

Infectious encephalitis: mimics and chameleons

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Accepted 17 December 2018
Published Online First
16 March 2019



ABSTRACT

'Query encephalitis' is a common neurological consultation in hospitalised patients. Identifying the syndrome is only part of the puzzle. Although historically encephalitis has been almost synonymous with infection, we increasingly recognise parainfectious or postinfectious as well as other immune-mediated causes. We must also distinguish encephalitis from other causes of encephalopathy, including systemic infection, metabolic derangements, toxins, inherited metabolic disorders, hypoxia, trauma and vasculopathies. Here, we review the most important differential diagnoses (mimics) of patients presenting with an encephalitic syndrome and highlight some unusual presentations (chameleons) of infectious encephalitis.

INTRODUCTION

'Query encephalitis' is a common reason for neurological consultation in hospitalised patients. Clinically, infectious encephalitis is characterised by acute onset of fever, altered mental status, focal neurological deficits and generalised or focal seizures.¹ It can be difficult to identify a specific cause, which remains undetermined in up to half of cases.¹ Historically, encephalitis has been almost synonymous with direct infection, but we now recognise parainfectious or postinfectious causes, as well as non-infectious causes. We also have to distinguish encephalitis from other causes of encephalopathy, including systemic infection, metabolic derangements, toxins, inherited metabolic disorders, hypoxia, trauma, epilepsy, thromboembolic stroke and other vasculopathies. It is essential to narrow the differential diagnosis, since starting treatment promptly can improve outcome and avoid unnecessary testing and treatments. Here we review the most important differential diagnoses (mimics) of patients presenting with an encephalitic syndrome and highlight some

unusual presentations (chameleons) of infectious encephalitis.

INFECTIOUS ENCEPHALITIS

Viruses cause most cases of infectious encephalitis, but bacteria (especially intracellular organisms such as *Rickettsiae*), fungi and parasites are also important. When evaluating a patient with suspected central nervous system (CNS) infection, it is essential to determine why this individual, in this place, has developed this disease at this time² (box 1). Infectious encephalitis can be sporadic, as with herpes simplex virus, or can be epidemic, as with many arthropod-borne viruses.¹ Age, geography, season, immunocompetence and psychosocial factors define the range of potential pathogens. All patients with suspected encephalitis should be tested for HIV, which not only predisposes to CNS infection but itself can cause meningoencephalitis during primary infection.³

The pattern of neurological involvement also provides important clues. Herpes simplex virus type 1, for example, preferentially affects the mesial temporal lobes. Deep grey matter involvement more commonly results from some flavivirus infections, such as with Japanese encephalitis and West Nile virus. Brainstem encephalitis, characterised by cranial neuropathies, dysautonomia and myoclonus, results from infection with certain arthropod-borne viruses, enteroviruses, listeriosis, brucellosis and tuberculosis. Encephalomyelitis presenting with acute flaccid paralysis can occur with enteroviruses such as poliovirus and EV-71, as well as flaviviruses.

Any patient with suspected CNS infection should have a lumbar puncture, unless contraindicated. The cerebral spinal fluid (CSF) profile can confirm the presence of inflammation and help to distinguish between different infectious causes. A lymphocytic pleocytosis is typical of viral encephalitis, although



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To cite: Toledano M, Davies NWS. *Pract Neurol* 2019;**19**:225–237.

Box 1 Important questions to ask in patients presenting with encephalitis, modified from Solomon *et al*¹

- ▶ Current or recent febrile or influenza-like illness.
- ▶ Rash.
- ▶ Sick contacts.
- ▶ Travel history.
- ▶ Contact with animals/animal bites.
- ▶ Exposure to mosquito or tick bites.
- ▶ Contact with fresh water.
- ▶ Consumption of unpasteurised dairy products.
- ▶ HIV risk factors.
- ▶ Immunocompetence status.
- ▶ Altered behaviour or cognition and personality change.
- ▶ Recent vaccination.

Box 2 Herpes simplex encephalitis mimics

Infectious

- ▶ Varicella zoster virus.
- ▶ Human herpes virus 6 (in the immunocompromised).
- ▶ Enterovirus.
- ▶ West Nile virus.
- ▶ Neurosyphilis.
- ▶ Tuberculosis.

Non-infectious

- ▶ Glioma/lymphoma/metastatic malignancy.
- ▶ Vasculitis.
- ▶ Autoimmune limbic encephalitis.
- ▶ Unilateral posterior reversible encephalopathy syndrome.

polymorphonuclear cells may predominate early in the disease. Certain bacterial infections such as listeriosis, brucellosis and tuberculosis also show a lymphocytic predominance but these are usually associated with higher protein, a low CSF/plasma glucose ratio and an elevated CSF lactate.¹ The CSF profile of immune-mediated and inflammatory encephalitis also mimics that of viral encephalitis. An acellular CSF is rare in infectious encephalitis but can be found early on and is more common in immunosuppressed patients. CSF eosinophilia occurs in coccidioidomycosis and certain parasitic infections of the CNS.

Herpes simplex virus encephalitis is the most common cause of sporadic encephalitis. Most cases are caused by herpes simplex virus type 1, but around 10% are caused by type 2.¹ The most distinctive presenting features are fever, disorientation, aphasia and behavioural disturbances, and up to a third of patients have convulsive seizures.¹

Neuroimaging can be negative acutely, but by 48 hours, over 90% of patients have MR brain imaging abnormalities and sensitivity approaches 100% at 3–10 days.⁴ T2-weighted and fluid-attenuated inversion recovery (FLAIR) images show markedly asymmetric but usually bilateral abnormalities in the limbic system, medial temporal lobes, insular cortices and inferolateral frontal lobes. Restricted diffusion on diffusion-weighted imaging (DWI) may be especially sensitive for early changes.¹ Although fairly characteristic, neuroimaging is not 100% specific, and clinicians should be aware of important imaging mimics (box 2) (figure 1).

CSF herpes simplex virus PCR is both highly sensitive and specific and usually establishes the diagnosis but can be negative if obtained acutely.¹ Repeated CSF examination 24–72 hours later is usually diagnostic.

NEUROLOGICAL CONDITIONS THAT MIMIC INFECTIOUS ENCEPHALITIS

We divide the mimics into parainfectious/postinfectious and non-infectious causes, although there is some

overlap. For example, autoimmune encephalitis can be triggered by infection but also occurs with malignancy, and although acute disseminated encephalomyelitis (ADEM) is generally considered to be post-infectious, there is not always an identified definitive infectious trigger.

Parainfectious and postinfectious encephalopathies

ADEM and acute haemorrhagic encephalomyelitis

ADEM is usually a monophasic, inflammatory demyelinating disorder of the CNS. It is more common in children but can occur in all ages.⁵ It is characterised by the abrupt onset of neurological symptoms days to weeks following infection or immunisation.⁵ Although there is not always a clearly identified precipitant, most cases have a non-specific flu-like illness preceding the onset of neurological symptoms.

Without a clear history of antecedent infection or vaccination, it can be difficult to distinguish ADEM from infectious encephalitis on purely syndromic grounds. ADEM is polysymptomatic and multifocal in presentation with symptoms and signs evolving over hours to days. Encephalopathy, optic neuritis and long tract signs are common. Most patients develop depressed level of consciousness ranging from lethargy to coma. CSF findings resemble those of viral encephalitis.⁵ Neuroimaging usually shows bilateral and asymmetric areas of increased signal in the subcortical white matter, brainstem, cerebellum, periventricular white matter and deep grey matter.⁵ The lesions vary in number and size and may enhance with gadolinium.⁵

Acute haemorrhagic encephalomyelitis is considered a hyperacute and more fulminant variant of ADEM. Like ADEM, it is commonly triggered by infection or vaccination. Brain imaging usually shows haemorrhagic lesions in the white matter.⁶ CSF examination often shows polymorphonuclear cells as well as numerous red blood cells (in the absence of a traumatic tap).

