Central nervous system infection: Radiological patterns

Overview
Infections of the central nervous system (CNS) can be highly debilitating and life threatening. A favourable prognosis relies on rapid recognition and early targeted treatment. Imaging plays a pivotal role in diagnosis and in assessing treatment response. Unfortunately, the overlap of disease patterns and radiological entities, together with the evolution of CNS infections, for example the emergence of multi-drug resistance and HIV, often makes diagnosis difficult or delayed. We aim to provide a pragmatic approach to adult CNS brain infections by reviewing common imaging patterns. Salient clinical and radiological features will be highlighted to differentiate from non-infectious disease mimics. Finally, we shall recognise the particular difficulties of diagnosing and monitoring CNS infection in the immunocompromised patient.

Approach
CNS infections have considerable radiological overlap with non-infectious disease. Correlation with patients’ demographic, clinical presentation and other investigations is essential. CT is limited in diagnosis; its main role is to provide rapid assessment of emergency complications such as hydrocephalus, raised intracranial pressure and haemorrhage. MRI is the primary study for detailed characterisation. Important sequences include: Fluid attenuated inversion recovery (FLAIR), T2-weighted, T1-weighted post-gadolinium and diffusion weighted imaging (DWI). We recommend classifying the imaging pattern into two broad categories: 1) diffuse and 2) focal. Within these groups it is important to delineate involved anatomical compartments, for example, meninges versus parenchyma. Defining whether the disease is multifocal also matters, as this implies haematogenous spread as opposed to a single focus which may signify local spread. Finally, serial imaging is vital. The evolution of imaging appearances not only helps to narrow differentials but follow-up imaging is essential to assess treatment response.

Diffuse pattern
Extra-axial
Extra-axial infections include meningitis and empyema. It is vital to review the paranasal sinuses, mastoid air cells and middle ear, as infection can spread from these sites.

Meningitis
Diagnosis of meningitis is primarily based on clinical findings like fever and signs of meningeal, plus laboratory tests, such as CSF analysis. Imaging is neither sensitive nor specific for meningitis; its main role is to judge risk of herniation from lumbar puncture and to assess complications such as hydrocephalus, venous thrombosis and ischaemia. There are, however, MR imaging findings which support the diagnosis. Abnormal subarachnoid hyper-intense signal can occur on FLAIR due to increased CSF protein, although this can be artefactual or present in other conditions like subarachnoid haemorrhage. Restricted diffusion in the cerebral sulci is similarly not specific but is more prevalent in bacterial as opposed to viral meningitis. Abnormal enhancement of the pia occurs in about 50% of patients. Fine, linear enhancement along the sulci is typical in bacterial and viral meningitis while thick, nodular enhancement in the basal cisterns is suggestive of tuberculosis (TB) or a non-infectious aetiology such as sarcoidosis and carcinomatous meningitis. Basal TB leptomeningitis is associated with an oblitative proximal intracranial arteriopathy, with infarcts most commonly in the basal ganglia and internal capsules (figure 1).

Empyema
An empyema is a collection of pus in either the extradural or subdural space. Causes include sinusitis, mastoiditis, meningitis and as a complication of surgery or trauma. Akin to extra-axial haematomas, extradural empyemas tend to be lentiform versus subdural collections which are crescentic. In both there is enhancement of the surrounding capsule. In subdural empyema the subjacent parenchyma can show abnormal signal due to local oedema and ischaemia, this is less frequent in extradural empyema and belies the greater risks associated with a subdural empyema (15% mortality). Although CT is often adequate for the diagnosis, restricted diffusion on MR is a reliable finding that differentiates from effusions and chronic haematomas which are often inseparable on CT (figure 2).

Parenchymal
Herpes encephalitis
Herpes simplex encephalitis (HSE) is the most common viral encephalitis. Patients present with fever, headache, seizures and focal neurology. Untreated HSE has a high mortality of 70% emphasising the need for prompt diagnosis and treatment. Imaging typically reveals bilateral, asymmetric involvement of the limbic system and insular. CT is often normal but can show ill-defined hypodensity and haemorrhage. MRI is superior in showing the extent of inflammation, best demonstrated by increased signal on FLAIR (figure 3). Associated haemorrhage manifests as foci of T1-shortening and susceptibility on gradient echo sequences. The presence of enhancement is variable. Restricted diffusion is an early, sensitive finding which occurs directly from local inflammation or secondary to seizure phenomenon.

