Benghazi Medical Center

HIV- Associated Neurocognitive Disorders

Prof. Ahmed Elhassi
Department of Infectious Diseases
Benghazi Medicine Center
Faculty of Medicine, University of Benghazi

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Learning Outcome

- Describe the neurocognitive burden of HIV
- Know the different types
- Understand the pathophysiology of neurocognitive disorders
- Describe the manifestations and apply tools in assessment of neurocognitive disorders
- Chose proper management of neurocognitive disorders

Overview

- Based on current World Health Organization statistics 2023, there are about 39 million PLWH
- 29.8million (%77) receive ART (WHO 2022)
- Despite the increased life longevity, neurologic complications remain common

- HIV can affect both the CNS and PNS
- With availability of ART, CNS complications due to opportunistic infections have decreased
- Manifestations of neurologic dysfunction other than OIs are still prevalent

- CNS is the organ most frequently affected by HIV after the lung

- At autopsy up to 80% of PLWH has CNS abnormalities
- **They are due to**

1. Effects of HIV itself
2. Immune dysregulation
3. Opportunistic Infections
4. Adverse effects of cART
5. Drug-drug interaction
6. Substance abuse

- Complications of the nervous system can occur in more than 50% of PLWH
- In 10–20% of cases neurologic manifestations are the presenting symptoms/signs of HIV infection
- Aseptic meningitis and acute demyelinating polyneuropathy occur within 10–20 days of systemic infection (25%)

Types of Neurologic Complications

- HIV-infected patients are susceptible to the same neurologic diseases as patients without infection in addition:

1. CNS manifestations:

- HIV-associated neurocognitive disorder (HAND)
- Vacuolar myelopathy
- Cerebrovascular disease
- Aseptic Meningitis

2. **Peripheral nervous system**:

- Distal symmetric polyneuropathy
- Mononeuropathy multiplex
- Chronic inflammatory demyelinating polyneuropathy
- Mitochondrial Toxicity

3. Infectious, autoimmune, neoplastic and those related to ART include:

- CNS lymphoma, Kaposi sarcoma
- Immune Reconstitution Inflammatory Syndrome of the CNS
- Progressive multifocal leukoencephalopathy
- Fungal infections ,Tuberculous meningitis, toxoplasmosis and Cytomegalovirus encephalitis

HIV-Associated Neurocognitive Disorders (HAND)

- Changes in memory, concentration, attention, and motor skills are common in patients with HIV

- ART has resulted in improved survival in PLWH, with age related cognitive changes, cognitive impairment has been increased

- When there is no alternate causes other than HIV infection, such impairments have been collectively classified as HIV-associated neurocognitive disorders (HAND)

- Cognitive dysfunction occurs in 50% or more of PLWH
- Before ART 20% of infected patients died with HAD
- After the introduction of ART fewer than 5% of patients have HAD
- Based on the CHARTER study, HAND still prevalent in PLWH (45%)

Nomenclatures

- The following terminology were proposed by (AAN/1991)
- HIV and AIDS dementia complex
- HIV-associated dementia
- HIV encephalitis and encephalopathy

They has been replaced by more clear definition,HIV-associated neurocognitive disorder (HAND)

