8 Neurological Illnesses Involved in Human Immunodeficiency Virus and Human T cell Lymphotropic Virus Infections

Manish Ramesh Patil and Imran Rizvi

Abstract

Human immunodeficiency virus (HIV) is a virus from the Lentivirus subgroup, of the Retroviridae family. Neurological involvement is frequent in pediatric human immunodeficiency virus infection and acquired immunodeficiency syndrome (AIDS). Direct invasion of the central nervous system by HIV type 1 (HIV-1) may result in HIV-1 associated encephalopathy, categorized as normal neurological findings, static encephalopathy, or as progressive encephalopathy. Aseptic meningitis, acute encephalitis (HIV-associated neurological disorder, HAND), and polyneuropathy typically occur earlier in the illness, whereas AIDS dementia complex often presents later. HIV/AIDS-associated encephalopathy is linked to HIV's tropism for macrophages or microglial cells, and for lymphocytes (CD4+). In HIV infection with neurologic manifestations, a CSF analysis and neuroimaging is mandatory for ruling out other opportunistic infections. The Retroviridae family also comprises of the Human T cell lymphotropic virus, HTLV. CNS involvement is principally from immunologically mediated insult. HTLV type 1 has a classical neurogenic presentation of myelopathy, labeled as HAM, HTLV-1-associated myelopathy, or as TSP, tropical spastic paraparesis. However, HAM/TSP is not the only neurological outcome that can result from HTLV-1 infection. Cases of complicated encephalitis have been reported in patients afflicted with HTLV type 1 infections.

Keywords

Human immunodeficiency virus · HIV-associated neurocognitive disorder · Myelopathy · Human T cell lymphotropic virus

M. R. Patil · I. Rizvi (✉)
Department of Neurology, King George's Medical University, Lucknow, Uttar Pradesh, India

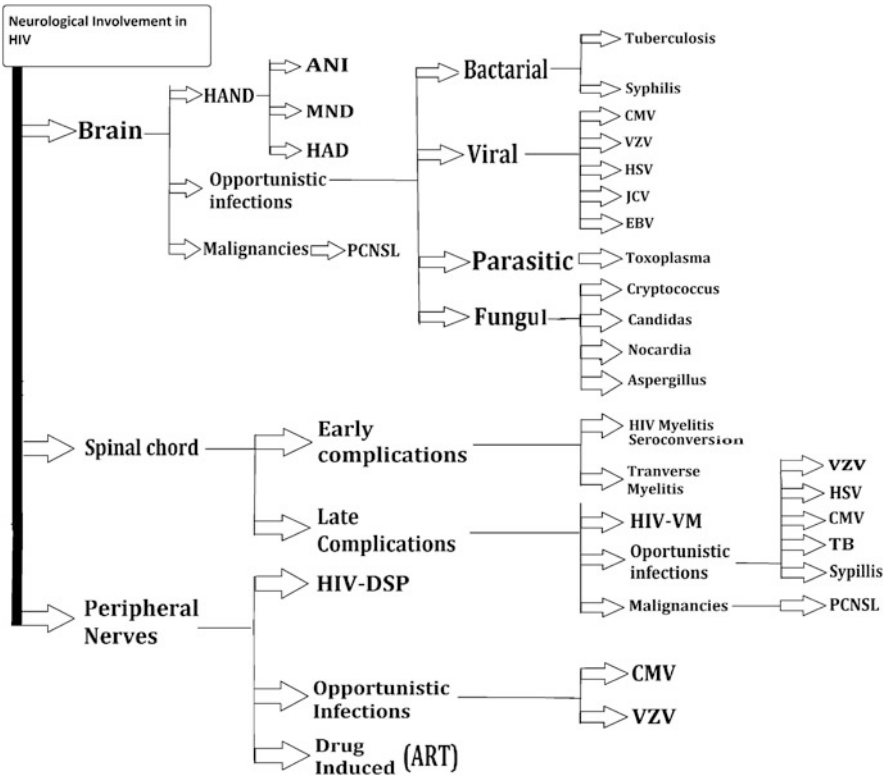
H. Sami et al. (eds.), *Viral and Fungal Infections of the Central Nervous System: A Microbiological Perspective*, https://doi.org/10.1007/978-981-99-6445-1_8

