

Neurocognitive symptoms in people with HIV

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Introduction

- Over the past three decades, the clinical presentation of HIV infection of the Central Nervous System (CNS) has evolved significantly
- The use of ART has significantly decreased the prevalence of severe forms of HIV-1 associated neurocognitive disorders (HAND)
- Neurocognitive dysfunction is however still reported with a very variable prevalence, ranging from 21% to 77.6%
- This very wide prevalence variance results largely from tests used to assess cognitive decline

What I hope to explore in this short talk

- Pathobiology of HAND
- The clinical presentation of HAND and how a neurologist might define this
- A bit on CSF biomarkers that might be helpful in investigating HAND
- Other causes of cognitive impairment in the older population living with HIV and how to recognise these clinically

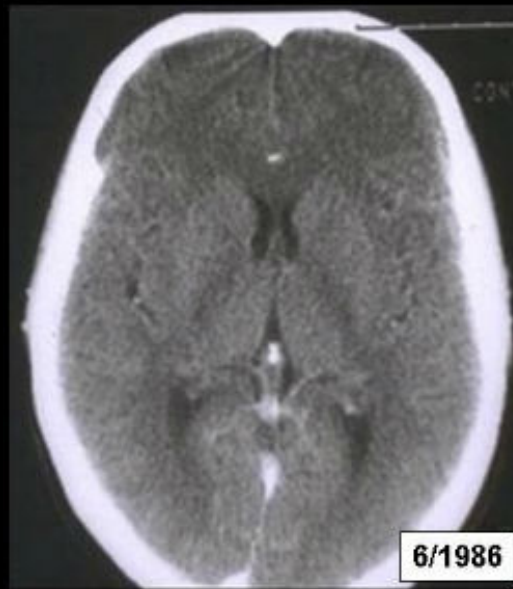
Definitions

HIV-associated neurocognitive disorder (HAND)

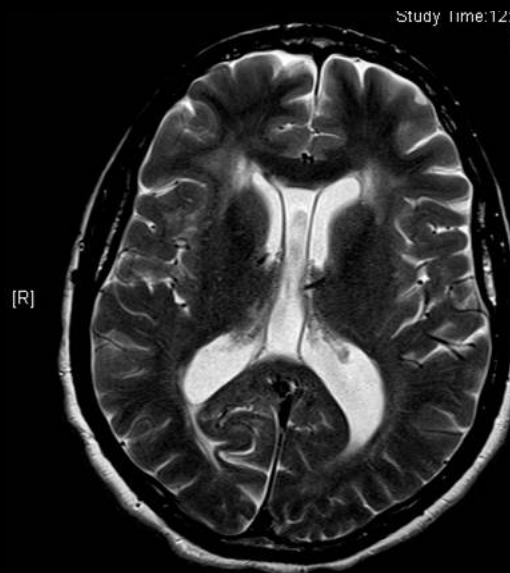
1. Asymptomatic neurocognitive impairment (ANI).
2. Mild-to-moderate symptoms, at which point it is referred to as mild neurocognitive disorder (MND).
3. In its most severe form, people may progress to HAD (HIV associated dementia)
 - For diagnosis of ANI, impairment does not interfere with daily function, whereas interference is mild for MND and marked for HAD

HIV-associated Neurocognitive Decline (HAND)

In the early stages of the AIDS epidemic, the most severe form of HAND was HIV-associated dementia (HAD) and typically occurred in patients with low CD4 counts. The onset was insidious and is similar to a vascular subcortical dementia with mental slowness, forgetfulness, poor concentration, changed behaviour with depression and mood swings and apathy.



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- HIV-associated **chronic inflammation and associated neurotoxicity of long term ART**, as well as the **aging** of the HIV-infected population are most likely to influence the pathogenesis of HAND
- Changing treatment patterns with the **very early use of ART** will most likely alter the prevalence of HAND by preventing the inflammatory process in the brain as a sanctuary site
- Population with cognitive concerns are the **older population started on ART later** and in whom other co-morbidities may play a role

- The underlying HIV neuropathogenesis, definitive causal pathophysiology of HAND and thus effective prevention or treatment remain elusive
- **HIV enters the brain early in the course of infection** and can be detected in brain macrophages, microglia and astrocytes in presymptomatic individuals, suggesting that these cell types are important reservoirs for the virus