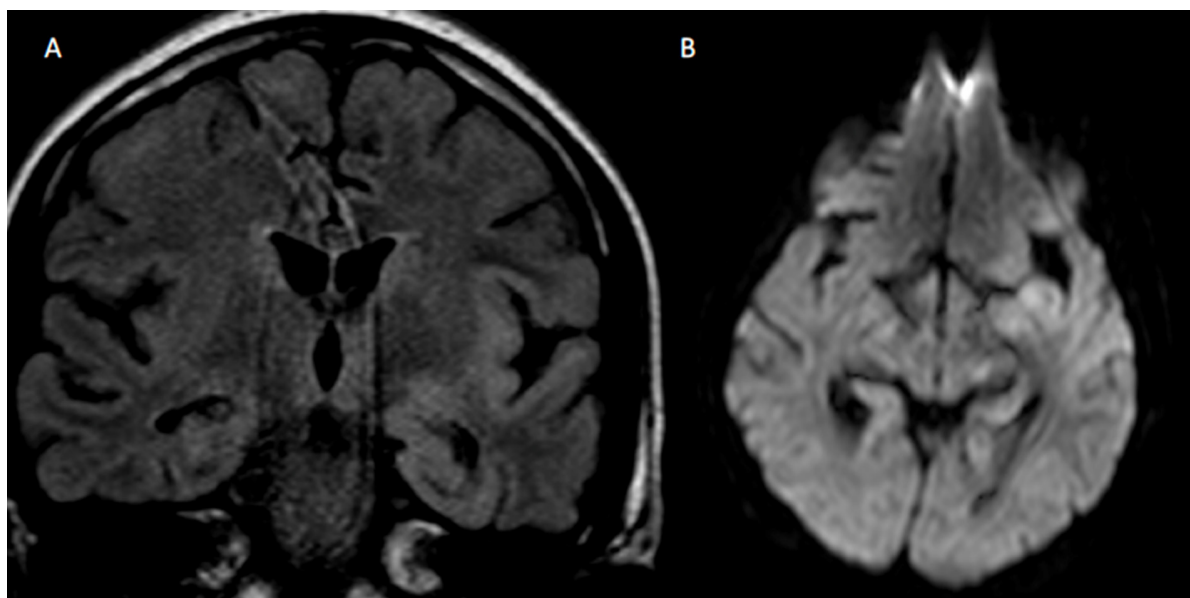


Figure 1 A young man presented with subacute cognitive decline, mood disorder and unwitnessed generalised tonic-clonic seizure. CSF examination showed a pleocytosis. The initial clinical diagnosis was herpes simplex virus encephalitis. Serological tests confirmed neurosyphilis. Brain imaging shows hyperintensity in left mesial temporal lobe on coronal T2 FLAIR (A) and restricted diffusion on axial diffusion-weighted imaging (B). FLAIR, fluid-attenuated inversion recovery.

Haemophagocytic lymphohistiocytosis syndrome

Haemophagocytic lymphohistiocytosis is a syndrome of excessive inflammation due to abnormal immune activation, probably caused by a lack of normal down-regulation of activated macrophages and lymphocytes.⁷ It can be either familial or sporadic. Systemic infection, rheumatological conditions or malignancy are common triggers in both familial and sporadic cases, and it is commonly associated with immunodeficiency syndromes. Although it usually affects infants, it can develop in children and adults of all ages. Clinically, it presents as a febrile illness with multiorgan dysfunction. Up to a third of patients have neurological involvement, including seizures, encephalopathy and focal deficits.⁷

In patients where neurological findings dominate the clinical picture, infectious encephalitis is likely. In the vast majority of cases, however, neurological symptoms are preceded by weeks of systemic symptoms. Cytopenias develop in up to 80% of patients. Serum ferritin is commonly elevated up to and above 10 000 µg/L. Liver function abnormalities and associated hypertriglyceridaemia and coagulation abnormalities are very common. MR brain scan abnormalities are non-specific and include parameningeal infiltration, subdural collections and necrotic changes. Findings consistent with posterior reversible encephalopathy syndrome are also very common. The CSF protein is frequently elevated, and half of cases have a lymphocytic pleocytosis. Histopathology from bone marrow, liver, spleen or lymph nodes may show haemophagocytosis. Elevated soluble CD25 (soluble interleukin-2 receptor alpha) and reduced natural killer cell function

support the diagnosis but may be available only at specialty laboratories.⁷

Influenza-related encephalopathy/encephalitis and acute necrotising encephalopathy

Influenza-related encephalitis/encephalopathy is a rapidly progressive encephalopathy that develops days after the onset of the first symptoms of influenza.⁸ Its pathophysiology remains unclear, and neither direct viral infection of the CNS nor a postinfectious inflammatory process appears to cause the condition. CSF studies are often normal, although a small number of cases have elevated CSF protein or mild pleocytosis. Similarly, there is only rarely any direct evidence of viral invasion on CSF and histopathology. The disease tends to affect children younger than 5 years of age, but there have been isolated cases in adults.^{8,9}

Several neuroimaging abnormalities may occur, ranging from scattered white matter abnormalities to diffuse brain oedema, but these changes are not specific. A more distinct imaging pattern is reversible focal swelling and restricted diffusion in the corpus callosum. This pattern can occur with influenza and other infections, as well as in certain metabolic disorders. It is usually associated with a benign course. This clinicoradiological syndrome is termed 'mild encephalitis/encephalopathy with reversible splenial lesion' (figure 2).¹⁰ Another pattern associated with influenza and other infections manifests as bilateral necrosis of the thalami and other regions, including the brainstem, cerebellum and cerebral white matter.⁸ This syndrome is termed 'acute necrotising encephalopathy' and has a more severe clinical course and worse prognosis.

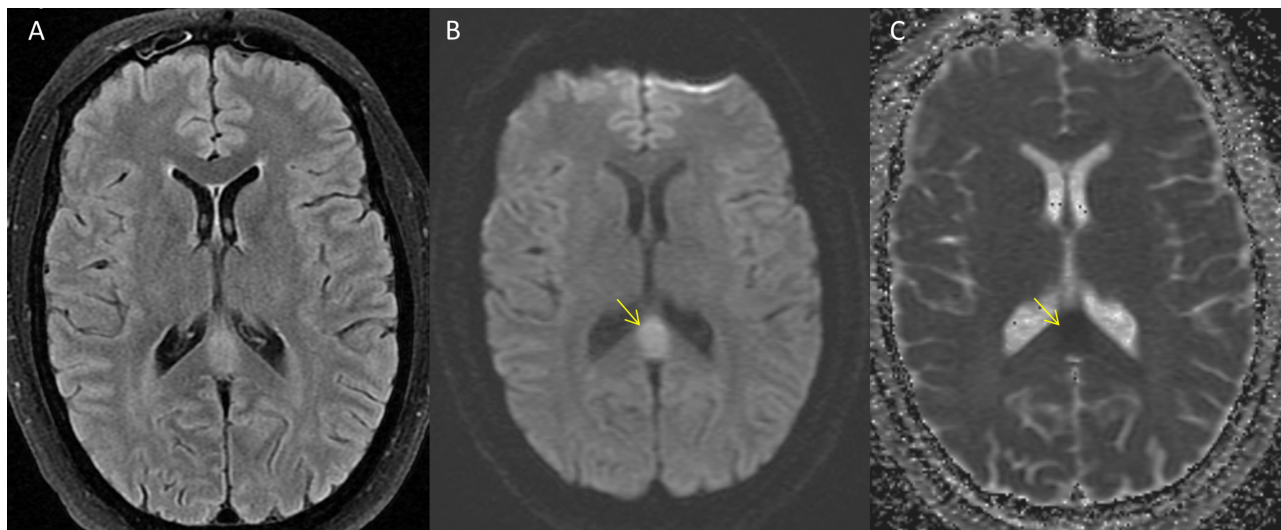


Figure 2 A patient with varicella zoster virus meningoencephalitis presenting with fever, headache and mild encephalopathy, which resolved with treatment. Brain imaging shows T2 fluid-attenuated inverse recovery hyperintensity in the splenium of the corpus callosum (A) with associated restriction on corresponding diffusion-weighted imaging (B) and apparent diffusion coefficient MAP (C). This clinicoradiographical picture has been named mild encephalitis/encephalopathy with reversible splenial lesion.

