

## NEUROIMAGING OF HIV AND AIDS RELATED ILLNESSES: A REVIEW

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### 1. ABSTRACT

Neuroimaging technology continues to unfold in a very exciting way, providing almost limitless information about the structural and functional integrity of the nervous system. In patients with an immunocompromised state such as those infected with human immunodeficiency virus (HIV) and subsequently developing acquired immunodeficiency syndrome (AIDS), neurologic complications represent an important manifestation requiring vigilance. Many of the central nervous system (CNS) disorders related to HIV and AIDS are treatable and without prompt diagnosis and treatment, will lead to significant morbidity or death. Neuroimaging plays an increasingly pivotal role in the early diagnosis and longitudinal monitoring of these conditions. The author intends to provide an overview of neuroimaging technology and its applications including various magnetic resonance imaging (MRI) and functional imaging techniques in the evaluation of patients with HIV and AIDS related CNS disorders. The role of neuroimaging in this population includes early detection of direct HIV infection, opportunistic infections, neoplasia, or cerebrovascular diseases. In addition, through a wide breadth of imaging techniques, the pathology, neurochemistry and metabolism of lesions can be studied to clarify the differential diagnosis, such as discriminating infection vs. neoplasia.

### 2. INTRODUCTION

The author intends to provide an overview of the applications of neuroimaging including primarily structural magnetic resonance imaging (MRI) and various functional imaging techniques in the evaluation of patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) related neurologic disorders. Advances in neuroimaging technology over the last three decades have allowed the non-invasive definition of a wide variety of pathologic processes that can be applied to the evaluation of patients with neurologic complaints. This neuroimaging revolution has led to a much more rapid and accurate diagnostic approach to patients with suspected central nervous system (CNS) complications of HIV infection or AIDS. Applications of neuroimaging in this population include early identification of lesions, differential diagnosis, and monitoring of treatment effects. There is increasing ability to detect direct HIV infection, opportunistic infections, neoplasia, or cerebrovascular diseases. Through advanced MRI and functional imaging techniques, the neurochemistry and metabolism of lesions can be studied to help differentiate infection vs. neoplasia. Relatively uncommon causes of CNS lesions in AIDS include vascular diseases/stroke, Kaposi sarcoma, metastasis, and pyogenic/bacterial abscesses. These are beyond the intended scope of this

article. The author strives for this review to be useful to trainees and practitioners in the clinical and imaging fields of general medicine, infectious diseases, and clinical neurosciences.

### 3. OVERVIEW OF NEUROIMAGING TECHNOLOGY

#### 3.1. Definition of techniques

The major modalities of neuroimaging include computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET), ultrasound/neurosonology (carotid and transcranial Doppler), myelography, and conventional (catheter) angiography. Both conventional (T1-weighted vs. T2-weighted, spin-echo vs. gradient echo) and advanced (echoplanar, diffusion, perfusion, spectroscopy, magnetization transfer) MRI techniques are available. Commercially disseminated in the early 1970s, computerized tomography (CT) produces images by detection of a collimated beam of X-rays through tissue in sequential slices. The most modern scanners use spiral technology, where the imaging is performed in a continuous helical fashion leading to higher resolution and faster scanning. MRI is based on the nuclear magnetic resonance spin and relaxation properties of hydrogen protons through the use of magnetic fields and radiofrequency pulses. One of the major advances in the past decade is the wide availability of echoplanar MRI, allowing ultrafast acquisition and a variety of new pulse sequences. Compared to MRI, CT has the disadvantage of ionizing radiation, decreased signal to noise, artifacts related to bone, and the inability to characterize neurochemistry and diffusion-related changes. The value of MRI has been enhanced by the development of advanced techniques such as diffusion, perfusion, and spectroscopy. CT is being rapidly replaced by MRI for most neuroimaging indications. Thus, in this review the author will focus on MRI rather than CT. Functional imaging techniques include functional MRI (fMRI), SPECT and PET. Functional MRI relies on the detection of blood oxygenation changes related to the performance of a task, and has purely research related role in the HIV population. Perfusion MRI uses the passage of gadolinium to measure blood flow and blood volume in the brain microvasculature. PET and SPECT are collectively categorized as nuclear imaging techniques, based on the radioactive tagging of molecules externally administered and imaged through the physiologic and pathologic uptake of these tracers by living tissue. The major role of PET/SPECT is to characterize metabolic changes in the brain related to mass lesions or cognitive changes in the HIV population.

#### 3.2. Conventional MRI

MRI became commercially available in the early 1980s and, by the late 1980s, could be performed with contrast to determine blood-brain barrier permeability. The first two decades of MRI technology were dominated by basic spin-echo or gradient-echo methods typically featuring T1-weighted and T2-weighted pulse sequences. T1-weighted images (T1WI) are sensitive to anatomic changes such as mass effect, midline shift, or sulcal

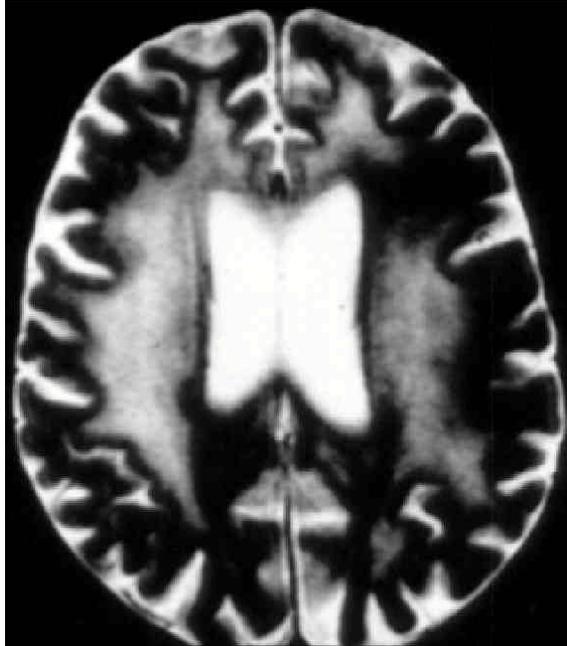
effacement and also to certain forms of hemorrhage, calcification or adipose. These images are also used to display the passage of intravenous gadolinium contrast into the meninges or across the blood-brain barrier. T2-weighted images (T2-WI) and their variations (e.g. proton-density images) are sensitive to nearly all CNS pathologies due to their sensitivity to prolongation of dephasing of water protons. Most CNS diseases are characterized by increased water content due to a variety of pathologic processes (edema, demyelination, inflammation, gliosis, tract degeneration, necrosis, etc.) and thus are depicted as bright on these images. Short-tau inversion recovery (STIR) for the spine and fluid-attenuated inversion-recovery (FLAIR) for the brain are techniques that take advantage of the sensitivity of T2-weighting in detecting increased water content, but also include inversion recovery pulses that suppress CSF. FLAIR images provide a high lesion contrast for intracranial disease in the HIV population (1) and other neurologic disease (2), but also present a unique set of technical challenges (3).

