Neurocognitive Disorders in HIV

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Financial Relationships With Commercial Entities

Dr Valcour has served as a consultant to Merck & Co, Inc, and ViiV Healthcare. (Updated 11/20/19)

Learning Objectives

After attending this presentation, learners will be able to:
• Recognize signs and symptoms of cognitive problems in aging people living with HIV infection
• Describe the challenges in diagnosing Alzheimer’s disease in aging people living with HIV infection
• Describe the inflammatory phenotype of cognitive issues in the setting of HIV infection
ARS Question #1

In studies designed to understand the frequency of HIV-associated Neurocognitive Disorders (HAND), which statement is true?

A. The frequency of HAND is similar now to what it was before the introduction of combination antiretroviral therapy.
B. The frequency of cognitive impairment among people with sustained viral suppression in blood is < 5%.
C. Progression of cognitive impairment is the most common course for people with HIV-related cognitive impairment with suppressed plasma HIV RNA.

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Key Points

- Impaired cognition remains an important challenge in the era of cART
  - Effects 1/3-1/12 of patients despite successful plasma viral suppression
  - Etiology is complex
  - Chronic inflammation underpins this continued mild/moderate fluctuating encephalopathy for many
  - Comorbidity is common
  - Cerebrovascular disease is a common comorbidity in older age
  - Co-occurrence of Alzheimer’s disease and other age-associated neurodegeneration is a reality
  - Distinguishing AD from HAND is one of the greatest challenges in geriatric neuroHIV

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Estimates of cognitive impairment

Despite suppression of plasma HIV RNA

- Switzerland (2010): 69% (aviremic for median of 48 months)
- Botswana (2010): 38% (98% on cART)
- Thailand (2010): 38% (2NN Cohort)
- US Military cohort (early treatment): 19%

Concern: Many studies continue to publish rates of cognitive impairment that include individuals not optimally treated
- CHARTER, for example, possibly representative at the time, but under-treated

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Prevalence of HIV-associated Neurocognitive Disorder (HAND)

Pre-cART
Post-cART

* Caveat: Post-cART rate is from a prevalence-type study and includes people without viral suppression - Truly representative of today's clinics

Modified from Nati Rev Neurosci 2007

Clinical presentation

Cognition
- Memory loss
- Concentration
- Mental slowing

Behavior
- Apathy
- Depression
- Agitation, Mania

Motor
- Unsteady gait
- Poor coordination
- Tremor

Clinical Features – Cognitive Profile

- Multiple cognitive domains can be involved, including memory
- Common to see attentional deficits
  - Re-reading, use of lists
- Information processing may be impaired
  - Keeping up with banter
- Course does not tend to be progressive in the setting of cART but may fluctuate
Progressive atrophy in older HIV+
Despite persistent suppression of plasma HIV RNA

- Seen largely in subcortical regions, including asymptomatic suppressed participants
- Seen in cerebellum, caudate, frontal lobe, total cortical gray matter, brainstem, and pallidum
- During acute HIV despite immediate therapy, reduced volumes over 2 years in putamen and caudate
  - Brain volume reductions seen during primary HIV (not on ART) including putamen despite treatment
- Two contrasting studies among younger individuals compared to demographically matched controls and a study where individuals with substantial cerebrovascular disease were excluded

The Role of Inflammation Despite Viral Suppression

Numerous studies demonstrate correlations to chronic inflammation
Among individuals optimally treated with plasma viral suppression

- In vivo brain imaging using ligands (PET)
  - TPSO binding (microglial activation) increased in HIV compared to controls and inversely associated with cognitive performance
  - Plasma markers and immunological markers
    - sCD163 and global performance
    - CD14+CD38- and CD16+CD38- (% CD14) and progressive worsening of memory performance
  - Additionally:
    - Chronic inflammation persists even when ARV started during acute HIV
      - CD163 links to brain pathology at autopsy

References:
Imaging studies show damaged integrity linked to inflammation. Further linked to cognitive impairment.

