Imaging of Infections of the Central Nervous System

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The central nervous system (CNS) has multiple protective mechanisms. The brain is protected internally by the meningeal coverings and a blood–brain barrier and externally by a bony cranium. Once invaded, the brain is susceptible to many different organisms. After invasion by a pathogen, the brain has a limited number of ways of reacting to infection. Bacteria generally cause meningitis, abscesses and empyemas. Viruses are associated with encephalitis and meningitis. Several different types of organisms can lead to granulomatous diseases. Fungi and parasites, which have become increasingly prevalent in the brain of immunocompromised patients, can cause meningitis or granulomas.

Pathogens may gain access to the CNS by various mechanisms. Haematogenous spread is probably the most common mechanism. The lack of a blood–brain barrier in certain CNS structures and the lack of valves in the facial and emissary veins may act as entrance points for pathogens.

Direct extension is also a common mechanism and may result from sinusitis, mastoiditis or otitis. The organism may be directly implanted into the CNS by trauma or surgery or may gain access perineurally along the nerve sheaths.

Early detection in CNS infections is essential because the brain is surrounded by the meninges and bathed in cerebrospinal fluid (CSF) which provide both a culture medium and a rapid means of dissemination during infection. Due to current improved antibiotic therapy and early detection with computed tomography (CT) and magnetic resonance (MR) imaging, infections and their complications have decreased.\(^1\) Contrast enhanced CT was the initial imaging technique that had significant effect on the mortality and morbidity of CNS infections by leading to early detection and prompt treatment. Enhanced MR imaging has further increased the sensitivity and allowed earlier detection of nearly all infectious processes.

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Meningitis and Ependymitis

Meningitis, an inflammation of the meninges, may be subclassified into leptomenigitis affecting the pia and arachnoid and pachymeningitis affecting the dura. Ependymitis, an infection of the ependyma, may result from leptomeningitis or from rupture of an abscess cavity directly into the ventricles.

Purulent meningeal infections are most commonly caused by one of three organisms: Neisseria meningitides, Haemophilus influenzae and Streptococcus pneumoniae. These organisms have a predilection for different age groups. In adults, S. pneumoniae and N. meningitides are the most common. In the elderly, S. pneumoniae is more commonly found. Haemophilus influenzae is prevalent in the first year of life. In the newborn group, beta-streptococcus and Gram-negative bacilli predominate.1

Viruses are a common cause of meningitis in all age groups, however 90% of patients are under the age of 30. Viral meningitis is usually an acute self-limiting illness. The specific infecting virus is dependent on the time of year, geographic location and age of the patient. The most common infecting viruses are enteroviruses, including the ECHO and Coxsackie viruses. Infections commonly occur in the late summer and early autumn.1

Granulomatous meningitis is most frequently caused by Mycobacterium tuberculosis and Cryptococcus neoformans. These organisms usually cause CNS infection in the course of haematogenous dissemination of infections originating in the lung.2

Tuberculosis (TB) is the most common non-purulent infection of the CNS. Leptomenigitis is the most common manifestation of this disease1 (Fig. 1). The TB organism creates a fibrous exudate that classically forms in the basal cisterns. This mass may partially or completely fill the cisterns compromising the cranial nerves and vessels that transverse this area.1-3 A study by Chang et al. of patients with diffuse active meningitis showed nine of ten to have cisternal obliteration.3 Sarcoidosis is a systemic disease of unknown aetiology that can cause a diffuse or localized granulomatous meningitis. This disease often involves the basilar cisterns as seen in TB.4

The advent of gadolinium contrast agents has made MR imaging the most sensitive imaging technique for the evaluation of meningitis and ependymitis.3,5,6 The CT findings in early or partially treated meningitis are usually normal. Positive MR imaging findings have been seen early in the course of the illness.6 Mathews found abnormal enhancement in his experimental animals between 13 and 29 h after inoculation and concluded that enhanced MR imaging is highly effective at demonstrating meningeal inflammation as well as its complications.6 Chang et al. concluded that T1- and T2-weighted precontrast and T1-weighted postcontrast scans are necessary in the evaluation of meningitis.7 Typically, the exudate appears as a mild hypointensity on the T1-images and as high intensity on the T2-weighted images. Magnetic resonance imaging with contrast demonstrates the changes in the meninges particularly well since subtle enhancement is not obliterated by the adjacent skull as in CT. However, CT may show small calcifications in the basal cisterns which are missed by MR imaging.3 There are usually few findings in viral meningitis on both CT and MR imaging.