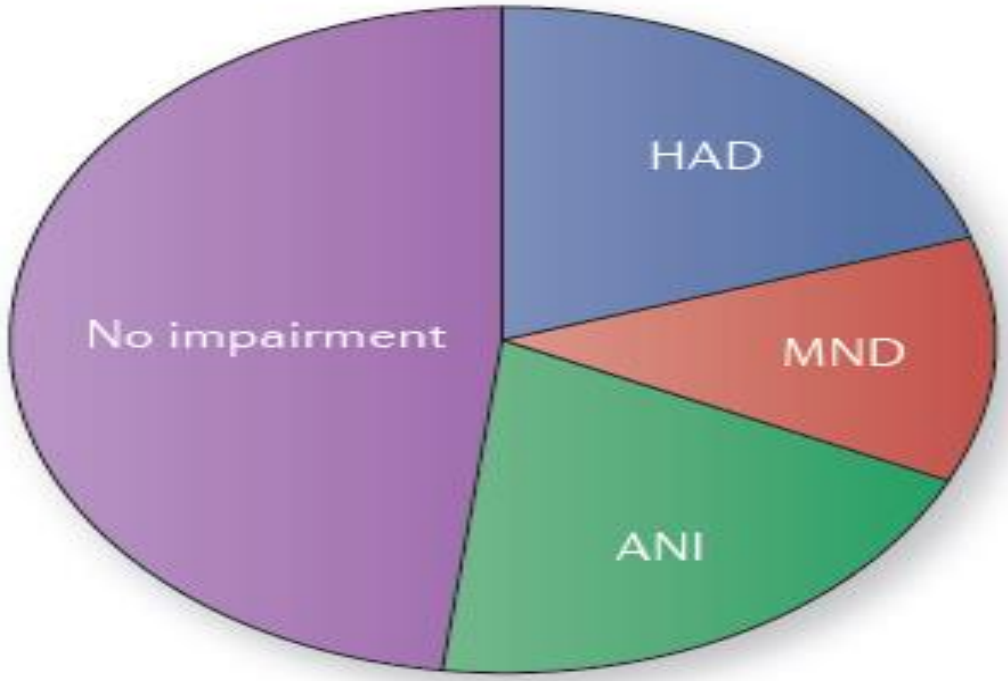
Frascati Classification

HAND Type	Prevalence in ART treated individuals	Diagnostic Criteria
Asymptomatic Neurocognitive Impairment (ANI)	30%	- ≥ 1 STD below the mean on 2 neurocognitive domains - no functional impairment
Mild Neurocognitive Disorder (MND)	20%-30%	- ≥ 2 STD below the mean on 2 neurocognitive domains - Mild to moderate interference in daily functioning
HIV Associated Dementia (HAD)	2%-8%	- ≥ 2 STD below the mean on 2 neurocognitive domains - Marked impairment in daily functioning

