

Imaging features of CNS involvement in AIDS

Efsun Şenocak, Kader Karlı Oğuz, Burçe Özgen, Aslı Kurne, Gülşen Özkaya, Serhat Ünal, Ayşenur Cila

ABSTRACT

Patients with acquired immunodeficiency syndrome (AIDS) are the subjects of a large part of routine neuroradiological work in the Western world currently. The World Health Organization announced that Turkish authorities had reported a cumulative total of 2544 HIV cases from 1985 to 2006, of whom 623 had developed AIDS and 140 had died. It is estimated that approximately one-third of AIDS patients develop neurological complications. The spectrum of diseases affecting the central nervous system (CNS) in AIDS patients comprises predominantly opportunistic infections and primary CNS lymphoma. Although to a lesser degree when compared with Western countries, the incidence of AIDS and related neurological diseases are on the rise also in Turkey. Therefore radiologists should recognize HIV-associated problems and their imaging features. In this review, we focus on imaging features of more common CNS diseases in HIV-seropositive patients. This essay has been prepared using radiological studies of the patients who had been managed in our hospital which is a tertiary care center with a highly motivated medical team for this peculiar disease in the years between 2002 and 2008.

Key words: • acquired immunodeficiency syndrome • magnetic resonance imaging • central nervous system infections • lymphoma

Human immunodeficiency virus (HIV) belongs to a subset of retroviruses called lentiviruses (or slow viruses), which means that there is an interval between the initial infection and the onset of symptoms. Upon entering the bloodstream, HIV infects the CD4+ T cells and begins to replicate rapidly. Acquired immunodeficiency syndrome (AIDS) is the final stage of HIV infection (1). The U.S. Centers for Disease Control and Prevention established the definition of AIDS as a condition, which occurs in HIV-infected persons with fewer than 200/mm³ CD4+ T cells and/or persons with HIV who develop certain opportunistic infections (2).

The brain may be affected by a variety of abnormalities in association with HIV infection. The spectrum of central nervous system (CNS) abnormalities can be divided into three main categories: HIV-associated lesions, opportunistic infections, and neoplasms. Although there is a considerable overlap in the imaging characteristics of different entities, some findings are found to be very suggestive of a particular disease and imaging modalities, mainly magnetic resonance imaging (MRI), play an important role in the diagnosis and follow up of AIDS patients with neurological disorders (3). In addition to infections and neoplasms, catabolic trend of the metabolism of these immunodeficient patients with consecutive thiamine deficiency may result in Wernicke encephalopathy (Fig. 1).

Pediatric HIV infection

Perinatal transmission is the most common route for HIV infection in infants and children. The virus can be transmitted from an HIV-infected mother to her child through pregnancy, birth or breastfeeding. In children, opportunistic infections and tumors are less common than in adults, occurring in 15% of cases (4). Reactivation is not often seen in pediatric patients, owing to their lack of prior exposure to pathogens, which results in a lower rate of infections. The most common CNS presentation of AIDS in children is encephalitis (5). On computed tomography (CT) and MRI, diffuse cerebral atrophy is the most common finding, occurring in 90% of cases. On non-contrast CT studies, basal ganglia calcifications are seen in one-third of infected children (Fig. 2) (4). These calcifications can be observed as early as 2 months of age (5). Foci of increased signal on T2-weighted (W) images that spare the U-fibers may be seen in the peripheral and deep cerebral white matter on MRI. Contrast enhancement is not a characteristic finding of these lesions and may be absent. Isolated reports of cerebrovascular disease in children with HIV have been described in the literature, including aneurysms, infarctions, and hemorrhage. Because most of these patients are asymptomatic during the early stages of the disease, screening of high-risk children is advisable for the early detection of cerebrovascular abnormalities (6).

From the Departments of Radiology (E.Ş. ✉ eurger@yahoo.com, K.K.O., B.Ö., A.C.), Neurology (A.K.), and Internal Medicine [Division of Infectious Diseases] (G.Ö., S.Ü.), Hacettepe University School of Medicine, Ankara, Turkey.

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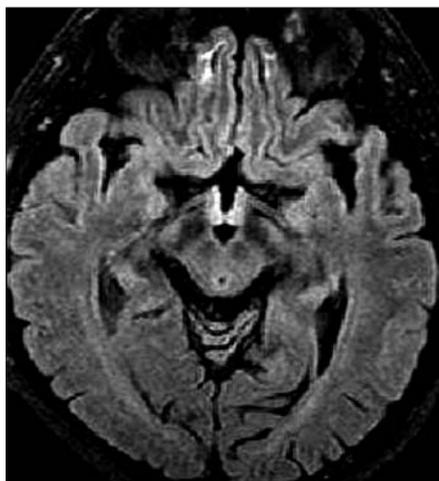


Figure 1. Axial FLAIR image of an AIDS patient with Wernicke encephalopathy shows hyperintense signal of the mammillary bodies.



Figure 2. A 1-year-old girl with developmental delay and fever. Axial non-enhanced CT image shows basal ganglia calcifications.