Familial and recurrent cases of acute necrotising encephalopathy following infection have been linked to mutations in Ran-binding protein 2.

Cerebral malaria

Cerebral malaria is a clinical syndrome defined as an otherwise unexplained encephalopathy in patients with malaria parasitaemia. It is almost always associated with *Plasmodium falciparum* infection. Risk factors include young age, pregnancy, HIV seropositivity and splenectomy.¹¹ In adults, cerebral malaria is more common in non-immune individuals than those living in endemic areas.¹¹ Cerebral malaria should be suspected in travellers returning from endemic regions who present with unexplained fever, even if they have been taking antimalarial prophylaxis.

Clinically, it presents with a prodrome of irregular fevers, malaise, abdominal pain, headache, anorexia, vomiting followed by encephalopathy, seizures and coma. In adults, neurological symptoms develop 7 days after symptom onset and rapidly evolve to coma. There are often signs of brainstem dysfunction. Retinal changes are very common in children and include macular and extramacular whitening, as well as orange or white discolouration of blood vessels representing areas of parasite sequestration.¹¹ Retinal haemorrhages are also very common in children and occur in 15% of adults.¹¹ CSF is usually normal or near normal. Associated haematological and metabolic abnormalities such as hypoglycaemia, anaemia, thrombocytopenia and acidosis are common. The diagnosis is made by examining thick and thin blood films, which may be negative initially especially in those who have been taking antimalarial prophylaxis.

Non-infectious encephalitis

Autoimmune encephalitis associated with paraneoplastic or neuronal surface antibodies

The term autoimmune encephalitis describes a heterogeneous group of neurological disorders associated with antineuronal autoantibodies.¹² These can be subdivided into two major groups based on the location of the target antigen. The first includes the classic paraneoplastic disorders, which are associated with antibodies targeting intracellular antigens (table 1). These antibodies are strongly associated with underlying malignancy but are not pathogenic. The second group is associated with antibodies targeting neuronal surface antigens (table 2). These antibodies are likely pathogenic and, importantly, patients in this group respond to immunotherapy. Cancer associations are variable but still relevant, as is the case between ovarian teratomas and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.¹³ A growing body of literature suggests that autoimmune encephalitis can occur as a parainfectious or postinfectious phenomena, best described in cases of anti-NMDAR following HSV encephalitis.¹³

The clinical spectrum of autoimmune encephalitis is highly variable. There are some well-described syndromes such as anti-NMDAR encephalitis and the limbic encephalitis associated with antibodies to leucine-rich-glioma-inactivated-1, a component of the voltage-gated potassium channel complex. Note, however, that many patients with autoimmune encephalitis do not present with a well-defined syndrome.¹³ The clinical spectrum of phenotypes associated with known antibodies continues to expand, and new antibodies are discovered. In addition, we increasingly recognise that there are well-described

Table 1 Antibodies to intracellular antigens

Antibody	Oncological association	Frequency of tumour	Response to immunotherapy	Neurological manifestations
ANNA-1 (anti-Hu)	Small-cell carcinoma.	>90%	Poor	Limbic, cortical encephalitis. Autonomic neuropathies, sensory neuropathy and other peripheral neuropathies.
ANNA2 (anti-Ri)	Small-cell carcinoma, breast adenocarcinoma and bladder cancer.	>60%	Poor	Brainstem encephalitis (opsoclonus–myoclonus, laryngospasm, trismus and cranial neuropathy) and cerebellar degeneration.
ANNA3	Small-cell carcinoma.	>60%	Poor	Limbic and brainstem encephalitis, sensory and sensorimotor neuropathies and myelopathy.
PCA2	Small-cell carcinoma.	>90%	Poor	Brainstem or limbic encephalitis and cerebellar degeneration.
Ma1, Ma2	Testicular (Ma2); breast, colon and testicular (Ma1).	>90%	Moderate	Ma2 Limbic encephalitis, diencephalitis, brainstem encephalitis; Ma1 and Ma2 brainstem encephalitis and cerebellar degeneration.
CRMP-5	Small-cell carcinoma and thymoma.	>75%	Poor	Encephalitis. Optic neuritis and retinitis, myelopathy, neuropathy and Lambert–Eaton myasthenic syndrome.
Amphiphysin	Small-cell carcinoma and breast adenocarcinoma.	>90%	Poor	Limbic encephalitis. Myelopathy, stiff-man syndrome and cerebellar degeneration.
GAD65	Thymoma; neuroendocrine tumours, breast or colon adenocarcinoma.	<10%	Moderate	Stiff-person syndrome, stiff-person phenomena, brainstem encephalitis and cerebellar degeneration.
GFAP	None described to date.		Good	Meningoencephalomyelitis, headache, papillitis and cerebellar ataxia.

ANNA, antineuronal nuclear antibody; CRMP-5, collapsin response mediator protein-5; GAD65, glutamic acid decarboxylase 65; GFAP, glial fibrillar acidic protein; PCA, Purkinje cell cytoplasmic antibody.

clinical phenotypes in patients in whom antibodies have not yet been identified.¹¹ In general, clinicians should suspect autoimmune encephalitis in patients presenting with subacute progressive encephalopathy and prominent new-onset psychiatric symptoms.¹³ New-onset seizures and cryptogenic status epilepticus can be part of the initial presentation but can also be the sole presenting symptom.¹² Abnormal movements, including orolingual and limb dyskinesias, dystonia, myoclonus and hyperekplexia occur more frequently in autoimmune encephalitis than in infectious encephalitis. Although autoimmune encephalitis can be preceded by a viral prodrome including fevers, fever is not a predominant feature.

MR scan of brain can be normal or show non-specific abnormalities; however, it may show findings suggesting limbic encephalitis, namely increased signal on T2-weighted FLAIR imaging of the mesial temporal lobes.¹³ In autoimmune limbic encephalitis, there is preferential involvement of the amygdala and hippocampus, and bilateral involvement is more symmetrical than in herpes simplex virus encephalitis. Restricted diffusion on DWI and haemorrhagic changes also suggest herpes simplex virus encephalitis. EEG can show generalised slowing or may identify subclinical seizures or non-convulsive status epilepticus. Finding extreme delta brush pattern on EEG strongly suggests anti-NMDAR encephalitis.¹⁴ CSF can show mild pleocytosis (usually fewer than 100 cells) sometimes with

transient elevations in oligoclonal bands or IgG index but it can also be normal.

Detecting a known autoantibody helps to establish the diagnosis and determines the need to screen for underlying malignancy. Conversely, failure to detect a known antibody does not rule out autoimmune encephalitis.

Bickerstaff's encephalitis

Bickerstaff's brainstem encephalitis is characterised by subacute onset of progressive impairment of consciousness, ataxia and bilateral, relatively symmetrical ophthalmoparesis.¹⁵ Bickerstaff's encephalitis usually follows an infectious prodrome, has a monophasic course and has a good prognosis. Additional clinical features include bilateral facial palsies, bulbar palsy, hyper-reflexia and pupillary abnormalities. MR scan of brain is usually normal, but a quarter of patients have brainstem abnormalities on T2-weighted and FLAIR imaging. Most patients have an elevated CSF protein, and half of patients have a mild lymphocytic pleocytosis.^{13 15} Finding anti-GQ1b antibodies in the serum supports the diagnosis, but this test is negative in up to 32% of patients.¹⁵

The absence of fever at the onset of neurological symptoms and the relative symmetry of findings usually help distinguish Bickerstaff's encephalitis from infectious rhombencephalitis. Nonetheless, it is important to rule out infectious causes.