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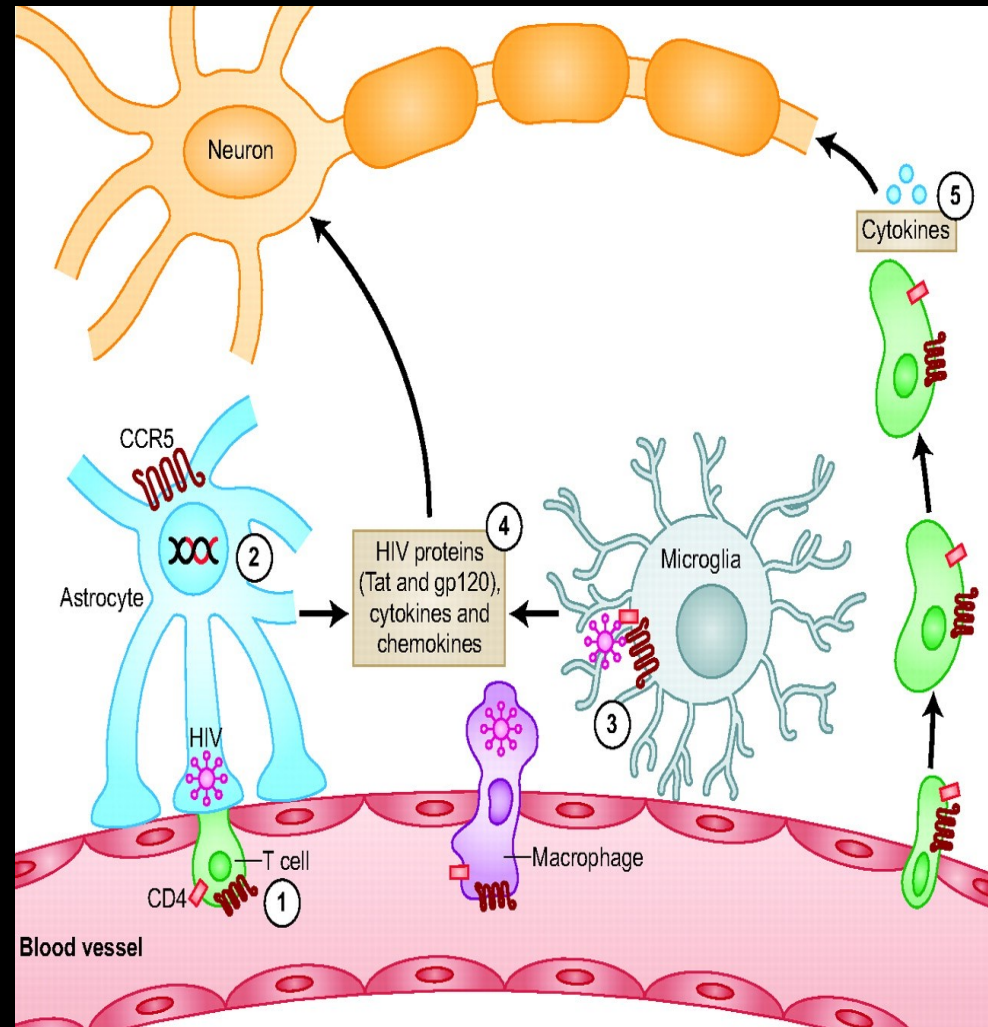
HIV can infect astrocytes by direct cell-cell contact with infected T cells through the virological synapse

2

After infecting astrocytes, HIV integrates into the genome where it remains latent

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HIV-infected macrophages enter the brain early after initial infection. Next, HIV infection spreads to perivascular macrophages and microglia, a process that occurs when HIV enters the cell after binding to the CD4-receptor–CCR5 co-receptor complex.