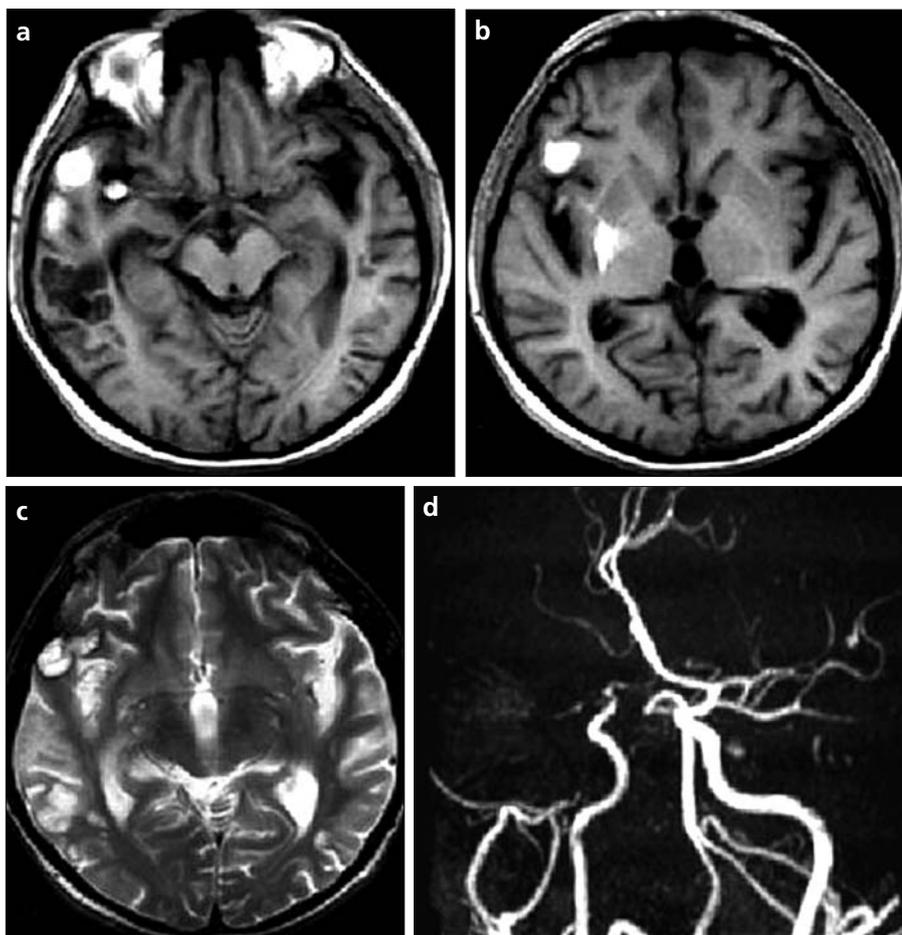


Figure 3. a–d. A 41-year-old male with numbness of the whole left side. T1-weighted axial MR images (a, b) demonstrate HIV vasculitis as hemorrhagic infarct of the right anterior temporal lobe and lentiform nucleus. There is also chronic infarct of the posterior temporal lobe. A small saccular small aneurysm at the middle cerebral artery (MCA) bifurcation is depicted (a). On axial T2-weighted MR image obtained a few months later (c), chronic stage of the previous hemorrhagic subacute infarct is seen with peripheral hemosiderin rim on the anterior temporal lobe; posterior chronic infarct is depicted again. MR angiography (d) shows occluded right MCA and a small saccular aneurysm on the anterior trunk of the left MCA.

HIV vasculitis

HIV-related vasculitis including a primary HIV vasculitis has been described in pathologic studies of AIDS patients. The lenticulostriate vessels are the most vulnerable (7). Joshi et al. (8) have suggested that the elastic lamina of vessels may be injured by elastases because of repeated infections. Shah et al. (5) postulated that the inflammation begins in the adventitia and involves the vasa vasorum, which leads to ischemia of the arterial wall, resulting in the destruction of elastic lamina and subintimal fibrosis. This panarteritis could then lead to stenosis and/or aneurysmal dilatation (9). Resultant infarcts or hemorrhages can occur (Fig. 3) (5).

HIV encephalitis

HIV encephalitis, also called AIDS-dementia complex (ADC) or HIV-associated dementia complex, is a progressive subcortical dementia, attributed to direct infection of the CNS with HIV (10). HIV causes an encephalitic illness in up to 60% of patients with AIDS and frequently coexists with other AIDS-related intracranial abnormalities (1). The pathogenesis of ADC is not completely understood. It is suggested that increased proliferation of HIV or a macrophage-initiated cascade of events even in the absence of a high viral load in the brain may lead to brain dysfunction and clinical dementia (10). Both CT and MRI have low sensitivity in identification of early disease due to the microscopic size of lesions. The most frequent radiological finding is atrophy of the brain (Fig. 4). On MRI, unilateral hyperintense lesions are usually present on T2W images, mostly in the frontal lobe, and progress to bilateral involvement. In the later stages, MRI reveals a diagnostic pattern of abnormalities: extensive and symmetric involvement of the deep white matter with typically spared cortical gray matter (Fig. 5). Contrast enhancement and mass effect are not features of lesions in HIV encephalitis (3). Among MRI techniques, magnetization transfer ratio (MTR) may be used to demonstrate macromolecular destruction (myelin and axonal loss) in HIV encephalitis and may help early diagnosis and in differentiation between progressive multifocal leukoencephalopathy (PML) by showing a degree of destruction which is more pronounced in PML (11). Wu et al. have proposed that dif-