Abbreviations

ADC	AIDS dementia complex
AFB	Acid fast bacilli
AKT	Anti Koch's therapy
ANI	Asymptomatic neurological involvement
CALAS	Cryptococcal capsular antigen with latex agglutination
cART	Combination anti-retroviral therapy
CBNAAT	Cartridge-based nucleic acid amplification test
CM	Cryptococcal meningitis
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
DSP	Distal symmetric polyneuropathy
EBV	Epstein Barr virus
ELISA	Enzyme linked Immunosorbent assay
FDG PET	Fluorodeoxyglucose positron emission test
HAART	Highly active anti-retroviral therapy
HAD	HIV-associated Dementia
HAND	HIV-associated neurocognitive disorders
HHV6	Human herpes virus 6
HIV	Human immunodeficiency virus
HIV-VM	Human immunodeficiency virus-vacuolar myelopathy
HTLV	Human T cell lymphotropic virus
IHDS	International HIV dementia scale
IRIS	Immune reconstitution inflammatory response
IVIG	Intravenous immunoglobulin
JC virus	John Cunnigham Virus
LFA	Lateral flow assay
MMSE	Mini mental status examination
MND	Mild neurocognitive disorder
MND	Motor neuron disease
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin's lymphoma
PCNSL	Primary CNS lymphoma
PCR	Polymerase chain reaction
PLWHA	People living with HIV AIDS
PML	Progressive multifocal leukoencephalopathy
SPECT	Single photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor

Neurological involvement is observed very frequently in retroviral infections like HIV and HTLV. The spectrum is quite broad and their comprehension is important due to high prevalence of HIV. In this era of HAART, there is a significant increase in longevity among PLWHA. These neurological observations are also increasing. They involve neurological systems at almost all the levels. In this chapter, we try to see them in an organized fashion. This in no way would attempt be an extensive record but intends to be a practical one.

Outline



8.1 Brain

Central nervous system comprises of brain and spinal cord. Involvement of CNS is seen from very early stages of HIV infection.

8.1.1 HAND (HIV-Associated Neurocognitive Disorders)

Cognitive involvement is very common among patients with HIV, even with invent of HAART, approximately half of the patients do suffer from cognitive involvement. This cognitive involvement may be due to the presence of HIV virus inside the central nervous system itself or due to the various opportunistic infections. The former type of cognitive involvement is referred as HIV-associated neurocognitive disorders.

Symptoms Patients suffering from HAND may be asymptomatic (ANI, i.e., asymptomatic neurological involvement) which can be demonstrated only with the detailed neuropsychological tests. Or they may have minimal affection so that daily activities are mostly unaffected (MND—mild neurocognitive disorder). The severe form where day-to-day activities are affected due to cognitive limitations is HAD (HIV-associated dementia). ADC (AIDS dementia complex) was the term used in pre-cART era, for slowly progressive form of subcortical dementia where attention, concentration, cognitive, and motor slowing were the main features (Clifford and Ances 2013). Now with HAART, executive functions (planning, organizing, monitoring, and correcting the tasks), language, memory (cortical functions) are the more commonly affected domains of higher mental functions. Initial mild personality changes, fall in occupational and social performances are better and earlier noticed by the family members. So, interviewing family members may provide deeper insight to the problem. HAND include this spectrum of asymptomatic to severe cognitive impairment seen in HIV patients.

Diagnosis Versions of MMSE (mini mental status examination), MoCA (Montreal cognitive assessment), CogState tools and The International HIV Dementia scale (IHDS), etc: the limitations to these are that they are time-consuming and less sensitive to very mild cognitive involvements. Neuroimaging (MRI) may show cerebral atrophy and signs suggestive of (mostly symmetric) white matter involvement.

