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REVIEW

HIV-Associated Neurocognitive Disorder (HAND): Obstacles to Early Neuropsychological Diagnosis

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Abstract: Despite the recent advances in HIV treatment, HIV-associated neurocognitive disorder (HAND) prevalence remains high, especially in the mild forms. Current recommendations endorse routine screening for HAND and early identification, but there are several obstacles in diagnosing and managing cognitive impairment in people living with HIV. The purpose of this review is to provide an overview of the concepts and diagnostic tools in the field of HAND and report on the strengths and limitations of currently available approaches.

Keywords: HIV infection, cognitive disorders, neuropsychology, cognitive test, screening

Introduction

Globally, 36.7 million people are living with human immunodeficiency virus (HIV).[1] Among them, millions of people have or are at risk of developing neurocognitive disorders. Before the introduction of combination antiretroviral treatment (ART), many patients with HIV, in the final stage of the disease, developed severe neurological impairments reunited under the umbrella term of AIDS dementia complex (ADC).[2,3] The introduction of combination ART in 1996 was a milestone in the history of HIV. However, although the effective antiretroviral treatment has decreased the severity of the neurological impairments, it did not decrease their frequency. Compared to the pre-ART era, the prevalence of HIV-associated neurocognitive disorder (HAND) in patients with HIV infection with systemic viral suppression is steady, but the non-demented forms of HAND account for the majority of the cases. Nowadays, patients with long-term infections, adherent to ART may present milder cognitive impairments.[2–4] The cases of dementia were reported to be relatively rare, with prevalence rates of 3–8%.[2–5]

Due to ART's significant impact on the central nervous system (CNS), diagnostic criteria for cognitive impairment were updated.[6] The term "HIV-associated neurocognitive disorders" (HAND) was proposed for the entire spectrum of neurocognitive diseases in the context of HIV as a replacement for ADC.[7]

The initial AAN criteria from 1991 comprised two diagnostic alternatives: HIV-associated dementia (HAD) and HIV-associated minor cognitive/motor disorder.[8] The epidemiological shift to milder forms of cognitive impairments prompted experts to reformulate the original diagnostic AAN criteria in order to better differentiate between demented and non-demented forms of the disease. Consequently, the current HAND classification comprises three degrees of severity: HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder

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(MND), and HAD. Although they were intended for use in research, the terminology has become widely used to refer to the clinical burden of disease.[9]

Screening and early diagnosis of HAND are essential in order to minimize the progression of ANI and MND to HAD, at which point there is a lower chance of complete recovery, even after ART is initiated or modified. Also, accurate detection is critical to the therapeutic and clinical management of people living with HIV (PLWH) with HAND, particularly for milder cognitive impairment forms. It enables adequate follow-up in patients who otherwise might not be targeted for neurological care.[10] An initial brief screening test, followed by a comprehensive neuropsychological evaluation in individuals with an impaired screen, is a cost-effective strategy. However, it is only useful if the screening test can detect at least mild HAND with good sensitivity and specificity.[10]

The purpose of this review is to provide an overview of the concepts and diagnostic tools in the field of HAND and report on the strengths and limitations of currently available neuropsychological approaches.

Epidemiology

Over the last 20 years, there were no significant changes in the overall prevalence of HAND in adults,[11] which is still high, estimated to occur in 30% to 60% of patients [1–6].[2–4,6,7,11] HAND prevalence varies by territory, being higher in Latin America and the Caribbean areas.[11–13] In CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER), a large cohort study, the prevalence of HAND was 47%, from which 33% of patients presented ANI, 12% presented MND, and only 2% associated HAD.[14–16] Nonetheless, the CHARTER cohort may not represent the entire HIV population. Although the study used minimal exclusion criteria to maximize generalizability, some limitations include the sample selection and the lack of demographically adjusted norms for the performance-based measures. The longitudinal component (eg, visits every six months, willingness to complete several assessments) may cause sample bias. For example, the highest functioning, working PLWH may not have time for participation, and the disabled patients might not participate due to physical or cognitive constraints.[17] Also, data were collected using both patient self-reports and clinician ratings, which could be subject to mode effects. In addition, the neurocognitive impairment was measured using GDS, which may not capture subtle forms of cognitive dysfunction.[18] Lastly, although the study includes one of the most comprehensive datasets on cognitive impairment in PLWH in the era of ART, the investigations were performed between 2003 and 2007, and the current HIV population may differ.[19]