- MCP-1 and neopterin broadly linked to abnormal brain integrity by diffusion tensor imaging (DTI)
- These DTI abnormalities link to worse cognitive performance

1. Chang et al, JAIDS 2019

The Role of Cerebrovascular Disease

Small Vessel Ischemic Disease in HIV

- Autopsy series in the US between 1999 to 2011
  - 50% of cases

Soontornniyomkij et al AIDS 2014
White matter lesion burden in aging with HIV

- Two patterns seen
- (1) Periventricular confluent lesions that are often described in small vessel ischemic disease (top)
- (2) Discrete lesions (bottom)

Studies demonstrating contribution of cerebrovascular disease to cognition in HIV

- White matter hyperintensities link to abnormalities on diffusion tensor imaging and are accelerated in HIV as well as to cognitive performance (age > 60)\(^1\)
- Some contrasting studies exist (no added burden due to HIV in age >60)\(^2\)
- May be particularly important for HIV over age 60 years
  - In HIV, the burden of white matter hyperintensities was predicted by age > 60 vs. < 60 years\(^3\)


Increased risk of symptomatic dementia associated with comorbidity

![Diagram](https://example.com/diagram.png)

- Theoretical increased risk associated with comorbidity such as CVD
Other potential contributors

- Co-morbidities – Infectious and non-infectious
- Psychiatric illness
- Medication effects
- Recreational drug use
- Others...

Distinguishing Alzheimer’s disease from HIV-related cognitive impairment

Increased risk of symptomatic dementia associated with co-morbidity
Hand (30-50%) Neurodegenerative disorders (e.g. AD, FTD, PSP)

80 years old

HAND

AD

• Increased risk?
• Altered phenotype?
• Accelerated course?

Why bother figuring out if it is HIV or AD?

• Sense of futility with each disease
  • Few effective pharmacological adjunctive treatments
• Planning for care
  • Clinical course vastly different between the two
• Clarity of diagnosis and optimal care
  • Currently, individuals living with HIV are at high risk for delayed diagnosis of Alzheimer's disease and other age-associated neurodegenerative disorders.

Course of AD in People Living with HIV

• Whether the course, features or timing of onset differ in HIV is unknown
• Pathology data worrisome that the course could be affected since multiple proteins have been reported to accumulate in brain tissue with HIV. These are also seen in neurodegenerative disorders
  • Amyloid – multiple lines of evidence for soluble amyloid and diffuse plaques (rather than neuritic plaques of Alzheimer’s disease (Reviewed in: Pulliam J Neuropharmac 2009; Mackiewicz JNV 2018)
  • TDP-43 seen in fronto-temporal dementia (Ellis Nature Reviews 2008)
  • Alpha-synuclein seen in Lewy Body Dementia (Kharlou JNV 2008)
ARS Question #2

When an older patient living with HIV presents with new cognitive problems, which will be most helpful in distinguishing HIV-related impairment from Alzheimer’s disease?

A. Brain imaging with distinct atrophy patterns that differentiate the two diseases
B. Cerebrospinal fluid analysis of HIV RNA levels
C. The pattern of neuropsychological testing with more clear deficits in 'subcortical' pattern in HIV
D. Cerebrospinal fluid Alzheimer’s disease markers of amyloid and tau

A Case Report

- 75 year-old right-handed man with 16 years of education
- Sought evaluation due to memory changes and because a brother died of Alzheimer’s disease at age 79 with symptoms “just like his”
- HIV history:
  - Diagnosed with HIV in the mid 1980s; nadir CD4 > 200 cells, no opportunistic infections
  - On integrase-based regimen for years, current, CD4 = 850 cells; UD plasma HIV RNA
Case Report – Cognitive Presentation

- Cognitive Symptoms
  - Subtle, insidious decline in his memory and executive functioning
  - Started 5-10 years ago and he feels they are progressing
  - Reports no functional problem currently
  - Has had depression since age 40, on treatment and both mild and stable
- Comorbidities:
  - Hyperlipidemia, hypertension, osteoarthritis, gout, and CAD with past MI

Case Report – Clinical Assessment

- Neurological exam:
  - Slow motor serial sequencing (Luria)
  - Lower extremity neuropathy – longstanding
- Neuropsychological testing
  - Montreal Cognitive Assessment (MoCA) Score of 24/30
  - Impaired visuospatial & executive functioning
  - Inefficient registering with reasonable memory

Case Report - MoCA

Marked dysfunction in executive performance and/or visual processing

Unexpected error in confrontation naming

Inefficient learning/registration, achieving only 4 of 5

Retention of learned material supportive of proper encoding
Neuropsychological testing – mixed picture

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Visual memory impairment
Language impairment
Manual dexterity and speed decreased, often seen in HIV

Case Report - Neuroimaging
Read as normal for age

Case Report - Next Steps?

