Central nervous system manifestations of HIV/AIDS: A pictorial essay

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Learning Objectives

• To review imaging appearances of a range of primary, opportunistic and malignant conditions that affect the central nervous system in HIV/AIDS

• To understand the impact of HAART on the epidemiology and imaging patterns of CNS conditions in HIV/AIDS.
Background

Sequelae of HIV/AIDS involving the central nervous system may result from one of four mechanisms:

1. direct consequence of the HIV virus
2. neoplasms related to host immunocompromise
3. opportunistic infections
4. treatment related effects

The introduction of Highly Active Anti Retroviral Therapy (HAART) has led to a dramatic decline in the incidence of HIV related infections and neoplasms. Nevertheless, these are conditions are still seen, most often in the setting of non-compliance with HAART or late presentation.

Direct effects of HIV virus on the central nervous system remain a common clinical entity (albeit with altered epidemiology), and furthermore, the post HAART era has brought with it a new concept - immune reconstitution inflammatory syndrome (IRIS).

Diagnosis of CNS conditions in HIV patients relies on imaging coupled with serological and CSF analysis, and correlation with the extent of immunosuppression, expressed as the declining CD4 count.
DIRECT CONSEQUENCES OF HIV

HIV encephalopathy

HIV encephalopathy is the consequence of direct neuronal damage by the HIV virus after it crosses the blood brain barrier, being carried by monocytes and lymphocytes - the "Trojan horse mechanism". The spectrum of resultant neurocognitive symptoms is wide, with imaging correlate seen predominantly at its severe end (i.e. with HIV associated dementia).

Imaging findings are non specific, and include symmetrical cerebral atrophy with patchy or diffuse T2 hyperintensity in the deep and periventricular white matter (Fig. 1 on page 11). There may be a frontal predominance which may involve the genu of the corpus callosum. There is no mass effect or enhancement with HIV encephalopathy.

The advent of HAART has resulted in up to 50% reduction in the incidence of HIV associated dementia. Paradoxically, as HAART treated patients also live longer, its prevalence may be increasing.

Summary:

Nonspecific, diffuse deep white matter disease resulting as a direct consequence of the HIV virus. There may be a paradoxical increase in its prevalence due to increased survival of the HIV positive population.

HIV associated vacuolar myelopathy

HIV associated myelopathy is a progressive spinal cord disorder seen in late-stage HIV infection and often but not invariably associated with HIV encephalopathy. It may be seen at any stage of HIV infection, but most commonly with CD4 counts <50 cells/µL. Pathological appearance resembles that of subacute combined degeneration of the cord, however the condition is not thought to be related to B12 deficiency.

Imaging appearance is of cord atrophy and T2 hyperintensity that may be diffuse or - like B12 deficiency - limited to the dorsal column (Fig. 2 on page 11).
There have been some reports regarding clinical improvement following antiretroviral treatment.

Summary:

Cord atrophy and diffuse or dorsal column predominant T2 hyperintensity in longstanding HIV, with potential for response to HAART. Imaging (and pathological) differential of subacute combined degeneration of the cord.

NEOPLASMS RELATED TO HOST IMMUNOCOMPROMISED

Primary cerebral lymphoma (PCL)

Non-Hodgkins lymphoma (NHL) is one of the AIDS defining neoplasms (the others being Kaposi's sarcoma and invasive cervical cancer). Although the incidence of lymphoma has decreased in the post HAART era, it remains higher than in the non HIV population.

In the HIV setting, there is a propensity for lymphoma to occur as a primary CNS neoplasm (PCL accounting for up to 15 percent of NHLs in HIV patients compared with 1 percent of NHLs in the general population).

Primary CNS lymphoma is most commonly a diffuse large B cell Non Hodgkins type. It usually occurs in the setting of infection with Epstein-Barr virus and marked immunosuppression, with CD4 counts of less than 100 cells/µL.

Histologically, lymphoma is a dense, cellular neoplasm and this accounts for its characteristic hyperdensity on CT, as well as its frequently low T2 signal and diffusion restriction. Surrounding oedema is generally mild.

Enhancement in CNS lymphoma is classically homogeneous (Fig. 3 on page 12). In the immunocompromised host however it may be heterogeneous (Fig. 4 on page 13) with areas of central necrosis, or indeed absent (Fig. 5 on page 14).

PCL is more commonly multifocal in the setting of HIV (in 30-80% of HIV patients compared to 20-40% of non-HIV patients with PCL). There is a predilection for basal ganglia and periventricular locations and subependymal spread.