Early ependymitis may not be visualized on MR imaging. If the infection progresses, a band of high signal intensity may surround the ventricles on the T2-weighted images representing an inflammatory response in the surrounding brain tissue and transudation of CSF from the ventricles through the denuded ependyma. Frequently the ventricles themselves will be enlarged secondary to obstructive hydrocephalus from the ependymitis.
or from communicating hydrocephalus secondary to an associated meningitis.\textsuperscript{12}

**Cerebritis and Bacterial Abscess**

Cerebritis is a focal area of inflammation of the brain usually resulting from bacterial or fungal infections. A cerebral abscess usually begins as cerebritis. Such an abscess develops in the brain parenchyma from a collection of purulent material surrounded by a fibrous capsule which forms as a result of tissue necrosis. Granulomatous infections of the brain parenchyma form focal nodules with histologic signs of chronic inflammation. These nodules may be caused by a variety of organisms, including bacteria, fungi, protozoans and spirochetes.

The progression from cerebritis to abscess formation is divided into four stages that take place over a 2–3 week period. Stage one is early cerebritis with a suppurative focus (1–3 days). Stage two is late cerebritis with increasing definition of a necrotic centre by neovascularity, fibroblastic infiltration and surrounding oedema (4–9 days). Stage three is early capsule formation with collagen encapsulation (10–13 days). Stage four is late capsule formation with increase in capsule thickness (beyond 14 days).\textsuperscript{4}

Brain abscesses are most commonly located in the frontal and temporal lobes and are less commonly found in the posterior fossa and parasellar areas.\textsuperscript{1} Most cerebral abscesses develop following dissemination from a distant site. Septic emboli may produce multiple areas of focal cerebritis or microabscesses (Fig. 2). This picture is commonly seen in patients with congenital heart disease, bacterial endocarditis, pulmonary infections and/or a history of intravenous drug abuse. Metastatic abscesses are usually located at the corticomедullary junction because the pathogens become lodged in the arborization of the arteries at this point.\textsuperscript{8} Other causes for abscess formation include direct extension from sinusitis or mastoiditis or implantation from surgery or trauma. Common bacterial pathogens include streptococci, staphylococci, Gram-negative species, and anaerobic bacteria such as *Bacteroides* and anaerobic streptococci. In debilitated and immunocompromised patients, a wide range of bacteria, fungi and protozoans can cause disease.

Tuberculomas and other granulomas usually have a similar pattern of development as do abscesses. However, granulomas may follow a longer time course with formation of a thicker capsule which later becomes solid. A tubercle is a small core of epithelioid cells surrounded by lymphocytes. Focal tuberculous cerebritis represents an area of inflamed parenchyma containing several small tubercles (Fig. 3). A true tuberculoma is formed by the conglomeration of multiple tubercles. The centre becomes necrotic and filled with caseous debris. Peripherally, a capsule of fibrous tissue and reactive gliosis is formed. Oedema is usually seen in the brain surrounding the lesion. Progression to true abscess formation, with a thin outer wall and central purulent material is rare (Fig. 4). The sarcoid granulomas are similar to tuberculomas in many ways. Sarcoid granulomas produce problems by mass effect; however, unlike tuberculomas, they do not develop caseous centres and are not associated with oedema.

Cryptococcal infections may form large parenchymal granulomas called torulomas which simulate tuberculomas. Toxoplasmosis infections may also form granulomas which have become more common because of the AIDS epidemic.

