity (predominantly axial) may be a feature of PERM
- Skin changes such as erythema nodosum, butterfly/discoid rash, or pseudofolliculitis suggest autoimmune causes

Investigation and Management

Management of rhomboencephalitis is tailored to the cause although it may be pragmatic to consider broad spectrum anti-microbials including viral and listeria cover in all cases presenting acutely or sub-acutely with rhomboencephalitis pending initial investigation results. Table 6 illustrates a framework to guide appropriately tailored investigations.

Table 6 – Investigations to consider in rhomboencephalitis
Infectious
Blood Blood serology and/or polymerase chain reaction (PCR) (see Table 1 for full aetiological agents) Blood cultures (bacterial infections including *listeria*)
Cerebrospinal fluid (CSF) Microscopy, culture & sensitivity for *listeria*, T*B* and others (see Table 1) Standard viral PCR and EBV/CMV/HHV-6 /TB PCR if immunocompromised or on clinical suspicion Consider *Whipple* disease polymerase chain reaction Consider bacterial 16S rDNA real-time PCR for a broad bacterial screen
Other Stool cultures/rectal swabs (enterovirus-71) Nasal/throat swabs (viruses including SARS-CoV-2, enterovirus and influenza) Sputum sample or early morning urine for TB microscopy, culture and sensitivity †*If recent exotic foreign travel or atypical presentation discuss with infectious disease team or microbiology for rarer infections*
Paraneoplastic
Intracellular antibodies Anti-Hu, anti-Ri, anti-Ma2, anti-Yo, anti-Tr, anti-amphiphysin and anti-GAD65
Cell surface antibody Anti-NMDA, anti-IgLON5, anti-glycine and anti-DPPX
Searching for the underlying malignancy Lactate dehydrogenase and blood film Serum α-fetoprotein or β-human chorionic gonadotrophin CSF cytology and flow cytometry (ideally obtain 10mls) Imaging as appropriate including: ultrasound ovaries/testes, MRI pelvis, chest X-ray, mammogram, CT chest/abdomen/pelvis or CT-PET.
Rheumatological
Autoimmune profile Anti-nuclear antibody, complements, anti-double-stranded DNA, extractable nuclear antigen, lupus anticoagulant (not if on anticoagulation), anti-cardiolipin and anti-beta2-glycoprotein-1
Sarcoidosis Serum/CSF angiotensin converting enzyme, CSF soluble interleukin-2 and chest imaging
Neuro-Behçet's syndrome HLA-B51, retinal fluorescein angiography/indocyanine green angiography, skin biopsy and pathergy test
Sjögren's syndrome Schirmer's test, salivary gland/mucosal lip biopsy or technetium-99m scialoscintigraphy
Para-infectious
Acute disseminated encephalomyelitis Anti-MOG antibodies
Bickerstaff's brainstem encephalitis Ganglioside antibodies including anti-GQ1b
If ongoing diagnostic uncertainty, consider brain biopsy

Biopsy and other neurosurgical interventions

Brain biopsy, particularly in the brainstem, has been considered a high-risk procedure. However, emerging data suggest that safety has improved and brainstem biopsy can have considerable clinical utility in selected cases, particularly where malignancy is considered in the differential diagnosis or there is ongoing diagnostic uncertainty.[37 38] The risk of the procedure needs to be weighed against the benefit of diagnostic clarity, treatment optimisation and avoidance of iatrogenic harm e.g. due to unnecessary immunosuppression. Where there is diagnostic uncertainty in a rapidly deteriorating patient, we recommend early discussion with neurosurgical colleagues to consider a biopsy, particularly where a target lesion is identified.[39]

Urgent repeat neuroimaging is indicated if a patient with a known brainstem syndrome develops new signs or reduced level of consciousness. Complications including hydrocephalus or haemorrhage may warrant neurosurgical management.[6] This is particularly relevant where the underlying cause of rhomboencephalitis is infective, most especially listeria and TB.

Conclusion

Rhomboencephalitis is an uncommon neurological condition with potentially devastating sequelae, particularly if left untreated. A structured and pragmatic approach when faced with this neurological challenge is therefore required. A careful and complete assessment of the history together with systemic and neurological examination are crucial to guide prompt initiation of appropriate investigations and treatment, as well as, where appropriate, early involvement of neurosurgical colleagues.