Importantly, there is considerable overlap in the appearance of CNS lymphoma and toxoplasmosis, with the two being potentially indistinguishable on imaging. This differential challenge is discussed further with the toxoplasmosis section.
Summary:

Multifocal lesions with mass effect but relatively mild oedema and imaging features reflecting high cellularity. Periventricular location, with or without subependymal spread. Variable and often incomplete enhancement in the immunocompromised setting.

Systemic lymphoma with CNS involvement

Unlike PCL in which almost all patients have parenchymal lesions, secondary CNS lymphoma will present as leptomeningeal metastases in two-thirds of patients (Fig. 6 on page 15), and as parenchymal lesions in one third.

CNS metastases in the HIV patient

CNS metastases from the other AIDS defining malignancies (i.e. Kaposi sarcoma and cervical cancer) are extremely rare.

Notably, there has been an increase in the incidence of non-AIDS defining cancers (e.g. lung and anal cancers and melanoma) in the HIV population since the advent of HAART, most likely due to the longer survival. Therefore, distant metastases must remain in the differential for any intracerebral mass lesion in an HIV patient.

OPPORTUNISTIC INFECTIONS

The decrease in frequency of HIV associated opportunistic infections post HAART has been dramatic. Nonetheless, patients continue to present with these complications, usually in the setting of a delayed diagnosis or non-compliance with therapy.

Toxoplasmosis

Toxoplasmosis is considered the most common CNS infection in patients with HIV. It is caused by the ubiquitous parasite, Toxoplasma gondii and occurs in patients with CD4 counts less than 100 cells/µL. Pathologically, infection typically results in a necrotizing encephalitis.

Imaging appearance is of multifocal mass lesions with a predilection for basal ganglia, thalamus, and corticomedullary junction (Fig. 7 on page 16). Unlike lymphoma, toxoplasmosis is generally hypo- to isodense on CT. On MRI, lesions are T2 hypo to isointense.
Enhancement pattern is ring or nodular. The "eccentric target sign" - a small eccentric enhancing nodule alongside an enhancing ring (Fig. 8 on page 17) is relatively specific for toxoplasmosis, but has a low sensitivity, being present in only 30% of cases.

**Toxoplasmosis vs primary cerebral lymphoma**

The common features of multiplicity, mass effect, enhancement and basal ganglia/corticomedullary location can make it very difficult, if not impossible to differentiate between these two entities.

Hyperdensity on CT favours lymphoma, as do solid enhancement and subependymal spread - when present. When a lesion is solitary, lymphoma is more likely.

Toxoplasmosis abscesses are often smaller and more numerous. Diffusion is greater in toxoplasmosis, however comparative analysis of ADC values demonstrates considerable overlap.

MR spectroscopy (MRS), MR perfusion or thallium SPECT may be of use. In lymphoma, there is typically elevation of choline on MRS, increased rCBV on perfusion and positive thallium SPECT. In contrast, the opposite should be seen in Toxoplasmosis. Lipid and lactate peaks are more suggestive of toxoplasmosis, but may appear with lymphoma if a necrotic area is sampled.

In some cases, diagnosis is made on followup, on the basis of improvement with toxoplasmosis therapy, in which case brain biopsy may be avoided.

**Summary:**

*Multifocal peripherally enhancing basal ganglia and corticomedullary junction lesions. Look for the eccentric target sign. Differentiation from lymphoma may require advanced imaging techniques, trial of therapy or biopsy.*

**Progressive multifocal leukoencephalopathy**

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disorder resulting from latent reactivation of the John Cunningham (JC) virus. It occurs with CD4 counts of 50-100 cells/µL.

MRI findings are of multifocal, bilateral but asymmetric areas of T2 hyperintensity involving predominantly periventricular and subcortical white matter, typically without mass effect or enhancement (Fig. 9 on page 18). Involvement of subcortical U fibres
is common. Occasionally there is cortical involvement. Diffusion restriction may occur at the leading edge in an acute lesion, and in late disease cystic changes may develop. There is some predilection for the parieto-occipital areas, basal ganglia and thalami.

**Summary:**

*Multifocal demyelinating disorder in advanced immunocompromise. Asymmetry is a key feature differentiating from HIV encephalopathy. Lack of mass effect and enhancement separate it from other common differentials such as lymphoma and toxoplasmosis.*

**CNS Tuberculosis**

CNS infection with acid-fast bacilli is usually from hematogeneous spread but may also result from direct extension. It usually occurs when CD4 count is <500 cells/µL.

CNS tuberculosis comes in a variety of forms. Tuberculous meningitis in HIV has a basal predominance, as it does in the immunocompetent.