Brain abscesses are a potentially fatal infection that may be treated successfully. Enhanced CT has been very beneficial in the early recognition of these lesions leading to a sharp decrease in mortality from 40% to less than 5%.\textsuperscript{9} Magnetic
resonance images are able to detect areas of cerebritis that are normal on CT. The components of an abscess are usually better differentiated on MR imaging. The central necrotic portion shows low signal on the T1- and cerebral oedema shows high signal on the T2-weighted images⁸ (Fig. 5). Follow-up after treatment with enhanced MR imaging has shown a more accurate assessment of healing and resolution of the abscess than CT.⁹

In cerebritis, CT may demonstrate low attenuation oedema and mass effect later in the course of the disease. Magnetic resonance imaging of early cerebritis shows low intensity on the T1- and high intensity on the T2-weighted images in the central inflammatory zone and surrounding oedema.⁸,¹² With the use of contrast, the sensitivity for the inflammation is increased (Fig. 2). Non-contrast T2-weighted images may overestimate the extent of early cerebritis because of high signal in areas of infected brain and reactive oedema. As the necrosis becomes more confluent, the centre shows low intensity on the T1- and is isointense to hyperintense on the T2-weighted images.⁸ In an abscess, the capsule shows low intensity on the T2-weighted images surrounding the isointense to highly intense central core. The exact degree of intensity of the central core may depend on the contents of the abscess (Fig. 5). Haines et al. concluded that pyogenic abscesses have a characteristic set of findings on MR imaging which should allow for early and accurate diagnosis.⁹

Magnetic resonance imaging is reported to be more sensitive than CT in detecting tuberculomas of the cerebral parenchyma.² Tuberculomas are seen as lesions isointense with grey matter on the T1- with central hyperintensity on the T2-weighted images. In some cases a hypointense ring is apparent within the wall of the tuberculoma on the T2-weighted images. Most lesions are outlined by a collar of high signal intensity due to oedema. Tuberculomas typically enhance with contrast in a solid or ring-like pattern (Fig. 3). A solid homogenous enhancement pattern suggests a granuloma rather than an abscess.² Such granulomas are best seen on enhanced T1-weighted images and are usually located adjacent to areas of marked meningeal enhancement.⁴ Sarcoïdosis is usually demonstrated as meningeal disease. However, granulomatoid parenchymal masses may develop from extension of the sarcoïd meningitis through the Virchow-Robin spaces.¹³ These sarcoïd granulomas resemble those caused
by TB; however, they do not have caseating centres and only rarely have associated oedema. Sherman & Stern reported that enhanced MR imaging is the preferred imaging technique in sarcoidosis because of the high prevalence of leptomeningeal involvement.  

Epidural and Subdural Empyema

Subdural and epidural empyemas are collections of purulent material most commonly caused by anaerobic streptococci, staphylococci and Gram-negative enterics. These subdural and epidural infections are uncommon, accounting for only 20–33% of all intracranial infections. Empyemas can result from the complications of meningitis or from haematogenous spread from a distant focus. Other causes include direct implantation through surgery or trauma. In adults, the most common cause is sinusitis or mastoiditis. In infants, a meningitis which induces an effusion is commonly the cause.

Extraaxial empyemas usually develop 1–2 weeks following sinusitis or mastoiditis by retrograde thrombophlebitis of the transdiploic veins. The thrombophlebitis progresses to an irreversible thrombosis of the dural sinuses and venous structures leading to secondary parenchymal infection and infarction. The high morbidity and mortality rate (25–50%) along with the clinical and radiologic findings are related more to the response of the cerebral vasculature and brain to the inflammatory response and less to the mass effect of the extraaxial collection. Prompt surgical treatment is a requirement since systemically administered antibiotics do not penetrate the subdural space in therapeutic amounts. Aggressive surgical therapy is also important in limiting the amount of neurologic deficits.