Imaging mimics include MCA infarcts, autoimmune encephalitis and gliomas. HSE typically spares the basal ganglia, which are commonly involved in MCA infarcts. Autoimmune encephalitis is often indistinguishable but is classically more symmetrical and gliomas are usually more indolent in presentation.
Rhomboencephalitis

Rhomboencephalitis is rare, life-threatening inflammation of the brainstem and cerebellum. The most common infectious cause is the bacteria Listeria monocytogenes. MRI shows ill-defined T2-hyperintensities, with variable restricted diffusion. Headache, parenchymal enhancement, which extends along the cranial nerves, is sometimes present. 46

Focal pattern

Pyogenic abscesses

Pyogenic abscesses evolve from cerebritis, a focus of infected parenchyma. Cerebritis presents radiologically as an area of swelling, with ill-defined T2-hyperintense signal, variable enhancement and restricted diffusion. As the infection coalesces an abscess sealed by a capsule forms. On CT this appears as a defined, hypodense lesion with an enhancing capsule. On MRI the cavity is typically T1-hypointense and T2-hyperintense and the capsule is T1-hyperintense and markedly T2-hypointense (figure 4). 2,9 The appearance of the capsule is related to paramagnetic haemoglobin degradation products which can cause a 'dual rim sign' on SWI, characterised by an outer hypointense ring and a contrasting inner concentric hyperintense rim of granulation tissue. This finding is specific for abscesses and can help differentiate from necrotic tumours. 17 Abscesses also exhibit thin, smooth, ring-enhancement while tumours usually have thicker, more nodular enhancement. 'Light bulb bright' restricted diffusion helps distinguish from tumours which are usually more variable on DWI. 13,21 Finally, abscesses often grow towards the ventricular system, hence the deepest part of the cavity wall is the thinnest. They may therefore rupture, causing secondary abscesses (Daughter cysts) or intraventricular extension and ventriculitis. 7 The latter is associated with high mortality and is suggested by ventricular wall enhancement and intraventricular or ependymal restricted diffusion. 7

Tuberculomas are granulomas, which due to haematogenous spread classically occur at the grey-white matter junction. Caseating granulomas have central T2-hypointensity and smooth ring enhancement whereas non-caseating granulomas are T2-hyperintense and solidly enhancing (figure 1). 2,9 Tuberculomas can develop into abscesses which, like pyogenic abscesses, exhibit central T2-hyperintensity and restricted diffusion. 2,9 Unlike pyogenic infections, TB abscesses tend to have thick, nodular capsules.

Neurocysticercosis

Neurocysticercosis is caused by the pork tapeworm Taenia Solium and is the most prevalent parasitic infection in the immunocompromised patient. 2,12 Parenchymal neurocysticercosis has four stages: 1) vesicular, 2) colloidal, 3) granular, and 4) calcified-nodular. 2,12 In the vesicular stage the parasite resides quiescently in cavities. These appear as discrete cyst-like lesions with intrinsic T1-hyperintense dots, which represent the scolex (head of the tapeworm). During the colloidal stage the parasite dies causing disruption of the cyst and a resultant local inflammatory response, associated with incomplete ring-enhancement and surrounding oedema (figure 5). 2,9 In the granular phase the cyst retracts, forming a ring or nodular enhancing granuloma with less surrounding oedema. Calcification of the granuloma demarcates the non-active calcified-nodular stage, characterised by punctate high density foci on CT and susceptibility on gradient echo or SWI. The presence of multiple cysts at different stages of development is highly suggestive of neurocysticercosis. 2,14

Infrequently, grape-like collections of cysts (racemose) can form in the subarachnoid space, these can rupture causing basilar meningitis and vasculitis. 24 Intraventricular cysticercosis is difficult to detect and is often most conspicuous on FLAIR sequences. Occasionally ventricular cysts can cause obstructive hydrocephalus. 25