Figure 4. A 34-year-old male with loss of orientation to time. Axial T1-weighted MR image shows cerebral cortical atrophy, the most common finding of HIV encephalopathy.

fusion tensor imaging (DTI) measurements acquired in the corpus callosum splenium were significantly associated with dementia severity and with motor speed, a sensitive marker of early cognitive decline in patients infected with HIV (12). On CT scans, abnormal areas of white matter may show decreased attenuation (13).

Opportunistic infections

Toxoplasmosis

Toxoplasma encephalitis occurs in 15–50% of HIV-infected patients (3). Any neurological sign indicative of CNS involvement should lead to neuroimaging studies in HIV-infected patients, as toxoplasmosis is the most frequent and easily treatable opportunistic infection (14). Until proven otherwise, HIV/AIDS patients presenting with focal neurological complaints should be accepted as having CNS toxoplasmosis (15). The corticomedullary junction, basal ganglia, and thalamus are most frequently involved; less commonly the brainstem may be affected (1). Typical CT findings of toxoplasmosis abscesses are multiple iso- or hypodense lesions, enhancing in a ring or nodular pattern with perifocal vasogenic edema and mass effect. The lesions may be hyperdense if hemorrhagic (1). MRI is superior to CT in detecting the lesions and identifying the disease extension. On T2W MRI, the majority of the lesions are hyperintense; however, iso- or hypointense lesions, as well as a mixed pattern, may be found. T1 sig-

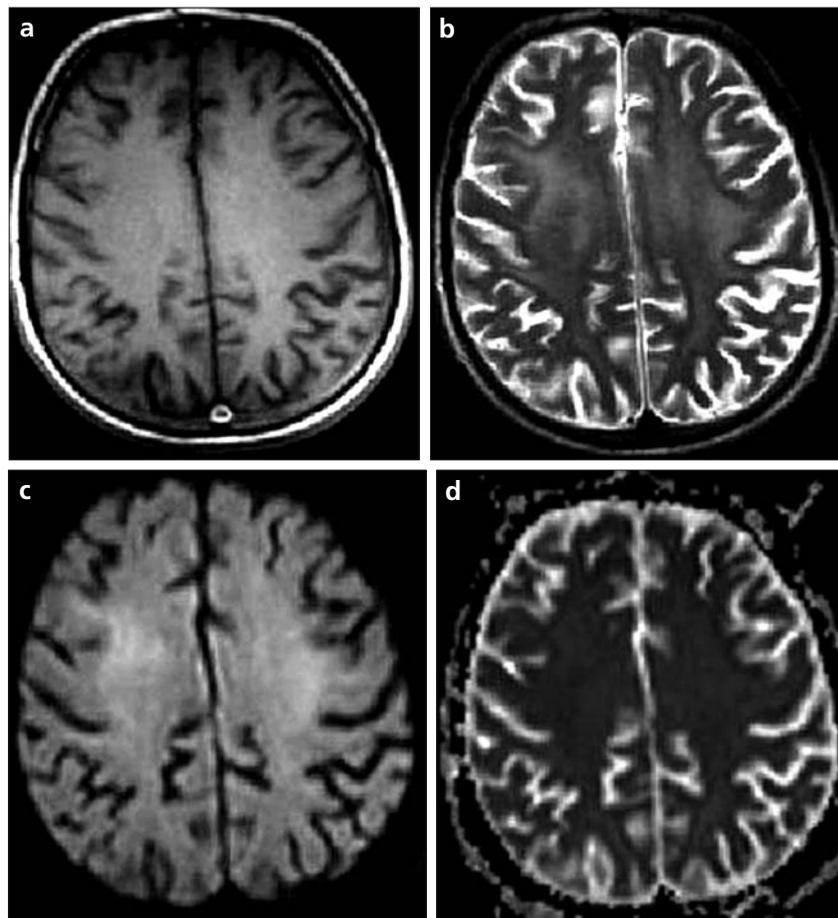


Figure 5. a–d. A 34-year-old male with loss of orientation to time. Axial T1-weighted MR image (a) does not reveal any abnormal signal intensity. Symmetrical and diffuse hyperintensity of the white matter is demonstrated on axial T2-weighted MR image (b); there is a T2 shine-through effect on trace diffusion-weighted image (c), and no apparent change of apparent diffusion coefficient (ADC) value on ADC map (d), and no mass effect compatible with HIV encephalopathy.

