HIV-Associated Neurocognitive Disorders (HAND)

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Educational Objectives
By the end of the session, learners will be able to:

1. Describe three categories of HIV-associated neurocognitive disorders (HAND) and two features that distinguish them from other neurodegenerative disorders
2. Outline an appropriate workup for HIV-associated neurocognitive disorders (HAND)
3. Apply an interdisciplinary approach to the treatment of HIV-associated neurocognitive disorders (HAND)
4. Model informative counseling for caretakers regarding prognosis

Suggested reading:

CASE ONE:

Mr. Wander is a 61-year-old gentleman with past stroke without sequelae, hepatitis C virus (HCV) infection not on treatment, HIV diagnosed at age 37 on efavirenz, tenofovir and emtricitabine, who presents to the emergency room stating “a man who takes care of horses” gave him a pill which made him ill. He denies other specific complaints or symptoms. He reports that he takes “approximately 4 medications daily” but is unable to elaborate the name, dosage and timing of any of his medications. His last CD4 is 170 cells/mm³ and his viral load is undetectable. He has prior meningoencephalitis due to toxoplasmosis.

Mr. Wander is your clinic patient whom you met for the first time 6 months ago – he missed his last follow-up appointment. The emergency room doctor calls you at the clinic to see if you can help provide more background information.
Questions:

1. **What are HIV-associated neurocognitive disorders (HAND)?**
   - HIV-associated neurocognitive disorders (HAND) describes the spectrum of cognitive deficits among HIV-infected patients after other differential diagnoses are excluded, such as delirium, central nervous system (CNS) infections or malignancies, cerebrovascular disease, substance use disorders, various dementia syndromes including Alzheimer’s and vascular dementia, nutritional deficiencies, and endocrine disorders.

2. **What are different types of HAND, and how would you figure out which type Mr. Wander has?**
   - There are 3 types of HAND based on the “Frascati criteria” (1) – proposed in 2007 by the working group supported by the National Institutes of Health (NIH) to assist in diagnosis and categorization for clinical/research purposes:
     - **Asymptomatic neurocognitive impairment (ANI)** – defined by a score of at least 1 standard deviation below the mean on at least 2 cognitive areas on standardized neuropsychological testing without observable functional impairment.
     - **Mild neurocognitive disorder (MND)** – defined by a score of 1 standard deviation below the mean on at least 2 cognitive areas on standardized neuropsychological testing with mild impairment of daily functioning.
     - **HIV-associated dementia (HAD)** – defined by a score of at least 2 standard deviations below the mean on at least 2 cognitive areas on standardized neuropsychological testing with marked impairment in activities of daily living.
   - To figure out which type of HAND Mr. Wander has, the level of impairment needs to be explored. If other potential causes of cognitive deficits are ruled out, Mr. Wander potentially has HIV-associated dementia, since he has at least a marked impairment in his ability to correctly manage medications, possibly also in other domains if history is taken further.

3. **What is the pathophysiology of HAND?**
   - HIV disseminates to the CNS soon after primary infection via infected monocytes that cross the blood-brain barrier to replenish perivascular macrophages. The infection of these brain macrophages and microglial cells results in activation and altered production of cytokines and chemokines even after years of durable viral suppression, leading to abnormal neuronal pruning. The basal ganglia and nigrostriatal structures are usually affected early in the course of the dementia.

4. **How common is HAND?**
   - Epidemiological data is limited, but based on a study by Heaton et al (2), the prevalence ranges from 25% (post-ART) to 52% (pre-ART). Neurocognitive deficits are more common in HIV-infected patients than the uninfected.
regardless of level of viral suppression, disease state, or ART status (ART has been associated with a decrease in prevalence of HAD but not of HAND overall).

