

CLINICAL VIGNETTE
2018; 4:2



HIV: AETIOPATHOGENESIS & CNS COMPLICATIONS

Editor-in-Chief: Prof Olufemi Idowu
*Neurological surgery Division, Department of
Surgery, LASUCOM/LASUTH, Ikeja, Lagos, Nigeria.*



Copyright- Frontiers of Ikeja Surgery
2018; Volume 4:2

**HIV:
AETIOPATHOGENESIS
AND CNS
COMPLICATIONS**

DR ARABAMBI B.

**Department of Medicine,
Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria**

OUTLINE

- Introduction
- Epidemiology
- Pathophysiology
- Classification
- Investigations
- Treatment
- Conclusion

INTRODUCTION

- Single stranded enveloped RNA virus
- Genus- Lentivirus; Family- Retroviridae
- HIV 1- Virulence high, Infectivity high, Global
- HIV 2- Virulence low, Infectivity low, West Africa, India
- HIV infection to AIDS spectrum
- Transmitted sexually and non-sexually
- Causes progressive immunosuppression
- 40% with neurologic complications
- 80% with neuropathologic findings at autopsy

EPIDEMIOLOGY OF HIV

| World region ^[15] | Estimated prevalence of HIV infection (adults and children) | Estimated adult and child deaths during 2010 | Adult prevalence (%) |
|---------------------------------|---|--|----------------------|
| Worldwide | 31.6 million – 35.2 million | 1.6 – 1.9 million | 0.8% |
| Sub-Saharan Africa | 21.6 million – 24.1 million | 1.2 million | 5.0% |
| South and South-East Asia | 3.6 million – 4.5 million | 250,000 | 0.3% |
| Eastern Europe and Central Asia | 1.3 million – 1.7 million | 90,000 | 0.9% |
| Latin America | 1.2 million – 1.7 million | 67,000 | 0.4% |
| North America | 1.0 million – 1.9 million | 20,000 | 0.6% |
| East Asia | 580,000 – 1.1 million | 56,000 | 0.1% |
| Western and Central Europe | 770,000 – 930,000 | 9,900 | 0.2% |

EPIDEMIOLOGY

- 2016 burden in Nigeria – 3.2 million
- Nigeria- 2nd highest burden in the world, only to South Africa, 6.8 million
- Steady decline in prevalence since 2005
- Highest prevalence in Rivers state with 15.2%
- Lowest in Ekiti at 0.2%

PATHOPHYSIOLOGY

- Principally infects activated CD4 cells
- Secondarily infects macrophages- important in the CNS manifestations
- Incorporates into host cell DNA with reverse transcriptase
- HIV crosses blood brain barrier and enters CNS early
- Immune suppression leads to opportunistic infections
- HIV has no proofreading enzymes to correct for RNA to DNA conversion errors- frequent DNA base substitutions and rapid genetic mutation- propensity for copying errors is a major reason that HIV frequently develops resistance to therapy

STAGES OF HIV

| STAGE | CHARACTERISTICS |
|-----------------------|--|
| Primary HIV infection | Asymptomatic, seroconversion |
| Stage 1 | Asymptomatic, persistent generalized lymphadenopathy |
| Stage 2 | Weight loss <10%, Herpes zoster, recurrent oral ulcers, onychomycosis, seborrheic dermatitis |
| Stage 3 | Chronic diarrhea >1month, oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis |
| Stage 4 | Pneumocystis jirovecii pneumonia, oesophageal candidiasis, disseminated TB, lymphoma, CNS toxoplasmosis, progressive multifocal leukoencephalopathy, invasive cervical carcinoma |

MECHANISM OF NEURONAL INJURY

• VIRAL FACTORS

- Gp120
 - Synaptodendritic injury
 - Reactive astrocytosis
 - Microgliosis
 - Loss of large pyramidal neurons
- Transactivator of transcription (Tat)
 - Mitochondrial dysfunction
 - Dendritic loss

• HOST FACTORS

- Cytokines and chemokines produced by activated immune cells
- Varies between individuals
- Partially reversible