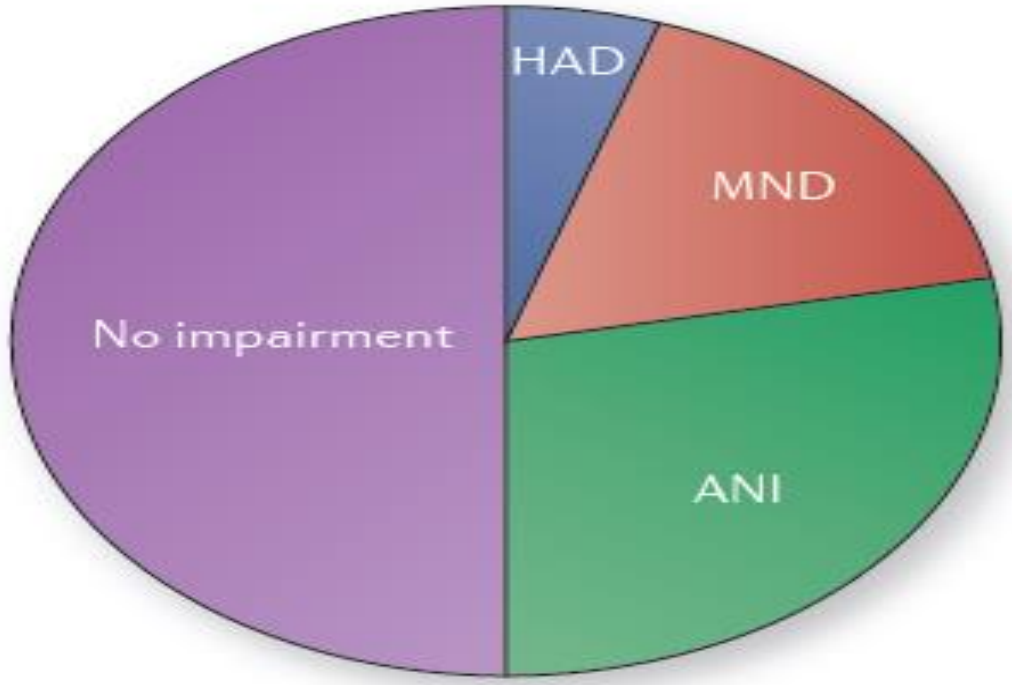
Antinori et al, Neurology, 2007

Prevalence

Pre ART



Post ART



Grant et al, Neurology, 2014

Risk Factors

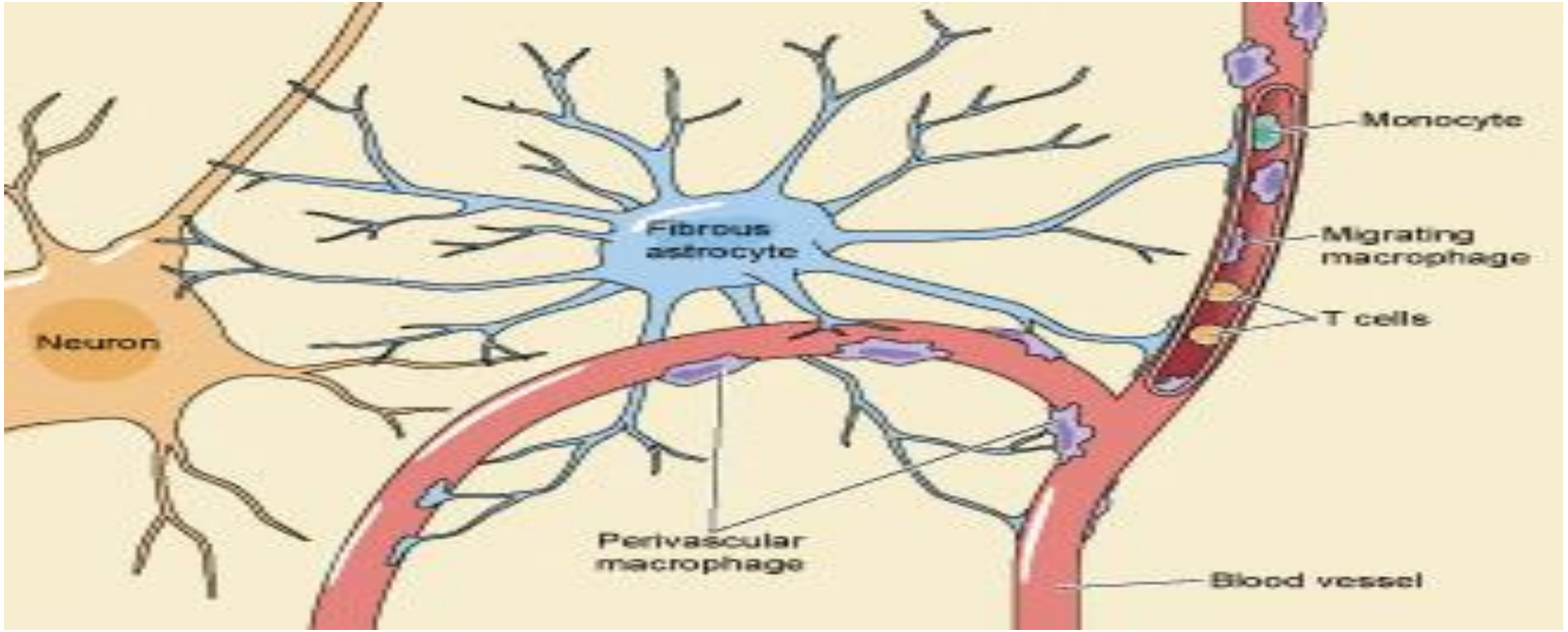
- Low CD4 nadir
- Advanced age
- Hepatitis C comorbidity
- Substance abuse, particularly amphetamines
- Cerebrovascular risk factors
- Psychiatric disorders
- Sleep disorders

Pathogenesis

- Continuous CNS inflammation due to HIV infection which lead to neurodegeneration
- HIV neurotoxicity (The brain is a pocket reservoir for HIV persistence)
- And disruption of brain glutamate metabolism and neurotransmission