Another recent meta-analysis on HAND subtypes revealed a prevalence of 23.5% for ANI, 13.3% for MND, and 5% for HAD. Moreover, HAND prevalence was independent of the current CD4 count, the proportion of participants receiving ART, or those with HCV co-infection.[20]

Clinical Findings and Cognitive Profile of HAND

The most frequently reported cognitive dysfunction in patients with HAND is decreased speed of information processing, followed by other common signs and symptoms of cognitive impairment such as attention and memory deficits or executive dysfunctions.[2,3,21] Some of these abnormalities are closely related and may coincide. For example, the ability to store a piece of information for temporary processing is dependent on attention functions.[3,21] Moreover, individuals with HAND often present deficits in reasoning, problem-solving, planning, and shifting between tasks translating into impaired executive functions. In addition, they may exhibit language problems, particularly impaired fluency, which is also partially related to executive dysfunction and mental slowness.[21,22] Also, some HAND patients have reported sensory-perceptual impairments, with difficulties in interpretation of visual, auditory, or sensorial stimuli.[21] In everyday practice, these common neurologic manifestations detected in people living with HIV (PLWH) remain an important issue to be addressed.

Diagnosis of HAND

The HAND is classified by Frascati criteria, based on several psychometric tests, in three degrees of cognitive impairment: ANI, MND, and HAD.[6] For ANI diagnosis, the patient should score ≥1 standard deviation (SD) below the normative data in at least two of five cognitive domains; the deficits should not interfere with daily functioning (usually detected by assessing the Instrumental Activities of Daily Living). In contrast to the ANI diagnosis, MND also

requires neurocognitive impairment in at least two of five cognitive domains, but the everyday functioning is affected.[6] The diagnosis of HAD requires an impaired performance of 2 SD below the normative data, in at least two cognitive areas, with marked day-to-day functional impairment. Also, HAND cannot be accounted for a virus-independent preexisting condition or age-associated diseases.[6]

Some of the international guidelines on HIV have specific sections addressing neurocognitive impairment.[23] They recommend a thorough assessment, including the clinical examination and medical history, neuropsychological evaluation, cerebral magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and screening for depression.[24–26] The HAND diagnostic algorithm includes neuropsychological tests which assess several domains: attention/working memory, language, abstraction/executive, speed of information processing, learning and recall memory, motor and sensory-perceptual skills.[6] Although all guidelines make reference to the Frascati criteria, there is no consensus on the specific tests that should be used as part of the cognitive evaluation.[27] Several preferred tests for each cognitive domain were endorsed by Antinori et al.[6] In addition, the Mind Exchange Working Group advocated that the tests should be validated in the language and culture of the patients, and the interpretation of the results should be made under normative data that are specific to each population.[25]

Despite the broad recommendations on the Frascati criteria, some researchers challenged their validity and use criteria.[28,29] Since there are no highly sensitive and specific screening tools that can be used in everyday clinical practice and there is no consensus on the management of asymptomatic patients, some scientists argued against a neuropsychological assessment for ANI. Moreover, a positive result might cause anxiety and depression to some patients and prompt further expensive investigations.[29] In addition, some research indicates that there is no association between the use of ART with estimated high CNS effectiveness and the neurocognitive functions.[30–32] Therefore, screening and assessment for ANI may be an unnecessary and expensive procedure in the diagnostic algorithm.[29] Since ANI is "asymptomatic," the diagnosis of ANI may have only a limited clinical value.[29]