#### 3.3. Diffusion and perfusion MRI

Diffusion-weighted (DWI) and perfusion-weighted (PWI) MRI techniques have been studied most extensively in patients with stroke (4, 5) in whom they have shown the ability to detect ischemia and tissue at risk more sensitively than conventional MRI and CT. In addition, both techniques have applications to the HIV population. DWI is based on the use of specialized gradients and echoplanar scanning capability in the detection of water diffusion. Water molecules in healthy tissue are in constant random diffusion (Brownian motion). DWI can detect either increases or decreases in the randomness, velocity and direction of this water diffusion. By imaging with multiple diffusion gradient strengths in multiple orthogonal planes, apparent diffusion coefficient (ADC) maps can be calculated which provide a physiologic estimate of the water velocity. DWI and ADC maps of the brain can be acquired simultaneously in approximately 30 seconds on most modern platforms. Restricted diffusion (decreased ADC) is typically hyperintense on DWI and hypointense on ADC scans vs. normal neural tissue. Increased diffusion (increased ADC) is usually hypointense on DWI and hyperintense on ADC maps. Causes of restricted diffusion include cytotoxic edema, inflammation/pus, high viscosity, and spongiform change. Causes of elevated diffusion include cystic change, vasogenic edema and necrosis. DWI is useful in the HIV population to study intracranial infectious vs. neoplastic mass lesions and for the early detection of stroke (e.g. due to vasculitis or meningitis). PWI scans depict perfusion of the brain microvasculature after a rapid intravenous bolus of gadolinium contrast that causes a paramagnetic susceptibility effect (4, 6, 7). One of the uses of PWI is to complement the information obtained by DWI in patients with acute stroke (4, 5). However, PWI is also useful in the HIV population to examine the blood flow and, in turn, the metabolic characteristics of intracranial mass lesions and cortical changes related to cognitive dysfunction (6).

#### 3.4. Magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (MRS) can non-invasively characterize the neurochemical profile



**Figure 1.** HIV encephalitis in a 35 year-old man. Hyperintense lesions are noted on this conventional spin-echo T2WI, located in the periventricular white matter and centrum semiovale, with relative sparing of the subcortical (arcuate) U-fibers. The lesions are “fluffy” or “cotton-like” and poorly circumscribed, showing confluence and a diffuse appearance. Cortical atrophy is apparent as indicated by enlargement of the subarachnoid spaces (cortical sulci) and lateral ventricles. The central atrophy is especially prominent. The white matter lesions were poorly appreciated on T1WI (not shown) and non-enhancing (not shown). There is no associated mass effect.

of brain tissue (7). An excellent review on the technical aspects and physics of MRS has been recently written (8). Most MRS studies of the brain are obtained by proton spectroscopy with water suppression and either a single-voxel or multi-voxel technique. MRS may be performed effectively with many clinical 1.5-T MRI scanners and commercially available software. The time required for one MRS acquisition is typically less than eight minutes. The data obtained are both quantitative (area under the curve) or semi-quantitative using the intrasubject ratio of one peak to another. The peaks are expressed as parts per million (ppm). MRS abnormalities include the demonstration of a pathologic metabolite that is not normally present or is usually only minimally detected (e.g. lactate/lipid). More commonly, MRS will show an abnormal quantity (increased or decreased) of a metabolite that is usually present (e.g. choline). In a clinical MRS brain study the metabolites of interest are myo-inositol (3.6 ppm), choline (3.25 ppm), creatine (3.0 ppm), glutamine/glutamate (2.2 to 2.4 ppm), N -acetyl-aspartate (NAA, 2.0 ppm), and lactate/lipids (1.33-0.9 ppm). NAA is a marker of neuronal and axonal integrity. Choline is thought to represent phospholipid membrane biosynthesis and cellular proliferation. Creatine (Cr) reflects cellular energy and typically acts as a reference peak. Increased

macromolecular (lipid and lactate) peaks indicate areas of cellular necrosis and anaerobic metabolism. The most common clinical role of MRS is the discrimination of neoplastic from nonneoplastic processes (9) and early detection of viral infection, which is pertinent to the HIV population.

## 4. HIV RELATED CONDITIONS

### 4.1. HIV encephalopathy

The HIV organism has been identified in the brains of patients with systemic HIV infection or AIDS, located intracellularly in multinucleated giant cells or microglia/monocytes. Direct effects of HIV infection of the brain will be referred to as HIV encephalopathy in this review. Such HIV related brain disease is thought to occur in two stages. The first stage occurs subclinically at the time of initial HIV infection (10), characterized by small (<1 cm) multifocal white matter lesions. These are typically localized areas of hyperintensity on T2WI throughout the cerebral white matter. Reported in about one-third of seropositive asymptomatic patients, these nonspecific lesions remain unchanged over time and are thought to represent gliosis caused by primary HIV infection (11). The second stage of HIV infection in the brain is characterized by progressive subacute encephalitis and brain atrophy, also known as the AIDS dementia complex, HIV-1-associated dementia, or HIV-1-associated cognitive/motor complex (10-25). Both MRI and CT can effectively screen for cerebral atrophy, present in virtually all patients with clinically significant HIV encephalopathy (7, 17, 24, 26). Central atrophy (ventricular enlargement) predominates over cortical atrophy (sulcal prominence) (Figure 1). One hypothesis maintains that activated brain macrophages and microglia release the excitotoxin quinolinic acid which contributes to neuronal injury and tissue loss, especially in regions of the brain vulnerable to excitotoxic injury in HIV infected individuals (the striatum and limbic cortex) (26). Regarding the white matter lesions of HIV encephalopathy, the pathological correlation includes multinucleated giant cells and microglial nodules with demyelination and vacuolation (19). Neuroimaging-pathologic correlation has shown that the lesions are hypodense on CT scans, isointense to mildly hypointense on T1WI, and markedly hyperintense on T2WI (Figure 1). The lack of significant hypointensity on T1WI is helpful in differentiating HIV encephalopathy from progressive multifocal leukoencephalopathy. Lesions typically begin in the periventricular white matter and centrum semiovale with sparing of the subcortical U-fibers. The lesions are most commonly symmetric, “fluffy” or “cotton-like,” and are poorly circumscribed, typically becoming confluent and diffuse (Figure 1). Mass effect or enhancement is typically absent. Involvement of the internal capsules, basal ganglia, thalamus, and cerebral peduncles typically occurs as the disease progresses (11, 17, 19).