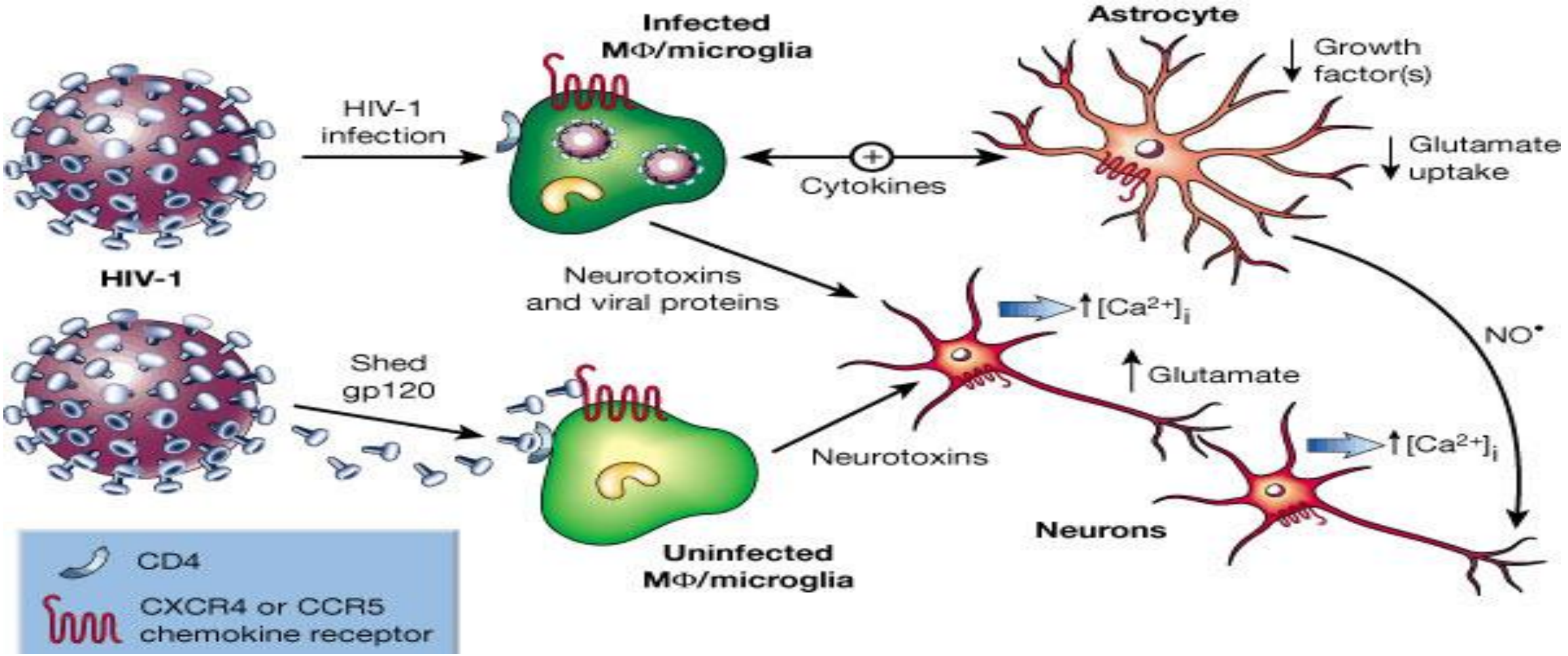
Saylor D et al, Nat Rev Neurol, 2016

HIV Neuropathogenesis



Dave R, Pomerantz RJ. (2005). HIV neuropathogenesis: persistent infection, persistent questions. Science & Medicine.

HIV Neuropathogenesis



Kaul, Garden & Lipton (2001). Pathways to neuronal injury and apoptosis in HIV-associated dementia. *Nature* 410, 988-994.