In contrast, some arguments support the concept of ANI. Several studies demonstrated that ANI is associated with both poor treatment adherence and a high unemployment rate (6,23).[33] Furthermore, ANI can be a risk factor for progression to a more severe neurocognitive disorder.[17] According to some studies, ART with high CNS effectiveness decreases the levels of HIV RNA in the cerebrospinal fluid (CSF) and improves cognitive function.[34] In addition, some ART was demonstrated to present neurotoxic effects.[35] Also, recent research has revealed that patients with ANI present grey and white matter abnormalities,[36] and modified blood plasma biomarkers (ie, nadir CD4 count, neopterin, and neurofilament light chains).[12]

The current laboratory tests are very effective and can quantify HIV RNA down to 20 copies per milliliter of plasma.[37] The CNS represents one of the major targets of HIV, and neurological complications could generate severe disability and a severe prognosis. Neuroimaging data show that lesions have a typical "subcortical" pattern, with abnormalities, especially in the basal ganglia, thalamus, cerebellum, and cortical motor circuits.[38,39] Early in the disease, MRI can detect enlargement of ventricles and the cortical sulci.[40] Nonetheless, the main use of neuroimaging is the exclusion of diseases mimicking HAND.[7] The modern neuroimaging techniques such as MR spectroscopy, magnetization transfer ratio (MTR), diffusion tensor imaging (DTI), and voxel-based morphometry are not yet used in clinical routine. However, several studies have reported the correlation of structural and biochemical changes with parameters of neurocognitive functions.[7,41–44]

Guidelines for Cognitive Assessment

Neuropsychological assessment of five cognitive domains requires highly trained personnel, is time-consuming, expensive, and unavailable in many healthcare centers.[6] Hence, brief screening tests with good psychometric properties that are easily accessible and can be administered by clinical staff in various settings would be advantageous. Notwithstanding, most HIV guidelines do not make any specific recommendations on screening for cognitive impairment. Furthermore, in the guidelines that present recommendations, there is a substantial variation that reflects the uncertainties in the literature.[23]

The European AIDS Clinical Society (EACS) endorses the screening of all PLWH without confounding comorbidities like severe psychiatric illness, abuse of illicit drugs or alcohol, active CNS opportunistic infections or other

neurological diseases, and sequels of CNS disorders.[24] The screening should be done at the time of diagnosis and before initiating ART. After that, the cognitive testing is indicated based on the symptoms, according to the indications. For screening, EACS proposes three questions: "Do you experience frequent memory loss?" "Do you feel that you are slower when reasoning, planning activities, or solving problems?" and "Do you have difficulties paying attention?". If a patent answers "Yes" to at least one question, the test is positive, and there is a need for further assessment.[24]

On the other hand, the consensus report of the Mind Exchange Program supports screening in the first six months after diagnosis, before starting ART. Afterward, screening is recommended every 6–12 in high-risk individuals or every 12–24 months in PLWH with low risk. If the patient shows clinical deterioration, neuropsychological testing should be performed immediately.[25] As the resources for neuropsychological testing are limited in many settings, a probable clinical diagnosis of HAND could be based on questionnaires, brief screening tests, functional assessments, and limited neuropsychological assessments. Patients with particular characteristics could then be referred for a complete neuropsychological evaluation.[25] In addition, some preferred screening tools like the HIV Dementia Scale (HDS) and the International HIV Dementia Scale (IHDS) are endorsed.[25]

The Italian Society for Infectious and Tropical Diseases recommends conducting tests like Montreal Cognitive Assessment (MoCA) and Cogstate for all patients with cognitive symptoms.[26]