nal depends on lesion characteristics, e.g., presence of hemorrhage or calcification (Fig. 6). Pathological contrast-enhancement on imaging is absent or faint with CD4 counts below 50/mm³, and becomes more pronounced as the count increases—that is, when the patient becomes more able to develop an immune/inflammatory response (1). Imaging modalities are also important in follow-up. If the lesions remain stable or increase in size 10–14 days after beginning of a specific treatment, immediate brain biopsy is indicated to exclude lymphoma (3), as distinction between lymphoma and toxoplasmosis lesions is often difficult and may be impossible in some cases on imaging studies. Brain single photon emission computed tomography (SPECT), 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), or MR spectroscopy (MRS) may help in diagno-

sis. On thallium 201 (TI 201) SPECT, in patients with lymphoma abnormal increased uptake of TI 201 is usually seen, whereas in toxoplasmosis no uptake is found (3). On FDG-PET, high FDG uptake most likely represents lymphoma, which should be biopsied for confirmation rather than treated presumptively as infectious (16). On MRS, lactate and lipids are elevated, with reduction or absence of all normal brain metabolites in toxoplasmosis lesions, whereas a prominent increase in choline could be observed in lymphoma (Fig. 7) (2).

Cryptococcosis

Cryptococcus neoformans is the most common intracranial fungal infection and third commonest infecting pathogen in AIDS (1). Cryptococcal meningoencephalitis is still associated with an overall mortality rate of 20%

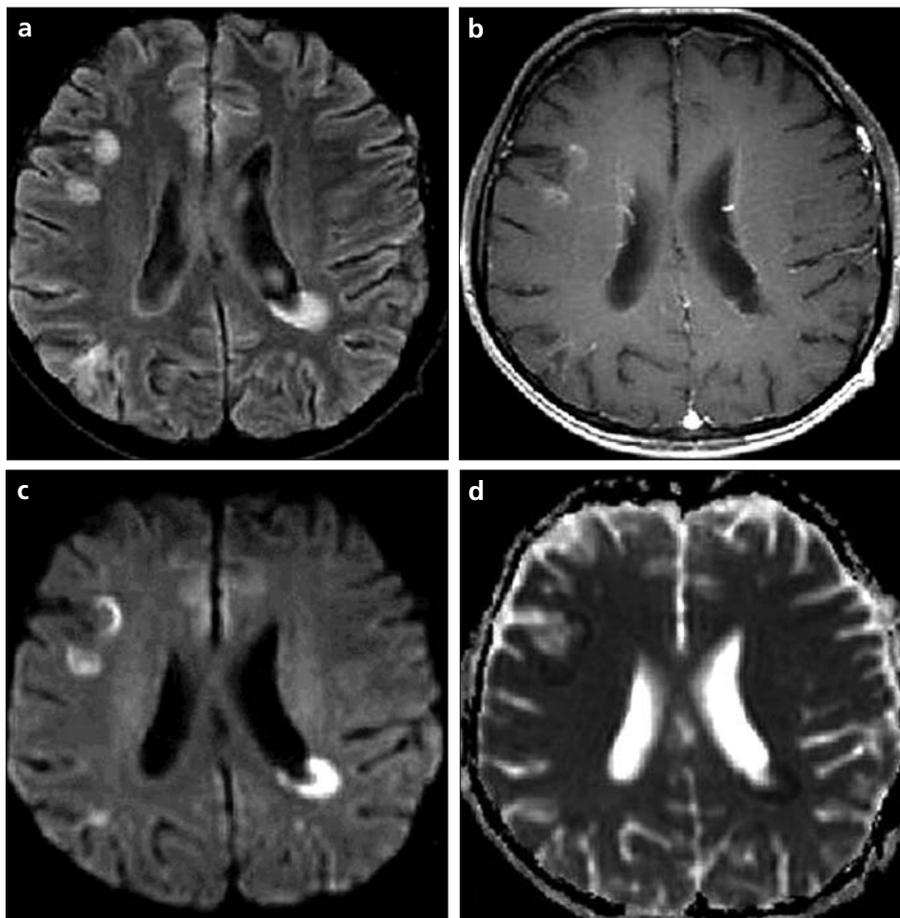


Figure 6. a–d. A 39-year-old male with loss of consciousness. Axial FLAIR MR image shows toxoplasmosis lesions in the corticomedullary junction of the right frontal and parietal lobes and posterior periventricular white matter on the left, (a) which enhance peripherally after gadolinium administration (b). Lesions show restricted diffusion on diffusion-weighted imaging (c, d).

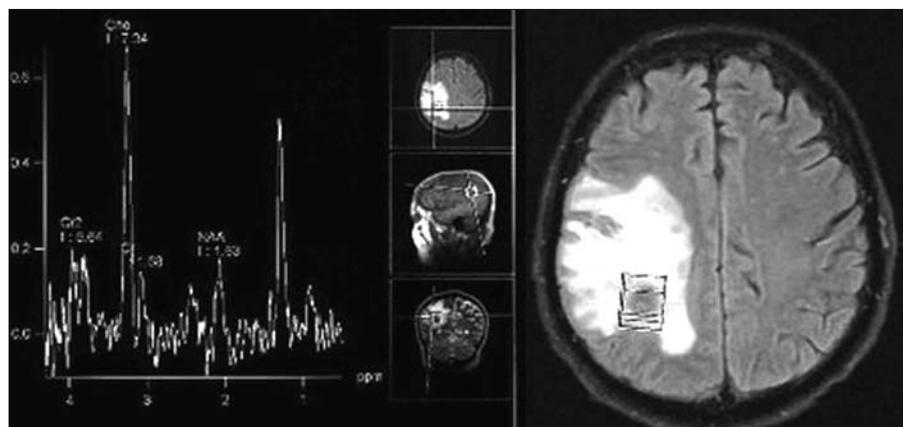


Figure 7. On MR spectroscopy of the right parietal lymphoma lesion, a prominent increase in choline is observed with decrease in N-acetyl-aspartate. The lesion has a high lipid peak.