• COFACTORS

- Coinfections
 - HCV
- Comorbidities
 - Nutritional deficiency, vascular risk factors
- Social factors
 - Alcohol, smoking, drug abuse
- Psychological factors

CLASSIFICATION OF CNS COMPLICATIONS

- Direct complications
- Opportunistic complications
 - Neoplastic
 - Non-neoplastic
- Treatment related complications
 - Neurological Immune Reconstitution Inflammatory Syndrome (NeuroIRIS)
 - Drug side effect (e.g. didanosine neuropathy, protease inhibitors dyslipidemia)

DIRECT COMPLICATIONS

- Aseptic meningitis
- HIV associated neurocognitive disorder (HAND)
- Stroke
- Vacuolar myelopathy
- Peripheral neuropathy and myopathy

OPPORTUNISTIC COMPLICATIONS

- Neoplastic
 - Primary CNS lymphoma
 - CNS Kaposi sarcoma
- Non-neoplastic
 - Tuberculous meningitis, tuberculomas
 - Cryptococcal meningitis, cryptococcomas
 - CNS Toxoplasmosis
 - Neurocysticercosis
 - Progressive multifocal leukoencephalopathy
 - CMV encephalitis

HAND SYNDROME

Classified based on severity

- Asymptomatic Neurocognitive Impairment (ANI)- mild impairment in two or more cognitive areas without impairment of everyday functioning
- Mild neurocognitive disorder (MND)- mild cognitive interference in everyday functioning
- HIV associated dementia (HAD)- moderate to severe impairment in two or more areas with severe impairment of functioning; *Prospective memory – “remember to remember”

Other aetiology of dementia must be ruled out

Subcortical dementia with motor and cognitive slowing

- Motor skills, cognitive skills, verbal fluency (pre cART)
- Prospective memory impairment (post cART)

Presentation similar to Alzheimer disease

MARKERS OF HAND

Blood

- Low CD4 count
- Plasma soluble CD14
- CD 163

CSF

- Neopterin and IgG index
- IL-6, IL-8, CCL2 (persistent)
- Neurofilament protein
- Tau

Functional neuroimaging

STROKE IN HIV

- Both ischemic stroke and intracerebral hemorrhage possible
- HIV associated vasculopathy
 - Vasculitis
 - Atherosclerosis
 - Antiphospholipid syndrome
- Protein C & S deficiency
- Cardioembolism
- Dyslipidemia
- Hyperviscosity
- Hemorrhage
 - Thrombocytopenia
 - Vasculitis/aneurysm
 - Mycotic aneurysm

HIV VACUOLAR MYELOPATHY

- Seen in advanced disease
- Impaired ability to utilize vitamin B12 involved
- Features of dorsal and lateral column dysfunction with sphincter involvement
- No back pain

