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Review Article

Central nervous system manifestations in HIV: magnetic resonance imaging pictorial review

Lipika Gupta[1], Archit Gupta[2]*

[1]Department of Radiodiagnosis, NEIGRIHMS, Shillong, Meghalaya, India
[2]Department of Radiodiagnosis, SNMC, Agra, Uttar Pradesh, India

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***Correspondence:**
Dr. Archit Gupta,
E-mail: architgrmc@gmail.com

ABSTRACT

Human immunodeficiency virus (HIV) is a member of the *Retroviridae* (retrovirus) family. It is associated with immunodeficiency, neurological diseases and neoplasms. With the use of antiretroviral therapy (ART), the prognosis of people who are infected with HIV has improved, and the incidence of HIV-related central nervous system (CNS) diseases has markedly decreased. In spite of that the mortality from HIV-related CNS diseases remains significant. Magnetic resonance imaging (MRI) has improved the perspective for people with HIV with the help of early diagnosis and prompt treatment. There are various conditions which come under the spectrum of CNS manifestations of HIV for e.g., HIV encephalopathy, progressive multifocal leukoencephalopathy (PML), HIV-related primary CNS lymphoma (PCNSL), CNS toxoplasmosis, other diseases caused by opportunistic infections like CNS cryptococcosis, CNS tuberculosis and immune reconstitution inflammatory syndrome (IRIS). Each condition shows certain specific MRI features which aid in diagnosis. Although, distinguishing between HIV-related CNS diseases based on imaging alone is sometimes difficult, in this review, we discuss the spectrum and imaging features that can contribute to their early differentiation.

Keywords: HIV, HIV-AIDS related central nervous system diseases, Magnetic resonance imaging

INTRODUCTION

The development of an identifiable neurologic syndrome in an HIV-infected person is the end result of a chain of events, determined by the properties of the virus itself, interactions with the environment (including treatment) and the genetic characteristics of the host. HIV-associated neurological syndromes can be classified as primary HIV neurological disease (in which HIV is both necessary and sufficient to cause the illness), opportunistic neurologic diseases (in which HIV interacts with other pathogens, resulting in opportunistic infections and tumors), and treatment-related neurological disease (such as IRIS).[1] MRI, a minimally invasive and a highly reliable imaging technique, is one of the best imaging tools for not only diagnosing but also monitoring the HIV-related CNS diseases. This article thereby reviews the spectrum and imaging features of CNS diseases in HIV-AIDS.

The neurological illness observed in HIV positive patients are divided into primary and secondary.

Primary illness includes distal asymmetric polyneuropathy (DSPN), AIDS dementia complex (ADC), acute inflammatory demyelinating polyneuropathy (AIDP) and stroke syndromes.

Tuberculous bacterial meningitis, cryptococcal meningitis, toxoplasmosis, PML and neurosyphilis are the secondary neurological illnesses.

Primary CNS lymphoma and Kaposi sarcoma are the two HIV associated malignancies.

These conditions can also be classified based on MRI pattern like diffuse and bilateral involvement seen in HIV encephalopathyl; focal brain lesions in CNS toxoplasmosis, primary CNS lymphoma, progressive multifocal leukoencephalopathy; meningitis/ meningoencephalitis seen in CNS-cryptococcosis and CNS tuberculosis and others patterns those seen in IRIS and HIV related cerebral infarction.[2]

There is a correlation between the serum CD4- positive T-lymphocyte counts and risk of HIV related CNS diseases. A cell count >500 cells/mm^3 has same risk as in immunocompetent host. Count between 200-500 cells/mm^3 shows increased risk if HIV-associated neurocognitive disorders (HAND) and cell count of <200 cells/mm^3 has shown increased risk of toxoplasmosis, HIV encephalopathy, cryptococcosis, PML and primary CNS lymphoma.[2]

HIV encephalopathy

HIV encephalopathy is considered a neurocognitive disorder caused by HIV. In early course of the infection, patients usually have no cognitive symptoms. However, in later stages, they show cognitive symptoms. The pathological correlation shows leukoencephalopathy characterized by diffuse myelin and axonal degeneration.[3] Since, in many cases, the symptoms improve with ART, it is essential to diagnose the disease at the earliest.[4,3]

