HIV-associated neurocognitive disorders

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HIV infection is associated with disturbances in brain function referred to as HIV-associated neurocognitive disorders (HAND). This literature review outlines the recently revised diagnostic criteria for the range of HAND from the earliest to the more advanced stages: (*i*) asymptomatic neurocognitive impairment; (*ii*) mild neurocognitive disorder; and (*iii*) HIV-associated dementia. Relevant literature is also reviewed regarding the differential impact upon component cognitive domains known to be affected in HAND, which in turn should ideally be targeted during clinical and neuropsychological assessments: psychomotor and information processing speed, learning and memory, attention and working memory, speech and language, executive functioning and visuospatial functioning. A discussion outlining the neuropsychological tools used in the diagnostic screening of HAND is also included. The central mechanisms of HAND appear to revolve primarily around psychomotor slowing and cognitive control over mental operations, possibly reflecting the influence of disrupted fronto-striatal circuits on distributed neural networks critical to cognitive functions. The accurate assessment and diagnosis of HAND depends on meeting the need for statistically sound neuropsychological assessment techniques that may be used confidently in assessing South African populations, as well as the development of relevant norms for comparison of test performance data.

South Africa continues to be home to the world's largest population of people living with HIV.[1] In developed countries such as the USA, the introduction of highly active antiretroviral therapy (HAART) as the mainstay of HIV treatment has resulted in impressive reductions in the incidence of severe HIV-associated neurocognitive disorders (HAND) and impacted favourably on survival rates in patients with HIV infection.[2] Neurocognitive impairments, however, do not present universally among all HIV-infected persons. Neuropsychological signs and symptoms of at least mild extent have been found in approximately 30% of persons with asymptomatic HIV infection and about 50% of individuals with AIDS.[3] Furthermore, despite the apparent reduction in the incidence of HIV-associated dementia (HAD), the incidences of milder forms of HAND appear relatively stable and may even have increased in individuals who are not immunosuppressed.[4] Therefore, despite the remarkable improvements in the USA, HAND will probably remain a public health concern of increasing severity in South Africa, given that the majority of adults and children in the region in need of antiretroviral therapy do not have access to it.

This article reviews the current diagnostic nosology for HAND and the neuropsychological domains typically affected by the HIV disease. The review concludes with a discussion of the commonly used neuropsychological screening tools for the detection and diagnosis of HAND.

Diagnostic nosology for HAND

The diagnostic nosology for HAND was revised and amended in 2007 using recommendations from the US National Institutes of Health working group.[5] The revisions emphasised that documented neurocognitive disturbance was an essential feature in the diagnosis of HAND, and specified more precise criteria for three syndromes: (*i*) asymptomatic neurocognitive impairment (ANI); (*ii*) HIV-associated mild neurocognitive disorder (MND); and (*iii*) HAD. These syndromes are discussed in turn below.

Asymptomatic neurocognitive impairment (ANI)

This previously unclassified phenomenon is estimated to represent the majority of HAND cases (over 50% of diagnosed cases) and 21 - 30% of asymptomatic HIV-infected individuals.[6] ANI refers to mild slowing in mental acuity and loss of concentration, quantified as less than 1 standard deviation (SD) below the mean of demographically adjusted normative scores in the presence of intact everyday functioning. The fall-off is so subtle that it is best assessed with the use of neuropsychological assessment tools. This exercise of early assessment and diagnosis acts as way to pre-identify patients at further risk of later and more significant cognitive as well as functional decline. The rationale of early identification premises that as effective treatments for neurological complications are developed, intervention at this early stage of HAND might represent the best chance to achieve remission, or at least delay the rapid progression of this debilitating disease.

Mild neurocognitive disorder (MND)

A diagnosis of MND requires evidence of mild to moderate neurocognitive impairment that represents at least 1 SD below the mean of demographically adjusted normative scores. To satisfy the diagnostic criteria, such impairment should occur in at least 2 cognitive domains in the presence of mild functional fall-off. The requirement of mild functional impairment is satisfied when at least 2 of the following criteria are met: (*i*) patient or informant report of decline in at least 2 instrumental activities of daily living (bathing, dressing or financial management); (*ii*) unemployment or a significant reduction in job responsibilities secondary to reduced cognitive abilities; (*iii*) decline in vocational functioning (e.g. increased errors, decreased productivity, or greater effort required to achieve prior levels of productivity); (*iv*) patient or informant report of increased problems in at least 2 cognitive ability areas in day-to-day life (this criterion cannot be used if based only on the self-report of an individual with current depression, since depression may bias self-report); and (*v*) scores of 1 SD below the mean on a performance-based laboratory measure of everyday functioning (e.g. medication management).[7]

HIV-associated dementia (HAD)