Toxoplasmosis

Toxoplasmosis, caused by the protozoa Toxoplasma gondii, is the most common opportunistic infection in AIDS. 24 Focal-to-focal transmission from undercooked meat is the main source. Symptoms include fever, headache and altered consciousness. Neuroimaging shows ring-enhancing lesions with surrounding oedema and a predilection for the basal ganglia and corticomedullary junction (figure 6). The 'eccentric-target sign' relates an asymmetric mural nodule and, although it only occurs in 30% of cases, has high specificity when present. 27

Toxoplasmosis has overlapping imaging appearances with CNS lymphoma. Features that favour lymphoma include hyperattenuation on CT, subependymal spread, corpus callosum involvement and restricted diffusion on MR. 28,29 If toxoplasmosis is suspected, treatment is initiated after which an interval decrease in lesion size is expected by two to three weeks. If the lesion is unchanged or increased in size then lymphoma or an alternative diagnosis should be considered. Advanced imaging is also useful. MR spectroscopy typically shows raised choline in lymphoma while lactate and lipid peaks are greater in toxoplasmosis. 28,29 On perfusion imaging, lymphomas typically have elevated relative cerebral blood volume. 31

CNS infection in the immunocompromised patient

HIV in combination with advances in oncology, autoimmune disease treatment and organ transplantation has resulted in a global increase in the number of immunocompromised patients. These patients are vulnerable to both atypical opportunistic and common non-opportunistic infections which, due to variable immune responses, are often diverse in behaviour and radiological pattern. Here we shall specifically review HIV-associated neurocognitive disorder (HAND), progressive multifocal leukoencephalopathy (PML) and immune reconstitution syndrome (IRIS).

HIV-associated neurocognitive disorder

HAND encompasses all neurocognitive diseases associated with direct HIV infection. HIV penetrates the CNS early in infection and even with highly active anti-retroviral therapy (HAART) the CNS can act as a sanctuary for ongoing HIV replication. 34 Resultantly cognitive impairment is common despite good virologic response to therapy. Severe HAND is characterised by subcortical dementia, with cognitive, behavourial and motor abnormalities. Imaging features include diffuse cerebral atrophy and symmetric T2-hyperintensity in the periventricular and deep white matter with no enhancement (figure 7). Symmetric involvement differentiates from PML which is typically asymmetric. 7 These appearances are non-specific and include toxic and metabolic leukoencephalopathies, nevertheless if this image pattern is present the radiologist should always recommend testing for HIV.

Progressive multifocal leukoencephalopathy

PML is a demyelinating disease caused by the opportunistic JC virus. HIV infection has the greatest risk of PML but the disease has also emerged in many other immunocompromised conditions. Recently, the therapeutic promise of the multiple sclerosis immunotherapy natalizumab has been tempered by the observed increased risk of PML. 37,38 PML is characterised by progressive neurological decline and without treatment death usually occurs within months.

MRI shows asymmetric, multifocal, T2-hyperintense white matter lesions with characteristic involvement of the subcortical U-fibres (figure 7). 25 The lesions do not typically...
enhance and are not associated with mass effect. The presence of restricted diffusion is a sign of active disease progression.36

Immune reconstitution inflammatory syndrome
IRIS can occur after commencing HAART in patients with HIV. It is characterised by dysregulated immune reactivation stimulating an excessive inflammatory reaction to pre-existing infectious and non-infectious antigens.37 Infectious antigens include PML and TB. Presentation usually occurs soon after starting HAART and is typified by paradoxical clinical deterioration despite improving CD4 counts and reducing viral loads. Imaging appearances are highly variable and dependent on the associated antigen. PML-IRIS is characterised by multiple white matter lesions which, unlike conventional PML, are associated with increased mass effect and atypical enhancement (figure 7). TB-IRIS is associated with increased leptomeningeal enhancement and large enhancing tuberculomas.38 Inconstant imaging features make it challenging to differentiate from other diseases like lymphoma.

Summary
CNS infections are an expansive disease group with varied clinical and radiological presentations. Imaging is vital for a prompt diagnosis and early life saving treatment. Ultimately, CNS infections remain a challenge and are not always ‘classical’ in their imaging presentation. Close correlation with clinical features and other investigations must be emphasised but infection should always be considered as a cause for a neurological presentation.