despite appropriate antifungal therapy (17). Imaging findings are nonspecific, and most often CT and MR images are normal. Nevertheless, meningitis with mild dilatation of the ventricular system or rarely nodular meningeal

enhancement on contrast-enhanced images may be detected. Dilated Virchow-Robin spaces filled with fungi result in the formation of nonenhancing cystic lesions, predominantly seen symmetrically in the basal ganglia

and thalamus. As expected, these lesions are of low density on CT scan, hypointense on T1W MR images and hyperintense on T2W MR images. Another pattern of cryptococcal CNS infection is a solid or ring-like contrast-enhancing parenchymal mass, cryptococcoma, which is extremely rare and found preferentially in the ependyma of the choroid plexus. These findings, although nonspecific, are very suggestive of CNS cryptococcosis in the appropriate clinical setting (3). Between 2002 and 2008 we did not observe an abnormal imaging finding attributable to cryptococcal infection among our AIDS patients.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a fulminating opportunistic infection of the brain that occurs in approximately 4% of AIDS patients; it is caused by the JC papovavirus (18). Primary infection with JC virus occurs in childhood and remains latent. In the setting of severely altered cellular immunity, this virus causes extensive myelin breakdown and white matter destruction, because of its targeting of the oligodendrocytes, the cell responsible for the production of myelin (18). The lesions are typically multifocal hypodensities on CT scans, and hyperintense patchy areas on T2W MR images, which start subcortically (the site of highest blood flow), then extend into the deep white matter. They demonstrate rapid progression in size, resulting in confluence of the lesions (3). Extensive white matter high signal on T2W /FLAIR imaging with sparing of the cortical gray matter is the hallmark of this infection (Fig. 8) (1). There is a lack of mass effect (3). Contrast enhancement, however, especially when faint and peripheral, does not exclude a PML diagnosis (14, 18) and has been considered by Berger et al. to be one of the factors predictive of prolonged survival in AIDS patients with PML, along with higher CD4 counts, possibly because of the patient's ability to mount a better response (19). The lesions may show a central area of marked hypodensity on CT, or they may show hyperintensity on T2W MR images, resembling necrosis (3). While a posterior location has been used as an imaging sign favorable to the di-

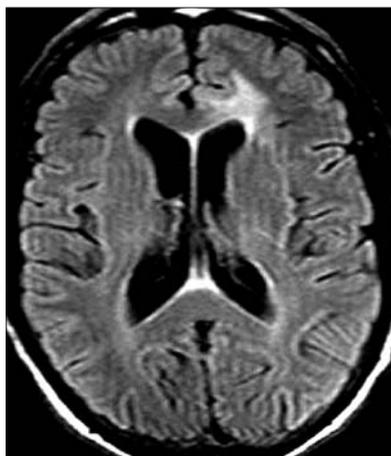


Figure 8. A 12-year-old boy with seizures and headache. Axial FLAIR MR image shows hyperintense signal in the left frontal and periventricular white matter consistent with progressive multifocal leukoencephalopathy.

agnosis of PML, such a location has not been deemed pathognomonic of PML (18). In PML, MTRs are very low (11). DTI also allows quantification of the degree of tissue injury, and these measurements can be used to guide and monitor treatment (20).

Cytomegalovirus infection

Cytomegalovirus (CMV) exists in latent form in general population. As many as 90% of adults have antibodies to it; CMV infection is typically the result of reactivation (1). Radiographic studies of CMV infection in the CNS are nonspecific and, in almost all cases, CT and MRI do not reveal any abnormality (3). Atrophy and ventricular enlargement are present in 40% of the cases (14). Brain involvement is usually in the form of encephalitis, with preferential involvement of periventricular regions and brainstem. Ventriculitis, infarcts, and meningitis are other manifestations. Less commonly, spinal cord, cranial nerves, and the peripheral nervous system may be affected. CT findings, if present, include diffuse white matter hypodensities, ependymal enhancement, and focal ring-enhancing or nodular-enhancing lesions (1). Foci of increased signal on T2W sequences are typical on MRI. Necrotic ventriculitis may cause periventricular subependymal enhancement around the lateral ventricles, septum pellucidum, corpus callosum, and the fornices (Fig. 9); or demyelination may result in diffuse white matter