The British HIV Association (BHIVA) endorses screening for cognitive impairment within the first three months of HIV diagnosis and on an annual basis afterward.[45] In addition, any event that might trigger or exacerbate cognitive difficulties, warrant neuropsychological assessment. In older patients (50 years and over) with symptoms of cognitive impairment, cardiovascular risk factors and current/prior alcohol dependence should be considered.[45] This approach is also supported by the Infectious Diseases Society of America guidelines.[46] The World Health Organization (WHO) recommends routine screening for PLWH from key populations. However, the methods and timing are not specified.[47]

If the patients present with a positive screening test, further neuropsychological testing is necessary, with the use of tests that explore multiple cognitive domains, including verbal fluency, executive functions, speed of information processing, attention and working memory, verbal and visual learning, and memory, motor skills, and evaluation of daily functioning. If the presence of cognitive dysfunction is confirmed, the guidelines recommend a neurological examination, cerebral MRI, and CSF examination to exclude other pathologies. Also, the assessment of CSF HIV viral load level and, if appropriate, evidence for genotypic drug resistance (GDR) in a paired CSF and plasma sample may be necessary.[24] After exclusion of other possible causes of cognitive impairment, a diagnosis of HAND is made, and the clinicians must take specific treatment measures.[24]

Screening for Cognitive Impairment

Importance of Screening

Since more PLWH gain access to effective ART, with increased life expectancy, screening for HAND is critical for their health, quality of life, and developing optimal management strategies.[48,49] Furthermore, as HIV patients become older, they are at a higher risk of developing dementia compared with the general population. With aging, there is a decline in the incidence of CNS opportunistic infections, which may affect cognition. However, HIV infection is a vascular risk factor, and other etiological factors for cognitive dysfunction should also be considered. These include conditions like Alzheimer's disease, cerebral small vessel disease with vascular dementia, dementia with Lewy bodies, hydrocephalus.[7]

Screening for cognitive impairment is the first step of clinical decision-making. It can enable the clinicians to determine which patients are most likely to have HAND, detect early signs of cognitive dysfunction, and determine if there is a need to adjust the ART regimen. Also, screening tools may aid in allocating the resources effectively and tracking and monitoring the cognitive functions.[48] In addition, educating the patients on the impact of HAND and strategies to minimize it may improve health outcomes and ART adherence.[48]

Psychometric Properties of Screening Tests

Several essential factors need to be considered when choosing a test: sensitivity and specificity, other psychometric properties like the positive and negative predictive values, and the optimal diagnostic cut-off.[48]

Sensitivity is the ability of the test to classify a patient as having the disease correctly; meanwhile, specificity is the ability of the test to correctly identify an individual as being free of disease.[50,51] A test with high sensitivity and low specificity will accurately detect the patients who have the disease (true positives) and produce a high number of false positives (individuals without the disease but who screen positive for it). Suppose the screening tool has a sensitivity lower than the specificity. In that case, the test will better detect the true negative patients (those who do not have the disease) than the truly positive patients. Other important parameters of a test are the positive predictive value (PPV proportion of individuals with a positive test and who do have the disease) and the negative predictive value (NPV - the proportion of patients who tested negative on the screening test, without the disease). A high PPV indicates that the screening instrument is more able to detect the patients with a true cognitive impairment. A high NPV indicates that the test has high accuracy in classifying the individuals without cognitive impairment (true negatives).[48] However, it is essential to keep in mind that PPV depends on the prevalence of the disease in the population and will increase as prevalence increases.[48] Other important information is provided by the likelihood ratios for positive results (LR+), representing the increase in the likelihood of a diagnosis of HAND after a positive screening test, and the likelihood ratios for negative results (LR-), indicating the decrease in the likelihood of a diagnosis of HAND after a negative screening test. The larger LR+, the more informative the test is. An LR+ >1 indicates an increase in the odds of having HAND in a patient with a positive screening result. If LR+ is 1, it argues against the diagnostic value of the test, and nothing has been learned by ordering the test.[52] Conversely, the LR- indicates a decrease in the probability of having a disease after a negative test. If the LR- is <1, the post-test odds of the disease being present are decreased. The smaller the LR is, the more informative the test result is. An LR- of 1 signifies that the test is useless because the probability of having the disease has not changed after the administration of the diagnostic test.[52]

Choosing the Screening Test

Although several tests are available to screen for cognitive impairment, many have a series of limitations to routine use. The tests may be time-consuming, expensive, or may necessitate trained personnel. In addition, some tests may have low accuracy in detecting the milder forms of HAND, and there may be a lack of normative data for this specific population.[27,48] All these limitations may impede their use in routine clinical practice.