5. **To investigate risk factors related to Mr. Wander’s neurocognitive deficits, what questions should you ask on the history? Your answer should address HIV-disease factors, comorbidities and host genetic factors.**

   - **HIV-disease factors:** Studies suggest that severe immunosuppression may cause irreversible neurocognitive deficits regardless of subsequent viral suppression or immune reconstitution. As a result, it is important to ask about prior HIV history. The following disease factors confer higher risk of HAND:
     - Lower nadir CD4
     - Lower CD4 cell counts
     - Older age at seroconversion
     - Duration of HIV infection
     - Presence of a prior AIDS-defining diagnosis

   - **Comorbidities:** Certain medical problems have been associated with HAND, although they are not causal and inflict neurological damage independently of HIV. Patients should be assessed for the following conditions:
     - Anemia
     - Vascular disease
     - Hepatitis C virus has independent neurotoxic effects from proinflammatory cytokines induced by HCV core protein
     - Metabolic abnormalities including increased waist circumference and insulin resistance similar to metabolic syndrome

   - **Host genetic factors** have not been shown in prior studies to play a role. A genome-wide association study by Levine et al (3) did not detect an association between apolipoprotein E4, chemokine receptor CCR2, monocyte chemoattractant protein-1, or any other polymorphisms with HAND.

   - **Mr. Wander has multiple risk factors.** His current CD4 level is low at 170 cells/mm$^3$. He also was infected in the past with Toxoplasmosis, an AIDS-defining illness. All of these factors suggest that he has had severe immunosuppression for many years, which has been reported to have long-lasting effects on neuropsychiatric performance. He also has vascular disease and hepatitis C infection, which causes neuronal damage independent of HIV.

6. **What clinical features would you look for on Mr. Wander? What kinds of problems in his daily activities might you find? Your answer should address cognitive deficits, mood disturbances and motor symptoms.**

   - **HAND symptoms are primarily characterized by subcortical dysfunction, manifested as speed impairment in cognitive functions, depressive symptoms and movement disorders.**
     - **Cognitive deficits:** HAND involve attention and working memory impairment, executive dysfunction (reading comprehension, mathematical skills), slow informational processing, poor attention/concentration. However, absence of higher cortical
dysfunction such as aphasia, agnosia, apraxia and its fluctuating
course (waxing/waning) help distinguish HAND from other
neurodegenerative disease, such as Alzheimer’s dementia.

- **Manifestations of cognitive deficits**: Patients may report problems
  with instrumental activities of daily living (IADLs). Medication and
  finance management may be affected by impaired memory/attention,
  executive dysfunction and poor attention/concentration. Grocery
  shopping and cooking may be hard to perform and unsafe with
  executive dysfunction.

- **Mood disturbances**: Affective disturbances associated with HAND
  may be an early manifestation of HAD, which include apathy,
  lethargy, loss of sexual drive, and diminished emotional
  responsiveness, anhedonia, irritable mood, insomnia, weight loss,
  restlessness and anxiety. These symptoms may progress to psychosis
  with paranoid ideas and hallucinations. However, patients usually
  lack crying spells or reported sadness, which distinguish it from major
  depressive disorder.

- **Manifestations of mood disturbances**: Patients may report insomnia,
  and reverse sleep-wake cycle. Apathy, lethargy, diminished emotional
  response, anhedonia and loss of sexual drive may result in seclusion
  from life partners or the surrounding community. Patients may become
  less active with subsequent physical deconditioning and a decline in
  mobility. Loss of appetite may manifest as weight loss and failure to
  thrive. Irritable mood, restlessness, anxiety, paranoid ideas and
  hallucinations may result in behavioral issues that impede medical
  care and create caretaker burden.

- **Motor symptoms**: Patients with HAD have marked difficulties with
  smooth limb movements especially in the lower extremities, resulting
  in unsteady gait, which is also affected by leg weakness. HAND also
  cause motor changes including bradykinesia, dysdiadochokinesia,
  hyperreflexia, tremor and frontal release signs such as grasp, root,
  snout and glabellar reflexes.

- **Manifestations of motor symptoms**: Motor symptoms more profound
  in the lower extremities may result in falls. Problems with fine motor
  movements such as bradykinesia and tremor in upper extremities may
  result in difficulties with activities of daily living (ADLS), such as
  dressing, eating, personal hygiene/grooming.
CASE ONE CONTINUED:

As we know, Mr. Wander does not know the name, timing and dosage of his medications, even though he manages them on his own. When questioned further, Mr. Wander reports he does not shop for grocery or cook, and simply eats most of his meals out, usually at McDonald’s since it is cheap, although you notice that he has lost 20 lbs since his last visit with you 6 months ago. He thinks he has been paying rent, but does not remember when he last did that. He used to like going out for walks and sitting outside with his friends, but has not done so since he fell on the sidewalk last month which resulted in the fear of falling and increased weakness. He appears disheveled, and reports tooth pain that makes it difficult for him to chew. Mr. Wander has no recreational drug use.