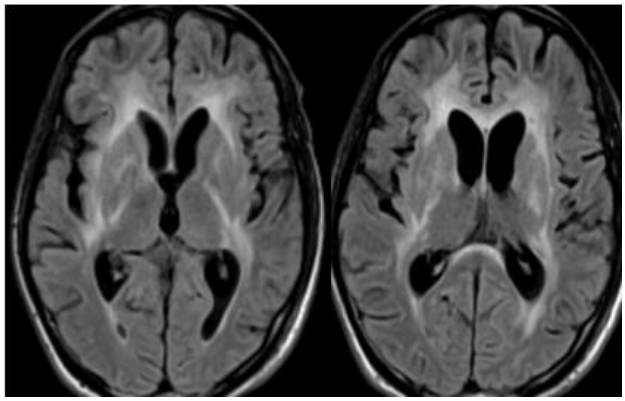

Figure 1: HIV encephalopathy; axial FLAIR (fluid-attenuated inversion recovery) image demonstrating diffuse parenchymal atrophy with periventricular white matter hyperintensity (plaques of white matter demyelination).[5]

HIV encephalopathy is seen on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, where we see an increased signal in bilateral deep white matter, rarely, involving the subcortical structures or the brain stem. This finding is usually apparent in the advanced stages of the disease and is usually followed by progressive brain atrophy (Figure 1).[5]

CNS toxoplasmosis

Toxoplasma gondii is an intracellular parasite that is the most common etiological agent of focal CNS disease in patients with HIV-AIDS in western countries.[6] The relative incidence of CNS-toxoplasmosis was 72% in 1991 which drastically decreased to 19% in 1996 due to improvement in treatment.[7] The seroprevalence of antibodies against *T. gondii* varies substantially among different geographic regions, with a prevalence of ~11% in the United States and 50-80% in certain European, African and Latin American countries.[8] Humans may contract the infection by eating undercooked meat (pork and lamb) containing tissue cysts or by consuming food or water contaminated with oocysts. In patients with HIV, it primarily arises due to reactivation of a latent infection with the most common manifestation being focal encephalitis.

The definitive diagnosis of CNS-toxo requires an appropriate clinical syndrome, detection of the parasite in clinical samples and identification of one or more mass lesions on radiological imaging.[8] In patients with severe immunosuppression, a negative result of antibodies does not exclude the diagnosis of CNS-toxo because up to 20% of the patients with HIV, may not have detectable antibody titers.[5]

The distinctive MRI findings of CNS-toxoplasmosis are multiple masses, representing *T. gondii* abscesses of approximately 2-3 cm in diameter, with ring contrast enhancement and surrounding vasogenic edema (Figure 2). The most common sites being the basal ganglia, thalamus, subcortical white matter, and cerebellum.[5,9] Typical contrast enhancement may not be seen if the serum CD4-positive T lymphocyte count is <50 cells/mm^3.

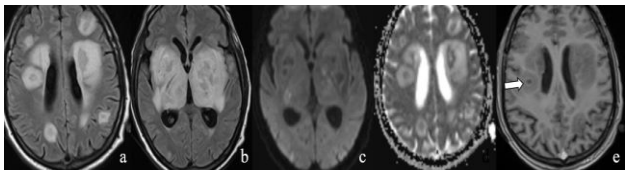

Figure 2: CNS toxoplasmosis; axial FLAIR MRI images; (a and b) multiple masses with surrounding vasogenic oedema in bilateral basal ganglia, thalami and subcortical white matter; (c) diffusion weighted imaging showing mild peripheral diffusion restriction corresponding to low value on (d) ADC map; (e) post-gadolinium T1 axial image demonstrating ring enhancement (white arrow).[5,9]