Clinical Features

- Executive dysfunction
- Memory
- Disruption of attention
- Processing speed
- Multitasking
- Impulse control
- Judgment

Diagnosis

- The diagnosis of HAND is a clinical one
- The Frascati criteria developed in 2007 by Antinori and his colleagues allowed for uniformity in the diagnosis of HAND
- Use of imaging to exclude other causes

A. The Frascati Criteria for the classification of HIV Associated Neurocognitive Disorders[1]

Classification	Criteria
Asymptomatic Neurocognitive Impairment (ANI)	NP impairment in ≥ 2 cognitive domains that cannot be explained by opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects. No reported or demonstrated functional decline.
Mild Neurocognitive Disorder (MND)	At least mild NP impairment (>1 SD below a demographically appropriate normative mean), involving ≥2 cognitive domains AND Reported or demonstrated mild functional decline that cannot be explained by confounding conditions.
HIV-Associated Dementia (HAD) Note: Severity of NP impairment and functional decline must both meet these standards in order to diagnose the person as having HAD. If either NP impairment or functional decline is mild, the condition should be classified as MND.	≥ Moderate NP impairment (>2SD below a demographically appropriate normative mean) on > 2 cognitive domains.* AND Reported or demonstrated major functional decline that cannot be explained by confounding conditions. *Alternatively, one domain could be more severely impaired (>2.5 SD below the mean) and another less severely impaired (>1 SD below the mean)

Adapted from Antinori et al 2007

B. Calculation of the Global Deficit Score[2]

Calculate z score for each neurocognitive test using normative means

↓

Convert to T score

↓

Transform T score to deficit score

↓

Average deficit scores to arrive at final Global Deficit Score

A conversion table for converting T scores to deficit scores

T score	Deficit score	Impairment descriptor
≥40	0	Normal
39-35	1	Mild
34-30	2	Mild-to-Moderate
29-25	3	Moderate
24-20	4	Moderate-to-Severe
≤20	5	Severe

Adapted from Carey et al 2010

Imaging

- Differentiating of slow progression of HIV-associated dementia, myelopathy, or neuropathy from an acute new-onset process such as infection must be diagnosed rapidly and appropriate treatment initiated urgently

- **CT, MRI and MR spectroscopy**
- **SPECT** (thallium-201 single-photon emission computed tomography)
- **FDG-PET**(18-fluorodeoxyglucose positron emission tomography)
- **Open biopsy with decompression**