7. What else should you consider to obtain Mr. Wander’s complete history?
   - Collateral stories from others should always be obtained in patients with dementia, since their report may be unreliable and not reflective of the true extent of disease. In patients without family members or caretakers, consider talking to neighbors, landlords or friends.

CASE ONE CONTINUED:

Concerned that Mr. Wander does not remember when he last paid rent, you ask to call his landlord to obtain further information. The landlord reports that Mr. Wander has always been a bachelor and never married or has children. He never has visitors and lives alone in the apartment. Mr. Wander started to miss his payments about a year ago, but was able to pay retroactively after being reminded. Lately, the landlord has reminded him a few times but still has not received payments for the last 2 months. Mr. Wander is close to being evicted since he is not able to pay rent. The landlord recalls stories of the police delivering Mr. Wander to the apartment after being found lost in his neighborhood, and an incident in which Mr. Wander set off the fire alarm because he left the stove on.

8. What would you focus on during the physical exam? How would you distinguish HAND from other neurodegenerative disorders, such as Alzheimer’s?
   - Look for exam findings that may suggest other diagnoses, including fever (CNS infection), focal neurological symptoms (CNS infection or malignancy, stroke), paresthesias or sensory deficits (B12 or nutritional deficiencies), waxing and waning disturbance in consciousness (delirium), symptoms related to thyroid or adrenal disorders.
   - Screening for depression and assessment of its severity are important, since depression affects quality of life and medical compliance. A screening Patient
Health Questionnaire (PHQ-2) with subsequent diagnostic PHQ-9 can be done in the office. Other tests to consider include Geriatric Depression Scale (GDS) or the Major Depression Inventory (MDI).

A detailed neurological exam and brief but appropriate cognitive testing can help distinguish HAND from other neurodegenerative disorders:

- On neurological exam, frontal release signs such as grasp, root, snout and glabellar reflexes suggest the presence of HAND. Other suggestive features include dysdiadochokinesia (impaired rapid alternating movements, such as rapid pronation/supination of the hands).
- Brief but appropriate cognitive testing can be performed in less than 10 minutes to help delineate the types of deficits present.
  - To test for executive dysfunction prominent in HAND, consider the Montreal Cognitive Assessment (MoCA), the International Dementia Scale or the HIV Dementia Scale. Avoid the mini-mental status exam (MMSE), since it does not thoroughly test executive function, not to mention that it has become proprietary and costs $1 per use.
  - Absence of higher cortical dysfunction such as aphasia, agnosia, apraxia and its fluctuating course (waxing/waning) help distinguish HAND from other neurodegenerative disease, such as Alzheimer’s dementia. Aphasia and agnosia are tested on the MoCA. There is little consensus on the proper method to test for apraxia, which is the inability to execute learned purposeful movements. Many exercises have been suggested, such as asking patients to pretend to brush teeth, use a hammer, but most have not been validated and translate poorly to clinical outcomes.

CASE ONE CONTINUED:

On exam, Mr. Wander has a temperature of 98.6, blood pressure of 140/90, heart rate of 76, respiratory rate of 16, and oxygen saturation of 99% on room air. He is alert without fluctuation in consciousness, although he is only oriented to place and person. He has no focal neurological symptoms or sensory deficits, but is hyperreflexic diffusely with the inability to perform rapid pronation/supination of his hands.

He scores 6/27 on PHQ-9 and 20/30 on the MoCA, losing points in clock-drawing, memory, attention, sentence repetition, delayed recall and orientation.