The pathognomonic signs for CNS-toxo are an eccentric target sign on contrast-enhanced T1-weighted images and a target sign on T2-weighted images. The target sign is seen as concentric high and low signal areas.[10] An eccentric target sign is characterized by a ring-enhancing lesion with an enhanced eccentric nodule (Figure 3). The ring corresponds to an inflammatory vascular zone at the

edge of a necrotic lesion and the eccentric nodule is a cluster of thickened vessels.[11,12]

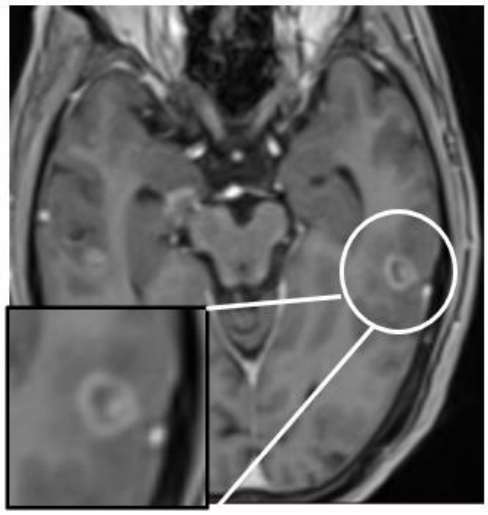

Figure 3: Eccentric target sign seen on contrast-enhanced T1-weighted axial image in CNS toxoplasmosis.[11,12]

Primary CNS lymphoma

PCNSL accounts for up to 15% of non-Hodgkin lymphomas in HIV-infected individuals.[13] The incidence of PCNSL in HIV-infected individuals is 2-6%, 1,000 times higher than that in the general population.[14] Affected individuals typically have serum CD4-positive T lymphocyte counts <50 cells/mm^3.

HIV-related PCNSL is characterized by lesions (solitary>multiple), having a larger diameter (usually ≥4 cm), most commonly involving the basal ganglia/periventricular region and corpus callosum.[15] HIV-related PCNSL is more aggressive than that in immunocompetent patients as it more frequently exhibits central necrosis and spontaneous haemorrhage within the lesion.16 Contrast enhancement is often irregular and peripheral, forming a ring-like enhancement (Figure 4) similar to that seen in CNS toxoplasmosis.

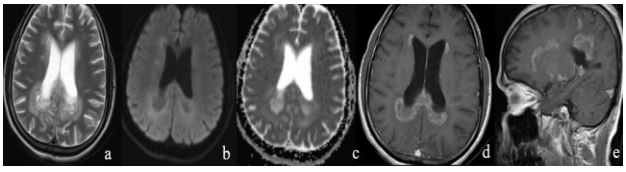

Figure 4: PCNSL; axial T2 weighted MRI image (a) multifocal heterogeneous lesions in bilateral periventricular region with involvement of splenium of corpus callosum showing patchy peripheral diffusion restriction on DWI image; (b) corresponding to low signal on (c) ADC map; axial (d) sagittal; (e) post contrast MRI images showing peripheral enhancement with central non-enhancing areas and leptomeningeal spread.[15,16]

PML

PML is a subacute, progressive, demyelinating disease caused by infection due to JC virus which causes oligodendrocyte damage.[2] It has a worldwide distribution and seroprevalence of 39-69% among adults in the general population. Primary JC virus infection is asymptomatic in childhood, however, in adulthood it can get reactivated in a state of severe immunodeficiency.[17]

The MRI finding for PML is the presence of asymmetrically located white matter lesions typically involving the subcortical U-fibres (Figure 5). The lesions show a low signal on T1-weighted image and a high signal on T2-weighted images.[18] Contrast enhancement is generally negative, but sometimes subtle enhancement may be seen at the margins of the lesions. It may be challenging to differentiate PML from other diseases like multiple sclerosis or gliomatosis with imaging findings alone. However, subacute lesions showing progression on repeat imaging together with worsening clinical symptoms and the uniquely uneven degree of demyelination within the lesion is often diagnostic of PML.