Treatment No definitive therapy is available for HANDs at present. HAART is the mainstay of the treatment for viral control. Various adjuvant therapies have been tried like SSRI, memantine and are of questionable benefit.

8.1.2 Opportunistic Infections

The opportunistic infections involving CNS are bacterial like tuberculosis; viral like CMV, JC, Virus, etc: parasitic like toxoplasma, etc., or fungal like cryptococcus, nocardia, etc.

8.1.2.1 Tuberculous Meningitis

The risk of tuberculosis infection increases from 10 to 30% depending upon the stages of HIV over lifetime as compared to HIV uninfected population. There is inflammation, increased pro-inflammatory cytokines, free radicles in chronic HIV infection. So, there is reduction of glutathione which normally scavenges free radicles, which possibly increases susceptibility for CNS tuberculosis (Wilkinson et al. 2012). CNS tuberculosis may present as tuberculous meningitis, tuberculomas, and tuberculous abscess. The spinal cord involvement is also common as myelitis and arachnoiditis. It is pragmatic to investigate every patient of tuberculous meningitis for HIV with ELISA and not to content with mere card tests. In India, tuberculous meningitis is a common presenting illness of HIV infection. The course observed may be more fulminant as compared to the immune-competent individuals.

Symptoms Fever, headache, vomiting, blurring of vision, double vision, alteration of sensorium, seizure, limb weakness, cranial nerve paresis.

Signs neck stiffness, Kernig's sign (when trying to extend a knee of a lower limb flexed at hip and knee, elicits pain and discomfort at neck due stretching of the inflamed meninges), Brudzinski's sign, cranial nerve palsy, papilledema, limb paresis, etc.

Investigations CT/MRI brain with contrast-may show meningeal post contrast enhancement, tuberculomas, abscess, infarcts, hydrocephalus (communicating or noncommunicating depending on whether the CSF flow is affected at arachnoid granulations or between the ventricles of the brain) (Image 8.1). CSF evaluation may

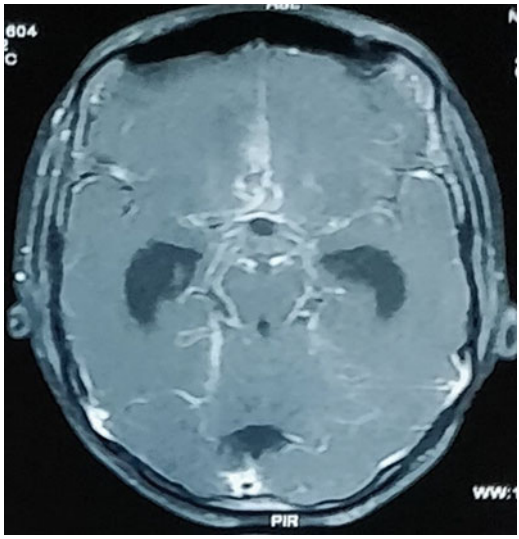


Image 8.1 MRI (T1 GAD enhanced) brain image of patient with TBM, showing leptomeningeal (pia and arachnoid mater) enhancement. And communicating hydrocephalus

show elevated cell count (mostly lymphocytes), elevated protein, and low sugar levels. AFB staining may show acid fast bacteria, CSF CBNAAT may be positive.

Treatment AKT (anti Koch's therapy) (first line: Isoniazid, Rifampicin, Ethambutol, pyrazinamide, Streptomycin), second line drugs used in case of drug resistance or drug-related side effects. Adjuvant use of steroids. Treatment of tuberculosis in HIV needs special caution as simultaneous administration of AKT and ART may lead to paradoxical deterioration in clinical status due to hyperactivation of the immune response leading to IRIS (Immune reconstitution inflammatory response).