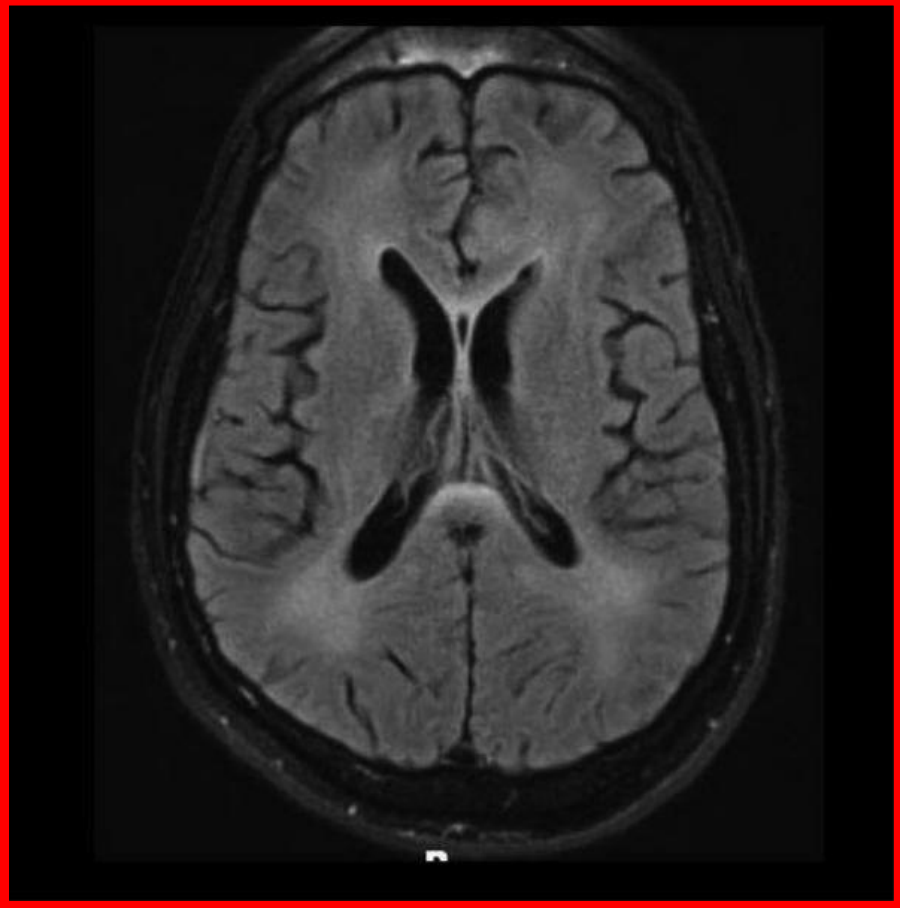
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

- Demyelinating disease
- Infection of oligodendrocytes by JC virus (Small non-enveloped double stranded DNA virus)
- May occur during immune recovery following initiation of cART
- Unifocal presentation with background multifocal pathology
- Focal insidious symptoms behavior, speech, cognitive, motor (hemiparesis, head tremors), visual impairment

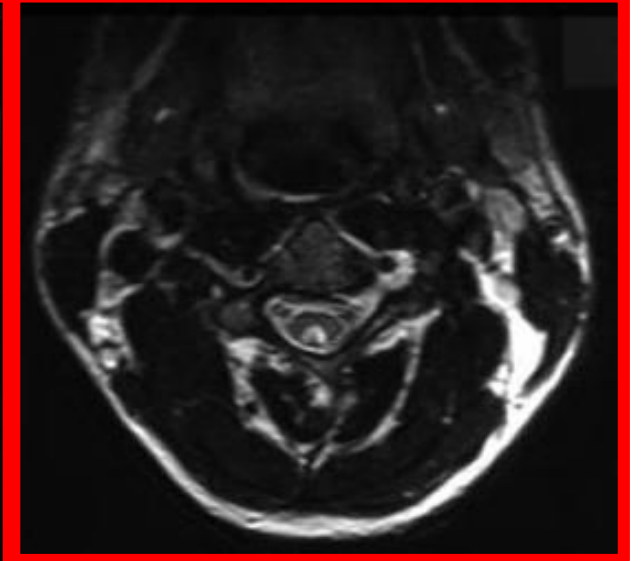
INVESTIGATION

- Neuroimaging
 - MRI/CT
 - MRS- decreased N-acetyl aspartate (neuronal loss), increased choline (membrane turnover), increased myoinositol (glial cell marker)
 - Functional imaging- PET, SPECT
- CD4 count, Viral load
- CSF analysis
- Serology
- Lipid profile
- Vitamin B12 assay
- Brain biopsy- single lesion with negative serology