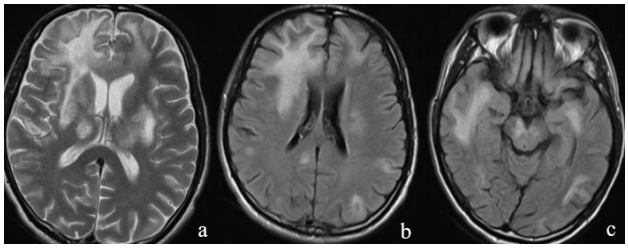

Figure 5: Progressive multifocal leukoencephalopathy; axial T2 weighted (a) FLAIR (b and c) bifrontal, left parietal and bitemporal white matter hyperintensities with involvement of the subcortical white matter/U-fibres.[18]

CNS cryptococcosis

HIV infection is considered the most common risk factor for cryptococcosis infection that is caused by a fungi known as *Cryptococcus neoformans*. *Cryptococcus spp.* enters the human body by inhalation, and in most of the cases it is eliminated by host defense mechanism. However, in some cases, especially in HIV-infected immunocompromised patients, it may lead to lung infection (pneumonia) and then subsequent CNS dissemination resulting in meningoencephalitis. Even though HIV infection is the major risk factor for CNS-cryptococcosis, spread to the CNS is also seen in HIV-negative immunocompromised as well as immune-competent individuals.[19]

The radiologic manifestations of CNS-crypt vary and are frequently minimal. MRI findings are non-specific or, most often, normal.[20] In HIV-infected patients presenting with fever, CNS-cryptococcosis should be considered

irrespective of positive or negative MRI findings.[21] The positive imaging findings in CNS-crypt correspond to three main forms i.e., gelatinous pseudocysts, meningitis/meningoencephalitis and a granuloma called cryptococcoma (Figure 6).

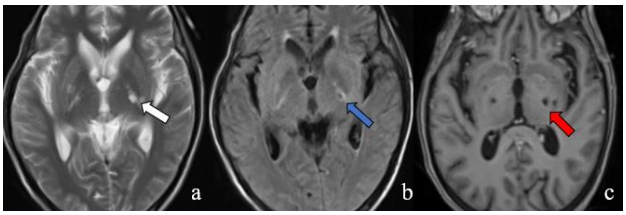

Figure 6: CNS cryptococcoma; axial T2 weighted (a), FLAIR; (b) T1 post contrast; (c) MRI showing few lesions in bilateral lentiform and caudate nuclei appearing hyperintense on T2WI (white arrows) and showing incomplete suppression on FLAIR (blue arrow); on post contrast study, few lesions show subtle peripheral enhancement.[22]

Meningitis/meningoencephalitis is the primary lesion of CNS-crypt and is more pronounced at the basal cisterns. If the meningeal infection spreads along the perivascular spaces, gelatinous mucoid-like cryptococcal capsular polysaccharides accumulate in the dilated perivascular spaces and form small cysts known as gelatinous pseudocysts. These cysts have a "soap bubble appearance" on MRI, exhibiting a low to intermediate signal on T1-weighted images, a high signal on T2-weighted images, and a low signal on FLAIR images.[22] They are often found in the basal ganglia, thalamus, and midbrain. However, in patients with severe immunosuppression, the only positive imaging findings pointing towards CNS-crypt maybe mild/non-enhancing cystic lesions and bilateral symmetrical perivascular space enlargement.

CNS tuberculosis

CNS-TB is caused by *Mycobacterium tuberculosis*. The primary infection is in the lung which gets disseminated through the bloodstream to the brain. The most common manifestations of CNS-TB are meningitis, tuberculoma and abscess and can be seen separately or simultaneously.[5,23] In 2017, 10 million people developed tuberculosis globally, amongst which 9% of the population had HIV.[24]

In patients with CNS-tubercular meningitis, characteristic neuroimaging findings include hydrocephalus, basilar exudates, periventricular infarcts and cerebral parenchymal tuberculomas, which might be seen together or separately.[23,25-27] Meningitis is more frequent in those infected with HIV than non-HIV tubercular infection. In contrast to CNS-crypt, CNS-TB frequently presents as hydrocephalus and meningeal contrast enhancement, especially in the basal cisterns and their presence is strongly suggestive of tuberculous meningitis (Figure 8). Tuberculomas with caseous necrosis show a ring-shaped contrast enhancement, whereas those without caseous necrosis usually show a homogeneous contrast enhancement (Figure 7).[5]