HAD represents the most severe form of HAND and is characterised by at least moderate to severe cognitive impairment that represents less than 2 SD below demographically adjusted normative means in at least 2 cognitive domains, in addition to a marked decline in the ability to complete activities of daily living. The functional impact resulting from HAD is particularly impairing. Two of the following functional deficits are required to fulfil the diagnostic criteria: (*i*) unemployment due to cognitive impairment; (*ii*) patient or informant report of dependence in at least 2 activities of daily living related to cognitive problems; (*iii*) patient or informant report of declines in at least 4 cognitive ability areas in day-to-day life; and (*iv*) performance at least 2 SD below the mean on a performance-based laboratory measure of everyday functioning (or 1 SD below the mean on 2 functional tests).[7]

Despite a marked decrease in the incidence of HAD after the advent of HAART (15 - 50%), it continues to be a significant cause of morbidity in HIV-infected patients. The prevalence, on the other hand, has increased due to the increased survival of HIV-infected patients resulting from the widespread use of HAART.[4]

The neurocognitive profile of HAND

The cognitive deficits resulting from HAND can be global; however, psychomotor skills, speed of information processing, executive functions, episodic memory, attention/working memory, language and sensory perception are most commonly affected by HIV infection. These cognitive domains, typically targeted in the assessment of HAND, are discussed below.

Motor skills and information processing

Severe movement abnormalities and psychomotor deficits can sometimes be observed in patients with HAD, most notably in the form of bradykinesia (slowed movement), hypomimia, action/postural tremor and hand agility, as well as bradyphrenia (slowed information processing).[7] HIV-associated motor slowing is often seen in gait velocity,[8] finger tapping[3] and manual dexterity.[9] Most neuropsychological tests are multi-factorial; in other words, they will probably provide information regarding a patient's performance on a number of different cognitive domains. Slowed information processing speed can therefore be observed on tasks with and without motor demands. HIV-associated cognitive and motor slowing deficits are often exacerbated when controlled processing demands are increased, such as under conditions of divided attention.[10] Furthermore, impaired performance on traditional tests of information processing speed could arise from a variety of deficits, including attention, visuoperception, working memory, praxis and basic motor skills.

Learning and memory

In addition to psychomotor slowing, episodic deficits in both verbal and visual memory are considered highly sensitive indicators of HAND. These episodic memory difficulties among HIV-positive individuals appear highly prevalent, with most estimates ranging from 40% to 60%.[11] Generally these impairments tend to be in the mild to moderate range, but they may worsen as the disease progresses, particularly with the onset of HAD.[12] A significant proportion of HIV-infected patients display evidence of impaired immediate and delayed recall of information in the presence of relatively better ability to recognise the information when presented to them.[13] Conversely, a smaller percentage of HIV-infected individuals (mainly those with HAD) exhibit evidence of rapid forgetting.[14]

HIV infection is also associated with frequent prospective memory complaints, especially in aspects of daily functioning.[14] Prospective memory entails one's ability to successfully execute a future intention and involves the formation, maintenance, retrieval and execution of a future intention.[7] It is essential for independent living and plays a critical role in daily duties such as employment, household responsibilities (e.g. financial management), social functioning and health care (e.g. medical compliance).[7] On performance-based tests of prospective memory, including both time- and event-based tasks, HIV-positive individuals demonstrate mild to moderate impairment with many omission and perseverative errors.[15]

With regard to semantic memory, HAD seems associated with mild deficits in memory for famous faces and public events.[16] The impact of HIV infection upon other aspects of declarative memory (e.g. semantic, autobiographical, emotional) as well as non-declarative (i.e. implicit) memory appear quite poorly understood given a lack of empirical inquiry.

Attention and working memory

As is the case with other neurocognitive domains, the severity of the attention/working memory impairment among individuals with HAND appears to be determined by the severity of the HIV disease and the complexity of the task (or the attentional load) presented during the assessment.[7] During the early stages of the disease, basic attention and concentration skills appear relatively unscathed; however, during the later stages mild to moderate deficits tend to appear in persons with HAND.[17] It appears that HIV is associated with mild deficits in basic attentional processes, which are amplified when processing demands are increased.[7]

Additionally, a number of studies examining working memory (the ability to create a memory representation for temporary processing and storage) abilities of HIV-infected persons reveal the occurrence of difficulties with both visual and verbal working memory tasks.[18-20] Furthermore, a number of studies have showed that attention/working memory deficits are among the strongest predictors of cognitive complaints among HIV-positive persons, predictive of medication adherence and significantly associated with driving ability (particularly the number of driving accidents in the past year) and dependence in activities of daily living.[7]

Executive functioning

When compared with other cognitive domains, fewer studies have examined the underlying cognitive processes of executive dysfunction in HIV. This is surprising given the prevalence of executive deficits and their association with important functional outcomes. It is widely accepted that HIV is associated with executive dysfunction across neurocognitive impairment profiles, especially in the later stages of the disease.[21] Executive dysfunction is strongly associated with impairments in everyday functioning, abstraction and novel problem-solving difficulties, deficits in social planning, and impairment in semantic event sequencing.