Advanced MRI methods, including DWI, PWI and MRS have recently revealed interesting information about HIV encephalopathy. Chang et al. (15) showed that patients with early stage symptomatic HIV encephalopathy had bilaterally decreased blood flow in the inferior lateral

frontal and medial parietal cortex and increased blood flow in the posterior inferior parietal white matter on PWI scans. These perfusion abnormalities correlated with the level of neuropsychologic dysfunction. Thus, PWI may assist in the diagnosis and monitoring of HIV encephalopathy.

MRS may show a decreased NAA/Cr ratio in the frontal gray matter of patients with early stage symptomatic HIV encephalopathy (22). White matter lesions of HIV encephalopathy are characterized by increased myo-inositol, increased choline, and decreased NAA (14). These neurochemical changes offer the ability to non-invasively monitor therapeutic effects of antiviral therapy. For example, Chang et al. (14) showed that highly active antiretroviral therapy (HAART) led to a reversal of initially increased choline in the midfrontal cortex and basal ganglia. The initially elevated myo-inositol in the frontal white matter and basal ganglia also decreased. Simone et al. (25) studied MRS of the centrum semiovale in 60 seropositive HIV patients, 25 of whom had HIV encephalopathy. The remaining patients had other HIV related brain lesions. Decreased NAA was present in all patients vs. normal controls. However, the NAA/Cr ratio was significantly lower in progressive multifocal leukoencephalopathy and lymphoma than in HIV encephalopathy and toxoplasmosis. All patients showed a significant increase in the choline/Cr ratio regardless of lesion subtype. The presence of a lipid peak was more common in lymphomas (71%) than in other HIV subgroups. A lactate peak was common in progressive multifocal leukoencephalopathy, but uncommon in other HIV subgroups. Thus, MRS of the white matter shows a high sensitivity in detecting brain involvement in HIV related diseases including HIV encephalopathy. The pattern may have partial specificity for lesion subtype, especially in the presence of marked decreased NAA or increased lactate or lipid peaks. MRS is more sensitive than conventional MRI in detecting HIV related brain injury in asymptomatic individuals (27). DWI also has the potential to reveal early cerebral abnormalities in HIV infected individuals, with particular ability to image the altered tractography of injured white matter fibers (28).

Functional imaging techniques such as SPECT and PET have also provided interesting insight into the pathophysiology of HIV encephalopathy (22). These methods have shown that metabolic abnormalities precede both the clinical and structural effects of the disease.

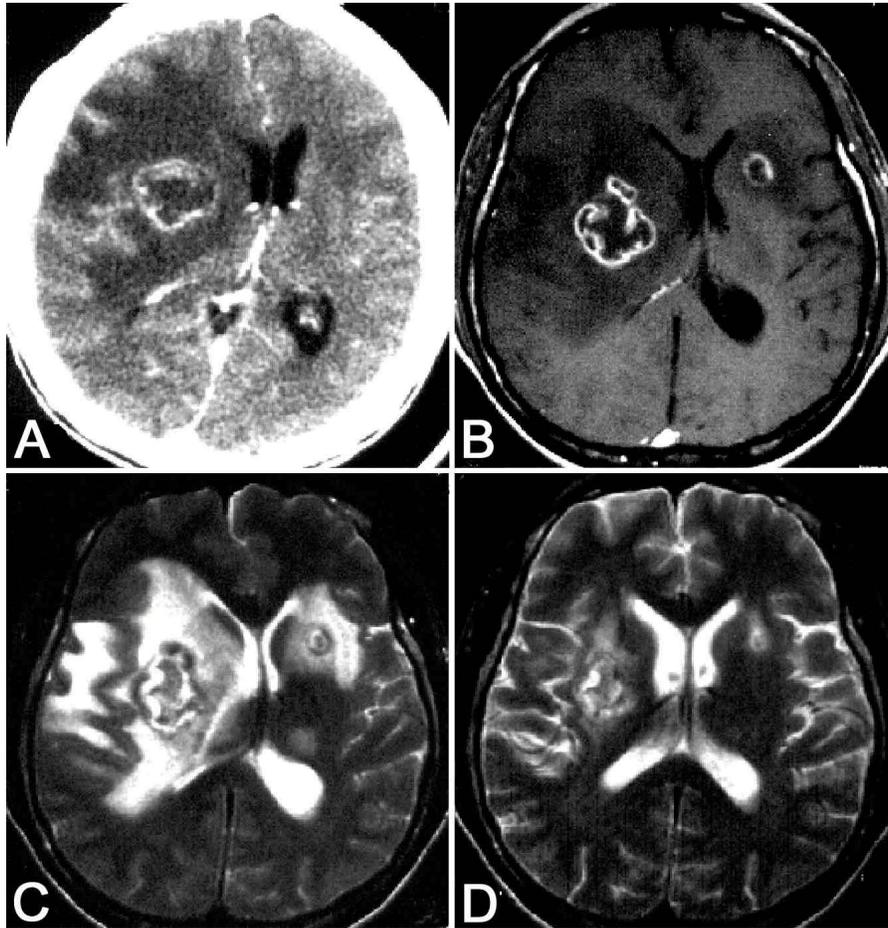
### 4.2. Vacuolar myelopathy

Spinal cord disease in patients with HIV infection or AIDS can occur due to a variety of causes, such as vacuolar myelopathy (VM), opportunistic infection, or neoplasia (29-37). The etiology of VM is unclear, appearing to be linked partially but not completely to direct infection of the cord by HIV. The most common cause of spinal cord disease among patients with AIDS or those infected with HIV is VM. Patchy vacuolation and tract pallor of the lateral and posterior columns followed by gliosis, demyelination and necrosis is the pathologic hallmark. Spinal MRI typically shows cord atrophy, involving the thoracic cord with or without cervical cord