Postoperative and posttraumatic empyemas, in contrast to otorhinologically induced empyemas, occur months to years after the initial incident with few or minimal signs and symptoms. The benign course is due to formation of a limiting membrane from the previous surgery or trauma which acts as a barrier protecting the underlying CNS structures. Because of the fulminant nature of extraaxial empyemas, prompt recognition is a necessity. Weingarten et al. concluded that MR imaging is superior to CT for demonstrating these lesions by enabling more sensitive detection, more accurate localization and more complete delineation of the disease.  

Superficial lesions are particularly easier to detect due to the absence of bony artifacts with MR imaging (Fig. 6). Magnetic resonance imaging also allows the differentiation between benign and purulent effusions, because on both
Figure 6. Sinusitis and a large epidural empyema in a young boy. Coronal MR scan (600/15) following the administration of gadolinium. There is a bifrontal extraaxial collection which crosses over the falk cerebri into both frontal lobes. The inner enhancing rim of the empyema is well shown (arrowheads). There is also considerable enhancement in the visualized ethmoid sinuses which are inflamed.

the T1- and the T2-weighted images, a higher signal intensity will be seen with empyemas. Posttraumatic empyemas are hypointense on both the T1- and the T2-weighted images when compared to most chronic subdural haematomas. Also, MR imaging is more specific in differentiating subdural from epidural empyemas. A hypointense medial rim is seen in epidural collections, but not in subdural effusions. Improvement in prognosis can be expected with the use of MR imaging because of early and accurate diagnosis as well as the ability to monitor therapy.  

Encephalitis

Encephalitis is an inflammatory disease of the brain and may be caused by bacteria, fungi, protozoans or viruses. The majority of diffuse infections of the CNS are viral in origin. The infection of the brain typically occurs during the initial exposure; however, some viruses like the herpes virus can cause disease many years after the primary exposure. Virulent organisms are able to bypass the body’s defence mechanism and produce general inflammation. The brain responds to these virulent organisms with an infiltrate of inflammatory cells along a perivascular distribution. Neuronal destruction results in cytotoxic and vasogenic oedema with the subsequent formation of glial nodules (Fig. 7).

Herpes simplex virus (HSV) type I is an important cause of encephalitis producing a fatal fulminant necrotizing meningoencephalitis in 50–70% of cases. The onset of symptoms may be abrupt or evolve over several days, with headache and fever being the most common early findings. Studies have shown that early diagnosis and treatment increases survival and decreases morbidity. Pathologically, HSV encephalitis is characterized by haemorrhagic necrosis involving one or both temporal and frontal lobes. This pattern is thought to result from the entry of the virus into the trigeminal ganglia which lie near the temporal lobes. HSV type II is an important cause of encephalitis in neonates and does not have preference for the temporal lobes.  

The CT scan may be normal in early encephalitis. Specific CT findings of temporal lobe oedema with mass effect and contrast enhancement may appear later. Magnetic resonance imaging is able to detect subtle changes in brain water due to oedema, which aids in earlier diagnosis and

Figure 7. Cytomegalovirus encephalitis in a 2-month-old infant with AIDS. Axial MR scan (3000/120). There are multiple patchy and confluent lesions scattered throughout the white matter. The lesions extend laterally from the walls of the ventricles into the corona radiata and central white matter of both cerebral hemispheres. More inferiorly, there is extension bilaterally into the subcortical white matter tracts. (not shown). The pattern is fairly symmetric bilaterally consistent with a widespread infection.
shows the extent of the disease more fully. Findings on MR imaging of abnormal signal in the temporal lobes and variable extension into the frontal lobes with sparing of the basal ganglia are highly characteristic of HSV infections.\textsuperscript{12} Also, MR imaging is better able to monitor the resolution of the disease as a result of early treatment.\textsuperscript{11}

Subacute sclerosing panencephalitis is a slowly progressive and fatal encephalitis. The disease usually occurs 3–10 years following a measles infection and is believed to be caused by this virus.\textsuperscript{14} Pathologically both grey and white matter are involved. In the grey matter, gliosis and perivascular infiltration by lymphocytes are found. Demyelination of variable degrees and gliosis are usually seen in the white matter. Eosinophilic inclusion bodies are often found in oligodendrocytes and neural cells in the cortex. These changes are also found in the caudate nucleus, putamen, globus pallidus, pons and thalamus.