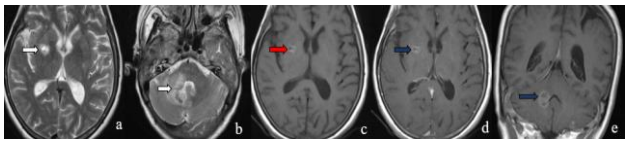

Figure 7: Caseating tuberculomas; axial T2 weighted image (a and b) few ill-defined areas of hyperintensities in right basal ganglia, right middle cerebellar peduncle and the right cerebellar hemisphere (white arrows); axial T1 weighted image; (c) peripheral rim of hyperintensity around the lesion in the right basal ganglia (red arrow); on post contrast (d and e) conglomerate peripheral rim enhancement is seen in the lesions (blue arrows).[5]

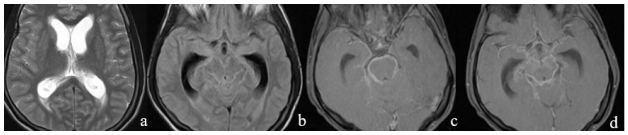

Figure 8: Tubercular meningitis (TBM) with hydrocephalus and basal exudates; axial T2 weighted (a) showing mild dilatation of bilateral lateral ventricles; axial FLAIR; (b) hyperintensities in basal cisterns (s/o exudates); on post contrast study (c and d), there is extensive enhancement of the leptomeninges and basal exudates along the basal cisterns - suprasellar, prepontine, crural, ambient and sylvian fissures.[23,25-27]

Inflammation due to infection can also involve the small blood vessels leading to impaired circulation and vasospasm which may lead to infarction, often bilateral in the basal ganglia.

IRIS

IRIS is a major complication related to anti-retroviral therapy and is a consequence of excessive activation of the immune system against persistent antigens (paradoxical IRIS), viable pathogens (unmasking IRIS), or self-antigens.[27,28] Predisposing factors associated with IRIS development are a serum CD4-positive T lymphocyte count of <50 cells/mm^3. Its prevalence ranges from 7.8 to 13%, and onset occurs 1-1.5 months after initiation of ART.[22,23,28,30]

CNS-IRIS has an acute onset and rapid progression from symptom onset to death. The syndrome may be recognized by the development of new onset symptoms or worsening of existing ones (e.g., opportunistic infections) despite adequate treatment and serological response. Specific abnormalities can be found on radiological imaging-MRI or computed tomography

imaging.[31] Patients should also be monitored for other opportunistic infections that may develop during therapy. Among HIV-related CNS diseases, PML and CNS-cryptococcosis are the most frequently encountered diseases. IRIS develops in at least 18% of HIV-infected patients with PML after starting ART. Dealing with IRIS is especially difficult in these patients as ART is the only effective therapy for PML.[28]

On MRI, a transient increase in parenchymal abnormalities with a high signal on T2-weighted or FLAIR images, peripherally restricted diffusion on diffusion-weighted imaging and presence of enhanced areas on contrast-enhanced T1-weighted images can be valuable clues to diagnose CNS-IRIS. However, a negative MRI finding alone cannot exclude the diagnosis.[28] Although CNS-IRIS is a diagnosis of exclusion, MRI can be useful for early recognition, thereby improving the patient prognosis.

CONCLUSION

HIV can damage any part of the neuraxis either directly or indirectly. Clinical suspicion, radiological imaging and serology together help in accurately diagnosing the infections. There is also equal importance of public education and preventive measures in case of HIV. The survival of these patients can be prolonged with appropriate management of the opportunistic infection and HIV itself. It is important to recognize the primary causal factor because proper therapy dramatically alters the morbidity and also improves the quality of life of these individuals.

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