Visuoperception

It has generally been believed that spatial cognition remains largely unaffected by HIV infection. Some investigations employing standard clinical tests of visuospatial functioning were unable to detect significant impairment and as such supported this early hypothesis. However, recently the conclusions drawn from this early data have been questioned.[7] More recent works now support the likelihood that subtle deficits exist in spatial cognition in HIV infection; however, the underlying aetiology remains unclear. Neuro-imaging research suggests that cortical thinning of parietal and frontal lobes is associated with cognitive impairment,[22] but thorough investigations of spatial cognition in HIV are still needed to clarify the exact nature and origin of this impairment.

Speech and language

There appear to be very few large-scale investigations examining the basic aspects of speech and language in HIV infection in adults, as only a few case studies are available in the literature. Despite a lack of conclusive empirical evidence, the limited data available indicate that basic receptive (e.g. auditory comprehension) and expressive (e.g. repetition) language functions are generally within normal limits in HIV infection, although mild difficulties in the more complex aspects of expressive language may be observed.[23] If present, general expressive language deficits tend to be mild in the asymptomatic stage, but may exacerbate with progression of the disease.[24]

Mild impairment in the pragmatic aspects of communication may also be evident, including turn-taking during conversations (e.g. inappropriate interruptions), poor lexical selection, and reduced fluency.[25] Verbal fluency impairment is the most frequently identified language deficit in HIV and is estimated to occur in approximately 40% of the population, albeit at generally mild presentations that may increase to moderate severity among individuals with more advanced HIV disease.[26]

Neuropsychological screening tools for HAND

Neuropsychological assessments are important tools for the purposes of diagnosing and categorising the effects of HIV on the central nervous system. Such methods are particularly useful in resource-limited settings such as South Africa where sophisticated neuro-imaging technology is often unavailable. When assessment tools are psychometrically sound (i.e. reliable and valid), and appropriate normative data are available for the population assessed, they can be quite sensitive to the nuances of even milder forms of cognitive impairment. The following neuro-psychometric tools have been used in the assessment of HIV-related cognitive disturbance:

The Mini-Mental State Examination (MMSE) was developed for the purpose of distinguishing Alzheimer's dementia from other dementing disorders and as such consists of items that specifically intend to tap 'cortical' functions. The MMSE is not ideal for the assessment of HAND as sub-cortical processes are primarily affected; milder forms of HAND cannot be reliably detected, and age, education and cultural background appear to impact on its psychometric validity.[27]

The HIV Dementia Scale comprises four items, an anti-saccadic eye movement error task, timed alphabet, verbal memory and copying a cube.[28] It is more sensitive to subcortical functions and has been validated in South Africa,[29] but can be difficult for non-neurologists to administer without the necessary training.[27]

The International HIV Dementia Scale (IHDS) consists of three subtests: timed alternating hand sequence, timed finger tapping, and recall of four items after 2 minutes. The IHDS has been recommended as an appropriate screening tool for neurocognitive disorder in general primary care settings as it is brief (can be completed in 2 - 3 minutes), the patient does not need knowledge of English, it can be performed by non-neurologists, and it does not require any special equipment other than a stop-watch.[27] Despite these advantages and the fact that it was developed specifically for resource-limited settings, validation studies are needed to confirm its appropriateness for the local South African population.

The Montreal Cognitive Assessment (MoCA) is a one-page 30-point test administered in 10 minutes and particularly adept at accessing milder forms of cognitive impairment, more so than the MMSE. Details on the specific MoCA items are as follows. The short-term memory recall task involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task and a three-dimensional cube copy. Multiple aspects of executive functions are assessed using an alternation task adapted from trail making test B, a phonemic fluency task, and a two-item verbal abstraction task. Attention, concentration and working memory are evaluated using a sustained attention task (target detection using tapping), a serial subtraction task, and digits forward and backward. Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros), repetition of two syntactically complex sentences, and the aforementioned fluency task. Finally, orientation to time and place is evaluated.[30] Work to develop local normative data for this test is currently underway.

More elaborate neuropsychological test batteries may be used for more complex cases or when time constraints are not an issue; however, in the absence of local population norms their appropriateness and utility are questionable. Singh[27] and colleagues have collected population norms for the following bedside tests: digit span forward, digit span backwards, trail making test A and trail making test B. The neuropsychology battery utilised at Lentegeur Psychiatric Hospital in the assessment of dementia is detailed elsewhere.[31]

Conclusion

The development of effective treatments for HIV have improved worldwide survival rates but at the same time have raised prevalence rates as well as increased the cognitive and functional impacts of the disease. The latter now represent a significant public health issue in South Africa. Concerted research efforts have shed some light on the cognitive profile of HAND, the central mechanisms of which appear to revolve primarily around psychomotor slowing and cognitive control over mental operations.[7] Further clarification of these cognitive mechanisms is needed, especially those underlying executive dysfunction and planning deficits. These appear to play a central role in a number of aspects of everyday functioning. Future research efforts should focus on the efficacy of cognitive and behavioural remediation strategies of HAND as well as standardisation of neuropsychological assessments that assist in measuring problematic cognitive symptoms.

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