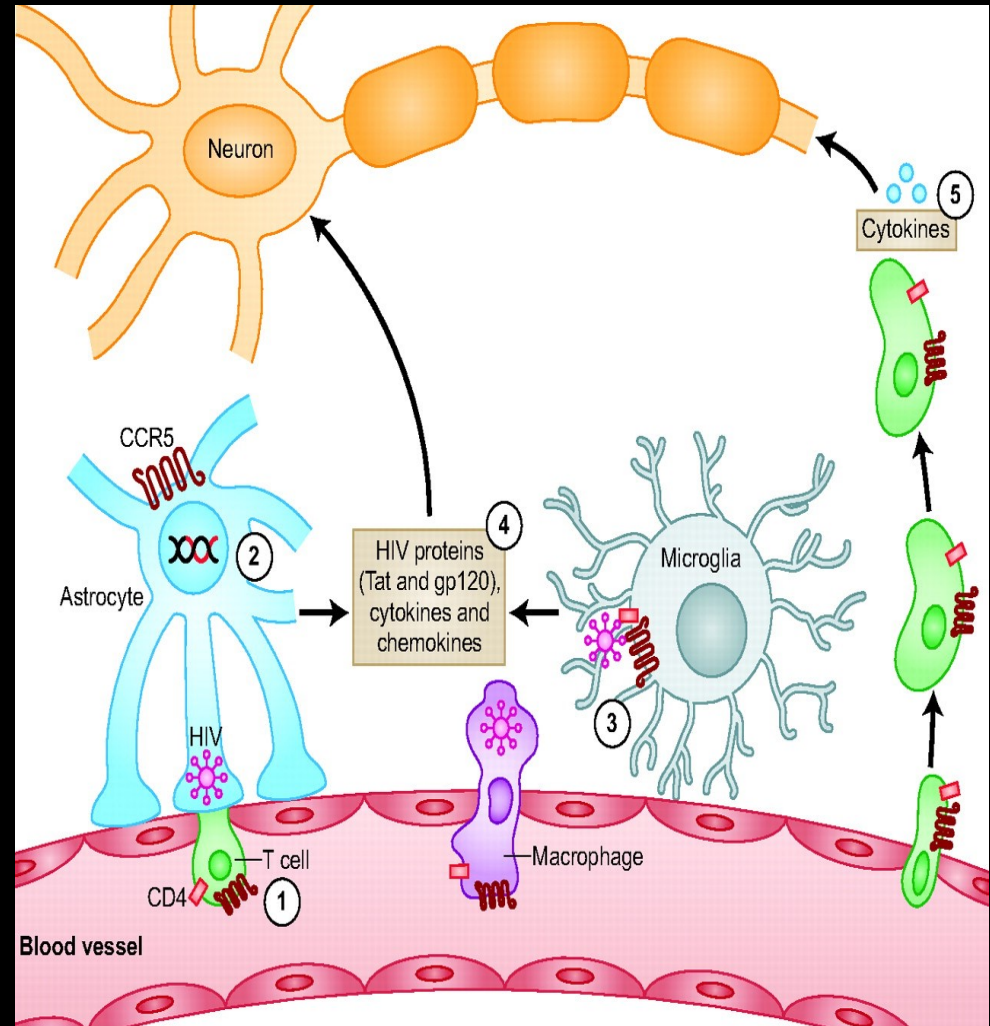


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HIV-infected astrocytes and microglia cause neuronal injury indirectly by releasing soluble toxic viral proteins (Tat and gp120) and pro-inflammatory molecules (cytokines and chemokines)

5

Ongoing low levels of HIV replication in the CNS despite the use of cART promotes the entry of chronically activated T cells, which cause neuronal injury indirectly by releasing pro-inflammatory cytokines



Evidence

- Good evidence that HAND in a milder form that HAD exists and relates to an inflammatory process - (Heaton et al., 1995, White et al., 1995, Sacktor et al., 2002, Giancola et al., 2006, Tozzi et al., 2007, Heaton et al., 2011).
- Are there other factors to consider especially co-morbidities

CSF biomarkers in HIV

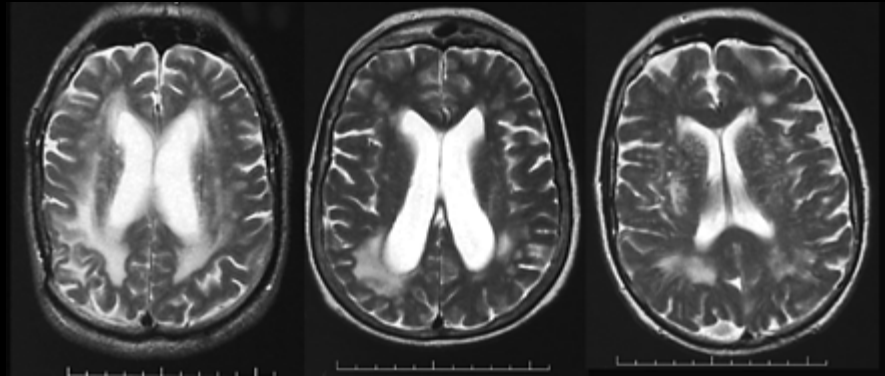
- CSF Neurofilament light chain (NFL) has emerged as a sensitive marker for assessing ongoing axonal damage in HIV infected patients
- Increased levels of NFL were seen in HAD, but also in neuroasymptomatic patients with or without ART, indicating that a subclinical axonal degeneration and immune activation, as measured by correlation to CSF neopterin, is a feature across the spectrum of HIV-infected patients
- Albumin ratio correlates with NFL, suggesting compromised BBB integrity

Does having HIV infection increase risk of developing other neurodegenerative pathologies such as AD and PD?