8.1.2.2 CNS Toxoplasma Infection

Toxoplasma is obligate intracellular parasite. Infection is acquired mainly via contaminated water and food or vertical transmission. Tachyzoites are the rapidly replicating and bradyzoites are slow replicating forms. There is constant transition between these forms. Few of these intermediates may evade the host immune response leading a possible persistent infection. Brain is the main organ where bradyzoites encyst, other being skeletal muscle, cardiac muscles, spinal cord, and retina. Vast necrosis of midline and periventricular structures, i.e., Corpus callosum, septum pellucidum, fornix, and basal ganglia were observed during autopsy of the affected patients. (Horowitz et al. 1983) Seroprevalence for toxoplasma among immunocompetent and immunocompromised population is reported to be between 15–67% in different studies. Geographical differences are hypothesized to be the cause for these differences (Basavaraju 2016). Immunocompromised hosts are highly susceptible to toxoplasma mainly through reactivation of the latent infection. Basal ganglial contrast (central or ring) enhancing lesions in such patients should raise suspicion for toxoplasma and guide further evaluation.

Symptoms May be associated with fever, headache, altered sensorium, psychosis, dementia, seizure, focal neurological deficit as limb weakness, sensory deficit, etc.: other extracranial toxoplasma manifestations like chorioretinitis (diminution of vision, blurring of vision, scotomas, eye pain, etc.), pneumonitis like illness may accompany.

Signs Focal neurological deficits may be elicited. Chorea if present is considered as pathognomic.

Diagnosis In suspected cases (mostly immunocompromised individuals with CD4 count $<100/\mu l$) if there is positive toxoplasma serology (IgM and IgG ELISA, CFT), symptoms and signs suggesting meningoencehalic involvement (neck stiffness, Kernig's sign, or focal deficit and suggestive neuroimaging; diagnosis of CNS toxoplasmosis is contemplated. Positive response (takes approximately 2–4 weeks) to the treatment may be considered as diagnostic evidence. Biopsy of the lesion provides definitive diagnosis, but may not be feasible in each suspected case.

Radiological diagnosis can be done with CT brain and MRI. Out of these, contrast enhanced MRI offer better visualization and sensitivity of the early lesions. Hypodensities, ring or central enhancing lesions with perilesional edema mainly affecting basal ganglia, cortical, and cerebellar regions are noted. 'Eccentric target sign' where nodule is noted at the rim of the enhancing ring on contrast enhanced T1 weighted imaging is highly specific but unusual radiological sign of toxoplasma. The 'concentric ring sign' with alternating hypo and hyperintense rings may be seen on T2 weighted imaging.

Treatment Sulfadiazine, pyrimethamine, folinic acid, and clindamycin are the first choices for the treatment. Other drugs which may be used are atovaquone, azithromycin, clarithromycin, and dapsone are used. Chemoprophylaxis with co-trimoxazole or dapsone and pyrimethamine is advisable for immunocompromised patients.

8.1.2.3 CNS Fungal Infections

The fungi capable of causing CNS pathologies fall under three major morphological categories like yeasts, dimorphic fungi, and molds; these morphological characteristics are important determinants of their clinical manifestations. Small Yeasts (e.g., Cryptococcus, histoplasmosis, sporotrichosis, blastomycosis, coccidiomycosis) cause leptomeningeal involvement. Whereas large yeasts like candida involve brain parenchyma predominantly manifesting as abscesses and granulomas. Those with large branched hyphae like Aspergillus, Zygomycosis invade blood vessels causing strokes or involve orbit, paranasal sinuses, and skull bones (Nathan et al. 2021).