Tuberculoma can have a variety of radiological features depending on whether they are caseating or not, and whether there is a liquid or solid center. There may be calcification after treatment. A caseating tuberculoma with a liquid centre can be difficult to differentiate from a tuberculous abscess. An abscess is however more likely to be solitary and/or large.

Spinal involvement of tuberculosis manifests as CSF loculation with obliteration of the spinal subarachnoid space. There may be loss of cervicothoracic spinal cord outline and matting of the lumbar nerve roots with nodular enhancement.

**Summary:**

*Tuberculosis can involve multiple regions of the CNS with a variety of radiological features. This can occur at any CD4 level, however generally less than 500 cells/µL.*

**Cytomegalovirus (CMV)**

This ubiquitous herpesvirus does not produce clinical disease in most people with an intact immune system, and remains latent until CD4 counts fall below 50 cells/µL. As with other opportunistic infections, the introduction of HAART resulted in a decreased prevalence of CMV infection and increased survival in AIDS patients.
On imaging, CMV is often seen as a meningoencephalitis or ventriculitis with ependymal, subependymal and periventricular T2 hyperintensity, with or without enhancement (Fig. 10 on page 20).

Parenchymal cerebral involvement is generally nonspecific, with diffuse white matter CT hypoattenuation/ T2 hyperintensity without mass effect, secondary to demyelination.

**Summary:**

*Ventriculitis with or without enhancement in the severely immunocompromised.*

**Fungal Infection**

The most common fungal infections affecting the HIV population are *Cryptococcus* and *Aspergillus* species.

**Cryptococcal Infection**

*Cryptococcus neoformans* is an encapsulated, ubiquitous yeast like fungus found in soil.

Infection occurs with CD4 counts <100 cells/µL. Pathologically, there are three main forms of cryptococcal infection: meningitis, gellatinous pseudocysts and cryptococcomas.

Imaging findings are often minimal, with the most frequent being a nonspecific hydrocephalus.

Cryptococcal meningitis is seen as focal or diffuse meningeal enhancement.

*C. neoformans* pseudocysts occupy and dilate perivascular spaces resulting in the appearance of rapidly growing, nonenhancing "cysts", with variable enhancement (Fig. 11 on page 19). Cryptocccomas are rare mass like parenchymal lesions with nodular enhancement. They have a predilection for the basal ganglia, thalamus, and cerebellum.

**Summary:**

*Variable pattern of cerebral involvement, with the most characteristic being due to perivascular gellatinous pseudocyst formation.*

**Aspergillosis**
Aspergillus species are ubiquitous septate hyaline molds, which may infect the brain via a haematogenous route from lung foci in patients with CD4 counts less than 150. The primary cerebral process is therefore a vasculopathy, which may result in infarction, haemorrhage or parenchymal invasion with abscess formation.

The presence of haemorrhage associated with parenchymal lesions should therefore prompt this differential. Cerebral aspergillosis lesions will have variable ring enhancement and restricted diffusion within the wall, but not the core - importantly differentiating them from pyogenic and tuberculous abscesses.

**Summary:**

*Haematogenous and angioinvasive spread results in the presence of haemorrhage, and/or cerebral abscess formation.*

**TREATMENT RELATED EFFECTS**

**Immune Reconstitution Inflammatory Syndrome**

Immune Reconstitution Inflammatory Syndrome (IRIS) is the paradoxic worsening of clinical and/or radiological illness which may occur when a patient with a low CD4 count and high HIV viral load is commenced on HAART. It typically develops in the first 2 to 12 weeks after starting antiretroviral therapy.

It is thought to result from restoration of the previously suppressed inflammatory immune response to the existing infectious/non-infectious antigens. IRIS has been reported with multiple HIV related conditions, including PML, tuberculosis, cytomegalovirus (CMV), Cryptococcus and Kaposi's sarcoma.

Generally, imaging features include increased oedema, mass effect and enhancement in regions that were previously normal on imaging, or exhibited considerably less florid disease (*Fig. 12* on page 21). Treatment includes corticosteroid therapy, whilst continuing antiretrovirals.

**Summary:**

*Paradoxic worsening of the clinical and radiologic disease in a severely immunocompromised patient commenced on HAART.*
Fig. 1: HIV encephalopathy. Confluent, symmetric periventricular white matter T2/FLAIR hyperintensities - non specific but out of keeping with age in this 50 year old male with progressive cognitive decline. The symmetry and lack of mass effect and enhancement are important in excluding coexisting opportunistic infections.