References
Figure 1
Tuberculosis. 25-year-old woman increased confusion. (A) Axial T2W and (B) T1W post-gadolinium images demonstrate a small tuberculoma with central T2-hypointensity and a smooth ring of enhancement. (C) Axial T1W post-gadolinium image of the same patient shows marked, thick, nodular basal cistern enhancement reflecting severe leptomeningitis. (D) Axial DWI demonstrates bilateral areas of restricted diffusion in both basal ganglia, consistent with secondary infarcts. (E) A year later after poor treatment compliance axial T1W post-gadolinium and axial T2W. Note the temporal horn dilation. (F) Image demonstrates numerous basal tuberculomas. (G) Coronal CTA image of same patient demonstrates severe attenuation of the intracranial arteries in keeping with obliterative arteriopathy.

Figure 2
Subdural empyema. 30-year-old woman headache two weeks after surgical excision of glioma. (A) Axial T2W image demonstrates a small left subdural effusion day one after surgery. (B) Axial CT on re-presentation two weeks later, note slight interval increase in depth of left subdural collection. (C) Axial DWI shows diffusion restriction in the subdural collection confirming empyema. (D) Axial T1W post-gadolinium demonstrates marked enhancement of the meninges surrounding the collection.
Figure 3
HSV encephalitis. 37-year-old woman with fevers and seizures. (A) Axial T2W images show asymmetric hyperintense signal and swelling in the right temporal and frontal lobes, insula and hypothalamus. (B) Axial T1W post-gadolinium shows ill-defined enhancement of the hypothalamus and frontal lobe. (C) Axial DWI and ADC maps demonstrate restricted diffusion in the right temporal and frontal lobes. (D) Subsequent CT six days after initial MRI shows new parenchymal haemorrhage in the right temporal lobe.

Figure 4
Pyogenic abscess. 42-year-old man with meningism and right hemiparesis. (A) Axial T2W image demonstrates an abscess in the left corona radiata which has a hyperintense cavity with a hypointense capsule. There is surrounding hyperintense signal reflecting oedema. (B) Axial T1W post-gadolinium shows smooth, thin enhancement of the abscess capsule. (C) Axial DWI demonstrates intra-cavity restricted diffusion. (D) Coronal T1W post-gadolinium shows the abscess growing towards the lateral ventricle, note the capsule is thinnest at this point.
Figure 5
Neurocysticercosis. Colloidal neurocysticercosis. (A) Axial T2W demonstrates a hyperintense cyst in the left corona radiata with surrounding oedema (B) T1W post-gadolinium images of the same patient, shows associated ring enhancement. Note a separate non-enhancing lesion in the left posterior parietal lobe in keeping with vesicular neurocysticercosis. (C) Sagittal T1W demonstrates intrinsic T1-shortening in the posterior parietal lobe lesion in keeping with a scolex. (D) Axial CT demonstrates several punctate calcifications reflecting calcified-nodular neurocysticercosis. (E) Axial FLAIR images of different patient shows a grape-like cluster of cysts closely related to the left lateral ventricle in keeping with rare ‘racemose’ form.

Figure 6
Toxoplasmosis. 42-year-old man, increased confusion. (A) Axial T2W shows a heterogeneous irregular lesion in the left basal ganglia with surrounding oedema and associated mass effect. (B) T1W post-gadolinium images demonstrates irregular ring enhancement.
Figure 7
CNS infection in the immunocompromised. (A) Progressive multifocal leukoencephalopathy. Axial T2W images demonstrate multifocal, asymmetrical white matter lesions. (B) T1W post-gadolinium image of the same patient shows no associated enhancement. (C) HIV-associated neurocognitive disorder. Axial T2W image demonstrates diffuse cerebral atrophy and symmetric T2-hyperintensities in the periventricular and deep white matter. (D) Immune reconstitution inflammatory syndrome. Axial T2W demonstrates nodular hyperintensities in the left middle cerebellar peduncle initially thought to be PML. (E) Axial T1W post-gadolinium image of the same patient shows associated contrast enhancement atypical for PML and suggestive of PML-IRIS.