Key points

- ⇒ Rhomboencephalitis typically presents with encephalopathy ± long tract signs, cranial nerve deficits and/or cerebellar dysfunction
- ⇒ Suspected infection should prompt enquiry about snorting cocaine which can create an artificial portal of entry
- ⇒ The most common cause is listeria and early, empirical treatment should be considered
- ⇒ Specialist review of MRI-brain scans can refine the differential diagnosis
- ⇒ Neurosurgical intervention including diagnostic biopsy and emergency treatment of hydrocephalus may be required

Further Reading

1) Jubelt B, Mihai C, Li TM, Veerapaneni P. Rhombencephalitis / brainstem encephalitis. Curr Neurol Neurosci Rep. 2011;11(6):543-52. doi: 10.1007/s11910-011-0228-5. PMID: 21956758.

2) Moragas, Mireia MD, Martínez-Yélamos, Sergio MD, Majós, Carles MD, et al. Rhombencephalitis, Medicine 2011;90(4):256-261. doi: 10.1097/MD.0b013e318224b5af

3) Kickingereder P, Willeit P, Simon T, et al. Diagnostic value and safety of stereotactic biopsy for brainstem tumors: a systematic review and meta-analysis of 1480 cases. *Neurosurgery* 2013;72(6):873-81. doi: 10.1227/NEU.0b013e31828bf445 [published Online First: 2013/02/22]

Competing interests

The authors have no competing interests to declare

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References

1. Dubow JS, Singer S, Segal AZ. Rhomboencephalitis due to cocaine-induced bony erosion of skull base. *Neurology* 2011;77(13):1313. doi: 10.1212/WNL.0b013e318230209a [published Online First: 2011/09/29]
2. Slifman NR, Gershon SK, Lee JH, et al. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. *Arthritis and rheumatism* 2003;48(2):319-24. doi: 10.1002/art.10758 [published Online First: 2003/02/07]
3. Ruggieri S, Logoteta A, Martini G, et al. Listeria monocytogenes-Induced Rhombencephalitis in a Patient With Multiple Sclerosis Treated With Dimethyl Fumarate. *JAMA Neurol* 2018;75(6):762-63. doi: 10.1001/jamaneurol.2018.0368 [published Online First: 2018/04/04]
4. Canham LJW, Manara A, Fawcett J, et al. Mortality from Listeria monocytogenes meningoencephalitis following escalation to alemtuzumab therapy for relapsing-remitting Multiple Sclerosis. *Mult Scler Relat Disord* 2018;24:38-41. doi: 10.1016/j.msard.2018.05.014 [published Online First: 2018/06/10]
5. Abbs A, Nandakumar T, Bose P, et al. Listeria rhomboencephalitis. *Pract Neurol* 2012;12(2):131-2. doi: 10.1136/practneurol-2011-000085 [published Online First: 2012/03/28]
6. Gerstein S, Gautam-Goyal P, Goyal S. A case of Listeria monocytogenes meningitis complicated by Hydrocephalus and Intraventricular hemorrhage: A review of treatment options and outcomes. *IDCases* 2020;19:e00704. doi: 10.1016/j.idcr.2020.e00704 [published Online First: 2020/04/01]
7. Hossain MZ, Akhaddar A, Turgut AT, et al. Brainstem Tuberculosis. In: Turgut M, Akhaddar A, Turgut AT, et al., eds. Tuberculosis of the Central Nervous System: Springer 2017:103-18.
8. NICE. Tuberculosis. 2016 doi: https://www.nice.org.uk/guidance/ng33
9. Rossi A, Martinetti C, Morana G, et al. Neuroimaging of Infectious and Inflammatory Diseases of the Pediatric Cerebellum and Brainstem. *Neuroimaging Clin N Am* 2016;26(3):471-87. doi: 10.1016/j.nic.2016.03.011 [published Online First: 2016/07/18]
10. Jubelt B, Mihai C, Li TM, et al. Rhombencephalitis / brainstem encephalitis. *Curr Neurol Neurosci Rep* 2011;11(6):543-52. doi: 10.1007/s11910-011-0228-5 [published Online First: 2011/10/01]
11. Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. *J Infect* 2012;64(4):347-73. doi: 10.1016/j.jinf.2011.11.014 [published Online First: 2011/11/29]
12. Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci* 2020;11(7):995-98. doi: 10.1021/acschemneuro.0c00122 [published Online First: 2020/03/14]
13. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of medical virology* 2020;92(6):552-55. doi: 10.1002/jmv.25728 [published Online First: 2020/02/28]
14. Wong PF, Craik S, Newman P, et al. Lessons of the month 1: A case of rhombencephalitis as a rare complication of acute COVID-19 infection. *Clin Med (Lond)* 2020 doi: 10.7861/clinmed.2020-0182 [published Online First: 2020/05/07]
15. Khoo A, McLoughlin B, Cheema S, et al. Postinfectious brainstem encephalitis associated with SARS-CoV-2. *J Neurol Neurosurg Psychiatry* 2020 doi: 10.1136/jnnp-2020-323816 [published Online First: 2020/07/09]
16. Ho M, Chen ER, Hsu KH, et al. An epidemic of enterovirus 71 infection in Taiwan. Taiwan Enterovirus Epidemic Working Group. *N Engl J Med* 1999;341(13):929-35. doi: 10.1056/NEJM199909233411301 [published Online First: 1999/09/25]