CT scan

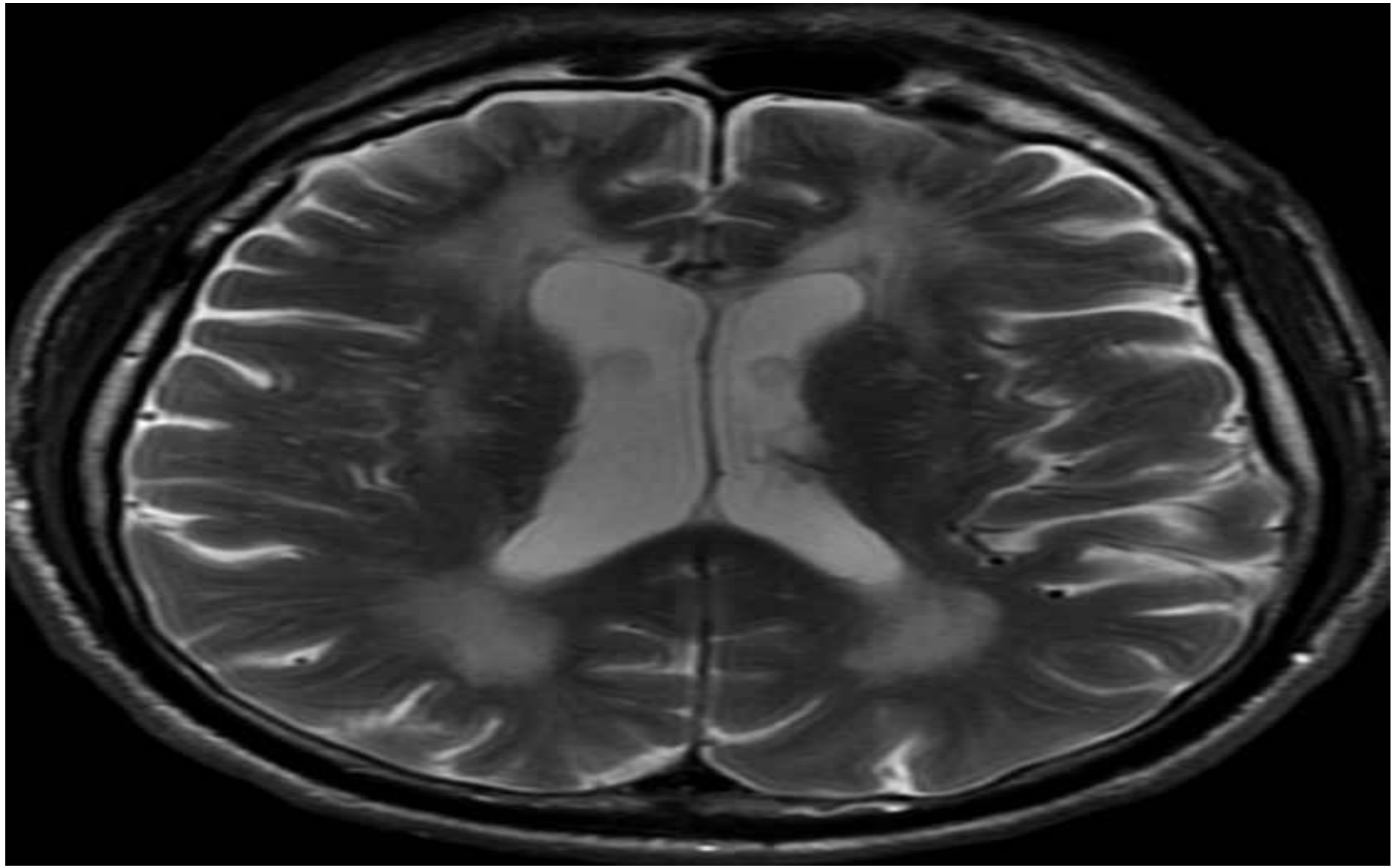
- Diffuse and symmetric cerebral atrophy, out of proportion in keeping with the age of the patient
- Symmetric periventricular and deep white matter hypoattenuation

MRI

Symmetric periventricular and deep white matter T2 hyperintensity with relative sparing of the subcortical white matter and posterior fossa structures, confluent or patchy, no mass effect, no enhancement

MR spectroscopy

- Shows decreased N-acetyl aspartate and increased choline peaks and changes in the glutamate and glutamine levels



Case courtesy of Dr Roberto Schubert, Radiopaedia.org.

Treatment of HAND

- There is no specific treatment for HAND
- Early and effective control of HIV replication is an important management tools for HAND
- Choosing ART with effective CNS penetration and minimum neurotoxicity becomes paramount in patients with HAND

Treatment of HAND

Management of symptoms	
Encourage to remain appropriately active	Medication adherence assistance
Structured routines	Determine level of supervision
Memory aids	Identify supports
Simplify complex tasks (e.g., drug regimens)	Fall prevention
Write instructions for patients and caregivers	Familiar environments
Cognitive skills building	

Prognosis and Prevention of HAND

- HAND is dependent on its severity
- Patients with HAD associated with worse prognosis
- Recent data from the Multicenter AIDS Cohort Study found that PLWH had no more decline in neuropsychometric tests than age-matched controls suggests that cognitive deterioration in HAND patients is not widespread
- Prevalence was observed with dual and INSTI-based regimens along with a more recent ART initiation

- Antinori A, et al. Declining prevalence of HIV-associated neurocognitive disorders in more recent years and associated factors, in a large cohort of ART-treated HIV-infected individuals. Clin Infect Dis 2022 Aug

Take-home messages

- CNS manifestation of HIV infection is common.
- It may be the presenting symptoms of the HIV infection and the degree of immunodeficiency correlate well with CNS presentation.
- In the era of ART neurocognitive disorders are more common than opportunistic infections.
- Psychosocial and psychiatric assessment should be part of care in PLWH.
- Carful selection and early use of ART will minimize the CNS symptoms.

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