A recent review identified that only in five years, 23 studies presented data on 18 different screening tests for HAND or the neurocognitive impairment associated with it, several of which were novel computer-based or mobile devices.[48] However, few screening tools have been developed and validated specifically for HAND.

The HDS[53] and the IHDS[54] present adequate psychometric properties only in more advanced, symptomatic forms of HAND. The scales are relatively insensitive to the milder neurocognitive impairments that prevail in the combination ART era.[55] Researchers estimate for the HDS an overall sensitivity of 42% and specificity of 91% in identifying subjects with HAND.[10,56]

The IHDS was explicitly designed for use in international, resource-limited settings.[54] The scale has the advantage that it is adequate under different cultural, linguistic, and educational conditions. In addition, it can be integrated with ease within a clinical visit, and no specific training is needed for its use. The IHDS assesses three main cognitive domains: memory, motor speed, and psychomotor functioning.[54] A recent systematic review found that the threshold of 10 is the most useful for optimal HAND screening (including ANI, symptomatic HAND, and HAD), with fair diagnostic accuracy.[57] For HAND screening, the test had a sensibility of 61.9% and a specificity of 67.5%. The sensibility was 61.8% for symptomatic HAND detection, but with a higher specificity of 73.6%. The test presented a specificity of 85.6% in patients with HAD and a sensibility of 58.1%.[57]

The Mini-Mental State Examination (MMSE) is a highly used instrument in clinical practice for detecting cognitive impairment, and clinicians are familiar with it. However, several studies demonstrated that the test is unreliable in detecting HAND.[55,58,59]

Another first-choice tool for detecting cognitive impairment is MoCA test which is highly sensitive and specific for the older adult population.[60] The main advantages of this test are that administration time is typically 10 minutes, and it is widely available in multiple languages. In addition, in order to minimize practice effects, three versions have been developed. Also, training is available online. The test assesses short-term memory, attention, working memory, and

frontal-executive functions frequently affected in PLWH. However, in patients with HIV, the MoCA has been used with variable results. A systematic review found that a lower threshold than the original cut-off of 26 is probably more helpful for an optimal screening, as it lowers false positive rates and improves the diagnostic accuracy.[27] The optimal cut-off score was 23, with a sensitivity of 44% and a specificity of 79%.[27] Therefore, using a certain threshold in MoCA will depend on whether sensitivity or specificity is more important in a given context.

Although the paper-and-pencil screening tests present certain advantages, there are also some limitations to their use. They are prone to human error, both in administration and scoring. Besides, they have to be manually entered into electronic medical records, which is also time-consuming and prone to errors. Some studies indicate that computer/tablet/mobile-based neurocognitive testing may be suitable for detecting mild forms of HAND. Bloch et al used an updated version of CogState to identify subjects with HAND and found it has a sensitivity of 76% and specificity of 71%.[61] For MND and HAD, the sensitivity was 100% and the specificity 98%. However, it must be taken into consideration that modern screening tests may require additional expenses.[61] Future research is needed to determine their accuracy and feasibility in detecting HAND to be incorporated in clinical settings.[62,63] Nonetheless, computerized screeners, such as CogState[64] and NeuroScreen,[65,66] offer new promising options to screen for HAND.