17. Solomon T, Dung NM, Kneen R, et al. Japanese encephalitis. *J Neurol Neurosurg Psychiatry* 2000;68(4):405-15. doi: 10.1136/jnnp.68.4.405 [published Online First: 2000/03/23]
18. Khanal D, Singh T, Rabinstein A. Epstein Barr Virus encephalitis in adults: a case series (P1.293). *Neurology* 2016;86(P1.293)
19. Fuller GN, Guiloff RJ, Scaravilli F, et al. Combined HIV-CMV encephalitis presenting with brainstem signs. *J Neurol Neurosurg Psychiatry* 1989;52(8):975-9. doi: 10.1136/jnnp.52.8.975 [published Online First: 1989/08/01]
20. Bulakbasi N, Kocaoglu M. Central nervous system infections of herpesvirus family. *Neuroimaging Clin N Am* 2008;18(1):53-84; viii. doi: 10.1016/j.nic.2007.12.001 [published Online First: 2008/03/06]
21. Odaka M, Yuki N, Yamada M, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barre syndrome. *Brain* 2003;126(Pt 10):2279-90. doi: 10.1093/brain/awg233 [published Online First: 2003/07/09]
22. Atherton DS, Perez SR, Gundacker ND, et al. Acute disseminated encephalomyelitis presenting as a brainstem encephalitis. *Clin Neurol Neurosurg* 2016;143:76-9. doi: 10.1016/j.clineuro.2016.02.014 [published Online First: 2016/02/24]
23. Sarbu N, Shih RY, Jones RV, et al. White Matter Diseases with Radiologic-Pathologic Correlation. *Radiographics : a review publication of the Radiological Society of North America, Inc* 2016;36(5):1426-47. doi: 10.1148/rg.2016160031 [published Online First: 2016/09/13]
24. Bourke D, Woon K. Craniectomy for acute disseminated encephalomyelitis. *Pract Neurol* 2020 doi: 10.1136/practneurol-2020-002705 [published Online First: 2020/09/27]
25. Schabitz WR, Rogalewski A, Hagemeister C, et al. VZV brainstem encephalitis triggers NMDA receptor immunoreaction. *Neurology* 2014;83(24):2309-11. doi: 10.1212/WNL.0000000000001072 [published Online First: 2014/11/08]
26. Armangue T, Spatola M, Vlagea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol* 2018;17(9):760-72. doi: 10.1016/S1474-4422(18)30244-8 [published Online First: 2018/07/28]
27. Hacohen Y, Absoud M, Hemingway C, et al. NMDA receptor antibodies associated with distinct white matter syndromes. *Neurol Neuroimmunol Neuroinflamm* 2014;1(1):e2. doi: 10.1212/NXI.0000000000000002 [published Online First: 2014/10/24]
28. Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. *Neurology* 2017;88(18):1736-43. doi: 10.1212/WNL.0000000000003887 [published Online First: 2017/04/07]
29. Montagna M, Amir R, De Volder I, et al. IgLON5-Associated Encephalitis With Atypical Brain Magnetic Resonance Imaging and Cerebrospinal Fluid Changes. *Front Neurol* 2018;9:329. doi: 10.3389/fneur.2018.00329 [published Online First: 2018/06/06]
30. Carvajal-Gonzalez A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. *Brain* 2014;137(Pt 8):2178-92. doi: 10.1093/brain/awu142 [published Online First: 2014/06/22]
31. Hara M, Arino H, Petit-Pedrol M, et al. DPPX antibody-associated encephalitis: Main syndrome and antibody effects. *Neurology* 2017;88(14):1340-48. doi: 10.1212/WNL.0000000000003796 [published Online First: 2017/03/05]
32. Dalmau J, Graus F, Villarejo A, et al. Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 2004;127(Pt 8):1831-44. doi: 10.1093/brain/awh203 awh203 [pii] [published Online First: 2004/06/25]
33. Uygunoglu U, Zeydan B, Ozguler Y, et al. Myelopathy in Behcet's disease: The Bagel Sign. *Ann Neurol* 2017;82(2):288-98. doi: 10.1002/ana.25004 [published Online First: 2017/07/28]
34. Joseph FG, Lammie GA, Scolding NJ. CNS lupus: a study of 41 patients. *Neurology* 2007;69(7):644-54. doi: 10.1212/01.wnl.0000267320.48939.d0 [published Online First: 2007/08/19]