Magnetic resonance imaging of subacute sclerosing panencephalitis shows lesions in the white matter of decreased intensity on the T1- and increased intensity on the T2-weighted images. Lesions of increased signal are seen in the white matter on the T2-weighted images that are not seen on CT.\textsuperscript{14}

Encephalitis may occur following viral illnesses or vaccinations. In some cases, no specific virus can be recovered from the CNS. Postinfectious encephalitis (PIE) has been described following measles, varicella or rubella infection or vaccination. It is clearly a non-infectious autoimmune disorder and consists of lesions showing increased signal on the T2-weighted images. Computed tomography may be normal or show areas of decreased attenuation within the white matter. Treatment with corticosteroids often results in improvement in the outcome. Unlike multiple sclerosis, there rarely are recurrent episodes of PIE.

### Immune Deficiency Related Infections

The frequency of neurologic symptoms from infections has become more evident with the current increase in immunosuppression due to organ transplantation, aggressive cancer chemotherapy and AIDS. Approximately one-third of AIDS patients have neurologic signs and symptoms during the course of the illness and 10–20% have neurologic complaints prior to the manifestation of AIDS. Neurologic involvement is even higher in autopsy cases where 73–80% have histologic evidence of severe disease.\textsuperscript{15,16} Neurologic involvement may be related to the direct effects of the human immunodeficiency virus (HIV), or secondary to infections or neoplasms. It is often difficult to ascribe a particular problem to a specific agent because multiple pathogens may be present. Both systemic and CNS infections contracted by AIDS patients are usually not bacterial in origin, but caused by opportunistic organisms.

The most common CNS infection in AIDS is caused by the neurotropic HIV virus. This virus causes both a subacute encephalitis (producing a progressive dementing encephalopathy) and a chronic meningitis. The centrum semiovale is the most common site of involvement, but all white matter tracks may be affected.\textsuperscript{17} Clinically, the subacute encephalitis progresses to a subcortical dementia known as AIDS dementia complex (ADC) which occurs in more than one-half of the patients with AIDS.

Magnetic resonance imaging in early HIV encephalitis shows bilateral areas of increased signal intensity in the deep white matter on the T2-weighted images. Late findings included atrophy and areas of diffuse increased signal intensity in the periventricular region, centrum semiovale and frontal lobes. No mass effect or enhancement with gadolinium is seen. In a study by Olsen \textit{et al.}, a diffuse white matter pattern was seen in 70% of 33 patients and was the most common finding.\textsuperscript{19} Early CT findings may be normal. Late findings include atrophy and diffuse decreased attenuation of the deep white matter, which does not enhance.\textsuperscript{17–19} For detecting these abnormalities, MR imaging is significantly more sensitive than CT. A diffuse periventricular white matter pattern on MR imaging in patients with AIDS strongly suggests ADC and further evaluation is usually not indicated.\textsuperscript{19}

Progressive multifocal encephalopathy (PML) is a viral infection affecting 2–7% of all AIDS patients.\textsuperscript{15,20} The disease is caused by a papovavirus and results in demyelination with necrosis of the white matter.\textsuperscript{15} Electron microscopy shows the oligodendrocyte nuclei to be filled with viral particles. These oligodendrocytes are the cells responsible for the maintenance and production of myelin. Clinically, PML develops insidiously and evolves relentlessly until the patient’s death in about 6 months or more.\textsuperscript{21} The centrum semiovale is frequently affected with extension into the cortical and subcortical areas of the cerebral hemispheres with a predilection for the parietooccipital areas.\textsuperscript{15,21} This involvement may help explain many of the neurologic symptoms seen with PML such as visual loss, aphasia, hemiparesis, ataxia and other focal findings.\textsuperscript{17,21}