- Modification of ARVs for greater CNS penetration?
  - No evidence to support this approach for a 10-year course
  - Most people are undetectable – thus CSF HIV RNA seldom linked to impairment
- Initiation of cholinesterase inhibitors for Alzheimer’s disease?
  - Would be empiric and possibly wrong
- Watch and wait
  - Natural longitudinal course is likely to distinguish the two over 3 years
  - Could implement broad recommendations without diagnostic clarity
  - Reasonable, but would you want this for yourself?
- CSF assessment for neurodegenerative biomarkers or referral to a specialist?
Neuropsychological Testing

- Considerable overlap between HAND and Alzheimer’s disease
- Cannot rely on cortical vs. subcortical pattern
- Memory is one of many domains that can be perturbed in HAND
- Encoding vs. retrieval of information may help distinguish error-prone/impulsive in HAND confounds recognition memory


Structural Brain Imaging

- Machine learning approach to differentiate 15 HAND vs. 80 Mild Cognitive Impairment due to Alzheimer’s disease
- Eight regions show promise to differentiate HAND from MCI (machine learning was >90% accurate)

Zhang et al, Haman Brain Mapping 2016

CSF Alzheimer’s disease biomarkers

Insufficient to differentiate HAND from AD

- Patients with HIV dementia have abnormalities in a-beta, t-tau, and p-tau similar to AD
- Some a-beta and tau alterations in HIV dementia
- Amyloid-beta alterations in HAND similar to mild AD, total tau measures may help differentiate
- Substantial overlap in a-beta and t-tau, p-tau measures may help differentiate

Case Report - Next Steps?

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- Initiation of cholinesterase inhibitors for Alzheimer’s disease?
  - Would be empiric and possibly appealing
  - Natural longitudinal course is likely to distinguish the two over 3 years
  - Could implement broad recommendations without diagnostic clarity
  - Reasonable, but would you want this for yourself?
- CSF assessment for neurodegenerative biomarkers or referral to a specialist?

Summary Points

- Impaired cognition remains an important and frequent challenge in the era of cART
- Cognitive impairment affects one-third to one-half of patients despite successful plasma viral suppression
- Chronic inflammation underpins this continued mild/moderate fluctuating encephalopathy
- Cerebrovascular disease is a common comorbidity among older people living with HIV and it contributes to the cognitive burden

Summary Points

- Due to advancing age of people living with HIV, the likelihood for Alzheimer’s disease (AD) will increase
- Like people without HIV, the rate of AD is likely to increase exponentially with age – whether the overall rate is higher in people living with HIV is unknown
- Distinguishing AD from HAND is an urgent issue with few data to define a clinical approach
- Alzheimer’s disease biomarkers including PET imaging and brain imaging are not likely to be enough, used individually, CSF AD biomarkers may add clarity
- Patterns of neuropsychological testing deficits overlap between the two diseases
What can we do now?

To screen or not screen

- Controversy exists
- Screening tools are not great
  - International HIV Dementia Scale is not useful – WOULD NOT USE
  - Mini Mental State Exam (MMSE) does not target HIV-related changes (more designed for AD) – WOULD NOT USE
  - Montreal Cognitive Assessment test (MoCA) has some association
  - Computer or tablet based measures may hold promise, particularly for longitudinal patterns

Treatment recommendations:

1. Adherence to antiretroviral medications with persistent plasma viral suppression
2. Referral to a specialist if Alzheimer’s disease or other age-associated neurodegenerative disorders is considered
3. Consideration for CSF escape (rare), particularly in more rapid and progressive presentations
4. Minimize polypharmacy and address medications that can impact cognition
   - Beers criteria available online
Treatment recommendations

- Compensatory measures
  - Given an underlying attentional and speed component, many patients respond to use of lists, reminders, alerts
  - Limiting multitasking
- Disclosing to friends when possible
  - Re: challenges keeping up with conversation/banter
- Reassurance on likely trajectory
- Empowerment with knowledge that symptoms are due to HIV and occur in others

The Lancet Commission: Potentially modifiable risk factors
- Up to 35% of dementia risk is potentially modifiable
  - Hearing loss
  - Hypertension
  - Obesity
  - Smoking
  - Depression
  - Physical inactivity
  - Social isolation
  - Diabetes

Thank you