involvement, and, less commonly, intramedullary cord lesions (35-37). The cord lesions are usually hyperintense on T2WI and isointense to mildly hypointense on T1WI. The lesion pattern may be diffuse (35) or restricted to the posterior columns (36). Some authors have argued that HIV myelitis is an entity distinct from VM (37) and that HIV myelitis should be suspected when lesions involve gray and white matter spinal cord areas (37). Enhancement is typically absent. Normal MRI may be seen in VM, especially when the myelopathy is clinically mild (35). MRI-histologic correlation has indicated that the nonenhancing hyperintense lesions on T2WI in the posterior columns represent extensive vacuolation (36). In addition to VM/HIV myelitis, other causes of myelopathy and spinal neuroimaging abnormalities in the HIV population include bone lesions (epidural masses, spine infection), opportunistic infections of neural tissue (e.g. cytomegalovirus polyradiculitis, herpes radiculitis/myelitis, tuberculosis, toxoplasmosis, fungal infection), and neoplasia (e.g. meningeal or intramedullary lymphoma, extradural leiomyoma) (34, 37).

## 5. TOXOPLASMOSIS

Acquired cerebral toxoplasmosis is parenchymal infection caused by *Toxoplasma gondii*, which occurs in the HIV population (7, 38-43) and in other immunocompromised hosts (44). In addition to being the most common opportunistic CNS infection in patients with AIDS, it is the most common cause of intracranial mass lesions. The spinal cord may also be affected, although much less commonly than the brain (34, 37, 45). Typically presenting with fever, headache, confusion, focal neurologic signs or seizures, cerebral toxoplasmosis is often encountered in the emergency setting. For this reason, CT is frequently used as an initial diagnostic modality, though MRI is more sensitive in detecting the disease (Figure 2) (38, 39). On noncontrast CT scans, acute or subacute lesions typically appear hypodense with surrounding vasogenic edema (Figure 2) (38). Chronic lesions appear calcified on CT scans, especially after treatment (42). On MRI (Figure 2), lesions are most commonly multiple and affect the deep central gray nuclei and lobar gray-white junction (7, 38-44). Other common locations include the posterior fossa, cerebral cortex, and periventricular white matter. Toxoplasmosis lesions typically appear isointense to hypointense on T1WI and hypointense to hyperintense on T2WI. Prominent edema and mass effect are typically seen. The edema is often disproportionately large relative to the lesion size. However, rarely, non-edematous lesions without mass effect may be seen, especially in non-AIDS cases (44). On T2WI, the masses may be difficult to distinguish from the surrounding edema. Or, a central isointense or hypointense core may be noted on T2WI giving a "target" appearance (Figure 2). The optimal conventional imaging study for toxoplasmosis is MRI with intravenous gadolinium contrast administration, as the lesions characteristically enhance (43). Avid enhancement is the rule and ringlike or nodular enhancement patterns are most commonly noted (Figure 2), while smaller lesions may show a homogeneous pattern. However, fulminant involvement



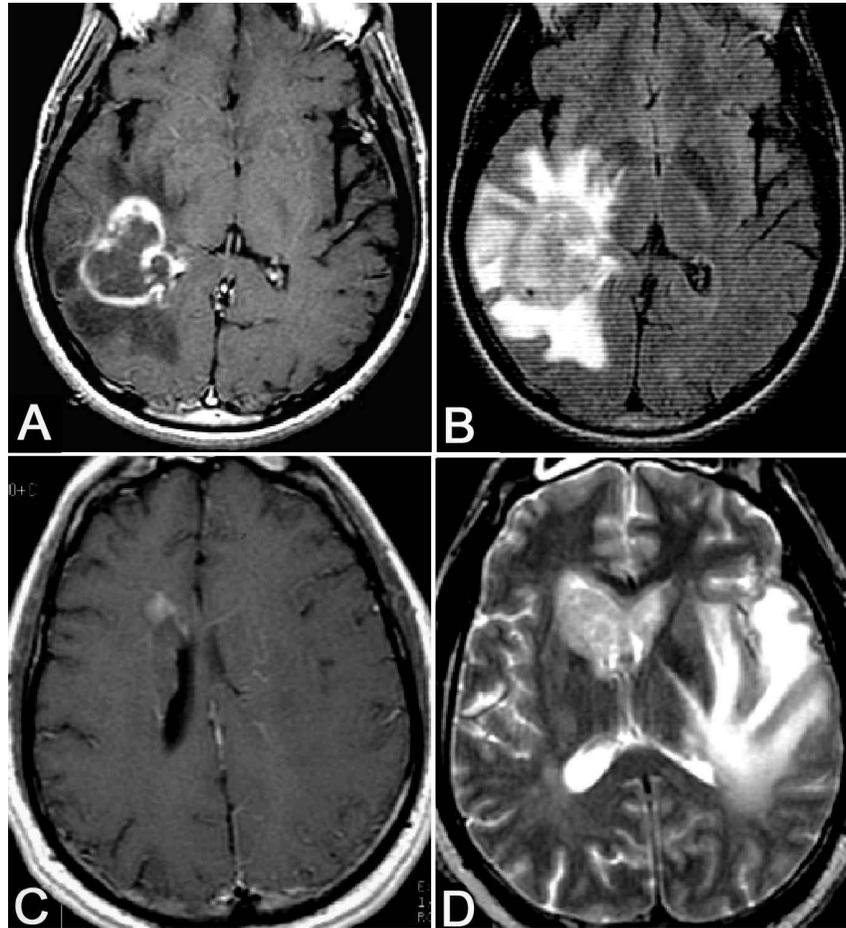
**Figure 2.** Toxoplasmosis in a 44-year-old man with AIDS and a CD4 count of 91 presenting with several days of generalized weakness, malaise, fever, headaches, and new onset seizures. Serial studies are shown before and after antibiotic therapy (adapted in part from reference 7). (A-C) Initial scans, pre-treatment. Edematous lesions appear centrally hypodense on CT (A) and centrally isointense to hypointense on T1WI (B) and hypointense to markedly hyperintense on T2WI (C), exerting moderate to severe mass effect. Severe surrounding edema is noted which is much larger than the size of the lesions. On T2WI (C), a central and concentric hypointense core gives a “target” appearance to the lesions. A third subtle lesion is apparent on T2WI in the thalamus (C). Note the relatively poor sensitivity of CT vs. MRI for the lesions in the left hemisphere. After contrast administration on both CT (A) and MRI (B), avid ringlike and nodular enhancement is noted. (D) T2WI shows marked improvement in each of the lesions 2 weeks after the completion of anti-toxoplasmosis medical therapy.

may occur despite a paucity of enhancement (44). MRI plays a central role in monitoring the response to antibiotic therapy and for prognosis (Figure 2) (38-40, 43). MRI improvement is typically noted 14 days after treatment. Beginning a few months after antibiotic treatment, toxoplasmosis lesions typically become calcified or hemosiderin-laden (7, 42) and appear focally hypointense on T1WI and T2WI. The role of advanced imaging techniques in the diagnosis of toxoplasmosis is discussed below (see Section 7).

