NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Assessment, Diagnosis and Treatment of HIV–Associated Neurocognitive Disorder (HAND)

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Differential diagnosis: conditions which may present with cognitive changes or delirium

- Substance use: intoxication/withdrawal
- Psychiatric disorders (major depression & psychosis)
- Metabolic or systemic disorders (hepatic encephalopathy, B12 deficiency, uremia)
- CNS opportunistic infections (CMV encephalitis, cryptococcal & tuberculous meningitis, CNS toxoplasmosis, PML)
- Systemic infections
- Brain tumors (lymphoma & metastatic disease)
- Other causes: neurosyphillis, substance-induced dementia, vascular dementia, brain injury, Alzheimer disease, & hydrocephalus
- Medication adverse effects: antiretroviral (ARV) medications (especially efavirenz), psychotropics, interferon, anticholinergics

Pathogenesis of HIV-Associated Neurocognitive Disorder: Trojan Horse theory of HIV entrance into the CNS*

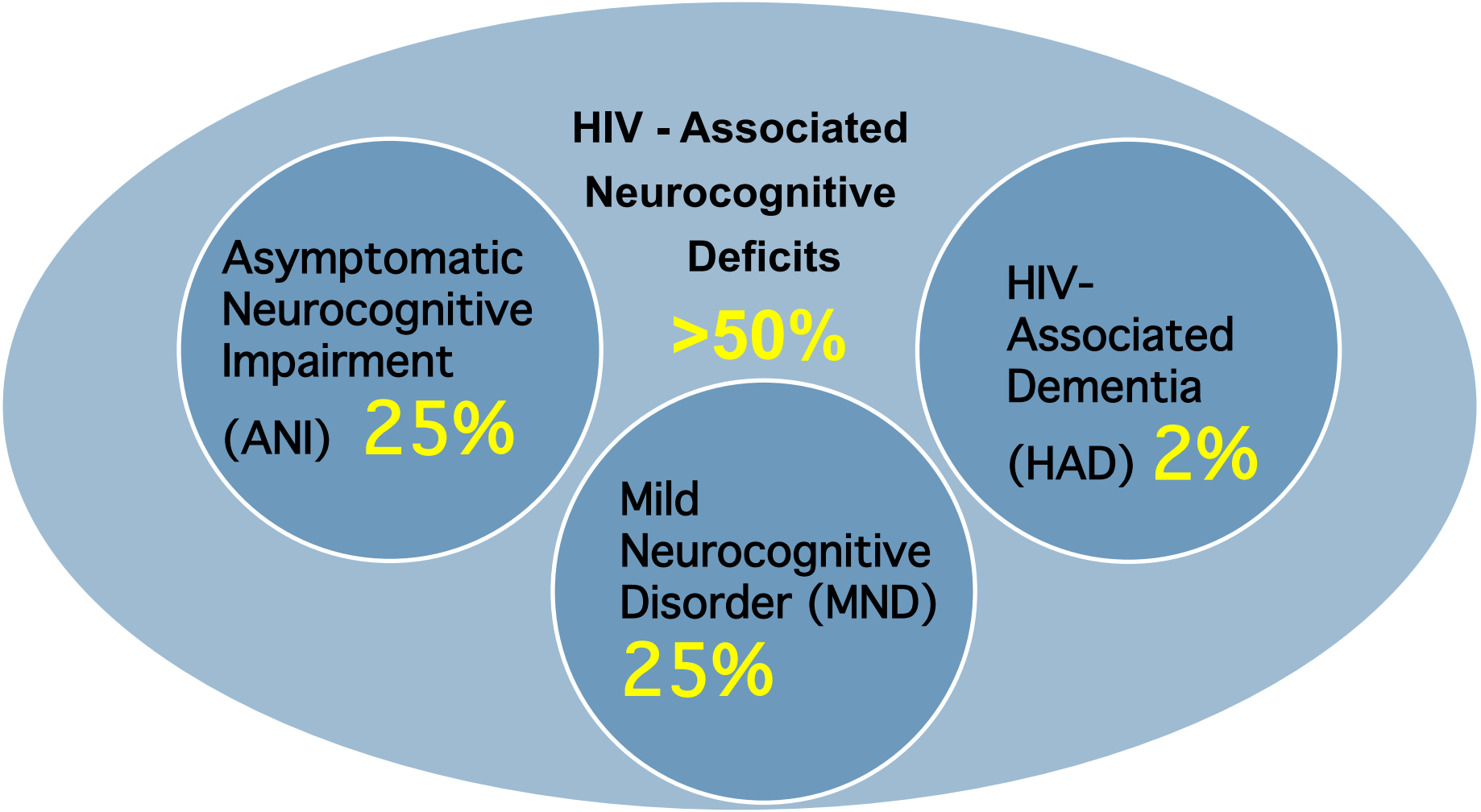
- HIV enters CNS w/in 2 wks of primary infection, crosses BBB by infected monocytes which differentiate into macrophages (reservoir).
- Cell-free virus also enters by infecting endothelial cells of BBB and diffusing into CNS.
- Macrophages infect other cells in CNS (microglia, astrocytes & perivascular macrophages) by direct contact.
- Neurons do not become directly infected.
- Cognitive impairment is caused by gradually increasing neuronal damage due direct toxic effect of viral proteins, chronic inflammatory process & production of cytokines.