REVIEW

Table 2 Antibodies targeting neuronal cell surface and synaptic proteins

Antibody	Oncological association	Frequency of tumour	Response to immunotherapy	Neurological manifestations
VGKC complex LGI1	Thymoma, small-cell lung cancer.	<10%	Good	Limbic encephalitis, hyponatremia and faciobrachial dystonic seizures.
CASPR2	Thymoma	40%	Good	Isaacs syndrome, Morvan's syndrome and limbic encephalitis.
NMDAR	Ovarian teratomas, testicular germinoma and neuroblastoma.	Varies with age, sex, and ethnicity	Good	Psychiatric disturbances, dyskinesias, catatonia, central hypoventilation and autonomic instability, and opsoclonus–myoclonus.
AMPA	Thymic tumours, lung carcinoma and breast adenocarcinoma.	70%	Good	Limbic encephalitis and nystagmus.
GABA-A receptor	Thymoma, small-cell lung cancer and rectal cancer.	40%	Good	Status epilepticus, epilepsy partialis continua, psychosis, behavioural disturbances, orolingual dyskinesias and chorea.
GABA-B receptor	Small-cell lung carcinoma and other neuroendocrine neoplasia.	70%	Good	Limbic encephalitis and orolingual dyskinesias.
mGluR5 receptor	Hodgkin's lymphoma.	>90%	Good	Cerebellar ataxia and limbic encephalitis (Ophelia syndrome).
GlyR	Thymoma, breast cancer and Hodgkin's lymphoma.	<10% of published cases	Moderate	Progressive encephalomyelitis with rigidity and myoclonus, oculomotor disturbances, dysautonomia, hyperekplexia and respiratory failure.
DPPX	None described to date.		Moderate	Encephalitis, sleep disturbances, myoclonus, hyperekplexia, dysautonomia and gastrointestinal dysmotility.
IgLON5	None described to date.		Poor	Non-REM parasomnias, REM sleep behaviour disorder, apnoea, stridor and cognitive decline.

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; GABA-A, γ -aminobutyric acid--A; GABA-B, γ -aminobutyric acid-B; GlyR, glycine receptor; LGI1, leucine rich glioma inactivated protein 1; mGluR5, metabotropic glutamate receptor 5. NMDAR, N-methyl-D-aspartate receptor; REM, rapid eye movement; VGKC, voltage gated potassium channel;

A similar clinical picture can occur with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), a recently described inflammatory disorder affecting the brainstem. CLIPPERS is associated with a fairly distinctive imaging pattern characterised by punctate and curvilinear gadolinium enhancement 'peppering' the pons and adjacent structures including the midbrain, cerebellar peduncles and cerebellum.¹⁶

Vasculitis

CNS vasculitis usually presents with headache and subacute progressive encephalopathy. Its classification depends on whether it is confined to the CNS or is secondary to an infection or systemic inflammatory disease.¹⁷ Primary CNS vasculitis lacks the symptoms and signs of systemic involvement that usually accompany secondary vasculitis, such as fever, weight loss, oligoarthropathy, ocular inflammation or rash. Inflammatory markers are also usually normal. Most systemic vasculitides can cause secondary CNS vasculitis.¹⁷ Other systemic autoimmune or inflammatory

conditions can also rarely cause secondary CNS vasculitis; these include systemic lupus erythematosus, Sjögren's syndrome, cryoglobulinaemia and rheumatoid arthritis.¹⁷ Although most patients with these conditions already have a diagnosis before developing neurological symptoms, CNS vasculitis can rarely be the first manifestation of their disease. Serological testing, such as antinuclear antibody or antineutrophil cytoplasmic antibody, can help establish the diagnosis.

MR scan of brain usually shows multiple ischaemic infarcts of different ages in the cortex, subcortical white matter and deep grey matter. Other features include leptomeningeal enhancement, microhaemorrhages and diffuse white matter lesions that suggest small vessel ischaemia.¹⁷ Diencephalic and mesencephalic involvement is common in Behçet's disease, an inflammatory vasculitis that usually presents with recurrent oral and urogenital ulcers, uveitis, pathergy, oligoarthropathy and recurrent thrombosis. Isolated neurological disease is rare and can mimic infectious brainstem encephalitis.¹⁸

Angiography showing stenosis or ectasia with 'beading' of intracranial vessels can confirm a vasculopathy, but this finding has a sensitivity of only about 60%.¹⁷ Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning may be very valuable in identifying systemic large vessel vasculitis, but it still has no clear role in detecting CNS disease.¹⁷ Definitive diagnosis is made by histopathological analysis, but note that a biopsy, particularly 'blind' biopsy of the meninges, does not always yield a definitive diagnosis.¹⁷

Susac's syndrome or retinocochleocerebral vasculopathy is an immune-mediated microangiopathy characterised by subacute encephalopathy, sensorineural deafness, tinnitus and branch-retinal occlusion.¹⁹ MR scanning typically shows multiple lesions involving the central fibres of the corpus callosum, as well as the periventricular and subcortical white matter. Retinal fluorescein angiography that confirms branch-retinal occlusion can help to establish the diagnosis.¹⁹

Neuromyelitis optica (NMO) spectrum disorder

NMO spectrum disorder classically presents with attacks of bilateral or rapidly sequential optic neuritis and/or longitudinally extensive myelitis.²⁰ Non-opticospinal involvement, however, is now well described. This includes relatively NMO-specific syndromes such as intractable nausea and hiccoughs due to area postrema involvement, or symptomatic narcolepsy due to hypothalamic involvement, but rarely, non-opticospinal involvement can present with encephalopathy and seizures.²⁰

Brain lesions seen in NMO spectrum disorder typically occur in aquaporin-4 (AQP-4)-rich sites such as the area postrema, hypothalamus or periaqueductal brainstem. However, they may also occur in the deep white matter where they may have associated cloudy enhancement, or an appearance similar to lesions seen with posterior reversible encephalopathy syndrome.²⁰ Longitudinal extensive corpus callosum lesions are also seen. Leptomeningeal involvement is exceedingly rare and should prompt reconsideration of the diagnosis. CSF shows primarily a lymphocytic pleocytosis, although there may be elevated neutrophil and eosinophil counts. Detecting autoantibodies to AQP-4 confirms a diagnosis, although 20%–30% of patients are seronegative.²⁰ A subset of patients with seronegative NMO spectrum disorder disease has antibodies to myelin oligodendrocyte glycoprotein (MOG). MOG-IgG associated encephalomyelitis is now considered a disease entity in its own right, presenting with recurrent (although occasionally monophasic) optic neuritis, myelitis, rhombencephalitis, as well as ADEM-like presentations.²¹

Systemic lupus erythematosus

The reported range and prevalence of neuropsychiatric manifestation of systemic lupus erythematosus

varies widely, depending on the population studied, the case definition used or the methods used for screening.²² Patients may develop seizures, psychosis and encephalopathy, although they are rare.²² The pathophysiology is unclear, and it is still unclear whether the neuropsychiatric manifestations are secondary to vasculopathy, coexisting neural auto-antibodies, infection or toxic-metabolic effects from treatment. Neurological symptoms tend to occur after systemic manifestations of systemic lupus erythematosus, although sometimes they can be the first manifestation of the disease.²² Neuroimaging can be normal, show non-specific white matter abnormalities, leptomeningeal enhancement or findings consistent with posterior reversible encephalopathy syndrome. Elevated serum antinuclear antibody is sensitive but non-specific. Antibodies to double-stranded DNA or smith nuclear antigen, along with decreased complement can provide supportive evidence. Antiphospholipid antibodies, antibodies to beta-2-glycoprotein and lupus anticoagulant are associated with antiphospholipid syndrome, which occurs in up to 20% of patients with systemic lupus erythematosus and is characterised by recurrent ischaemic infarction, seizures and cognitive decline.²³

Neurosarcoidosis

Nervous system manifestations of sarcoidosis include cranial neuropathies, myeloradiculopathies including cauda equina syndrome, peripheral neuropathy and myopathy.²⁴ Some cases present with headache, encephalopathy, psychosis and seizures. Neurosarcoidosis occurs in approximately 5%–10% of patients with systemic sarcoidosis but can occur in up to 17% of patients without detectable systemic evidence of sarcoidosis.²⁴ Although its onset is usually subacute, it can rarely present as an acute illness.