8.1.2.3.1 Cryptococcal Meningitis (CM)

CM is accountable for approximately 15% of HIV AIDS-related deaths globally (Rajasingham et al. 2017). It mostly manifests as subacute meningoencephalitis, occurs due to inhalational infection by fungi of group basidiomycetes; encapsulated yeasts found in soil contaminated by bird (mainly pigeon) droppings (most common pathogenic species being *C. neoformans*, *C. gattii*). And is prevalent in population where HIV is rampant. It is also seen in patients with cell-mediated immunodeficiency due to various other causes like cytotoxic drugs, in organ transplant recipients, and in patients with hypogammaglobulinemia, liver disease, Cushing's syndrome, even immunocompetent individuals may suffer from CM.

Cryptococcus is the most common cause of fungal meningitis in humans both immunocompromised and immunocompetent (*C. gattii* mostly affects immunocompetent individuals) (Pyrgos et al. 2013). From lung and lymph nodes, these fungi spread to various organs through hematogenous and lymphatic route. Access to the subarachnoid space is achieved via transcellular migration across ependymal cells. As there is lack of complement mediated and soluble ant-cryptococcal factors in brain, there is predilection for CNS affection by cryptococci. As CM carries very high mortality in untreated cases, it should be considered as differential in all cases of lymphocytic meningitis (Williamson et al. 2016).

Symptoms Headache (most common and prominent feature), fever (may not be a feature in chronic course), alteration of sensorium, seizures, focal neurological deficits (cranial nerve palsies), visual disturbances.

Signs Neck stiffness, Kernig's sign may be present. papilledema, focal deficits.

Diagnosis CSF evaluation (lymphocytic pleocytosis, elevated protein and decreased glucose levels), India ink test of CSF have good sensitivity, CSF culture, CSF Ag LFA (lateral flow assay), detection of cryptococcal capsular antigen with latex agglutination (CALAS).

MRI brain may show dilated Virchow Robbin spaces, pseudocysts, contrast enhancing cryptococcomas (mainly involving basal ganglia) (though enhancing lesions are less common in immunocompromised individuals), less frequently leptomeningeal enhancement may be noted. Vascular infarcts, may be seen, etc.

Treatment Amphotericin B, flucytosine for induction phase, fluconazole, and flucytosine for consolidation phase and fluconazole for maintenance phase.

8.1.2.4 Opportunistic Viral Infections

8.1.2.4.1 Cytomegalovirus

Cytomegalovirus is the most important opportunistic virus causing neurologic complications in HIV patients. Other important ones are Epstein Barr virus (mainly its role in CNS lymphoma in HIV patients), varicella zoster virus, HHV-6, and JC virus (causing Progressive Multifocal Leukoencephalopathy). CMV is a human herpes virus, infects humans through close contacts, sexual intercourse, perinatally, through blood products and organ transplantations. Most CNS complications are caused by through the reactivation of prior infection due to immunodeficiency. Median CD4 count in CMV encephalitis is <20 cells/microliter. Encephalitis, myeloradiculitis, and neuritis are main neurologic disease manifestations seen in CMV infection. Focal cell aggregation and or necrosis; ventriculoencephalitis, which is the most distinctive clinical reflection of CMV encephalitis, presents with focal or diffuse ependymal inflammation and periventricular necrosis. Aggressive CMV-dependent dementia is also a noted clinical presentation of CMV.

Symptoms CMV encephalitis—Confusion, lethargy and progressive dementia. Focal neurological deficits and cranial neuropathies are commonly seen as opposed to HAND where focality is not a feature. Internuclear ophthalmoplegia, ataxia, and vertigo are also frequently noticed.

Signs Retinitis, pneumonitis, esophagitis, colitis, adrenalitis, etc., other signs of systemic involvement are commonly found. Along with this alteration of sensorium and evidence of dementia on dementia assessment tools. Focal neurological deficits,

cranial neuropathies and other peripheral neuropathies, and myeloradiculopathy might be noted.

Diagnosis CSF evaluation may suggest moderate rise in protein levels, polymorphic pleocytosis (more so in myeloradiculitis rather than ventriculomyelitis), positive Polymerase chain reaction for CMV is highly sensitive. Neuroimaging (MRI with contrast) may show cerebral atrophy, ventricular dilatation with periventricular contrast enhancement.