The T2-weighted MR images are more sensitive than CT or the T1-weighted images in detecting
the extent and number of white matter lesions. PML lesions usually do not enhance.22 PML should be considered in any patient with AIDS who has focal high intensity intracerebral lesions on the T2-weighted scans.31 Contrast is frequently helpful in PML patients because this lesion does not enhance and can be distinguished from toxoplasmosis which does enhance.19

Cytomegalovirus (CMV) is a member of the herpes virus group which often causes CNS abnormalities in immunosuppressed patients. The infection is frequently asymptomatic, although ventriculitis and/or focal, multifocal or diffuse encephalitis may occur. One author found CMV to have a predilection for involvement of the ependymal or subependymal regions.18 Magnetic resonance imaging shows both grey and white matter disease, ventriculitis and cortical atrophy.17 Studies done postmortem show focal hyperintense lesions without mass effect on the T2-weighted images (Fig. 7). These lesions most frequently represent necrosis or infarction often associated with CMV infections. The high rate of infarction is believed due to infection of the endothelial cells causing occlusion of the vascular lumen.16

Toxoplasma gondii is an intracellular protozoan that is found throughout the environment. Toxoplasmosis is the second most common cause of CNS infection in patients with AIDS. Central nervous system toxoplasmosis results from reactivation of a previously acquired infection in most cases. The resulting necrotizing encephalitis typically manifests as multiple thin-walled abscesses. In the immunocompromised AIDS patient, a thick abscess wall does not develop because of poor host defence mechanisms.17,23 Multiple lesions of increased signal intensity are seen on the T2-weighted images with areas of surrounding vasogenic oedema and enhancement with gadolinium. Toxoplasmosis lesions show either ring or solid enhancement and are usually 1–4 cm in diameter. Such lesions may be hard to differentiate from the high signal of surrounding oedema. Areas of decreased signal intensity from calcification or haemorrhage may be seen on the T2-weighted images, especially if the patient has received antibiotics. The basal ganglia are the site most frequently involved, but the white matter and the cortex are also commonly affected. A trial of antitoxoplasmosis antibiotics may help differentiate these findings from lymphoma which has a similar picture.17 Computed tomography is less sensitive for detection of focal masses but may show single or multiple ring enhancing lesions.15,18

Cryptococcosus, the most common fungal infection of the CNS in AIDS patients, ranks third after HIV and toxoplasmosis as a cause of CNS infection.24 Meningitis is the most common
manifestation of cryptococcosis. The pathology ranges from mild congestion to meningeal thickening and distention of the subarachnoid space by the abundant mucoid exudate. Fungi may enter the subarachnoid spaces and accompany the perforating arteries in the Virchow-Robin spaces. These give rise to small ‘soap bubbles’ or gelatinous pseudocysts in the adjacent parenchyma. The T2-weighted images show bilateral small, well defined foci of high signal intensity clustered around the region of the basal ganglia (Fig. 8). These lesions appear hypointense to isointense to grey matter on the T1-weighted images and may not enhance with gadolinium. Although the dilated perivascular spaces of Virchow-Robin are not always present, when seen they appear to be characteristic of cryptococcal involvement and may help in early diagnosis and treatment.

Other CNS infections, although not as common, have become increasingly prevalent due to AIDS. Fungal infections, including candidiasis, histoplasmosis, aspergillosis and coccidiomycosis have all been seen in AIDS patients. These diseases have the ability to produce fungal abscesses and granulomas both of which are rare in AIDS patients because of the altered immune response. Meningitis is the most frequent presentation and is usually blunt with little or no evidence of enhancement on imaging studies.

Neurosyphilis is a sexually transmitted disease caused by the spirochete Treponema pallidum. This disease has become increasingly prevalent due to the AIDS epidemic. Neurosyphilis usually takes the meningeal or vascular form. MR imaging findings consist of high signal intensity in the basal ganglia on the T2-weighted images with patchy enhancement of these regions with gadolinium. Stroke-like symptoms in young AIDS patients with MR imaging findings suggestive of vascular ischemia should alert clinicians to the possibility of meningovascular syphilis.

References