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Fig. 2: HIV myelopathy. Sagittal (A) and axial (B) T2 images in a patient with gradually progressive sensory neuropathy show atrophy of the cord and signal hyperintensity limited to the dorsal columns. The coexisting cervical degenerative deformity does not account for the extent and distribution of cord signal abnormality.

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Fig. 3: Primary CNS lymphoma in a 35 year old male, non compliant with HAART, who presents with a CD4 count of 113 cells/uL. (A) Non contrast CT; (B) FLAIR; (C) DWI; (D) post gadolinium. Multiple periventricular lesions are hyperdense on CT. MRI shows FLAIR hyperintensity that extends along the ependyma, homogeneous diffusion restriction suggestive of lesion hypercellularity, and homogeneous enhancement in the same characteristic distribution.

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Fig. 4: Primary CNS lymphoma with central necrosis in a 47 year old male with a CD4 count of 12. (A) Non contrast CT; (B) T2-weighted MRI; (C) DWI; (D) post gadolinium T1-weighted. There is an enhancing and diffusion restricting, peripherally located lesion with relatively mild surrounding oedema. A second lesion (not shown) was present in the cerebellar vermis. This appearance and multiplicity of lesions makes it difficult to differentiate between lymphoma and toxoplasmosis. In this case however the CT hyperdensity does favour lymphoma and the diagnosis was confirmed on biopsy.

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**Fig. 5:** Primary CNS lymphoma in 40 year old male with endstage HIV and concomitant disseminated intra-abdominal MAC and ileal Kaposi sarcoma. (A) FLAIR; (B) DWI; (C) T1-weighted and (D) post gadilinium T1 weighted MRI. There are T2 hyperintense lesions with mass effect and mild surrounding oedema in a periventricular distribution typical for cerebral lymphoma. There is however a striking lack of enhancement when comparing to the precontrast image, and lack of diffusion restriction. The appearance likely reflects the patient's profound immunocompromise. The patient passed away several days after this imaging. Post mortem confirmed primary cerebral diffuse large B-cell lymphoma.
**Fig. 6:** Secondary leptomegeal lymphoma in a 42 year old male, CD4 count 140 cells/uL. (A) post gadolinium sagittal; (B, C) T2-weighted axial MRI. There is irregular lumbar nerve root thickening and enhancement. There is also concurrent retroperitoneal lymphadenopathy, including a large nodal mass shown on image B.

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**Fig. 7:** Toxoplasmosis in 35 year old male, CD4 83 cells/mL. (A & B) FLAIR; (C) DWI; (D) post gadolinium T1 weighted MRI. Multiple lesions with peripheral enhancement and diffusion restriction, centred on basal ganglia and corticomedullary junctions.

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Fig. 8: Eccentric target sign of toxoplasmosis. Examples in two patients.

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**Fig. 9:** Progressive multifocal encephalopathy (PML). (A & B) FLAIR; (C) post gadolinium T1, (D) DWI. Asymmetric non-enhancing T2 hyperintensities, which extend to the subcortical U-fibres. Importantly there is no mass effect, despite the fairly extensive signal abnormality on the left, and the almost "mass-like" appearance of the lesion in the right frontal lobe. Some diffusion restriction is present at the margin of the left-sided lesion.

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**Fig. 11:** Cryptococcosis in a 40 year old male with a CD4 count of 116 cells/uL. (A) T2-weighted and (B) post gadolinium T1-weighted MRI. Multiple rounded T2 hyperintense foci, which are likely dilated perivascular spaces and multifocal enhancement in a perivenular distribution. CSF culture was positive for cryptococcus.

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**Fig. 10**: CMV ventriculitis. Ependymal enhancement in a patient with HIV complicated by CMV meningitis/ventriculitis.

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**Fig. 12:** PML-IRIS in a 42 year old male, CD4 count 74 cells/μL. (A & D) Initial T2 and post gadolinium T1 weighted images show asymmetric cerebellar white matter T2 hyperintensity without mass effect or enhancement. Diagnosis of PML was made. (B & E) 2 weeks later, HAART has been commenced and CD4 count is improving, but the patient is deteriorating clinically. There is now more extensive T2 signal change and new enhancement. This is in keeping with IRIS. (C & F) another 2 weeks later there is improved signal change and resolution of enhancement. The patient has been treated with corticosteroids.

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Conclusion

Imaging diagnosis in the HIV patient with cerebral pathology relies on the interplay between radiological findings and quantification of immunosuppression. The radiologist should be aware of the changing epidemiology of HIV complications in the post-HAART era.
Personal Information

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References