- **HAND**- Prominent white matter changes on FLAIR

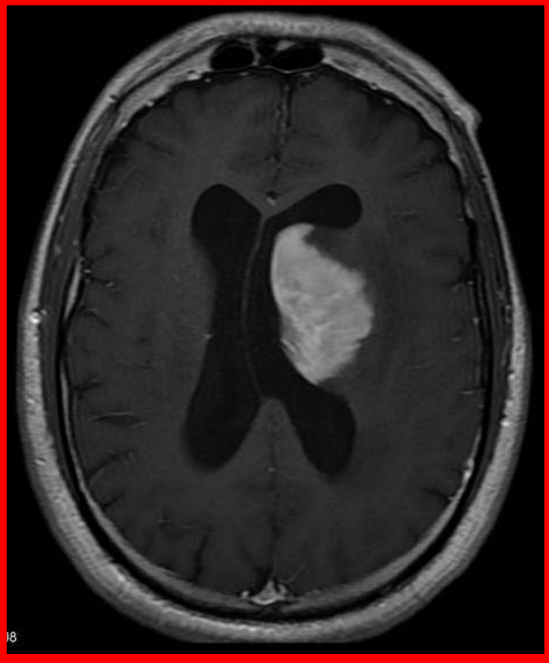


HIV Vacuolar myelopathy

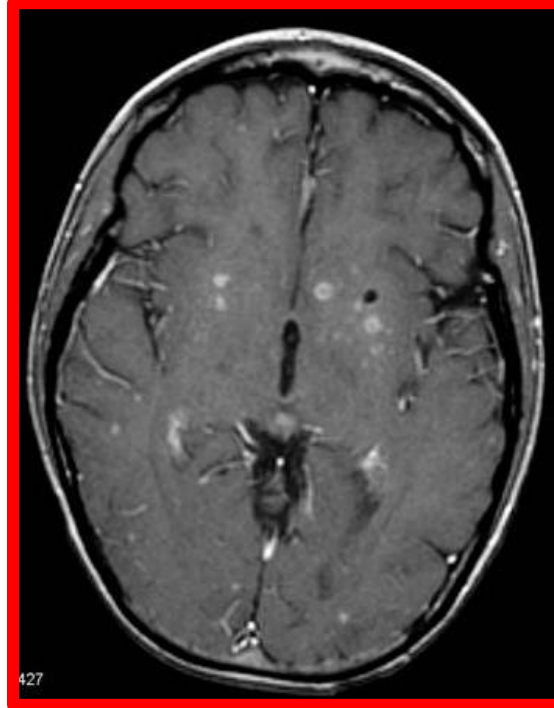


T2 hyperintensity in the posterior cord

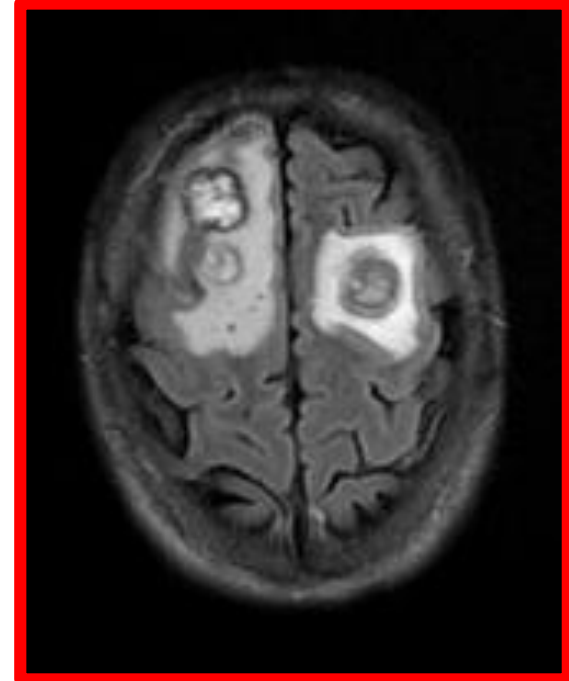
**Primary CNS
Lymphoma-single
homogenously
enhancing lesion**