Other possible limitations for the screening tests include the age of the participants in the diagnostic test accuracy studies in HIV populations. There are only a few studies on patients older than 50 years and children.[48,67]

Up to date, there have been developed and evaluated many screening tests for detecting HAND. Two reviews[10,68] reported that, by 2013, there had been a total of 36 studies examining 40 different screening tests, subtests, or short batteries of individual neuropsychological tests as screening tools for HAND. Also, a new review[48] found 23 additional studies presenting data on 18 different screening tests for HAND; several screeners were novel, based on a computerized assessment or mobile-based screeners (for a review, see Robbins et al. 2021;[48] Wilson 2021[69]). The strengths and the weaknesses of these screening tests are presented elsewhere.[10,48]

However, the studies investigating the use of screeners in PLWH present substantial variation in several key factors, hindering optimal screen validation and interpretation of the literature. For example, some studies included or excluded HIV patients without an optimal rationale, and various tools lacked construct validity assessment. The "gold standard" was heterogeneous among studies, with some researchers using non-standard definitions of impairment. In addition, the screen impairment definitions were variable, and some authors did not report important HIV or demographic characteristics. Furthermore, some studies included a control (HIV negative) group, and others did not.[10]

Finally, HAND screen validation studies did not include a measure of IADL status in their screening measure. This may be a significant limitation, as it impedes the optimal application of the current HAND criteria when assessing the ability of the test to differentiate between ANI and MND.[10]

Implementation of Screening Programs

The first essential step to developing and implementing a screening program is to evaluate its feasibility and acceptability.[48] For the development of a sustainable screening strategy, it is important to analyze the challenges of screening in a clinical setting, including time and space limitations, training of personnel, and costs. In addition, if the screening program is incorporated into clinical practice, it will have to prove a beneficial effect on patient outcomes.[48]

Extensive Neuropsychological Testing

As previously presented, the reference standard for the cognitive assessment is an extensive neuropsychological battery. Nonetheless, this approach also has several limitations. Besides the fact that it is time-consuming and necessitates trained healthcare professionals, it is more expensive and more challenging to implement in clinical settings.

Moreover, the current criteria for diagnosing mild cognitive impairment (ie, ANI) include a subjective complaint and functional independence, which have no analog in the DSM5 criteria. The Frascati criteria delineate three levels of HAND severity; in the case of ANI, asymptomatic means that patients do not have clinically significant difficulties in daily functioning.[6] However, studies investigating the extensive neuropsychological batteries used for HAND found that, in normal populations, without HIV infection, between 15% and 22% of individuals will have false-positive results.[70] Furthermore, 20% of a simulated normal population will present a score below the threshold used for HAND.[28] These

false-positive results are due to two common practices intended to increase the sensitivity of detecting the milder forms of cognitive dysfunction. First, extensive neuropsychological batteries involve multiple comparisons that will cause higher false-positive rates than a single test; the probability of a pathological score increases as the number of tests/each domain and the number of domains assessed increases. Second, the high threshold scores (*z* scores with a cut-off of 1 SD) will determine an increased overlap between critical portions of test-score distributions in persons with and without cognitive impairment.[28,70] Therefore, the price of the increased sensitivity will be a reduction of specificity. Consequently, the increased number of false-positive cases will determine biased estimates for prevalence, decreasing the power of analytical estimates.[70,71]

In addition, a reference standard with a high risk of bias will determine biased estimations of the accuracy of any index test (or screening test) in the diagnostic accuracy studies.

Nonetheless, the Frascati criteria are the most commonly used criteria for diagnosing HAND in medical settings and research; also, the validation of the milder forms of HAND, including ANI and MND, rely on neuropsychological assessment because of the paucity of longitudinal clinical-pathological correlation studies, and the lack of a gold standard antemortem biomarker or neuroimaging finding.