## 6. LYMPHOMA

Primary central nervous system lymphoma (PCNSL) is a lymphoreticular neoplasm confined to the CNS typically of the non-Hodgkin B-lymphocyte type (46). PCNSL affects immunocompromised patients, including

those with AIDS (46-50), but also occurs in immunocompetent individuals (51-53). This is the most common brain malignancy and the second most common cause of intracranial mass lesions in the HIV population. PCNSL has a highly variable appearance on CT or MRI studies. CT typically shows the disease as hypodense or hyperdense on noncontrast images and enhancing on post-contrast scans (49). On MRI (Figure 3), PCNSL is most commonly hypointense or isointense on T1WI and hypointense to slightly hyperintense on T2WI. The amount of associated edema and mass effect is usually disproportionately small given the tumor size (Figure 3). As with toxoplasmosis, MRI with contrast administration is the diagnostic study providing the highest yield in the evaluation of PCNSL. Intense contrast enhancement is noted in at least 75% of cases, but may be absent less commonly (7, 49, 52, 53). A wide variety of enhancement

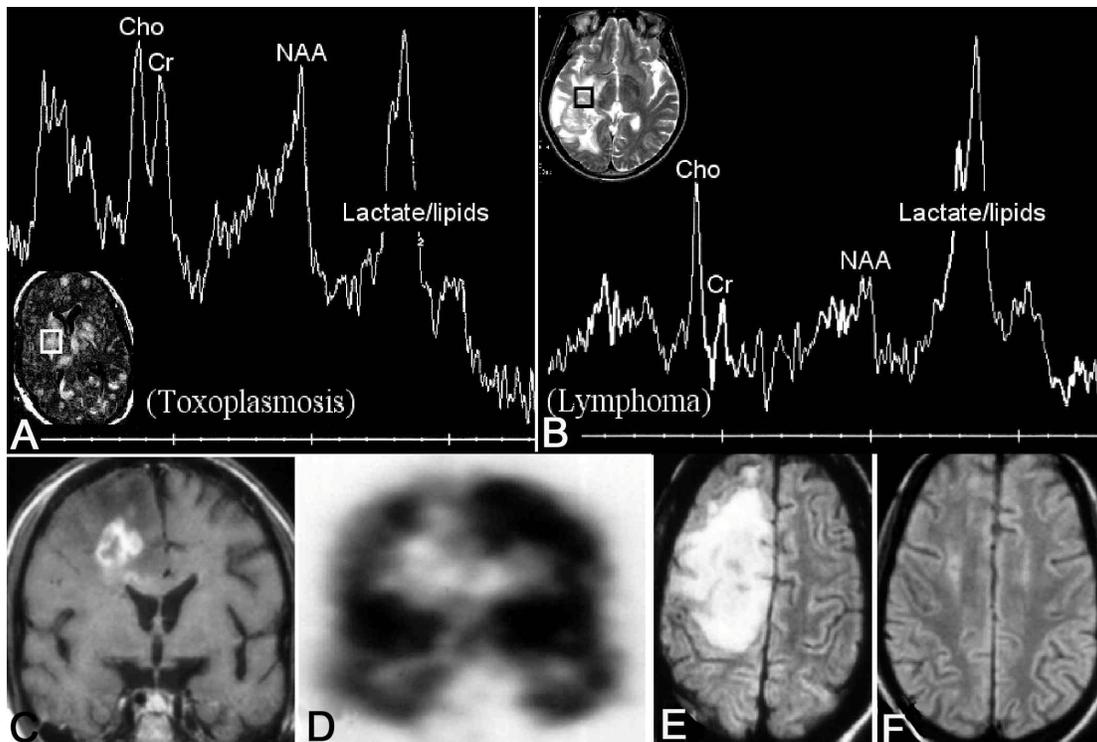


**Figure 3.** Primary CNS lymphoma in two patients with AIDS. Adapted from reference 7. A-B. 24 year-old man with AIDS and hemiparesis, headaches and visual symptoms. Postcontrast T1WI (A) FLAIR (B) and T2WI (Figure 4) show a solitary large ring-enhancing lesion with mild mass effect and moderate vasogenic edema. The hypointensity of the lesion on T2WI (Figure 4) is characteristic of lymphoma. Note that the mass effect and edema is less than expected given the size of the lesion, as is typical for primary brain lymphoma while much more edema and mass effect vs. lesion size is expected in toxoplasmosis (Figure 2). C-D. 30 year-old man with AIDS. Postcontrast T1WI (C) and T2WI (D) show left temporal lobe vasogenic edema, related to a temporal lobe mass lesion (not shown). There are also bilateral lesions in the caudate nuclei on T2WI (D), with periventricular and ependymal extension of enhancement on the right (C). The ependymal spread is characteristic of primary CNS lymphoma.

morphology may be seen, including homogeneous, nodular, and ringlike patterns (Figure 3). The detection of subependymal or leptomeningeal spread of disease lends diagnostic specificity for PCNSL (Figure 3). While the lesions of lymphoma may be multiple (Figure 3), a solitary brain mass in an HIV-positive patient is most likely PCNSL (Figure 3).

The MRI appearance tends to differ significantly in immunocompromised vs. immunocompetent individuals (7, 51), reflecting a more aggressive disease in the former. In the HIV population and other immunocompromised hosts, the enhancement pattern is highly variable. Most commonly, ring enhancement is noted (Figure 3) and, less commonly, homogeneous, heterogeneous, subependymal and gyriform enhancement is seen (Figure 3). In untreated patients, the doubling time of the MRI tumor volume is approximately two weeks. Hemorrhage is uncommon.