Treatment Antivirals like ganciclovir, foscarnet, and cidofovir.

8.1.2.4.2 Herpes Zoster Virus

Symptoms trigeminal nerve and multidermatomal radicular involvement is frequent with immunodeficiency. Radicular pain, dysesthesia, reddish papules, vesicles involving dermatomal distribution is seen.

Encephalitis with necrotizing vasculitis may present with altered sensorium, focal deficits and seizures, meninomyeloradiculitis, and retrobulbar optic neuritis are other reported manifestations.

Diagnosis CSF evaluation, CSF PCR. MRI Brain

Treatment Injectable acyclovir, steroids may be used.

8.1.2.4.3 PML (Progressive Multifocal Leukoencephalopathy)

It occurs due to infection of CNS oligodendrocytes by JC virus. It is seen in immunocompromised hosts like HIV infection, malignancies (especially lymphoid), patients on immunomodulator agents.

Signs and Symptoms Neurological symptoms develop slowly over weeks. Neuropsychological symptoms include affection of attention, concentration, cognitive and motor slowness (subcortical dementia), executive dysfunctions, visual disturbances, and motor deficits. Its course remains progressive, ultimately leading to death in months.

Diagnosis CSF evaluation, presence of JC virus in CSF by PCR, biopsy of brain.

MRI brain in early-stage show areas of patchy demyelination (non-contrast enhancing, asymmetric T1 hypo and T2 hyperintensities with no perilesional oedema or mass effect) in subcortical white matter (which progressively becomes more confluent and necrotic.

Treatment cART in HIV-affected patients. Steroids are used in PML IRIS patients with impending brain herniation (Weissert 2011).

8.1.2.5 Primary CNS Lymphoma (PCNSL)

Among the AIDS defining cancers (Kaposi sarcoma, PCNSL, NHL non-Hodgkins's lymphoma, Burkitt's lymphoma, and cervical cancer), PCNSL is frequent CNS involving cancer (Rubinstein et al. 2014). Approximately 15% of NHLs in HIV patients present as PCNSL. Mostly these are related to Epstein bar virus and thought to be due to ineffective immunoregulation. Supratentorial solitary or multiple mass lesions is a common presentation.

Symptoms and Signs Suggestive of raised intracranial tension (headache, vomiting, and blurring of vision), focal neurological deficits, seizures, alteration of sensorium, cranial nerve palsies.

Diagnosis Biopsy of the lesion with histopathological evaluation even though very sensitive diagnostic test. The yield drops vastly with the use of steroids. CSF cytology and flow cytometric immunophenotyping. CSF EBV DNA PCR (as HIV-associated PCNSL is consistently associated with EBV). FDG PET, SPECT.

MRI brain may show solitary or multiple hypo to isointense lesions on T1 weighted images. They are mostly located in periventricular regions with homogeneous contrast enhancement in immunocompetent patients whereas are located at cortical or subcortical regions with ring or heterogeneous less avid enhancement in immunocompromised patients. Periventricular location with subependymal and leptomeningeal spread is mostly observed.

Treatment Whole brain radiotherapy, high dose methotrexate-based chemotherapy.

8.2 Spinal Cord

Spinal cord injury mediated by HIV is mostly by indirect mechanisms like immune modulation, degeneration, and opportunistic infections and neoplasms. The pathological mechanism may involve necrosis, demyelination, or vasculitis. Acute transverse myelitis is seen mostly in early stages of seroconversion, whereas Vacuolar myelopathy and opportunistic infections are noted in late stages of illness.

Signs and Symptoms may present with difficulty in walking (weakness in lower limbs -spastic paraparesis, incoordination while walking-sensory ataxia, autonomic disturbances—bowel/bladder involvement etc.).