Biomarkers

Considering that standardized neuropsychological tests may present low accuracy in early diagnosis of HAND,[72] and differentiation of milder forms of HAND is often difficult, future research should focus on the identification of specific biomarkers. This would enable a better understanding of the pathophysiological mechanisms and guide the development of novel treatments.[14]

A recent review scrutinized the utility of four possible biomarkers, including neurofilament light (NFL) chain concentration, amyloid and tau proteins, resting-state functional MRI, and prepulse inhibition (PPI).[72] Although there are significant genotypic differences in NFL chain concentration, sAPPα, sAPPβ, amyloid β, total tau, phosphorylated tau, and the resting-state fMRI, there are several limitations to their use. Most of them require invasive procedures with high costs. Furthermore, some biomarkers, although promising, might lack of specificity. Therefore, their utility as diagnostic and prognostic biomarkers, especially for milder forms of cognitive impairment, may be questioned. Nonetheless, PPI appears to be a promising, brief, noninvasive diagnostic biomarker with high sensitivity (89.3–100%) and specificity (79.5–94.1%).[72] Also, it may serve as a prognostic biomarker for milder forms of HAND.

In the future, the use of multiple CSF or plasma markers, rather than a single protein, could provide a diagnostic biomarker for HAND with higher accuracy, but additional research is needed.[72]

HAND and Other Comorbidities

The HAND diagnosis is hampered by the possibility of the presence of several confounders. First, the new diagnostic criteria[6] recommend the assessment of IADL to distinguish between ANI and MND. Nonetheless, the methods to obtain evidence of IADL impairments have not been well established.

Second, a poor performance on cognitive tests may not be due to the direct effects of HIV on the CNS, as the presence of socioeconomic factors, low educational status, and comorbidities can also affect the results.[9]

The diagnosis of HAND implies that the impaired cognitive performance is due to HIV infection. Nonetheless, in clinical practice, there are three categories of PLWH with cognitive dysfunction: patients with neuropsychological impairments caused exclusively by HIV, patients with cognitive impairments due to a combination of factors (ie, HIV and comorbidities), and individuals in which the HIV brain pathology may not be contributing at all to the poor performance on cognitive tests.

Comorbidities have a significant impact on PLWH. For example, hypertension, hypercholesterolemia, and diabetes are risk factors for cerebrovascular disease and cognitive impairment. In the Multicenter AIDS Cohort Study (MACS), in older patients, a poor psychomotor speed performance was correlated with hyperglycemia and atherosclerotic disease (detected by increased carotid intima-media thickness).[73] Another study revealed that the risk of developing cognitive impairment is 6.2-fold higher in patients with HIV-associated pre-existent cardiovascular risk factors.[74]

The prevalence of cerebrovascular diseases increases with age. In PLWH, the cerebrovascular disease may be a consequence of both traditional risk factors (ie, smoking) and the metabolic and systemic effects of HIV and ART on endothelial function.[75]

Aging is another risk factor for cognitive impairment. With advances in ART and increase in life expectancy, PLWH now might present multiple geriatric syndromes in the setting of aging and increased multi-morbidity.[76] Some studies reported that PLWH over the age of 50 have a 7-fold higher odds of developing mild cognitive impairment compared to HIV-negative age-matched individuals. The authors concluded that HIV infection might accelerate cognitive aging and dementia.[77] Notwithstanding, it is difficult to predict which patients with mild cognitive dysfunction will progress to dementia in daily practice or what type of dementia they will develop.[14]

In addition, there are several common pathological features between Alzheimer's Disease (AD) and HAND. For example, Apolipoprotein E epsilon 4 (APOE-ε4) is a critical factor for developing AD.[14] In patients with HIV, the presence of at least one ApoE4 allele was found to be associated with decreased cognitive performance (eg, attention/working memory, executive functioning, fluency) and brain atrophy.[78,79] Furthermore, in patients diagnosed with HAND, especially above the age of 65, progressive symptoms and lack of impairment reversal may indicate AD overlap.[80] Therefore, differentiating AD from HAND may be essential, especially from a therapeutic point of view.