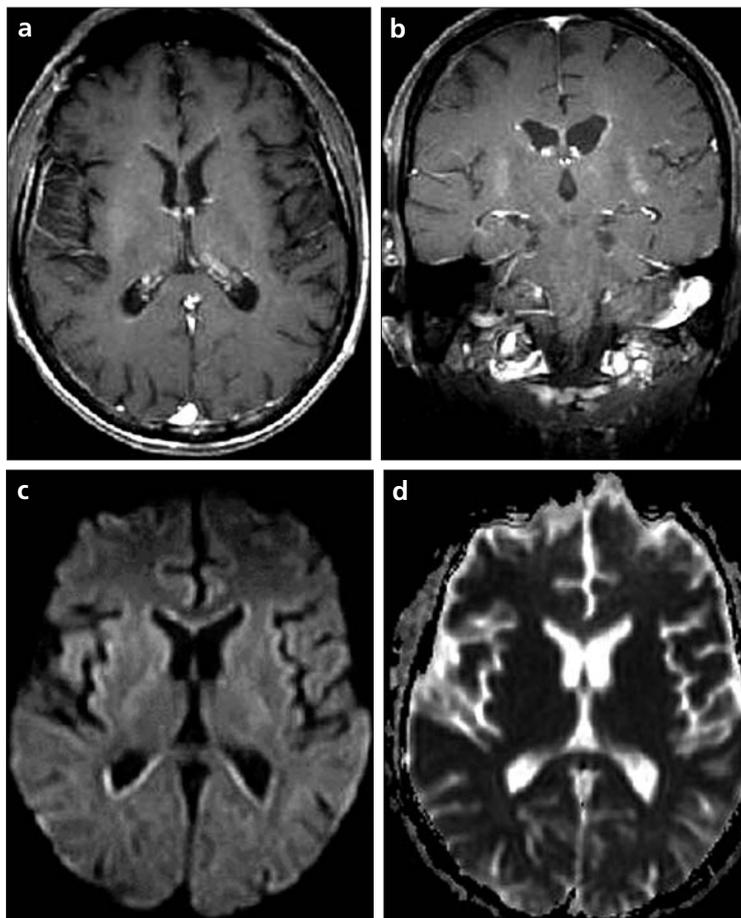


Figure 9. a–d. A 35-year-old male with tonic-clonic convulsions. Contrast-enhanced axial (a) and coronal (b) T1-weighted MR images demonstrate ventriculitis caused by *Cytomegalovirus* infection as periventricular ependymal enhancement. Diffusion-weighted MR image (c) and apparent diffusion coefficient map (d) demonstrate periventricular restricted diffusion.

abnormalities (3). Signs of ventriculitis on imaging studies are supportive of the diagnosis but are nonspecific as they can also occur in *Herpes virus* ventriculitis or lymphoma (14). Because of nonspecific neuroradiological features, the diagnosis of CMV infection must be confirmed by histological identification of typical intranuclear inclusions (owl's eyes) (3).

Tuberculosis

CNS tuberculosis has a high mortality (79%) among AIDS patients, underlining the necessity for an early diagnosis (3). As in the non-AIDS population, basal meningitis usually presenting with increased FLAIR intensity (suggestive of exudate and meningeal enhancement in the basal cisterns) and hydrocephalus are typical findings of CNS tuberculosis (Fig. 10) (3). Rupture of subependymal or subpial granulomata into the cerebrospinal fluid (CSF) or penetration of the walls of meningeal

vessels by hematogenous spread have been proposed for the pathogenesis of tuberculous meningitis (21). Communicating hydrocephalus, which is a common sequela of tuberculous meningitis, primarily results from obstruction of the basal cisterns by the dense inflammatory exudates. Occasionally, the hydrocephalus may be attributable to a focal parenchymal lesion with mass effect or entrapment of a ventricle by granulomatous ependymitis (3, 21). Tuberculomas may result from extension of CSF infection into adjacent parenchyma via cortical veins or small penetrating arteries or may result from hematogenous spread of systemic disease. They may be found anywhere both in the intra- and extra-axial spaces; the majority are said to be supratentorial. Tuberculomas may be solitary or multiple and may show nodular enhancement. Early tuberculomas appear hypointense whereas mature tuberculomas contain a hypointense center

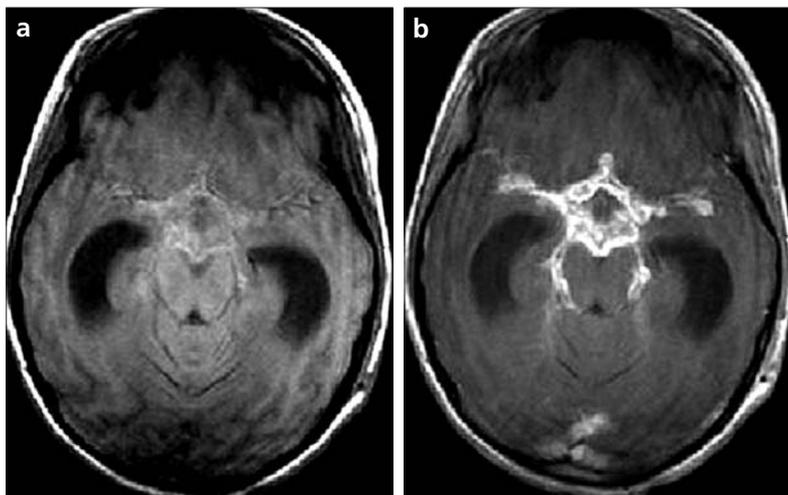


Figure 10. a, b. A 42-year-old male with fever and loss of consciousness. Axial FLAIR MR image (a) shows basal meningitis of tuberculosis infection presenting with increased signal intensity suggestive of exudates. Contrast-enhanced axial T1-weighted MR image (b) shows nodular meningeal enhancement in the basal cisterns; hydrocephalus is also depicted with dilatation of the temporal horns of the lateral ventricles.