**CNS Toxoplasmosis-
multiple lesions that
are ring enhancing**



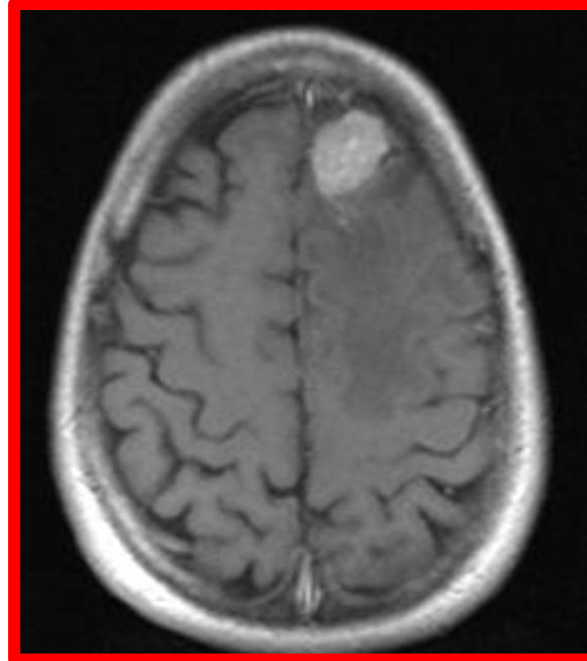
**CNS Kaposi
Sarcoma**



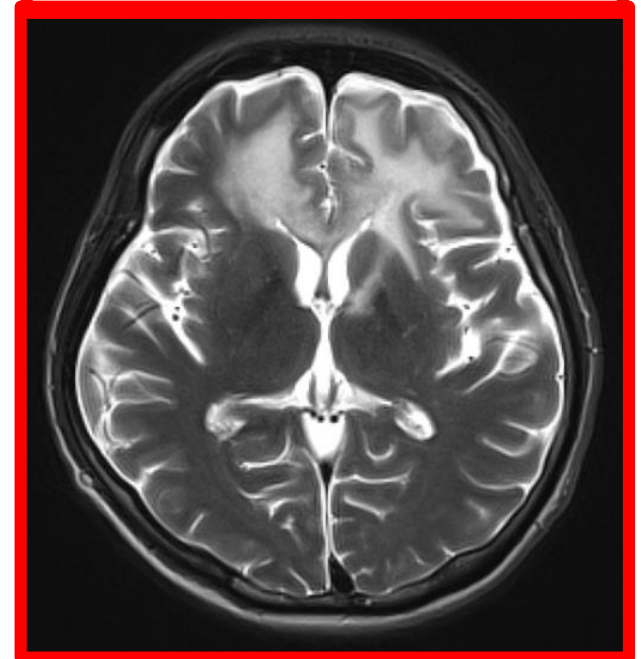
Cryptococcal meningitis



Tuberculoma



PML



NON-SURGICAL TREATMENT

- **COMBINATION ANTIRETROVIRAL THERAPY (cART)**- defined by the use of two NRTIs and a 3rd drug from any class. Choices defined by drug interactions, possible side effects and comorbidities; E.g. Dolutegravir + Abacavir + lamivudine
- ✓ Nucleotide/Nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine, Abacavir, Lamivudine, Emtricitabine, Tenofovir
- ✓ Non-nucleotide reverse transcriptase inhibitors (NNRTIs): Nevirapine, Efavirenz, Etravirine, Rilpivirine. *HIV 2 is naturally resistant to NNRTIs
- ✓ Protease inhibitors (PIs): Lopinavir, Indinavir, Nelfinavir, Amprenavir and Ritonavir
- ✓ Integrase inhibitors: Elvitegravir, Dolutegravir, Raltegravir
- **CORTICOSTEROIDS**- Lymphoma
- **RADIOTHERAPY**- Lymphoma
- **OTHERS**
- ✓ Treatment of underlying cause
- ✓ Symptomatic management
 - ✓ Seizure control
 - ✓ Psychiatric component
- ✓ Secondary prevention of stroke
- ✓ Monitoring

SURGICAL

- Biopsy- single lesion with negative serology
- Shunting- hydrocephalus
- Tumour excision

CONCLUSION

- HIV is a prevalent condition in Nigeria
- CNS involvement are common with HIV and can occur very early
- Can be due to the direct effect of the virus or opportunistic infections
- Appropriate evaluation is needed to determine the exact etiology and management
- Combined ART is the backbone of management

REFERENCES

- WHO classification system for HIV infection
- HIV/AIDS (CNS manifestations), radiopaedia.org
- Prityi R. CNS complications in HIV, Medscape.com
- Dawn McGuire. Neurologic manifestations of HIV.
- Ellis RJ et al. HIV infection and CNS: A primer
- Letendre SL et al. Neurologic complications of HIV disease and their treatment