- Putative biomarkers of AD pathology, including cerebrospinal fluid (CSF) proteomics— $A\beta$ /amyloid, tau, phospho-tau, and others, and amyloid PET neuroimaging are supportive of a clinical diagnosis of AD pathology in HIV-uninfected individuals
- CSF AD biomarkers in subjects with HAND reveals low amyloid levels in both diagnoses, increased phospho-tau in AD, and inconsistent tau levels in HAND
- HAND is *not* associated with increased CNS fibrillar amyloid as detected by amyloid PET imaging

- To date difficult to confirm and pathologies are different but in the aging population, both HAND and AD may co-exist
- HIV infection can be associated with neuronal damage and loss in distinct brain regions, including frontal cortex, substantia nigra, cerebellum, and putamen and features of neuronal apoptosis have been found in brains of HAD patients. Moreover, the localization of apoptotic neurons was correlated with signs of structural damage and closely associated with evidence of microglial activation, especially within subcortical deep gray structures

Vascular risk and vascular cognitive impairment



Mounting data suggests that HIV infection leads to an excess risk of developing cardiovascular disease

HIV infection and treatment are more directly linked to atherogenesis, endothelial dysfunction, and coagulation abnormalities, likely through inflammation and immune dysregulation

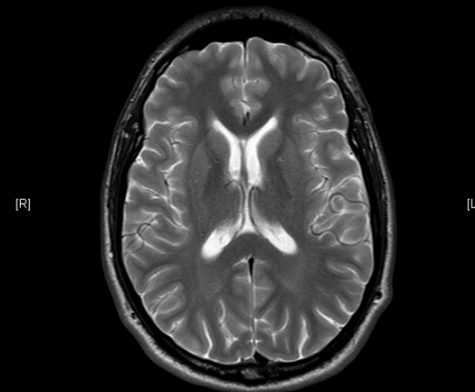
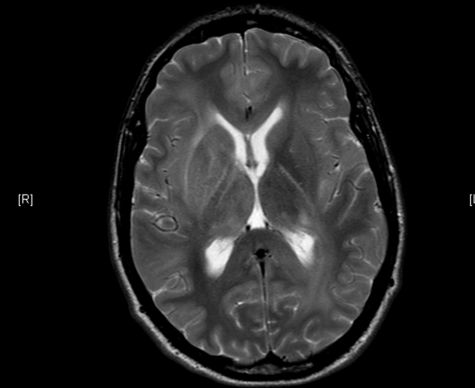
Same risk reduction strategies that are used in HIV-uninfected individuals should apply (statin therapy, blood pressure control, and management of diabetes, smoking cessation)

Clinical aspects

- most consistent with that of other ‘subcortical’ disorders (e.g., Huntington’s disease), with deficits especially in the areas of motor skills, processing speed, and executive functions
- Severity of attention/working memory impairment among individuals with HAND appears to be driven by HIV disease severity as well as complexity or “load” of the attention/working memory task
- HIV-associated deficits in episodic memory are readily observed on a variety of verbal (e.g., word lists and passages) and visual (e.g., simple and complex designs) tasks
- HIV-associated motor slowing is often seen in gait velocity, finger tapping and manual dexterity

A patient variably complaint on ART presents with headache and focal neurology including cognitive slowing

- Normal opening pressure of 16 cm/CSF
- WCC 168 (95% lymphocytes, 5% polymorphs)
- Glucose 3.6 mmol/l (serum glucose 5.1)
- Protein 5.5 g/l protein
- CSF HIV RNA 2128158 copies/ml
- Serum HIV RNA 7358 copies/ml
- Other viral PCR studies negative
- Unmatched OCB's in CSF



Conclusions

- Cognitive symptoms in patients with HIV may have multiple causes which include HAND, vascular change, medication, lifestyle, mood and other dementias of aging.
- CSF biomarkers and imaging are important to distinguish causes.
- Patients present with a subcortical type dementia different clinically from AD/PD