Gonzalez-Scarano & Martin-Garcia, 2005

HIV-Associated Neurocognitive Disorder (HAND)

- Prior to use of HAART: 20–30% w/ advanced HIV had sx of HIV-associated dementia (Gonzalez-Scarano, 2005).
- Since HAART:
  - Incidence of HAD has dramatically decreased.
  - Up to 40% of HIV+ patients continue to suffer from HAND (Antinori et al. 2007, Nabha et al 2013)
- CHARTER study 2003-07 (Heaton et al 2009). 1500 patients on HAART: > 50% w/ HAND.
  - 2% HAD
  - 25% MND
  - 25% ANI

AIDS Dementia Complex and Minor Neurocognitive Motor Disorder. New terminology



Risk factors for HAND

- Low CD4 count (<200)
- Level of plasma viremia, CSF viral load
- Lower nadir CD4 count
- Hepatitis C co-infection (and possibly active Hep B co-infection)
- Drug abuse/dependence (methamph)
- Ageing
- Diabetes
- Cardiovascular risk factors

Rackstraw 2011

HIV-Associated Neurocognitive Disorder and Dementia

- Subcortical dementia: brain regions most commonly damaged in HAD are the basal ganglia, deep white matter, hippocampus, and cerebral cortex. Characterized by:
  - Psychomotor slowing
  - Changes in mood and anxiety
  - Deficits in memory, verbal fluency
  - Deficits in executive functioning: abstraction, information processing, decision-making, attention
  - Deficits in olfaction are also common in HAD

Lindl 2010

Signs & Symptoms of HIV-Associated Dementia

- Memory deficits
- Distractibility & decreased attention/concentration
- Mood & personality changes: sadness, anger, irritability, or emotional lability
- Apathy, fatigue & social withdrawal
- Psychomotor slowness, poor balance, & clumsiness
- Executive dysfunction, apraxias & reduced speed of information processing
- Language problems
- Visuospatial difficulties
- Late stage: Psychotic symptoms, severe verbal memory, seizures, & mutism.

Diagnostic Criteria of HAD

The patient displays ≥ 2 of the following cognitive symptoms for >1 month:

- Impaired attention/concentration
- Slowing in processing information
- Difficulty with abstraction/reasoning
- Difficulty with visuospatial skills
- Impaired memory/learning
- Impaired speech/language

AND at least one of the following:

- Acquired abnormality in motor function by clinical examination or neuropsychological testing
- Decline in motivation, emotional control, or social behavior

Lindl 2010

Dx of Mild Neurocognitive Disorder

Diagnostic Criteria

- The patient displays at least 2 of the following sx for >1 mo: Impaired attention/concentration
  - Mental slowing
  - Impaired memory
  - Slowed movements
  - Impaired coordination
  - Personality change, irritability, or emotional lability
- And has mild-moderate impairment in daily function and ADLs.

Lindl 2010, Nabha 2013

Evaluation of Neurocognitive Deficits in HIV: Subcortical Dementia

- HAD: >2 SD below mean scores in 2 different cognitive domains & moderate-severe deficits in ADLs.
- Comprehensive neurocognitive testing of 5 cognitive domains:
  - Attention & speed of information processing
  - Working memory & learning/recall
  - Verbal/language
  - Abstraction/execution functioning
  - Motor skills
- MND: >1 SD below mean and mild ADL difficulties
- ANI = MND without ADL deficits

Screening tests for HAND: Subcortical Dementia Screening

- **HIV Dementia Scale**: 4 tests of memory, attention, psychomotor speed & contruction. 80% sens 91% specif, PPV 78%. Validated in English & Spanish only*. Score ≤10/16 is indicative of need for further testing.

- **Modified HIV Dementia Scale**: Score <7.5 = possible HAD.
  - Memory-Registration: (4 words: dog, hat, bean, red)
  - Psychomotor Speed: Ask pt to write alphabet in upper case letters horizontally across the page and record time. (<21 sec=6; 21-24 sec=5; 25-27 =4; 28-30=3; 31-33=2; 34-36=1. >36=0).
  - Memory Recall: give 1 point for each word recalled. Give 0.5 pt for recall after prompting.
  - Copy cube, record time. (<25 sec=2; 25-35 sec =1; >35 sec=0)

*Powers et al 1995. Wojna et al. 2007.