8.2.1 Diseases Affecting Spinal Cord in Early Stages of HIV

Primary HIV-Associated Transverse Myelitis Is noted in early stages of seroconversion. Mostly accompanied by constitutional features like fever, malaise, and backache, which gets followed by symptoms of acute transvers myelitis. Biopsy suggests specific multinucleated giant cells or microglial nodules. CSF may suggest lymphocytic pleocytosis. MRI may show T2 hyperintensities (dorsal spine is mostly involved). Steroid pulse therapy mostly shows clinical improvement.

Immune Mediated Transverse Myelitis Mimics CNS demyelinating disorder like multiple sclerosis and Neuromyelitis Optica spectrum disorder. With brain and spinal cord demyelinating lesions may also present with optic neuritis (painful loss of vision and painful eye movements). There is absence of characteristic multinucleated giant cells or microglial nodules and JC virus. Clinical picture suggestive of longitudinally extensive transverse myelitis may be seen. cART and steroids are used for the treatment.

HIV-Associated Motor Neuron Disease (MND) Presents with symptoms of both upper motor neuron (weakness, hyperreflexia, hypertonia) and lower motor neuron (weakness, atrophy, fasciculations) disorder. Even though exact pathology is unknown, histopathology of HIV-associated MND shows pathology other than ALS (amyotrophic lateral sclerosis). Those with HIV-associated MND present earlier and progress rapidly as compared to ALS. cART, intravenous IVIG show stabilization and clinical reversal.

8.2.2 Spinal Cord Involvement in Late and Uncontrolled HIV Stages

Vacuolar myelopathy (HIV-VM) is a very common entity seen due to direct viral pathology (Wuliji et al. 2019). Its prevalence is quite high up to 22–55% and does not carry good prognosis. There is formation of myelin sheath vacuoles and lipid-filled macrophage infiltration predominantly in lateral and posterior parts of the spinal cord with subsequent cord atrophy. This is mainly noted in lower thoracic spinal cord. Advanced disease may show complete demyelination, axonal degeneration, and astrocytic gliosis (Mongezi et al. 2021).

The viral particles were cultured from the spinal cord tissue, but immunohistochemical studies did not demonstrate them in the vacuoles.

HIV-VM is a diagnosis of exclusion. It has got subacute onset and slow progression. The possible causes of spinal cord involvement like infectious, inflammatory, demyelinating, compressive, and metabolic has to be considered and looked for through neuroimaging and CSF evaluation. There is no definitive treatment at present. c ART and symptomatic therapy is mostly provided (Robinson-Papp et al. 2019).

In humans, tropical spastic paraparesis and Japanese myelopathy are due to HTLV infection.

PCNSL is frequently associated with spinal cord involvement. The disease harbors poor prognosis.

CMV myeloradiculitis may present as acute transvers myelitis. When presenting with polyradiculitis may show LMN (lower motor neuron) type of weakness with bowel and bladder involvement. May mimic GBS (Guillain Barre syndrome).

Herpes simplex virus (HSV) sacral myeloradiculitis presents with perinium numbness with bowel bladder incontinence and progressive ascending paresis. And this too may mimic GBS. HSV may also cause severe necrotizing myelitis in HIV.

Varicella zoster may case radicular involvement. Retrograde spread may cause myelitis and encephalitis. It carries poorer prognosis.

Syphilis (Treponema Pallidum) and tuberculosis (Mycobacterium Tuberculosis) frequently cause extensive spinal cord and radicular involvement.

8.3 Peripheral Nerves

Peripheral neuropathy is one of the commonest complication seen in HIV patients. As the longevity among HIV patients is increasing with the advent of HAART, the prevalence of neuropathies is also increasing. Even though distal symmetric neuropathy is more frequent presentation, virtually all forms of peripheral neurological involvement can be seen in HIV. These include acute and chronic inflammatory demyelinating polyradiculopathies, mononeuropathies, mononeuropathy multiplex, cranial neuropathies, autonomic neuropathies, and ALS like motor neuropathies. And it is very difficult to distinguish between those due to direct viral injury and those due to antiviral drugs (Kaku and Simpson 2014). In pre-ART era, low CD4 count and viral load was associated with HIV DSP. But nowadays this correlation is not well established (Morgello 2004). Other factors like diabetes, hypertriglyceridemia, use of statins, older age, height, etc., play a more important role.