Multiple lesions are noted in 30% to 75% of cases (Figure 3). Differential diagnosis in the immunocompromised setting includes toxoplasmosis (see Section 7). It should be emphasized that MRI features such as a solitary lesion (Figure 3), non-enhancement, spontaneous hemorrhage, or diffuse white matter infiltration do not exclude PCNSL in this population (49). In immunocompetent patients, lesions are more often single and more likely to abut the ventricular system (51). Homogeneous enhancement is most commonly seen while more malignant appearances (ring/nodular enhancement, hemorrhage) are uncommon. Unusual manifestations of PCNSL include diffuse infiltration of the neuraxis without a focal mass or enhancement (49, 52); an MRI appearance mimicking viral encephalitis may also occur (53). Lymphoma of the spine and spinal cord occurs at a rate of 2-4% in the HIV population, most likely due to metastasis from the brain (34, 37). The intraspinal involvement may occur in



**Figure 4.** Toxoplasmosis vs. primary CNS lymphoma in AIDS: advanced imaging methods in 3 patients. A-B. Single-voxel MRS and representative thumbnail MRI slices with voxel localizer of patients with toxoplasmosis (A) and primary CNS lymphoma (B). In patient A, a mild increase in choline (Cho) to creatine (Cr) ratio, a moderate reduction in NAA/Cr, and lactate/lipid peaks are present. In patient B, a marked increased Cho/Cr, marked decreased NAA/Cr, and lactate/lipid peaks are present. The latter findings of severe Cho and NAA changes are consistent with malignancy rather than an infectious or inflammatory process such as toxoplasmosis. The patient shown in B is also shown in Figure 3. Adapted in part from references 7 and 44. C-F. Solitary toxoplasmosis – role of functional imaging. A 32 year-old man with AIDS developed acute headache, fever, leg weakness, and new onset seizures. MRI shows a solitary heterogeneously enhancing lesion (C) in the frontal lobe that is isointense to hyperintense on proton density T2WI (E) with copious surrounding edema. The differential diagnosis includes toxoplasmosis and primary CNS lymphoma. For further clarification, a resting brain neurulite (perfusion) SPECT scan (D) was performed and shows that the lesion is “cold” due to marked hypoperfusion (white areas). Thus, a presumptive diagnosis of toxoplasmosis was made and the patient received anti-toxoplasmosis treatment. Follow-up MRI (F) shows resolution of the lesion. Different images of this patient have been shown previously (7).

osseous, epidural, meningeal, radicular, and intramedullary areas (34, 37). The role of advanced imaging techniques in the diagnosis of PCNSL is discussed below (see Section 7) (Figure 4).

#### 7. DIFFERENTIATING TOXOPLASMOSIS FROM LYMPHOMA: ROLE OF ADVANCED IMAGING TECHNIQUES

The principal diagnostic consideration for an intracranial mass lesion in the HIV population is toxoplasmosis vs. PCNSL (Figure 4). It is important to rapidly diagnosis these entities so that prompt treatment can be initiated while limiting unnecessary invasive testing. Toxoplasmosis may be difficult to distinguish from PCNSL by conventional imaging methods, suggesting the need for a biopsy (Figure 4). MRI findings in favor of toxoplasmosis include multiple lesions, abundant edema, a hyperintense core on T2WI, the presence of hemorrhage, and involvement of the deep central gray matter nuclei (Figure 2). MRI findings suggesting PCNSL include a solitary lesion, subependymal enhancement (Figure 3), encasement

of the ventricles, homogeneous enhancement in lesions larger than 1 x 1 cm, and hypointensity in the core on T2WI (Figure 4). Despite these guidelines, the two entities cannot be reliably distinguished by conventional imaging. A successful trial of antitoxoplasma therapy provides a presumptive diagnosis, but brain biopsy is sometimes felt to be necessary in differentiating these two diseases.

However, advanced imaging methods have increased the ability to choose patients for biopsy vs. empiric medical therapy (Figure 4) (54-64). A variety of advanced MRI (16, 25, 54-60) and functional imaging methods (61-64) can non-invasively provide valuable information about the pathology of these lesions and increase diagnostic confidence (Figure 4). Toxoplasmosis lesions have been compared with PCNSL by dynamic contrast-enhanced fast MRI using heavily weighted gradient echo T1WI (59), DWI (16, 54), MRS (16, 25, 43, 55-58, 64) (Figure 4) or functional nuclear neuroimaging studies such as SPECT (Figure 4) (43, 61, 63, 64) or PET (62, 64).



**Figure 5.** Progressive multifocal leukoencephalopathy (PML) in 3 patients illustrate typical findings, including lesions that are markedly hypodense on CT (A), and hyperintense on FLAIR (B) and T2WI (C). As is characteristic of PML, lesions were markedly hypointense on T1WI and non-enhancing (not shown). Lesions follow the gray-white interface and prominently involve the subcortical U-fibers, while sparing the cortical ribbon, causing a “scalloped” or “heart of the gyrus” appearance.

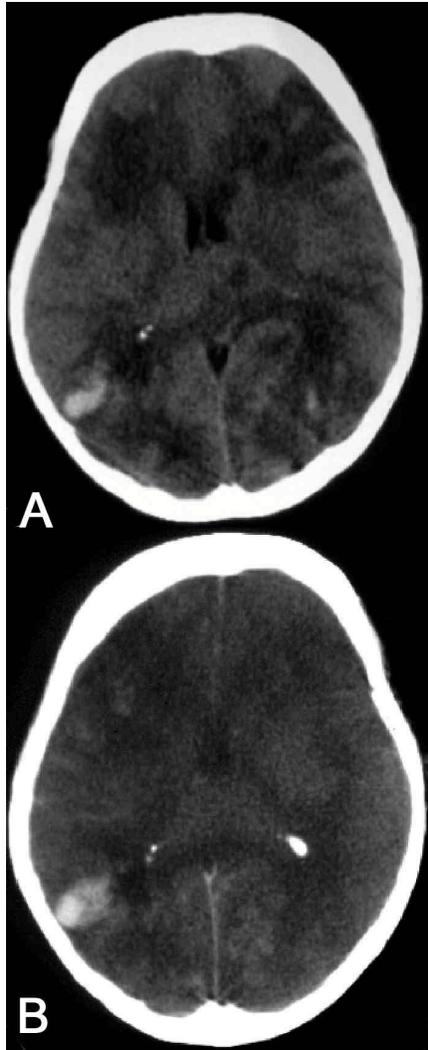
For example, using DWI and ADC maps, toxoplasmosis lesions have faster diffusion than PCNSL lesions (54). MRS may play a role in distinguishing toxoplasmosis from PCNSL; however this has been debated (16, 25, 43, 55-58, 64). Toxoplasmosis is generally

associated with mild increases in choline, mild to moderate decreases in NAA and the pathologic presence of lactate/lipid peaks (Figure 4), whereas PCNSL typically shows markedly increased choline, markedly decreased NAA, and lactate/lipid peaks (7, 55-58) (Figure 4). PCNSL lesions appear to show relatively low or normal blood volume on PWI scans (59) and thus this method will not likely assist in discrimination from toxoplasmosis lesions. Further study is necessary to more definitively characterize the role of advanced MRI techniques in the differential diagnosis of these two diseases in patients with AIDS.