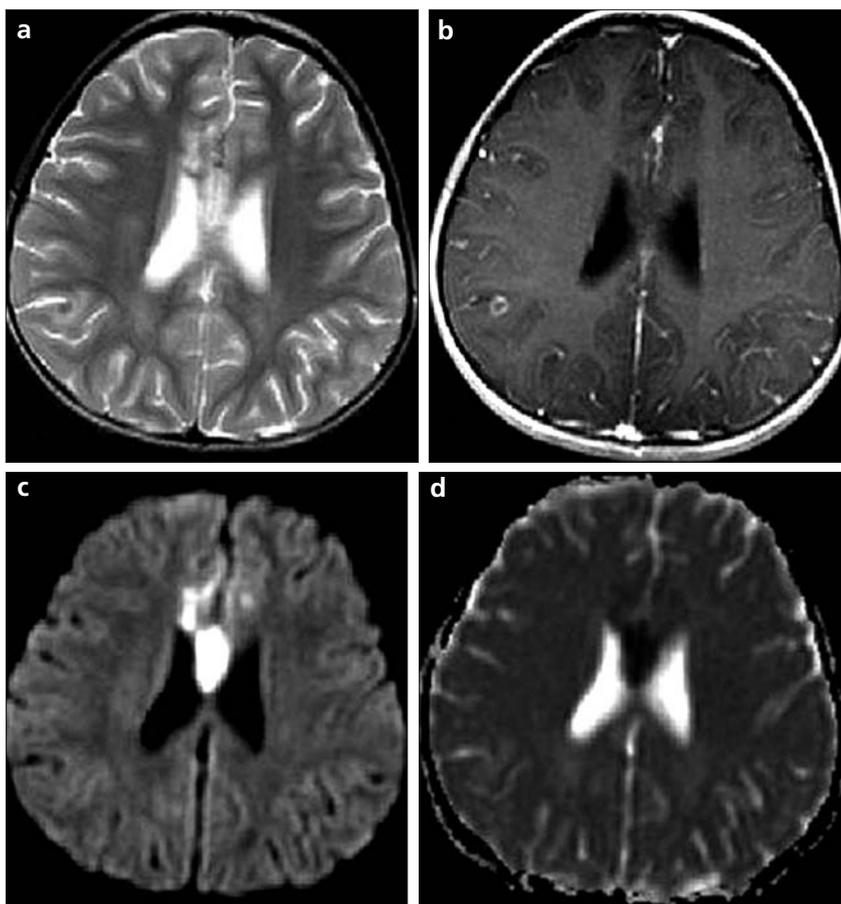


Figure 11. a–d. A 42-year-old male with fever and loss of consciousness. Axial T2-weighted MR image (a) shows tuberculoma of the right parietal lobe with hypointense center surrounded by hyperintense capsule that enhances peripherally on contrast enhanced axial T1-weighted MR image (b). Acute infarct of the corpus callosum with restricted diffusion is also depicted on diffusion-weighted MR image (c) and apparent diffusion coefficient map (d).

surrounded by an isointense capsule on T2W MRI sequences (Fig. 11) (21). Tuberculous abscesses are rare, tend to be larger than tuberculomas, and have a more accelerated clinical course. They are mostly multiloculated, and central liquefaction with pus formation appears hyperintense on T2W images. Significant edema and mass effect favor abscess. These ring-like enhancing lesions can pose problems in differentiation from abscesses of other etiologies, especially in the absence of associated findings such as basal meningitis, hydrocephalus, and basal ganglia infarcts (3, 21). Infarction (Fig. 11) is another common complication of CNS tuberculosis, a result of spasm and thrombosis as arterial vessels course through the gelatinous basal exudates. The most common locations are the regions of basal ganglia (1, 3). We used the MR images of a patient without AIDS to demonstrate the imaging findings of tuberculosis infection, as none of our AIDS patients had tuberculosis; however, one should keep in mind that imaging features reported are similar to those in the non-AIDS population.

Syphilis

It has been suggested that the natural history of syphilis is altered by HIV infection, because HIV-infected patients are more likely to progress to clinical neurosyphilis, and neurologic symptoms develop after shorter latent periods than in non-AIDS population (22). Typical imaging findings are ischemic infarcts in the perforator vessel territory of the basal ganglia or brainstem or in the large vessel territory of the middle cerebral artery. Syphilitic cerebral gummas are uncommon. They appear as isolated, peripherally located nodules on CT that appear isodense to cortex and enhance intensely following iodinated contrast material administration (1). On MRI, they are isointense to gray matter on T1W sequences, usually enhance homogeneously, and are hyperintense on T2W sequences. Cranial nerve involvement, particularly of the optic and vestibulocochlear nerves, has also been reported (1, 23).