References

Basavaraju A (2016) Toxoplasmosis in HIV infection: an overview. Trop Parasitol 6(2):129. https://doi.org/10.4103/2229-5070.190817

Clifford DB, Ances BM (2013) HIV-associated neurocognitive disorder. Lancet Infect Dis 13(11): 976–986. https://doi.org/10.1016/s1473-3099(13)70269-x

Horowitz SB, Bentson JR, Frank Benson D, Davos I, Pressman BD, Gottlieb M (1983) CNS toxoplasmosis in acquired immunodeficiency syndrome. Arch Neurol 40(10):649–652. https://doi.org/10.1001/archneur.1983.04050090085015

Kaku M, Simpson DM (2014) HIV neuropathy. Curr Opin HIV AIDS 9(6):521–526. https://doi.org/10.1097/coh.0000000000000103

Mongezi T, Sibi J, Jerry G, Lourdes de Fátima I-V, Tozama D, Humberto FS (2021) Atypical HIV-vacuolar myelopathy: a case report. Eur J Med Res 26(1):13. https://doi.org/10.1186/s40001-021-00483-0

Morgello S (2004) HIV-associated distal sensory polyneuropathy in the era of highly active antiretroviral therapy. Arch Neurol 61(4):546. https://doi.org/10.1001/archneur.61.4.546

Nathan CL, Emmert BE, Nelson E, Berger JR (2021) CNS fungal infections: a review. J Neurol Sci 422:117325. https://doi.org/10.1016/j.jns.2021.117325

Pyrgos V, Seitz AE, Steiner CA, Prevots DR, Williamson PR (2013) Epidemiology of cryptococcal meningitis in the US: 1997–2009. PLoS ONE 8(2):e56269. https://doi.org/10.1371/journal.pone.0056269

Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, Denning DW, Loyse A, Boulware DR (2017) Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis 17(8):873–881. https://doi.org/10.1016/s1473-3099(17)30243-8

Robinson-Papp J, Nmashie A, Pedowitz E, George MA, Sharma S, Murray J, Emma, Lawrence SJ, Machac J, Heiba S, Kim-Schulze S, Navis A, Roland BC, Morgello S (2019) The effect of pyridostigmine on small intestinal bacterial overgrowth (SIBO) and plasma inflammatory biomarkers in HIV-associated autonomic neuropathies. J Neurovirol 25(4):551–559. https://doi.org/10.1007/s13365-019-00756-9

Rubinstein PG, Aboulafia DM, Zloza A (2014) Malignancies in HIV/AIDS. AIDS 28(4):453–465. https://doi.org/10.1097/qad.0000000000000071

Weissert R (2011) Progressive multifocal leukoencephalopathy. J Neuroimmunol 231(1-2):73–77. https://doi.org/10.1016/j.jneuroim.2010.09.021

Wilkinson KA, Torok ME, Schwander S, Meintjes G (2012) HIV-associated tuberculosis 2012. Clin Dev Immunol 2012(2012):950964. https://doi.org/10.1155/2012/950964

Williamson PR, Jarvis JN, Panackal AA, Fisher MC, Molloy SF, Loyse A, Harrison TS (2016) Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol 13(1):13–24. https://doi.org/10.1038/nrneurol.2016.167

Wuliji N, Mandell MJ, Lunt JM, Merando A (2019) HIV-associated vacuolar myelopathy and HIV-associated dementia as the initial manifestation of HIV/AIDS. Case Rep Inf Dis 2019(2019):3842425. https://doi.org/10.1155/2019/3842425