Neuroimaging characteristics are protean and non-specific, although leptomeningeal and pachymeningeal enhancement correlates well with disease activity.²⁴ Serum ACE has poor sensitivity and specificity. CSF ACE concentration is also insensitive and only moderately specific. A CSF CD4/CD8 T cell ratio above 5 supports the diagnosis.²⁵ The definitive diagnosis of sarcoidosis requires histopathological demonstration of non-necrotising granulomas in affected tissue, but it may be challenging to obtain a suitable sample. FDG-PET may identify systemic sarcoidosis and help to identify a potential biopsy site.

Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)

The syndrome of transient HaNDL is a self-limiting condition that can mimic encephalitis. As the name suggests, patients usually present with episodes of severe migrainous headache, along with transient neurological deficits and lymphocytic pleocytosis.²⁶ The most frequent neurological deficits are hemiparesis,

hemisensory disturbances and aphasia, although there may be visual disturbances and encephalopathy.²⁶ In addition to the CSF pleocytosis, there is often a raised CSF opening pressure. Although it is usually monophasic, many patients have repeated episodes over the duration of the illness, which typically lasts 3 weeks but can last up to 3 months.²⁶

Toxic and metabolic encephalopathies

Septic encephalopathy

Septic encephalopathy is the most common cause of infection-associated encephalopathy and develops in up to 70% of patients presenting with sepsis.²⁷ Clinically, patients with septic encephalopathy develop confusion and inattention progressing to delirium, stupor and coma. There are usually no focal findings, and seizures occur less frequently than in patients with encephalitis. Myoclonus and asterixis, typical of metabolic encephalopathies, are rare. Neuroimaging is usually normal, although there may be scattered punctate ischaemic changes, presumably due to in situ thrombosis.²⁷ CSF is usually entirely normal or shows a mild elevation in protein.

Toxic syndromes

Many patients with ingestion/overdose have presenting clinical features suggesting encephalitis, including mental status changes and fever. Identifying a specific toxic syndrome can help to establish a diagnosis, especially when there is no immediately available history of exposure (table 3).²⁸ Serotonin syndrome, for example, is characterised by hyperthermia, flushing, agitation, hypertonia, myoclonus and clonus that is both spontaneous and induced (especially in the legs).²⁸ Neuroleptic malignant syndrome, which presents with hyperthermia, rigidity, bradykinesia and stupor, is another well-described toxidrome.²⁸ Withdrawal states, such as those from withdrawal from alcohol and other GABA-ergic substances can present with tachycardia, hyperthermia, confusion and hallucinations.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome is a heterogeneous clinical syndrome characterised by acute neurological symptoms arising in the setting of blood pressure fluctuations, autoimmune and metabolic disorders, infection, eclampsia, transplantation or exposure to immunosuppressant or cytotoxic drugs.²⁹ The sudden onset of seizures, encephalopathy and, less commonly, focal deficits can mimic encephalitis, especially when the encephalopathy arises in the setting of infection (usually systemic but rarely in the CNS). Neuroimaging can be very helpful in this regard as posterior reversible encephalopathy syndrome has a fairly distinct radiographic appearance. Classically, brain imaging shows relatively symmetrical signal abnormality involving the cerebral white matter of both cerebral hemispheres, particularly in the parieto-occipital regions. Other brain regions are also frequently affected, including the fronto-temporal lobes, basal ganglia, brainstem and cerebellum. Although less common, there may be gadolinium enhancement and restricted diffusion (figure 3). CSF commonly shows an elevated protein and sometimes a mild lymphocytic pleocytosis.

Mitochondrial encephalomyopathies

Mitochondrial diseases have a wide clinical spectrum. Of the various mitochondrial disorders that can present in adulthood, mitochondrial encephalomyopathy with lactic acidosis and stroke-like symptoms (MELAS) is the one most likely to mimic infectious encephalitis. MELAS belongs to a group of mitochondrial diseases caused by point mutations in mitochondrial DNA. Clinically, it presents with non-ischaemic stroke-like episodes resulting in hemiparesis, hemianopia, aphasia, encephalopathy and cortical blindness.³⁰ Focal and generalised seizures also occur.³⁰ Patients commonly have a prior history of migraine headaches, vomiting, muscle weakness, psychiatric disturbances, growth failure and hearing loss, but these may be masked by the more dramatic stroke-like presentation.³⁰ Fever can trigger these

Table 3 Toxic syndromes

Toxic syndrome (causative agents)	Vitals	Pupils	Other findings
Sympathomimetic (cocaine, amphetamines and pseudoephedrine)	Hyperthermia, tachycardia, tachypnoea and hypertension.	Mydriasis	Agitation, paranoia, diaphoresis, tremors and seizures.
Anticholinergic (tricyclic antidepressants, antihistamines and scopolamine)	Hyperthermia, tachycardia, tachypnoea and hypertension.	Mydriasis	Hypervigilance, agitation, dry flushed skin and urinary retention.
Serotonin syndrome (MAOIs, SSRIs, SNRIs, tricyclic antidepressants, triptans, tramadol and dextromethorphan)	Hyperthermia, tachypnoea, tachycardia and hypertension.	Mydriasis	Agitation, tremor, diaphoresis, hyperreflexia, clonus, myoclonus. Findings more prominent in lower extremities.
Neuroleptic syndrome (typical and atypical antipsychotics)	Hyperthermia, tachypnoea, tachycardia and hypertension.	Normal	Decreased level of awareness, mutism, lead-pipe rigidity and hyporeflexia.

MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

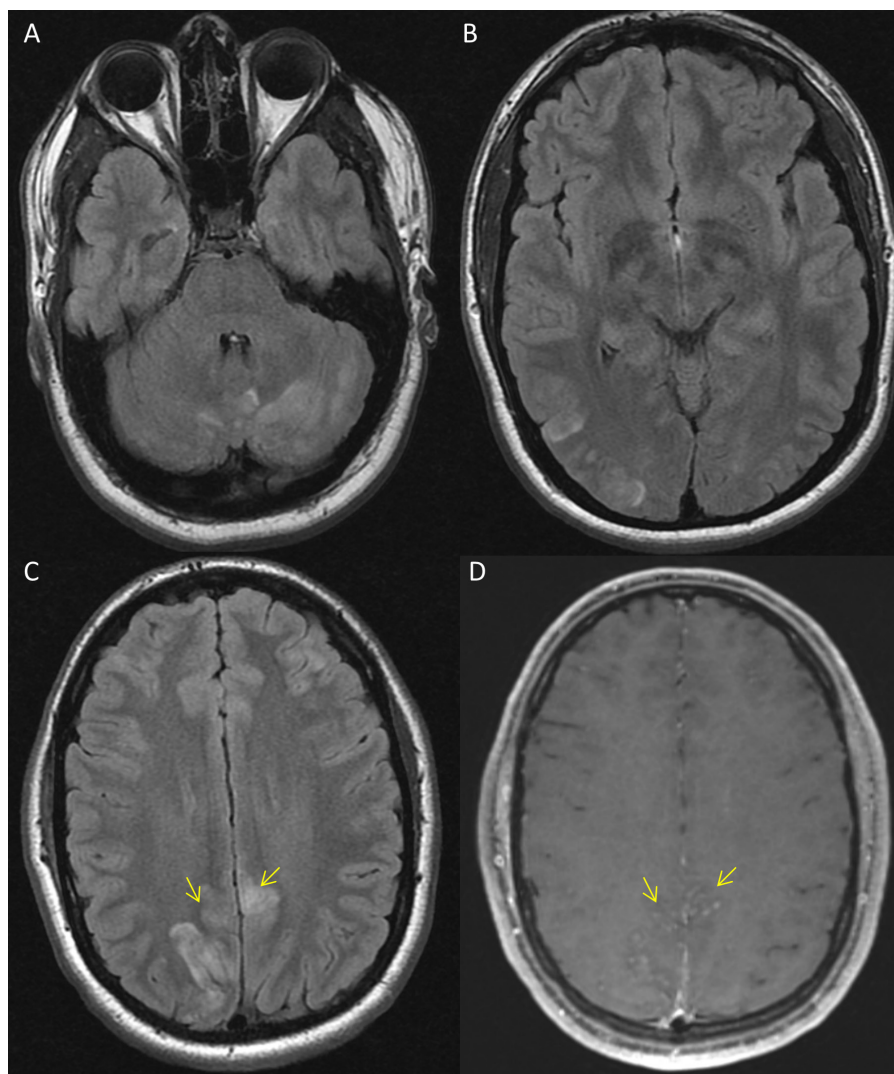


Figure 3 A young man presenting with seizures and encephalopathy a week after a viral illness. Blood pressure was labile at presentation. Brain imaging shows characteristic T2 fluid-attenuated inverse recovery hyperintensities in the cerebellar (A) and subcortical (B and C) white matter. The lesions in the parasagittal frontal lobes show associated punctate gadolinium enhancement (C and D). Repeated MR scan of brain 3 weeks later was normal (not shown). The clinicordiological features are in keeping with the posterior reversible encephalopathy syndrome.

stroke-like events, and its presence may lead clinicians to suspect encephalitis.