Lymphoma

Parallel with the rising frequency of AIDS, the prevalence of primary CNS lymphoma (PCL) has increased to 6% among AIDS patients (3). Unlike classical PCL, AIDS-related lymphoma can

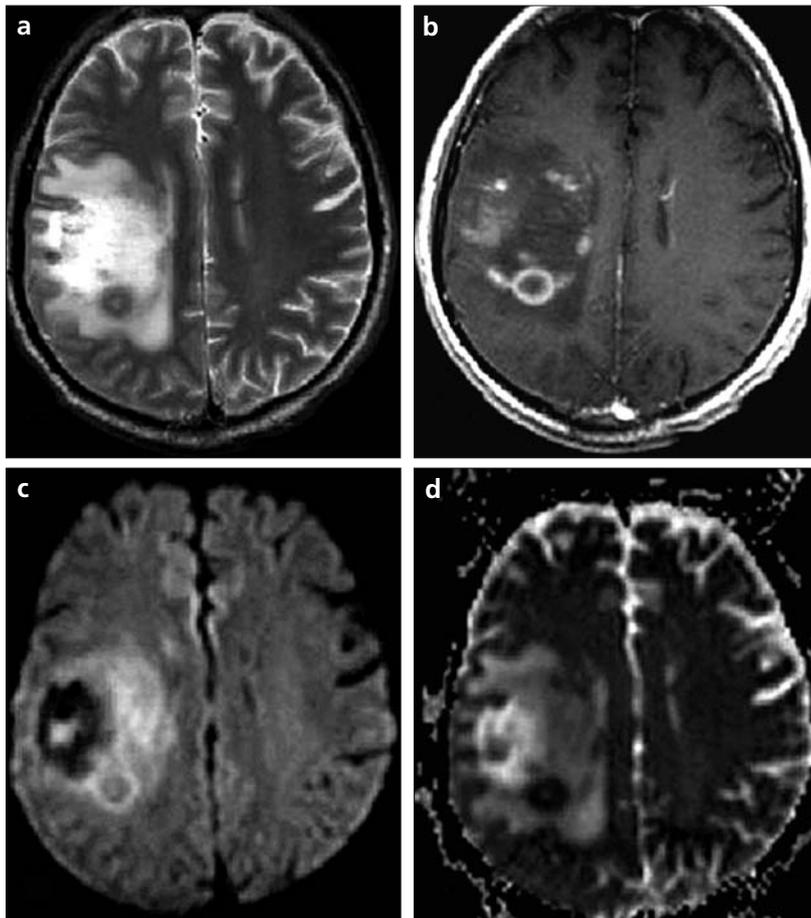


Figure 12. a–d. A 54-year-old male with left-sided weakness. Frontal and parietal diffuse edematous area is seen with hypointense nodular lesions on axial T2-weighted MR image (a). On contrast enhanced axial T1-weighted MR image (b), these lesions show nodular enhancement accompanied by linear enhancement at the margins of a lesion, tracking along perivascular spaces, highly suggestive of primary central nervous system lymphoma. Posterior larger lesion shows restricted diffusion on diffusion-weighted MR image (c) and apparent diffusion coefficient map (d).

be cortical, tends to involve gray and white matter, is associated with leptomeningeal thickening, and may induce vasculitis (1). PCL predominantly involves the basal ganglia, corpus callosum, periventricular white matter, frontal lobes, and thalamus; it is occasionally confined to the subependymal regions or can even be wholly intraventricular (1, 3). It is typically isointense to gray matter on T2W MR images, usually with a moderate peripheral edema. The iso-/hypointensity of the central areas is the result of necrosis due to the coagulation necrosis and thrombosis of the vessels. The lesion shows heterogeneous or ring-like, irregular nodular type enhancement (3). Linear enhancement at the margins of a lesion, tracking along Virchow-Robin perivascular spaces, is highly specific for PCL (Fig. 12) (24). A large (more than 3.5 cm in

diameter) prominently enhancing lesion, localized in the deep white matter, close to the midline, or a periventricular lesion, with a moderate degree of edema and mass effect with rapid progression, should be suggestive of PCL (3). The major differential diagnosis is toxoplasmosis, and, as mentioned previously, biopsy may be often indicated. SPECT, FDG-PET, and/or MRS may help in diagnosis, before performing interventional procedures or surgery.

Conclusion

CT and MRI are both excellent means of detection of cerebral lesions in AIDS patients, useful in initial diagnosis and in therapeutic follow-up evaluation. MRI has a higher sensitivity. Imaging findings of the lesions in HIV-infected patients may overlap, and differential diagnosis may be difficult; however,

certain imaging characteristics and localizations of lesions may favor the diagnosis. Adjunctive imaging tools such as proton MRS, perfusion-weighted MRI, CT, or MR angiography may help to identify certain pathologic abnormalities to highlight the diagnosis.

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