HIV, Aging and the Neurologic System

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Overview

• Review of HIV neuropathogenesis
• Current understanding of HIV and aging
  – Synergistic and/or parallel mechanisms to increased impairment
  – New findings in the past year
• Major areas where methodology can be improved
  – Focus on etiology/pathogenesis rather than just “impairment”, what is meant by age, existing limitations in assessment of function
Clinical Features

reflective of anatomic pathology

Cognition
- Memory loss
- Concentration
- Mental slowing
- Comprehension

Behavior
- Apathy
- Depression
- Agitation, mania

Motor
- Unsteady gait
- Poor coordination
- Tremor
Cognitive Impairment in HIV

Heavily focused on neuropsychological testing impairment

- Asymptomatic disease has unclear pathological relevance, but is associated with impaired function
No change in the frequency of cognitive impairment despite HAART

Caveats

- Less than 2% with dementia
- No specificity for etiology
- No requirement for symptoms
- Rare progressive disease
- Highest risk with
  - Comorbidity
  - Viral detectability/low CD4
  - age

Conference on Retroviruses and Opportunistic Infections 2009

Grant et al CROI 2009
Higher Frequency of Dementia in Older HIV Individuals.

- Consistently, studies identify greater rates of cognitive diagnoses with increased age.
- Most impairment in this study was thought to have contributions from other disease processes (parallel mechanisms).

**Hawaii Aging with HIV Cohort**

- Older: 50+
- Younger 20-39

*Neurology 2004*
Age related neurological changes extend beyond cognition

Parkinson’s disease – rate increased to 4-8 times normal for 50 year old individuals (but still accounted for only 3 observed cases out of 2500) Tisch 2009 Neurology
Synergistic effects of age and HIV

• Exceedingly difficult to prove due to confounding and tissue access
  – ? accumulation of proteins associated with neurodegeneration
  – ? increased processing speed deficits
  – No evidence for interaction with age and HIV on testing performance (Valcour 2011 JINS and Lucette 2011 J Neuropsychiatry Clin Neurosci)
Changes in brain oxygenation (activation) with stimulation

HIV and age effects noted without substantial interaction

Ances 2010 Neurology
Tau expression in hippocampus

Elevated despite viral control with HAART

What is due to HIV vs. other factors

Pre vs. Post HAART Era Amyloid Deposition

Age 24-75, mean age in mid 40s
UCSD and UCLA brain banks

Green et al AIDS 2005
11C-PiB binding

Cognitively normal HIV negative subject with low CSF β1-42 amyloid

Caveats: PiB binds only to neuritic plaques, thought to be a final stage in AD amyloidosis; age around 50 for both groups; no cognitive impairment

Cognitively normal HIV+ subject with low CSF β1-42 amyloid

Ances 2010 Neurology
Complete disconnect between CSF amyloid and PiB

Raises important questions related to amyloid processing in HIV

Ances 2010 Neurology
Parallel mechanisms: HIV and aging
Parallel mechanisms

• Cerebrovascular disease
  – carotid IMT and glomerular filtration rate were significantly associated with psychomotor speed, whereas IMT was associated with memory test performance (Becker 2009 Neurology)
  – Insulin resistance and diabetes associated with impairment (Valcour 2005 JAIDS)
79-year old male – impaired
(yet, asymptomatic)

3T Image
Summary

• Neuropsychological testing impairment rates are unchanged in the setting where HAART is available
  – Not specific to pathogenesis
  – Strongest predictors are non-adherence, resistance, comorbidities
  – Most impairment is “asymptomatic”

• Age is consistently a risk for medical diagnosis for impairment (although not necessarily for NP impairment with matched controls)
  – is at least theoretical risk for both synergistic and parallel mechanisms for increased risk for impairment
How can we improve?
Improved Disease Specificity

• Specificity for disease rather than “impairment” alone
  – Unique methodology employed for HIV will not due for understanding neurodegeneration

• It will be impossible to define pathogenesis without clear clinical characterization
  – Terms like Asymptomatic Neurocognitive Impairment are not sufficient
Risk for NP impairment in HIV

- Risk factors
  - Age
  - Low CD4
  - Detectable VL
  - Comorbidity

- Does not help us understand risk in people with long-term control

- Does not speak to mechanisms

Heaton 2010 Neurology
New focus

• Focus on patients with impairment despite “successful” treatment. Potential etiologies include:
  – Unmanaged comorbidities
  – Parallel diseases – Alzheimer’s disease
• Such work could define how current treatment approaches are insufficient
  – Reservoirs - CNS, monocytes
Address the issue of asymptomatic impairment

• Is this disease – probably
• ? Insight
• Poor proxy informants
• We will not be able to move forward with understanding dementia syndromes without clear data of functional consequences
How does one define old?

“Forty is the old age of youth; fifty the youth of old age.”

- Victor Hugo
What would doubling the risk for Alzheimer’s disease look like at age = 55?
UCSF 60+ HIV Cohort

Only one case of presumed AD – diagnoses completed by consensus panel using Alzheimer’s Disease Research Center (ADRC/INA?NIH) methodology
Is a focus on chronological age sufficient (appropriate)?

These patients are both 65 years old – are they equivalent?
- Survival factors, severity of past disease, exposure to medications, etc
- Quantifying factors that may be associated with age (Cohort effects) needs to be independent of simply relating everything to “age”
Clarification of the Question at hand

- “Accelerated” aging from a tissue stand-point? – probably difficult to prove
- Multifactoral etiology to impairment – probably important
- Risk for neurodegenerative disorders – probably necessary, but will require a truly old cohort
- Functional life expectancy?

J. Fries NEJM 1980