Functional nuclear imaging techniques show promise in differentiating toxoplasmosis from PCNSL (Figure 4) (43, 61-64). Initial work showed that thallium SPECT had a 94% positive predictive value in identifying PCNSL (61). Likewise, early work showed that FDG-PET has 90% accuracy in differentiating PCNSL (metabolically active) from toxoplasmosis (metabolically inactive) (62). Recent studies have extended these observations. Naddaf et al. (63) compared thallium and sestamibi SPECT in 17 patients with AIDS and intracranial enhancing lesions. Both SPECT techniques yielded no false-negative cases of PCNSL (sensitivity 100%). Of the 13 non-neoplastic cases, the thallium studies showed seven true-negative cases (specificity 54%) and the sestamibi studies showed nine true-negative cases (specificity 69%). The biopsies of the false-positive cases (toxoplasmosis) indicated healing after medical treatment. Pomper et al. (64) studied 10 such patients with PET and SPECT. All patients with positive (hypermetabolic) PET and SPECT findings had PCNSL (100% specificity). Thus, SPECT or PET seems to have a role as a screening tool in patients with enhancing mass lesions and AIDS. Hypermetabolic lesions are the best candidates for biopsy prior to the onset of therapy. Hypometabolic lesions are probably the best candidates for empiric antitoxoplasma therapy with close follow-up (Figure 4).

## 8. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy (PML) is a progressive, infectious, demyelinating disorder caused by the JC human polyoma virus. PML most commonly manifests in immunocompromised hosts and causes myelin injury by infection of oligodendroglia. Lesions on MRI (7, 65-73), reflecting areas of demyelination and axonal loss (70), are typically markedly hypodense on CT scans, markedly hypointense on T1WI, and hyperintense on FLAIR, and T2WI, with little or no mass effect (Figure 5). On post-contrast studies, lesions are usually nonenhancing or, rarely, mildly enhancing. The disease usually begins by involving the posterior subcortical lobar white matter at the gray-white junction. The subcortical (arcuate) U-fibers are affected while the cortical ribbon is spared. This results in the classic “scalloped” or “heart of the gyrus” sign (Figure 5). Multifocal, asymmetric involvement is most common (Figure 5). Progression of disease usually includes the development of lesions in the thalamus, basal ganglia, corpus callosum, and posterior fossa (7, 65, 70). The spinal



**Figure 6.** Aspergillus cerebritis: serial non-contrast CT in a fatal case. Bilateral intermixed hypodense and hyperdense lesions are seen in the bilateral frontal, parietal and occipital lobes. Hyperdense areas represent hemorrhage. Hypodense areas represent varying degrees of ischemia/infarction, cerebritis, and edema. The two scans are separated by three days. A. Original scan. Note that the repeat CT (B) shows the emergence of diffuse brain edema (note loss of sulcal and gray/white definition). Autopsy revealed systemic and multiorgan aspergillus infection with multiple brain abscesses, angioinvasion and hemorrhage.

cord may also be affected. Unusual manifestations include lesions limited to the brain stem (66) and prolonged survival (68, 69). Serial MRI may be useful in demonstrating the response of PML to medical therapy (65, 67, 69). Post et al. (72) studied the role of MRI in predicting long term survival in patients with PML related to AIDS. Mass effect, while uncommon, was the only MRI variable associated with shorter survival. Cortical atrophy, ventriculomegaly, and lesion topography or size was not of prognostic value. MRS in PML typically shows increased choline, decreased NAA, and the presence of lactate/lipids (25, 73).

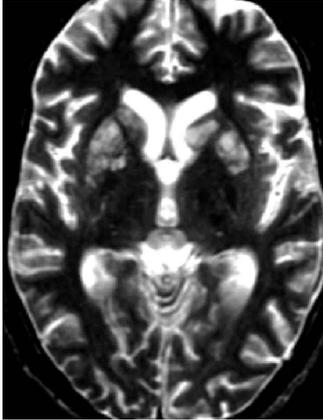
## 9. OTHER OPPORTUNISTIC INFECTIONS AND MISCELLANEOUS CONDITIONS

### 9.1. Neuroimaging of meningitis

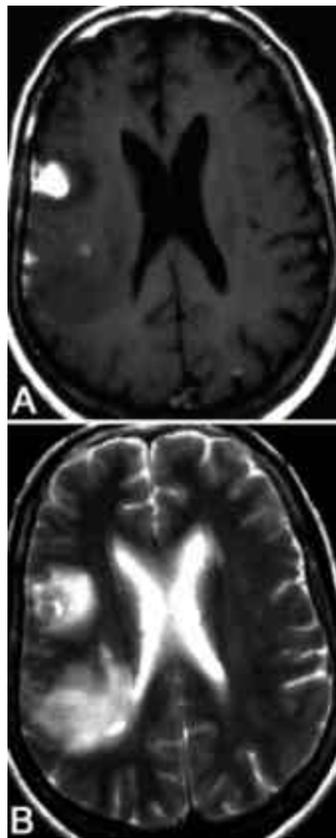
The author will first consider the general neuroimaging findings in meningitis, followed in subsequent sections by organism specific findings in AIDS. MRI is superior to CT for the evaluation of meningeal disease due to the lack of bone artifact (74). However, clinical and CSF data remain the cornerstone of diagnosing meningitis while the sensitivity or specificity of MRI remains unreliable (74-79). While noncontrast conventional MRI in uncomplicated infectious meningitis is usually normal, distention of the subarachnoid space or increased signal of the cisterns may be occasionally seen on proton density images. FLAIR is a sensitive MRI method for the evaluation of intracranial infections in the HIV population (1) and has higher sensitivity than T2WI for detecting meningitis (78). Abnormalities on FLAIR images suggesting meningitis include hyperintensity of the subarachnoid space and hyperintense vessels (7). On post-contrast MRI scans, homogeneous leptomeningeal enhancement of the falx, tentorium, convexities, and basal cisterns may be noted. Intravascular enhancement may also be seen (77). However, infectious meningitis may occur with normal intracranial enhancement in the setting of a mild inflammatory response (e.g. immunocompromised host, viral meningitis). It is also important to note that abnormal meningeal or intravascular enhancement, or FLAIR subarachnoid hyperintensity on MRI may occur in a variety of conditions other than infectious meningitis (3, 7, 77, 79, 80). Conventional MRI and CT are more useful tools for the diagnosis of the complications of meningitis, such as ventriculitis (81), hydrocephalus (82), infarction (83), cerebritis/abscess (84), myelitis (85) and subdural empyema (86). The use of DWI (87, 88) and magnetization transfer (76) may increase the sensitivity of MRI in diagnosing infectious meningitis and its ischemic complications. For example, hyperintensity of the meninges or brain parenchyma may be seen on DWI in meningitis (87, 88).