International HIV Dementia Scale (IHDS)

(Validated cross-culturally. Tests memory, motor speed & psychomotor speed. Sens 80% Sp 57%.)

1. **Memory-Registration:** 4 words to recall (dog, hat, bean, red) – 1 sec to say each. Then ask for all 4 words. Repeat if pt does not recall all immediately. Tell pt you will later ask for words.
2. **Motor Speed:** Have pt tap 1st two fingers of non-dominant hand as widely & quickly as possible. 4 = 15 in 5 sec; 3 = 11-14 in 5 s; 2 = 7-10 in 5 s; 1 = 3-6 in 5 s; 0 = 0-2 in 5 s. Score____
3. **Psychomotor Speed:** Have pt perform movements w/ non-dominant hand as quickly as possible: 1) Clench fist on flat surface. 2) Put hand flat on surface w/ palm down. 3) Put hand perpendicular to flat surface. Demonstrate & have pt perform 2x for practice. 4 = 4 sequences in 10 sec; 3 = 3 seq in 10 s; 2 = 2 seq in 10 s; 1 = 1 seq in 10 s; 0 = unable to perform. Score____
4. **Memory-Recall:** Ask pt to recall 4 words. For words not recalled, prompt w/ clue: animal (dog); piece of clothing (hat); vegetable (bean); color (red). Give 1 pt for each word spontaneously recalled. Give 0.5 pt for correct answer after prompting. Max=4 pts. Score____

Max score=12. Scores <10 should be evaluated further for possible dementia.

Sacktor et al 2005.

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HAD Screening Tests

- **Mental Alternation Test***: Ask pt to count to 20, say the alphabet, & then alternate between numbers & letters. (ie 1-A, 2-B, 3-C…) Score = # of correct alternations in 30 sec (max=52). Score <15 indicates need for further testing.

- MOCA

*Jones BN et al. 1993

3 simple screening questions for HAND*

1. Do you experience frequent memory loss?
2. Do you feel you are slower when reasoning, planning activities or solving problems?
3. Do you have difficulties paying attention?

Key Point: Early HAD differs from Alzheimer's in that it is more likely to present with behavioral changes and psychomotor slowing, progresses more rapidly, may be associated w/ CSF findings and is rarely associated w/ aphasia.

*Simioni et al, 2010

International Consensus Guidelines*

- All pts w/ HIV should be screened to assess neurocog fxn during first 6 months of HIV dx.
- High risk groups should be monitored q 6-12 months.
- Freq of monitoring should be increased in those w/ neurocog decline, not on HAART and those w/ poor immunological response and incomplete virologic suppression.
- Comprehensive neuropsych eval is the standard for eval of HAND.
- MRI and LP are part of complete eval for HAD

*Mind Exchange Working Group

Pharmacologic Management of HIV-Associated Neurocognitive Disorders (HAND)

- **HAART:** for tx & prevention of HAND. High CNS penetration.
- **Psychiatric Meds**
  - **Antidepressants:** SSRI or bupropion for comorbid depression, anxiety, or behavioral problems. Consider psychiatry referral.
  - **Stimulants:** Palliative agents to help manage sx of fatigue, decreased concentration, & memory deficits among patients with MND/HAD. Refer to psychiatrist for eval & initiation of tx. Starting dose is 5 mg/d. Max dose is 60 mg/d. They should be used with great caution for pts w/ hx of substance abuse.
  - **Antipsychotic medications:** for agitation/hallucinations. Consult w/ psychiatrist. Start at the lowest possible dose & increase slowly as needed.
  - **No Benzodiazepines:** ↑ confusion & ↓ concentration.

*U.S. DHHS HRSA HIV/AIDS Bureau Clinical Guide for HIV/AIDS Care. June 2012.

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Nonpharmacologic Management of MND and HAD*

- Structured routines, good nutrition, minimize use of alcohol & illicit drugs.
- Adherence to medical regimens is compromised:
  - Simplify complex tasks
  - Repeat information & write instructions
  - Ask patients to repeat info & instructions
  - Encourage use of medication adherence tools (pill boxes, alarms, blister packs or pre-filled medisets)
  - Encourage adherence support from family & friends

*U.S. DHHS HRSA HIV/AIDS Bureau Clinical Guide for HIV/AIDS Care. June 2012.

Potential adjunctive therapies for HAND

- Drugs that either specifically or non-specifically target suspected key pathways in HIV-induced neuronal injury.
- AIDS Clinical Trials Group focus on 3 of these drugs:
  - NMDA antagonist-- memantine
  - Antioxidants-- selegiline
  - Anti-inflammatory-- minocycline