Coinfections represent another risk factor for cognitive impairment. For example, patients with HIV and hepatitis C present an increased risk of cognitive dysfunction than PLWH without hepatitis.[81] Also, the patients with a sexually transmitted disease history (eg, syphilis or gonorrhea)[82] or with anti-cytomegalovirus antibodies were found to present cognitive impairments.[75]

Psychiatric conditions are well-known factors affecting cognitive abilities, likely to worsen HAND clinical presentation.[5,83] Depression, the most prevalent psychiatric comorbidity in HIV patients, was demonstrated to mimic cognitive dysfunction. In addition, it negatively impacts executive functions, short-term memory, and attention.[75] Apathy may also influence cognitive testing. Furthermore, neuropsychiatric conditions such as apathy are likely to be an expression of the disease. The initial AAN criteria recognized the progression of HIV infection with neuropsychiatric features; some of these are probably due to the underlying striato-frontal pathology, especially in older PLWH, with chronic HIV infection.

In addition, behavioral features like apathy, behavioral disinhibition, poor insight into difficulties, anxiety, and depression, poor decision-making (eg, poor financial management, impulsivity) may not be assessed quantitatively. Furthermore, such patients are usually excluded from research studies,[5] and downgrading these symptoms from the current diagnostic criteria may lead to reductions in sensitivity.[9]

Other possible comorbidities like ART neurotoxicity, nutritional and vitamin deficiencies, history of head injury, previous CNS infections, neurodegenerative diseases, birth trauma, and lifestyle factors such as alcoholism and illicit substance use are further factors that influence cognition.

Their presence increases the potential for misclassification of HAND. The pathology due to HIV and the associated diseases should be viewed as separate, overlapping entities.[9] They should be listed as specifiers (eg, cerebrovascular disease, psychiatric illness); where this categorization is not possible, they can be termed as "multifactorial" or due to "undetermined factors".[9]

Future Research

An early diagnosis and specific management of HAND are essential for the health status and the quality of life of PLWH. Currently, guidelines recommend using the Frascati criteria for good clinical practice, but extensive neuropsychological testing can be time-consuming, expensive, and requires trained personnel. Therefore, in clinical practice, screening for HAND plays a key role in managing HIV patients. Although screening tests may present lower diagnostic accuracy, they are likely to be more reliable than the information provided by patients or self-reports.[84,85] PLWH with abnormal screening test results should be further assessed for the underlying causes of cognitive dysfunction such as mood disorders, cognition impairing effects of ART, thyroid disease, syphilis, and B12 deficiency. Before referring patients for a complete neuropsychological evaluation, these possible comorbidities should be identified.[86] Therefore, a step-wise

protocol that includes cognitive screening would be easy to implement in daily clinical practice, guiding physicians on how to manage this complex problem.[86]

Also, a possible solution for the low diagnostic accuracy of the current tests could consist of a short battery of two or three screening tests (ie, IHDS and MoCA) that requires 10 to 30 min to complete. This could improve both sensitivity and specificity, allowing the use in settings with low resources.[87] In order to develop a screening tool that can reliably detect the presence of HAND, future research could compare the use of multiple brief screening tests with an extensive neuropsychological assessment. In addition, further cross-sectional studies are needed to investigate the optimum cut-off score for HAND for brief screeners like, for example, MoCA.[27] Also, the psychometric properties of the screeners should be investigated in PLWH with different cultural and educational backgrounds and speaking different languages.

Recent studies indicate that a mobile/tablet-based screening test presents significant advantages, being associated with high sensitivity and specificity. Therefore, further research should be done in this direction.[48,65,66]

Although there are over 2 million children living with HIV, little attention was paid to finding a suitable screening method for them, and further research is needed. Also, as the life expectancy of PLWH increases, studies should investigate the effects of aging and comorbidities in this population and the accuracy of the cognitive assessment tools in diagnosing HAND.

Last but not least, the investigation of diagnostic and predictive biomarkers for HAND has the potential for great clinical significance.

Disclosure

The authors report no conflicts of interest in this work.

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