35. Hirohata S, Matsueda Y, Arinuma Y, et al. FRI0385 Clinical characteristic features of brainstem encephalitis in neuropsychiatric systemic lupus erythematosus *Annals of the Rheumatic Diseases* 2018;77:726.
36. Weber MS, Derfuss T, Metz I, et al. Defining distinct features of anti-MOG antibody associated central nervous system demyelination. *Ther Adv Neurol Disord* 2018;11:1756286418762083. doi: 10.1177/1756286418762083 [published Online First: 2018/04/07]
37. Porretta E, Jefffrey SM, Jordan SL, et al. Safety and utility of brainstem biopsy and resection. *Journal of Neurology, Neurosurgery, and Psychiatry* 2016;87:e1.108–e1. doi: 10.1136/jnnp-2016-315106.196
38. Kickingereder P, Willeit P, Simon T, et al. Diagnostic value and safety of stereotactic biopsy for brainstem tumors: a systematic review and meta-analysis of 1480 cases. *Neurosurgery* 2013;72(6):873-81; discussion 82; quiz 82. doi: 10.1227/NEU.0b013e31828bf445 [published Online First: 2013/02/22]
39. Rice CM, Gilkes CE, Teare E, et al. Brain biopsy in cryptogenic neurological disease. *Br J Neurosurg* 2011;25(5):614-20. doi: 10.3109/02688697.2010.551677 [published Online First: 2011/04/20]

Figure Legends

Figure 1 – The rhombencephalon

Sagittal MRI-brain demonstrating the anatomy of the rhombencephalon or hindbrain**.** Highlighted structures include the pons (blue), medulla (red), cerebellum (green) and the mid-region of the fourth ventricle (orange).

Figure 2 – Listeria rhomboencephalitis

Sagittal T1-weighted MR brain scan reproduced with permission from Abbs et al Practical Neurology 2012;12:131-132

Figure 3 - Acute haemorrhagic leucoencephalitis

MRI brain T2WI (sagittal image) showed extensive brainstem involvement with hyperintense signal, reproduced with permission from Nabi et al, BMJ Case Reports 2016;2016:bcr2016217215

Figure 4 Seronegative autoimmune encephalitis

A & B) Axial T2 and Coronal FLAIR MRI demonstrating abnormal hyperintense signal in the pons, midbrain and also bilaterally within the hippocampi. C) Axial Post-Gd T1 MRI with patchy pontine enhancement (white arrow). D & E) Follow-up Axial T2 and Sagittal T1 MRI performed 22-months after first presentation demonstrating marked pontine atrophy (arrowhead) with bilaterally symmetrical linear hyperintensity within the pontocerebellar fibres (dotted arrows)

Figure 5 – Parenchymal brainstem neuro-Behçet's syndrome

Brain MRI shows lesions in the pons extending to bilateral middle cerebellar peduncles, which are hypointense on T1-weighted imaging (A), hyperintense on T2-weighted imaging (B), with

heterogeneous contrast enhancement (C) reproduced with permission from Yildiz et al BMJ Case Reports 2013;2013:bcr2013200738

Figure 6 – Rhomboencephalitis mimics

A) Lymphoma: Coronal FLAIR MRI - Abnormal signal hyperintensity demonstrated within the vermis and left paramedian vermis with minimal local mass effect. Lesion demonstrates abnormal restricted diffusion and homogenous enhancement (not shown) as expected in primary CNS lymphoma

B) Astrocytoma: Coronal T1 Post-Contrast MRI - Irregular peripherally enhancing and centrally necrotic lesion in the lower pons/upper medulla. Mild local mass effect with expansion of the involved structures.

C) and D) Osmotic demyelination syndrome: C) Axial Non-Contrast CT Head – Spherical hypodensity involving the central pons which is mildly expanded. D) Axial T2 – Well demarcated central pontine T2 hyperintensity with sparing of the periphery and the descending corticospinal tracts (white arrows)

E) and F) CLIPPERS: E) Axial T2 MRI – florid patchy and linear punctate hyperintensities demonstrated within the brainstem and bilaterally in the cerebellum with no associated oedema or local mass effect (white arrows). F) Sagittal T1 post contrast MRI Brain and upper cord – numerous enhancing punctate foci in the brainstem, cerebellum and the upper cervical spinal cord.