### 9.2. Fungal infections

Fungal brain infections in the HIV population and in other immunocompromised hosts display a myriad of manifestations on MRI (Figures 6, 7) (89-100). Fungi that proliferate in hyphal or pseudohyphal forms, such as aspergillus (Figure 6) and mucormycosis, are associated with hemorrhage, cerebritis and ischemia/infarction due to their angioinvasive potential. These fungi also commonly involve the orbits and paranasal sinuses. Fungi that reproduce in yeast forms, such as cryptococcus (Figure 7) and histoplasmosis, typically manifest as leptomeningitis with or without parenchymal involvement. Fungal meningitis is most commonly seen on MRI as a communicating hydrocephalus with diffuse nodular enhancement of the basal cisterns. Spread of infection along Virchow-Robin (perivascular) spaces of arterioles may occur in yeast infections leading to basal ganglia lesions (ischemia, cerebritis, or gelatinous pseudocysts) (Figure 7) or choroid plexus involvement. Spinal involvement may occur due to fungal infection in the HIV



**Figure 7.** Cryptococcal brain infection. T2WI of a 33-year-old woman with AIDS shows multiple tiny bilateral hyperintense lesions in the caudate and putamen. These lesions represent mucoid material secreted by the fungal organisms. Adapted from reference 7.



**Figure 8.** Tuberculosis of the brain with cerebritis and tuberculoma formation. MRI scans of a patient are shown including post-contrast T1WI (A) and T2WI (B). Heterogeneous lesions are seen in the frontal and parietal region, involving both cortical and subcortical areas. The intermixed hypointensities on T2WI most likely represent hypercellularity, free radicals, or both. Postcontrast axial T1WI shows parenchymal and leptomeningeal enhancement, representing both meningitis and sub-pial extension.

population with involvement of the leptomeninges, spinal cord, or both due to hematogenous spread (34, 89).

### 9.3. Tuberculosis

Intracranial tuberculosis may occur in a variety of forms on MRI (101-110), including meningitis, tuberculomas, cerebritis, and frank abscesses (Figure 8). Tuberculous meningitis is most commonly seen as a communicating hydrocephalus with diffuse nodular enhancement disproportionately affecting the basal cisterns. Intracranial tuberculomas are usually isointense on T1WI and mixed hypointense and hyperintense on T2WI (Figure 8). On postcontrast studies, ringlike or homogeneous enhancement is common (Figure 8). Frank abscesses are much less common than tuberculoma and are characterized by liquefactive necrosis and pus rather than caseating granuloma in the core (109). Magnetization transfer MRI adds sensitivity for detecting tuberculosis lesions of the brain and combined with MRS may assist in differentiating tuberculosis from other infections (104, 108). Gupta et al. (104) showed that pyogenic brain abscesses had elevated lipid, lactate, and amino acids on MRS studies while tuberculous lesions showed only elevated lipid/lactate. The magnetization transfer ratio of the wall of pyogenic abscesses was higher than that of a tuberculoma. Spinal tuberculosis may occur in the HIV population with involvement of the bony spine, epidural region, leptomeninges, spinal cord, or nerve roots (34, 109).

### 9.5. Neurosyphilis

Intracranial neurosyphilis may manifest on MRI as meningitis, cranial neuritis, cerebrovascular disease, or parenchymal gumma (111-116). Cranial nerves VII and VIII are most commonly affected when basilar meningitis occurs (112). Orbital involvement may also occur, particularly of the roof and supraorbital rim (112). The cerebrovascular disease is characterized by endarteritis of medium and large arteries (Heubner's arteritis) or, less commonly, small arteries and arterioles (Nissl-Alzheimer arteritis) (112). When vasculitis has occurred, neuroimaging studies typically reveal multiple areas of ischemia and infarction. Syphilitic gummas appear as discrete masses, ranging from a few millimeters to several centimeters in diameter typically involving the cerebral cortex (111, 112, 114, 116).

### 9.5. Cytomegalovirus

The incidence of acquired cytomegalovirus (CMV) encephalitis in patients with AIDS is decreasing in the HAART era (117). The most common forms of intracranial CMV infection include meningoencephalitis, white matter disease and ventriculitis/ependymitis (71, 118-122). CMV typically spreads through the nervous system along the meninges and nerve roots in the brain and spinal cord (71). The most common MRI presentation is brain atrophy and periventricular/subcortical diffuse and multifocal white matter hyperintensities on T2WI (120). The noncontrast MRI findings may resemble HIV encephalitis (121). However, specificity is added by the presence of periventricular (ependymal) or meningeal enhancement on post-contrast images (71, 120). Spinal

CMV infection is usually seen as diffuse enhancement of the leptomeningeal surface of the conus, cauda equina, and filum terminale with clumping of the intraspinal nerve roots in the thecal sac (71).

### 9.6. Other conditions

In this review, the author has chosen to focus on neuroimaging of the most common CNS complications of HIV and AIDS related diseases. The reader is referred to excellent reviews of neuroimaging of other manifestations, such as bacterial infections (123), viral infections (71), vasculitis (124), stroke (125, 126), spinal disease (34, 37, 127), and specific considerations in pediatric cases (128).

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