9. What work up would you order? Include all laboratory tests, procedures, imaging and testing that are appropriate.
- Laboratory tests: Similar to routine evaluation for other types of dementia, consider B12/folate level, thyroid-stimulating hormone (TSH), syphilis and hepatitis C in patients without known status, and complete metabolic panel. Substance abuse test should also be considered.
- Procedures/imaging: In contrast to routine evaluation for other types of dementia, in which brain imaging (unlikely to affect management) or lumbar puncture (low risks of CNS infection) are not necessary, these tests are crucial in patients with HIV. Lumbar puncture is warranted to rule out infection, such as neurosyphilis or cryptococcal meningitis, especially in patients with fever or CD4 count less than 200 cells/mm³. Brain MRI should be ordered to rule out infection, infarction or malignancy.
- Typical brain MRI findings include cerebral atrophy most often in the basal ganglia and frontal white matter in cortical regions. T2-weighted images usually demonstrate bilaterally symmetrical periventricular white matter hyperintensities.
- Neuropsychological testing is not recommended, since it is costly, time-consuming, stressful and unlikely to add useful information to in-office testing described above.

CASE ONE CONTINUED:

Laboratory results show that Mr. Wander’s hepatitis C titer is undetectable, and his liver function tests (LFT) are normal. Otherwise, B12/folate level, TSH, syphilis and lumbar puncture are unremarkable. Brain MRI does not show signs of infection, malignancy, or other neurodegenerative diseases, although chronic microvascular changes are present. However, there is no acute infarction. You diagnose Mr. Wander with HIV-associated dementia.

10. How would you treat Mr. Wander? Should you switch his regimen in the setting of newly-diagnosed HAD?
- ART is the mainstay treatment for HAND, choosing optimal regimen based on resistance patterns and side effect profile, with additional attention to CNS penetration effectiveness (CPE), since a few studies have shown that ART with higher CPE is associated with improved scores on neuropsychological testing, including improved concentration, speed of mental processing and mental flexibility (4).
- Among first line agents, emtricitabine, abacavir, ritonavir-boosted darunavir, raltegravir and dolutegravir have high CNS penetration. Other high CPE rank agents including zidovudine, nevirapine and ritonavir-boosted indinavir but these are no longer considered first-line agents.
- ART regimen should foremost be optimized based on resistance patterns and side effect profile. If Mr. Wander has reasons to switch regimens, such as virological failure or intolerance to side effects, then regimens with high CPE rank can be considered to replace what he is already taking. Otherwise, if Mr.
Wander has been stable on the current regimen, ART should not be switched solely to satisfy higher CPE ranks, since current data is still limited regarding its benefits on symptoms and progression of HAD.

CASE ONE CONTINUED:

With newly diagnosed HAD, you are concerned that Mr. Wander has not been taking his ART. As a result, you also repeat his CD4 and viral load, only to find that his CD4 is now 100 cells/mm$^3$ with a viral load of 150,000 copies/mL. Resistance testing shows that he is now resistant to efavirenz.

11. Would you switch Mr. Wander's regimen? What do you need to consider if you choose new agents for him?
   - Mr. Wander should be switched to other preferred ART regimen, with consideration of resistance patterns and side effects, less importantly CPE rank scores.
   - **Choosing a third agent**: Even though viral load was >100,000 copies/mL and integrase inhibitor may be associated with less toxicity in this population, Mr. Wander is at high risk of drug resistance due to noncompliance in the setting of his dementia, and protease inhibitor may be a safer option.
   - **Choosing a backbone**: Since his viral load was >100,000 copies/mL and dolutegravir will not be the third agent, tenofovir/emtricitabine should be used since there are conflicting reports on the efficacy of abacavir/lamivudine in patients with high viral load if dolutegravir is not the third agent.
   - Based on the reasoning above, and because boosted darunavir has a high CPE rank score, darunavir/ritonavir/tenofovir/emtricitabine may be an optimal choice for Mr. Wander.