Routine neuroimaging during an acute attack usually shows hyperintense T2 lesions in the grey and subcortical white matter, predominantly affecting temporal, parietal and occipital regions.³¹ The lesions cross vascular territories and spare the deep white matter. Although they may have associated enhancement, there is usually little to no restriction observed.³¹ CSF is usually acellular but may show a mild lymphocytic pleocytosis. Certain clues such as short stature, myopathy, cardiac abnormalities and family history of recurrent stroke should raise suspicion.³⁰ Blood and CSF lactate tends to be elevated during an acute attack.³⁰ MR spectroscopy showing a large lactate peak and low ratio of N-acetyl aspartate to creatine is supportive.³¹ The definitive diagnosis is through mitochondrial DNA studies.

Neoplasia

Temporal lobe tumours

Metastatic and primary CNS tumours can rarely present as acute encephalitis.³² Temporal lobe involvement may suggest herpes simplex virus encephalitis, but the MRI signal changes associated with tumours differ from viral encephalitis in that they tend to be unilateral and contiguous, although bilateral involvement can occur with gliomatosis or lymphomatosis cerebri (figure 4). Repeating imaging a few days after presentation can also be very helpful, as imaging changes in herpes simplex virus encephalitis evolve rapidly compared with those associated with neoplasm.

Intravascular large cell lymphoma

Intravascular large cell lymphoma is a rare subtype of large cell lymphoma that affects small blood vessels. Virtually any organ can be involved but CNS and cutaneous involvement is common, particularly in Western

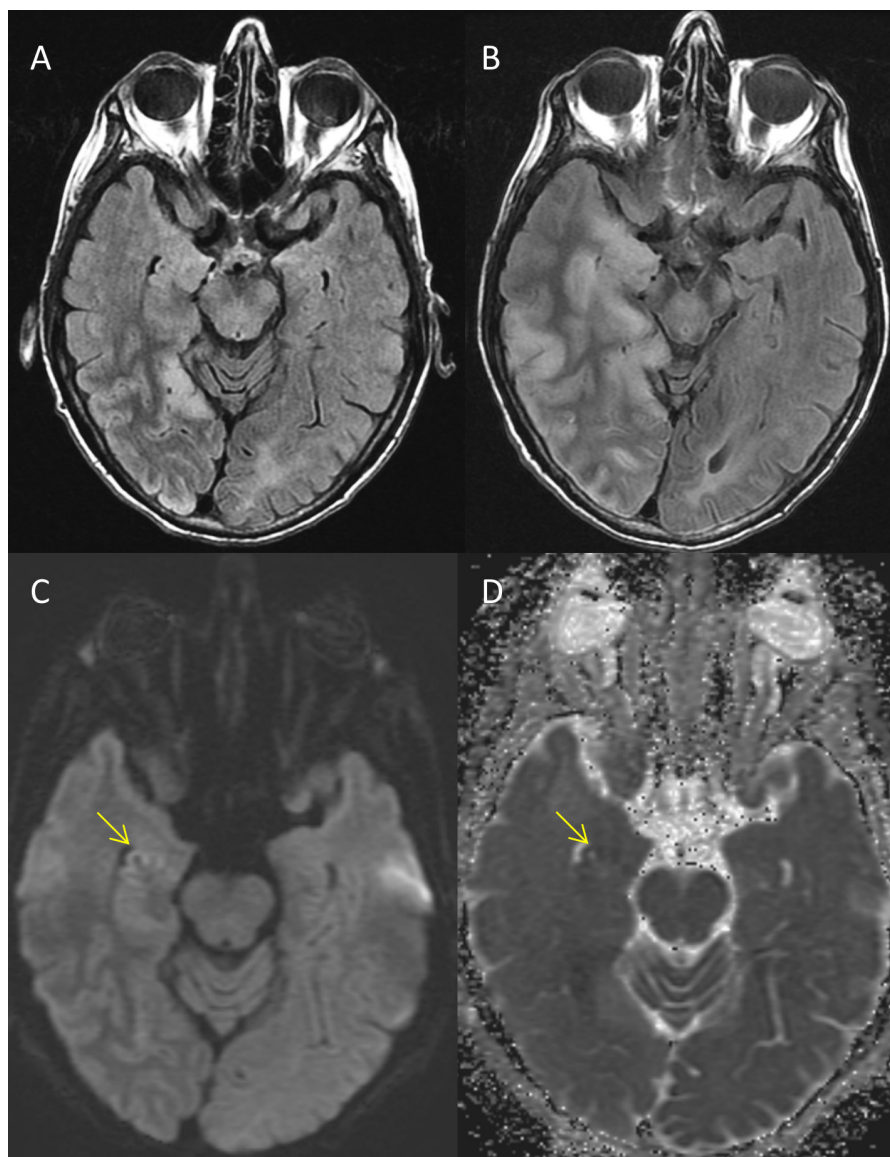


Figure 4 A patient presenting with seizures and encephalopathy. Brain imaging shows T2 fluid-attenuated inverse recovery (FLAIR) hyperintensity in the right mesiotemporal structures (A) with associated cortical restriction on corresponding diffusion-weighted imaging and apparent diffusion coefficient map (C and D, arrows). An MR scan of brain, repeated 3 weeks later due to persistent encephalopathy (D), shows significant expansion of the T2 FLAIR signal abnormality in the right cerebral hemisphere. Brain biopsy was consistent with gliomatosis cerebri.

countries.³³ Neurologically, it presents as a rapidly progressive encephalopathy. Constitutional B symptoms are very common as are skin manifestations.³³ Serum lactate dehydrogenase and beta-2-microglobulin are frequently elevated but are non-specific.³³ Neuroimaging can be normal or show bilateral but asymmetrical signal change involving subcortical white matter and deep grey matter structures. There may be associated gyriform, perivascular or homogeneous gadolinium enhancement, as well as restricted diffusion.

Stroke-like migraine attacks after cranial radiation (SMART)

SMART is a rare syndrome that occurs years after successful treatment of CNS neoplasia with therapeutic cranial irradiation. Clinically, it presents with

recurrent attacks of headache associated with seizures, confusion and focal deficits.³⁴ Neuroimaging shows increased T2 signal and swelling of cortical gyri with associated gadolinium enhancement within a previous radiation field.³⁴ Both the neurological deficits and imaging abnormalities usually reverse but permanent sequelae are possible (figure 5).

UNUSUAL PRESENTATIONS OF INFECTIOUS ENCEPHALITIS (CHAMELEONS)

Paralytic rabies and viral acute flaccid paralysis

Rabies virus is usually transmitted to humans by bites from animal vectors. There are two clinical forms of the disease. Encephalitic rabies is by far the most common, and it occurs in 80% of cases³⁵; paralytic

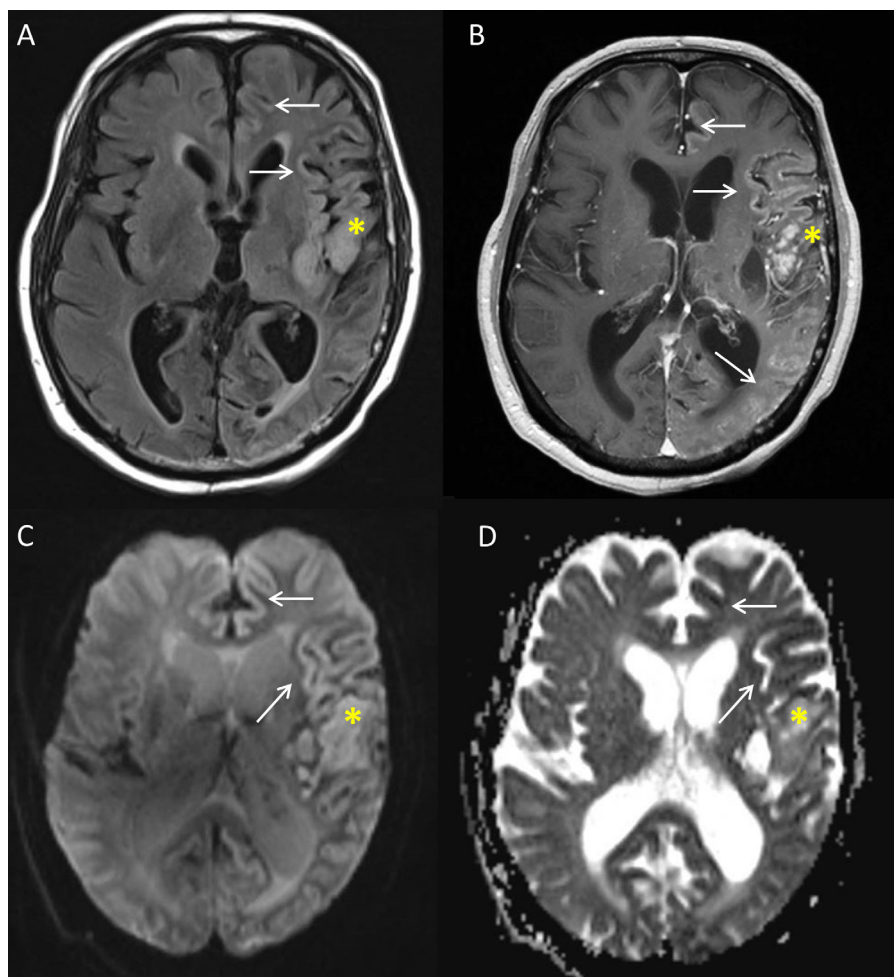


Figure 5 a patient with a history glioblastoma multiforme treated with chemoradiation 2 years before, presenting with a 2-day history of headache, aphasia and right hemiparesis. Brain imaging shows fluid-attenuated inverse recovery imaging hyperintensity and swelling (A, arrows) with associated gadolinium enhancement (B) and minimal restriction on corresponding diffusion-weighted imaging (C) and apparent diffusion coefficient MAP (D). An asterisk marks residual tumour.

rabies occurs in 20% of cases.³⁵ Typically, the onset of clinical disease is between 20 days and 90 days from the time of exposure, but there have been documented incubation periods longer than a year. The earliest neurological manifestations are usually paraesthesia, pain and pruritus near the site of exposure.

- In encephalitic rabies, this is followed by episodes of hyperexcitability, hallucinations, confusion and dysautonomia punctuated by periods of lucidity. Hydrophobia is a distinct clinical feature. Progressive neurological deterioration leads to paralysis, coma and death.
- In paralytic rabies by contrast, there is early prominent weakness that initially may affect only the bitten limb but invariably progresses to involve other limbs and bulbar muscles.³⁵ Sphincter dysfunction, pain, piloerection and sensory disturbances also occur. Hydrophobia is rare. Survival is longer, but patients eventually progress to coma and death. Clinically, paralytic rabies may resemble Guillain-Barré syndrome. A history of exposure to an animal bite may not always be clearly established. Symptoms at the local site, asymmetry,

piloerection and early bladder dysfunction help differentiate it from Guillain-Barré syndrome.

Other viruses that can present with flaccid paralysis include poliovirus, other enteroviruses (EV-70, EV-71 and EV-68)³⁶ and West Nile virus.³⁷ The presentation is usually asymmetric and preceded by a viral prodrome with or without meningismus. The MR scan of spine usually shows short segmental and longitudinally extensive spinal cord lesions. These preferentially involve the grey matter and are associated with haemorrhagic necrosis.^{36 37}

Symptomatic CSF HIV viral escape

Patients with HIV on combined antiretroviral therapy (cART) can present with neurological symptoms in the setting of suppressed peripheral viraemia and normal CD4 counts but 'discordant' elevation of CSF HIV RNA. Clinically, these patients tend to present with progressive cognitive decline, behavioural changes, ataxia, apraxia and focal deficits.³⁸ Occasionally, they can present acutely with encephalopathy and seizures. MR scan of

brain shows fairly symmetrical signal abnormalities in the cerebral, brain stem and cerebellar white matter with or without enhancement.³⁸ CSF can be normal or show mildly elevated protein and white blood cell counts. However, this disorder is characterised by dissociation between CSF and plasma virus concentrations. Those with complete plasma viral suppression have detectable CSF HIV RNA, while in those with low but measureable plasma, viral loads have CSF concentrations that is at least a log order different. Genotypic analysis of the CSF virus often shows resistance to components of the cART regimen.³⁸ Optimisation of the cART regimen usually results in clinical and radiological improvement.

Immune reconstitution inflammatory syndrome

CNS immune reconstitution inflammatory syndrome is defined by a pathological inflammatory response to either a previously treated (paradoxical) or a previously undiagnosed (unmasked) opportunistic infection.³⁹ Immune reconstitution inflammatory syndrome results from the restoration of a dysregulated immune response against pathogen-specific antigens. In the setting of HIV, it is characterised by paradoxical clinical deterioration following initiation of cART. Although immune reconstitution inflammatory syndrome can occur in the setting of HIV alone, it more commonly occurs in response to an opportunistic organism such as *Mycobacterium tuberculosis*, *Cryptococcus neoformans* or JC virus (the agent responsible for progressive multifocal leukoencephalopathy).³⁹ Paradoxical worsening, manifesting altered consciousness, focal deficits, cranial neuropathies and seizures, occurs on average 3–5 weeks after starting treatment but can develop months after treatment.³⁹ Brain imaging varies depending on the underlying infection, but associated gadolinium enhancement is common.

The histopathological hallmark of immune reconstitution inflammatory syndrome is CD8 T cell predominant inflammatory infiltrate along with evidence of underlying infection. CD8 T cell predominant infiltrates also develop in CD8 encephalitis, a rapidly progressive, sometimes fulminant, encephalitic illness that may occur in HIV seropositive patients on cART. These patients have no evidence of occult CNS infection, although some have shown concurrent CSF viral escape at the time of their illness.⁴⁰ Brain imaging usually shows extensive bilateral grey and white matter signal abnormality with associated perivascular gadolinium enhancement.⁴⁰

Varicella zoster virus (VZV) vasculopathy

VZV can cause a vasculopathy affecting both large and small cerebral blood vessels.⁴¹ Clinicians should suspect VZV vasculopathy in a patient with a recent history of herpes zoster or varicella infection who presents with stroke or altered mental status. The absence of the characteristic rash does not rule out VZV vasculopathy, especially in immunocompromised and HIV seropositive patients. The diagnosis is confirmed with VZV

Box 3 Infectious causes of vasculopathy

- ▶ Varicella zoster virus.
- ▶ Neurosyphilis.
- ▶ Tuberculosis.
- ▶ Nocardiosis.
- ▶ Angioinvasive fungal infections (eg, aspergillosis, fusariosis and zygomycosis).
- ▶ Cryptococcosis.

PCR. In patients with negative PCR, finding evidence of intrathecal synthesis VZV-specific IgG (measured with comparison with serum using an antibody index) is diagnostic.⁴¹ Box 3 includes other infectious causes of vasculopathy.

Atypical presentations of herpes simplex encephalitis

Immunocompromised patients with herpes simplex virus encephalitis can present with fewer prodromal symptoms and neurological deficits than those with preserved immune response.⁴² Absence of CSF pleocytosis is also more common in the immunosuppressed as is more widespread brain involvement, including brainstem and cerebellum.⁴² Extratemporal involvement, including of the brainstem, can also occur in HSV encephalitis secondary to herpes simplex virus type 2.¹

CONCLUSION

There is a broad differential diagnosis for a patient presenting with possible encephalitis. Infectious causes are common, but parainfectious and postinfectious, as well as non-infectious causes may also occur. Clinicians should also consider non-inflammatory encephalopathies secondary to systemic infection, toxins and metabolic disorders.

Key points

- ▶ Encephalitis is characterised by acute onset of fever, altered mental status, focal neurological deficits and generalised or focal seizures.
- ▶ CNS infection is a common cause of encephalitis, but immune-mediated causes are increasingly recognised.
- ▶ Non-inflammatory encephalopathies (related to systemic infection, metabolic disorders or toxins) can cause a similar clinical syndrome.
- ▶ Infectious encephalitis sometimes presents subacutely and without fever, making it more difficult to recognise.

Acknowledgements Thanks to Dr Christopher Carswell, consultant neurologist, and Dr Anastasia Gontsarova, consultant neuroradiologist, Imperial College NHS Trust, for sharing figure 1.

Contributors MT and NWSD contributed equally to the drafting of this manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or

not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Commissioned. Externally peer reviewed by Tom Solomon, Liverpool, UK, and Mark Ellul, Liverpool, UK.

REFERENCES

- 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;64:347–73.
- Davies N, Thwaites G. Infections of the nervous system. *Pract Neurol* 2011;11:121–31.
- Newton PJ, Newsholme W, Brink NS, *et al.* Acute meningoencephalitis and meningitis due to primary HIV infection. *BMJ* 2002;325:1225–7.
- Granerod J, Davies NW, Mukonoweshuro W, *et al.* Neuroimaging in encephalitis: analysis of imaging findings and interobserver agreement. *Clin Radiol* 2016;71:1050–8.
- Wingerchuk DM, Weinshenker BG. Transverse myelitis, and neuromyelitis optica. *Continuum* 2013;19:944–67.
- van der Knaap M, Valk J. Acute disseminated encephalomyelitis and acute hemorrhagic encephalomyelitis. *Magnetic resonance of myelination and myelin disorders*. 3rd edn. New York: Springer, 2005.
- Janka GE, Lehmborg K. Hemophagocytic syndromes—an update. *Blood Rev* 2014;28:135–42.
- Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. *Curr Opin Neurol* 2010;23:305–11.
- Goenka A, Michael BD, Ledger E, *et al.* Neurological manifestations of influenza infection in children and adults: results of a national British surveillance study. *Clin Infect Dis* 2014;58:775–84.
- Shah S, Keil A, Gara K, *et al.* Neurologic complications of influenza. *J Child Neurol* 2014;29:NP49–NP53.
- Postels DG, Birbeck GL, malaria C. Cerebral malaria. *Handb Clin Neurol* 2013;114:91–102.
- Toledano M, Pittock SJ, Epilepsy A. Autoimmune epilepsy. *Semin Neurol* 2015;35:245–58.
- Graus F, Titulaer MJ, Balu R, *et al.* A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391–404.
- Schmitt SE, Pargeon K, Frechette ES, *et al.* Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;79:1094–100.
- Wakerley BR, Uncini A, Yuki N, *et al.* Guillain-Barré and Miller Fisher syndromes—new diagnostic classification. *Nat Rev Neurol* 2014;10:537–44.
- Pittock SJ, Debruyne J, Krecke KN, *et al.* Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *Brain* 2010;133:2626–34.
- Scolding NJ. Central nervous system vasculitis. *Semin Immunopathol* 2009;31:527–36.
- Miller JJ, Venna N, Siva A. Neuro-Behçet disease and autoinflammatory disorders. *Semin Neurol* 2014;34:437–43.
- Buzzard KA, Reddel SW, Yiannikas C, *et al.* Distinguishing Susac's syndrome from multiple sclerosis. *J Neurol* 2015;262:1613–21.
- Flanagan EP, Weinshenker BG. Neuromyelitis optica spectrum disorders. *Curr Neurol Neurosci Rep* 2014;14:483.
- Kitley J, Woodhall M, Waters P, *et al.* Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. *Neurology* 2012;79:1273–7.
- Hanly JG. Diagnosis and management of neuropsychiatric SLE. *Nat Rev Rheumatol* 2014;10:338–47.
- Roldan JF, Brey RL. Neurologic manifestations of the antiphospholipid syndrome. *Curr Rheumatol Rep* 2007;9:109–15.
- Stern BJ, Aksamit A, Clifford D, *et al.* Neurologic presentations of sarcoidosis. *Neurol Clin* 2010;28:185–98.
- Marangoni S, Argentiero V, Tavolato B. Neurosarcoidosis. Clinical description of 7 cases with a proposal for a new diagnostic strategy. *J Neurol* 2006;253:488–95.
- Gómez-Aranda F, Cañadillas F, Martí-Massó JF, *et al.* Pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis. A report of 50 cases. *Brain* 1997;120(Pt 7):1105–13.
- Ziaja M. Septic encephalopathy. *Curr Neurol Neurosci Rep* 2013;13:383.
- Holstege CP, Borek HA. Toxidromes. *Crit Care Clin* 2012;28:479–98.
- Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol* 2015;14:914–25.
- El-Hattab AW, Adesina AM, Jones J, *et al.* MELAS syndrome: clinical manifestations, pathogenesis, and treatment options. *Mol Genet Metab* 2015;116:4–12.
- Saneto RP, Friedman SD, Shaw DW. Neuroimaging of mitochondrial disease. *Mitochondrion* 2008;8:396–413.
- Whitley RJ, Cobbs CG, Alford CA, *et al.* Diseases that mimic herpes simplex encephalitis. Diagnosis, presentation, and outcome. niaD collaborative antiviral Study Group. *JAMA* 1989;262:234–9.
- Ponzoni M, Ferreri AJ, Campo E, *et al.* Definition, diagnosis, and management of intravascular large B-cell lymphoma: proposals and perspectives from an international consensus meeting. *J Clin Oncol* 2007;25:3168–73.
- Lim SY, Brooke J, Dineen R, *et al.* Stroke-like migraine attack after cranial radiation therapy: the smart syndrome. *Pract Neurol* 2016;16:406–8.
- Jackson AC. Rabies. *Neurol Clin* 2008;26:717–26.
- Maloney JA, Mirsky DM, Messacar K, *et al.* MRI findings in children with acute flaccid paralysis and cranial nerve dysfunction occurring during the 2014 enterovirus D68 outbreak. *AJNR Am J Neuroradiol* 2015;36:245–50.
- Petersen LR, Brault AC, Nasci RS. West Nile virus: review of the literature. *JAMA* 2013;310:308–15.
- Ferretti F, Gisslen M, Cinque P, *et al.* Cerebrospinal fluid HIV escape from antiretroviral therapy. *Curr HIV/AIDS Rep* 2015;12:280–8.
- Johnson TP, Nath A. New insights into immune reconstitution inflammatory syndrome of the central nervous system. *Curr Opin HIV AIDS* 2014;9:572–8.
- Lescure FX, Moulignier A, Savatovsky J, *et al.* CD8 encephalitis in HIV-infected patients receiving cART: a treatable entity. *Clin Infect Dis* 2013;57:101–8.
- Nagel MA, Gilden D. Update on varicella zoster virus vasculopathy. *Curr Infect Dis Rep* 2014;16:407.
- Tan IL, McArthur JC, Venkatesan A, *et al.* Atypical manifestations and poor outcome of herpes simplex encephalitis in the immunocompromised. *Neurology* 2012;79:2125–32.