12. How would you monitor treatment?
   - Other than usual monitoring of antiviral potency, there are no specific guidelines on monitoring treatment for HAND. Cerebrospinal fluid (CSF) viral studies have been performed for research purposes, but have been difficult to translate to clinical practice since CSF viral studies are expensive and not widely available. Also, management based on CSF viral suppression is controversial and there is lack of evidence to support this practice.
   - For patients with HAND despite plasma and CSF viral suppression, ART management is controversial. A switch to ART regimens with a higher CPE rank may be appropriate in patients with persistent or progressive cognitive decline due to a possibility of very low level virus in the CSF that cannot be detected by standard testing.
   - For patients with detectable CSF virus despite plasma suppression (i.e. CNS escape), ART management is controversial. Current data is limited and does not suggest that CNS escape predicts progression of HAND. A regimen with higher CPE rank should only be considered if cognitive deficits are
substantial or progressive and the new regimen can maintain antiviral potency.

CASE ONE CONTINUED:

Based on test results, you decide to switch Mr. Wander to darunavir, ritonavir, tenofovir, and emtricitabine. However, you are still concerned that he would not be able to manage his medications, not to mention the fact that Mr. Wander may be evicted soon.

13. What would you do next?
   - The treatment of complex diseases such as HAND requires a multidisciplinary approach to be successful. Consider enlisting help from the following providers:
     - Social work: to help Mr. Wander with his finances, meal delivery, and accommodation with appropriate safety monitoring such as assisted living facilities, in-home increased supervision such as companions or home health aides.
     - Physical therapy and occupational therapy: to help with falls, deconditioning, devices to mitigate unsteady gait or upper extremity tremors. Therapy sessions can help get patients out of the house, keep them engaged and decrease seclusion.
     - Visiting Nurse Services (VNS): to help pre-pour medications and monitor for compliance. Ordering blister packs can also help reduce confusions regarding medications and increase compliance.
     - Psychiatrists: to help optimize treatment for depression.
     - Geriatricians: to help manage associated geriatric syndromes, such as falls, safety concerns, polypharmacy, and weight loss/failure to thrive.
     - Pharmacists: to help eliminate polypharmacy, reduce drug-drug interaction, ensure appropriate dosing, and simplify timing of medications to increase compliance.
     - Lawyers: to help with the process of appointing a guardian or power of attorney, considering Mr. Wander can no longer handle his own finances.
   - Advanced care planning is crucial in patients with dementia. It is important to have the discussion with Mr. Wander before he becomes too sick or too demented to communicate his wishes. A health care proxy should be appointed. Your friendly geriatricians can be helpful in this regard.
CASE ONE CONTINUED:

Since Mr. Wander has mild depression on PHQ-9, you decide to start him on anti-depressants without referring to psychiatry. You make a note to monitor him for signs of mania.

You refer Mr. Wander for physical and occupational therapy. Your social worker submits an application to an assisted living facility, and home health aid by VNS is provided.

You refer Mr. Wander to a geriatrician, who helps simplify all of his medications to twice per day and orders blister packs for him. She also helps determine that Mr. Wander would like one of his neighbors whom he sees everyday and whom he became friends with to be his health care proxy. She plans to see him back in one month to continue discussion regarding his wishes and manage his failure to thrive.

A month later, Mr. Wander returns for a follow-up visit with his home health aid, who asks when to expect cognitive improvement on the current treatment. She also wonders if anything can be done to prevent or delay further cognitive decline.

14. How would you counsel Mr. Wander’s home health aid?
   - The prevalence of HAD decreased in the post-ART era, suggesting that effective ART may help prevent HAD. However, based on current available data, it is unclear whether ART or viral suppression/immune reconstitution can lead to reversal of disease. Symptomatic improvement seems less likely in patients with more severe baseline dysfunction.
   - The progression of disease is currently unclear. It is debated whether the presence of HAND predispose to or are an early manifestation of HAD. Some patients continue to have only mild symptoms, while others progress to more severe disease. No intervention has been shown to delay or prevent the progression of HAD once it is already present.
   - A study by Vivithanaporn et al (5) showed that neurocognitive disorders represent a marker for increased mortality (hazard ratio 3.1).
   - Overall, the evidence that ART reduces the prevalence of severe HAND, the association of lower CD4 nadir with neurocognitive deficits, the improvement in cognition with ART in a subset of patients, and the association between severe impairment and lack of response to ART all suggest that ART would benefit patients with HAND, especially in the earlier stages of disease.
Additional reference: