HIV-associated neurocognitive disorders (HAND) in a South Asian population - contextual application of the 2007 criteria

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ABSTRACT

Objectives: To estimate the prevalence of HIV-associated neurocognitive disorders (HAND) among HIV patients in a multiethnic South Asian population, describe the pattern of neurocognitive impairment in HAND and the factors associated with HAND.

Design: A cross-sectional survey of HIV-positive outpatients and inpatients.

Setting: The sole referral centre for HIV/AIDS treatment in Singapore.

Participants: Inclusion criteria were HIV positive, age between 21 and 80 years old and at least 3 years of education. Exclusion criteria included concomitant delirium, serious systemic disease or major psychiatric illness. 265 patients did not meet criteria or declined to participate. The final sample size was 132.

Outcome measures: The primary outcome measure was cognitive impairment based on performance on the Montreal Cognitive Assessment, International HIV Dementia Scale and Instrumental Activities of Daily Living. The secondary outcome measure was the classification of impairment based on the 2007 updated research nosology for HAND.

Results: The prevalence of HAND was 22.7% of which 70% (15.9% of total) were asymptomatic neurocognitive impairment, 23.3% (5.3% of total) were mild neurocognitive disorder and 6.7% (1.5% of total) were HIV-associated dementia. Increasing age (OR 1.104, 95% CI 1.054 to 1.155, p<0.001), less education (OR 0.78, 95% CI 0.69 to 0.89, p<0.001) and low baseline CD4 count (OR 0.15, 95% CI 0.03 to 0.74, p=0.019) were associated with HAND. Delayed recall, language and abstract thinking were the domains most commonly affected, but impairment in visuospatial ability (RC 3.013, 95% CI 1.954 to 4.073, p<0.001) and attention (RC 2.205, 95% CI 1.043 to 3.367, p<0.001) were most strongly associated with HAND.

Conclusion: HAND is common among HIV patients in a South Asian sample, most of whom are asymptomatic. Older patients with less education and severe illness at diagnosis are at highest risk of HAND. Delayed recall is most commonly affected, but visuospatial dysfunction is most strongly associated with prevalent HAND.

INTRODUCTION

Much research attention has been given to HIV-associated neurocognitive disorders (HAND) in recent years because this entity has taken on clinical importance now that highly active antiretroviral therapy (HAART) has achieved marked reductions in AIDS-related morbidity and mortality. Majority of the available data have emerged from Western populations citing an incidence rate of 21% and prevalence rates of up to 39%³ with one study from the Asia-Pacific region reporting a prevalence of only 12%.² There is a strong body of evidence showing an adverse functional impact of HAND, with patients having difficulty with activities of daily living...
Application of HAND criteria in South Asian context

and requiring more assistance to ensure adherence to medications. They may even have difficulties maintaining employment, hence requiring more social assistance. HAND has also been shown to be associated with low nadir CD4 counts in the absence of central nervous system opportunistic infections and persists despite long-standing suppression of viremia. With evidence that HAART can improve neurocognitive functioning, early initiation of antiretroviral treatment in at-risk HIV-positive individuals may prevent neurocognitive impairment.

The prevalence of known HIV cases among the Singapore resident population aged 15 years and above was 0.1% in 2009. There is a cumulative total of 4845 HIV-infected Singapore residents as of end 2010. In 2010, 54% of the newly diagnosed cases already had late-stage HIV infection at the point of diagnosis, similar to the pattern in previous years. Due to the country’s strict drug laws, intravenous drug abuse accounts for only 2% of total cases. Previous local studies had identified older age and lower baseline CD4 counts as predictors of progression to AIDS and that the commonest AIDS-defining illnesses between 1985 and 2001 did not involve the central nervous system. Despite a previous study in South India that found mild-to-moderate neuropsychological deficits in a functionally normal HIV-positive group, yet the total burden of HAND in Singapore and other South Asian HIV-positive populations and its clinical significance is so far unknown.

This is the first study from a multiethnic South Asian population to estimate the local prevalence of HAND and to identify the demographic and clinical characteristics of individuals with HAND. Our secondary objective is to test the use of standardised cognitive screening and clinical assessment tools for detecting HAND in our local setting.

METHODS

Study participants

This study was a cross-sectional survey conducted in the Communicable Disease Centre of Singapore, which is the country’s referral centre for care and treatment of HIV/AIDS. Singapore has a multiethnic population consisting of Chinese, Malay and Indian races and represents a good reflection of the South Asian population. The study protocol had been approved by the Domain Specific Review Boards of the National Healthcare Group. The study was conducted from September 20 to October 15 of 2010 and included both inpatients and outpatients. Patients were eligible if they were HIV positive, aged between 21 and 80 years old and had at least 3 years of education. Exclusion criteria included patients with concomitant delirium, serious systemic disease or major psychiatric illness. Written informed consent was obtained from eligible patients.

Test battery

Participants were administered the Montreal Cognitive Assessment (MoCA), the International HIV Dementia Scale (IHDS) and the Lawton scale for Instrumental Activities of Daily Living by trained members of the study team. The MoCA has been validated locally with a cut-off score of 26/27 out of 30 for the diagnosis of Mild Cognitive Impairment, but these data are currently unpublished and under peer review (Ng, A et al, 2011). The Instrumental Activities of Daily Living has also been validated locally and shown to be cross-culturally applicable. However, the IHDS has not been validated outside of Africa but has been used in India to screen for HIV dementia in comparison with a HIV-negative group. As presence of depression was considered to be a potential confounder, depressive symptoms were measured by administering the Patient Health Questionnaire on all participants. To avoid interviewer bias, study team members who administered the tests were blinded to the clinical details at the time of administering the cognitive tests. Patients were classified as HAND or normal based on the clinical judgement of impaired performance in at least two domains of delayed recall, executive function, visuospatial function, attention, language function, abstract thought, orientation, motor speed and psychomotor speed, in addition to scores lower than recommended cut-offs on the MoCA and IHDS, and information on functional impairment which was ascertained using the stated instruments. Hence, validated total cut-off scores on the MoCA and IHDS were not used as the sole criterion of cognitive impairment in the application of HAND criteria. Demographic, relevant clinical data and laboratory data were obtained by retrospective chart review. Data included age, sex, acquisition risk for HIV, level of education, comorbid sexually transmitted infections and vascular risk factors such as hypertension, diabetes and dyslipidemia, hepatitis B and C coinfection and exposure variables of baseline CD4 cell count, current CD4 cell count, stage of illness at diagnosis, length of time since diagnosis, plasma HIV viral load and anti-retroviral therapy.

Statistical analyses

Comorbid sexually transmitted infections and vascular risk factors were analysed as categorical variables. Stage of illness was defined by the United States Center for Disease Control classification. CD4 counts were analysed by three groups of severity: >500, 200–499 and <200. Five participants with newly diagnosed illness and who had only one set of laboratory results for CD4 counts had the same data recorded for both baseline and current CD4.

The prevalence of HAND and its subtypes was first computed. The Students t test and $\chi^2$ test were used to compare continuous and categorical variables, respectively, between cognitively normal and subjects with HAND. Univariate logistic regression analysis was used to determine the variables associated with HAND. Multivariate logistic regression analysis was then performed to adjust for the effect of confounders. Subgroup analysis was not performed as the numbers in the group with the HAND outcome were insufficient for meaningful analysis.
RESULTS
During the study period, 400 patients were screened for eligibility. Two hundred and sixty-five patients either did not meet the inclusion criteria or declined to participate. Three were excluded because of concurrent delirium. A total of 132 patients gave written informed consent to participate in the study. Data from 132 participants were analysed. 90.9% of the whole sample was receiving antiretroviral treatment. Data on the eligible patients that did not participate are not available.

HAND was detected in 22.7% of the participants. Within this group, 70% (15.9% of total) had asymptomatic neurocognitive impairment, 23.3% (5.3% of total) had mild neurocognitive disorder and 6.7% (1.5% of total) had HIV-associated dementia. Table 1 shows the demographic and clinical characteristics of the two groups. HIV patients with HAND had a higher mean age (54.40 vs 43.45, p < 0.001) and lower mean years of education (8.03 vs 11.45, p < 0.001). Also, a larger proportion of patients with HAND had more severe stage of illness (stage C: 63.3% vs 31.4%, p = 0.006) and lower baseline CD4 counts at diagnosis (CD4 < 200: 80.0% vs 47.5%, p = 0.002). The two groups did not differ significantly in the presence of comorbid sexually transmitted infections and vascular risk factors. Univariate logistic regression analysis was performed for all the exposure variables and it showed that age (OR 1.104, 95% CI 1.054 to 1.155, p < 0.001), education (OR 0.78, 95% CI 0.69 to 0.89, p < 0.001), stage C of illness (OR 4.09, 95% CI 1.66 to 10.07, p = 0.002) and baseline CD4 count between 200 and 499 (OR 10.00, 95% CI 2.23 to 44.92, p = 0.003) were significantly associated with the presence of HAND (table 2). Depression as measured with the Patient Health Questionnaire-9 was found not to be associated with HAND. The OR for a history of central nervous system opportunistic infections was high at 3.67, was 1.15 for the log-transformed viral load and 1.92 for the presence of any vascular risk factor but all three were not statistically significant. Therefore, multivariate logistic regression was used to adjust for the confounders of age and education. Stage C of illness ceased to be associated with the presence of HAND, and the direction of association with a less severe baseline CD4 became more consistent with clinical reason (OR 0.15, 95% CI 0.03 to 0.74, p = 0.019).

The HAND group performed consistently and significantly worse than the cognitively normal group across all domains, except for the domain of orientation (table 3). Impairment in the domains of delayed recall, language, abstract thinking, motor speed and

### Table 1 Demographic and clinical characteristics by neurocognitive status, N = 132

| Characteristic                         | Normal, N = 102 (77.3%) | HAND, N = 30 (22.7%) | p Value |
|----------------------------------------|--------------------------|----------------------|---------|
| Age                                    | 43.45 (SD = 10.19)       | 54.40 (SD = 10.83)   | < 0.001 |
| Education                              | 11.45 (SD = 3.97)        | 8.03 (SD = 3.66)     | < 0.001 |
| Employment (n, %)                      |                          |                      |         |
| Professional                           | 40 (39.2%)               | 3 (10%)              |         |
| Blue-collar                            | 36 (35.3%)               | 13 (43.3%)           | 0.001   |
| Unemployed                             | 26 (25.5%)               | 14 (46.7%)           |         |
| Gender (n, %)                           |                          |                      |         |
| Male                                   | 86 (84.3%)               | 28 (93.3%)           | 0.362   |
| Female                                 | 16 (15.7%)               | 2 (6.7%)             |         |
| Race (n, %)                             |                          |                      |         |
| Chinese                                | 85 (83.3%)               | 28 (93.3%)           | 0.317   |
| Malay                                  | 8 (7.8%)                 | 0                    |         |
| Indian                                 | 6 (5.9%)                 | 2 (6.7%)             |         |
| Others                                 | 3 (2.9%)                 | 0                    |         |
| Stage of illness at diagnosis (n, %)   |                          |                      |         |
| A                                      | 62 (60.8%)               | 9 (30%)              | 0.006   |
| B                                      | 8 (7.8%)                 | 2 (6.7%)             |         |
| C                                      | 32 (31.4%)               | 19 (63.3%)           |         |
| Baseline CD4 (n, %)                    |                          |                      |         |
| <200                                   | 48 (47.5%)               | 24 (80.0%)           |         |
| 200–499                                | 40 (39.6%)               | 2 (6.7%)             | 0.002   |
| >500                                   | 13 (12.9%)               | 4 (13.3%)            |         |
| Current CD4 (n, %)                     |                          |                      |         |
| <200                                   | 23 (22.8%)               | 8 (27.6%)            |         |
| 200–499                                | 53 (52.5%)               | 16 (55.2%)           | 0.670   |
| >500                                   | 25 (24.8%)               | 5 (17.2%)            |         |
| Comorbid STI (n, %)                    | 43 (42.2%)               | 15 (50.0%)           | 0.447   |
| Comorbid vascular risk factor(s) (n, %)| 38 (37.3%)               | 16 (53.3%)           | 0.115   |

STI, sexually transmitted infection.
psychomotor speed were prevalent in at least two-thirds of the HAND group. The domains of visuospatial function, executive function and attention were affected the least frequently. However, logistic regression showed that impairment in visuospatial function, attention or language on the MoCA was most predictive for the presence of HAND (table 4).

**DISCUSSION**

Our study showed that one in five HIV-positive patients from a South Asian population can be expected to have HAND. The results indicate that patients with HAND tend to be older (mean 54.4 years), with fewer years of formal education (mean 8.0), and had extremely low baseline CD4 counts (CD4 \(< 200 \text{ cells/µl}\)). This is consistent with the previous studies. Length of time since diagnosis and current CD4 counts did not determine the diagnosis of HAND.

Other studies have not examined directly the association between duration of illness and the presence of neurocognitive impairment but have hypothesised that central nervous system injury begins very early in the course of HIV infection. Also, recovery of immuno-suppression does not appear to be protective for HAND, a finding that has been recently demonstrated. In our study, HAND was directly related to severely low baseline CD4 counts. The finding that nadir CD4 counts are a strong predictor for HAND has been shown in several studies. Because our study design is cross-sectional, we are unable to assess the effect of immune recovery or comment on nadir CD4 count. We assume that because patients present with late-stage HIV infection, baseline CD4 count is an approximate surrogate for nadir CD4 cell count.

Our study failed to show any statistically meaningful relationship between HAND and sexually transmitted infections, hepatitis B and C coinfection and vascular risk factors, unlike previous studies. This is most likely due to a small number in the HAND group. However, the effect of vascular risk factors would be an

### Table 2

| Variable                      | OR (95% CI)        | p Value | Adjusted OR (95% CI) | p Value |
|-------------------------------|--------------------|---------|----------------------|---------|
| Age (years)                   | 1.104 (1.054 to 1.155) | <0.001  |                      |         |
| Education (years)             | 0.782 (0.687 to 0.890) | <0.001  |                      |         |
| Years since diagnosis         | 1.024 (0.940 to 1.116) | 0.588   |                      |         |
| Stage at diagnosis            |                    |         |                      |         |
| A (Reference)                 |                    |         |                      |         |
| B                              | 1.722 (0.315 to 9.427) | 0.531   |                      |         |
| C                              | 4.090 (1.662 to 10.066) | 0.002   | 1.333 (0.369 to 4.815) | 0.661   |
| Baseline CD4                  |                    |         |                      |         |
| <200 (Reference)              |                    |         |                      |         |
| 200–499                       | 10.000 (2.226 to 44.919) | 0.003   | 0.151 (0.031 to 0.737) | 0.019   |
| >500                          | 0.437 (0.478 to 5.521)  | 0.437   |                      |         |
| Current CD4                   |                    |         |                      |         |
| <200 (Reference)              |                    |         |                      |         |
| 200–499                       | 1.152 (0.433 to 3.069)  | 0.777   |                      |         |
| >500                          | 1.739 (0.497 to 6.086)  | 0.387   |                      |         |
| History of CNS OIs            | 3.67 (0.70 to 19.21)  | 0.124   |                      |         |
| Log-transformed viral load    | 1.15 (0.94 to 1.40)   | 0.177   |                      |         |
| Vascular risk factors         | 1.92 (0.85 to 4.38)   | 0.118   |                      |         |

Adjusted OR, corrected for age and education. CNS OIs, central nervous system opportunistic infections.

### Table 3

| Score                      | Normal, mean (SD) | HAND, mean (SD) | p Value |
|----------------------------|-------------------|-----------------|---------|
| MoCA (total)               | 28.45 (1.45)      | 24.17 (3.20)    | <0.001  |
| MoCA (executive function)  | 3.82 (0.41)       | 3.03 (1.03)     | <0.001  |
| MoCA (attention)           | 5.95 (0.22)       | 5.63 (0.56)     | 0.004   |
| MoCA (language)            | 5.71 (0.54)       | 4.50 (1.08)     | <0.001  |
| MoCA (abstraction)         | 1.61 (0.55)       | 1.97 (0.67)     | <0.001  |
| MoCA (recall)              | 4.23 (0.97)       | 3.23 (1.19)     | <0.001  |
| MoCA (visuospatial)        | 0.93 (0.25)       | 0.40 (0.50)     | <0.001  |
| MoCA (orientation)         | 5.93 (0.29)       | 5.73 (0.64)     | 0.109   |
| IHDS (total)               | 10.92 (1.20)      | 8.65 (2.34)     | <0.001  |
| IHDS (motor speed)         | 3.49 (0.82)       | 2.60 (1.30)     | 0.001   |
| IHDS (psychomotor speed)   | 3.59 (0.75)       | 2.57 (1.33)     | <0.001  |

IHDS, International HIV Dementia Scale; MoCA, Montreal Cognitive Assessment.
imported area for future research as the baseline prevalence of metabolic diseases in Singapore is high. Our study also showed that a history of central nervous system opportunistic infections is possibly an important contributing factor despite the lack of statistical significance that we attribute to the small sample size, while other studies had actively excluded such patients. The viral load in plasma was traditionally thought to predict the presence of HIV-associated dementia but more recent studies have shown correlation with viral loads in the cerebrospinal fluid while there is peripheral viral suppression. Currently, it is not local practice to measure HIV RNA in the cerebrospinal fluid and great difficulties with getting consent for lumbar punctures from future research subjects are anticipated.

HAND is currently conceptualised as having a subcortical pattern with an argument for bradykinesia and bradyphrenia being the cardinal features of HAND. There is also general agreement that the most prevalent impairments in HIV are in the domains of Learning, Abstraction/Executive Functioning, Attention/Working Memory and Motor Functioning, whereas Verbal Functioning/Language is relatively spared. The pattern of cognitive impairment in South Asian patients with HAND does not appear to fit into a discrete subcortical pattern as previously thought. In fact, both cortical and subcortical functions are frequently affected, and this is consistent with a recent study demonstrating both cortical and subcortical neurodegeneration. It is not clear from this study whether this is due to effects of HAART, as suggested by other studies. Even though it is possible to analyse the Central Nervous System Penetration Effectiveness (CPE) scores of the HAART regimen of the study subjects, the cross-sectional methodology limits meaningful interpretation of the results as many other confounders such as duration of treatment and the timing of treatment initiation need to be considered. Future longitudinal studies should evaluate the differences in the cognitive profile of HAND in patients with and without HAART.

An important limitation of this study is the relatively small sample size. However, previous prevalence estimates were too imprecise for an a priori sample size calculation. There was also potential response bias that was not dealt with in the study methodology. Patients who did not consent to participate in the study may have had characteristics that would skew the prevalence rate in either direction. This study is also limited by the lack of published normative data on the cognitive tools used. However, the authors have used demographically appropriate data wherever possible. Another limitation is the lack of exclusion of subjects with substance or alcohol use. However, based on the demographics of the local HIV population, substance or alcohol use is relatively uncommon.

However, we feel that this study is important as it provides the first data we have among multiethnic South Asian patients on HAND. Our centre sees the majority of HIV/AIDS patients, and thus, the study prevalence likely approximates the true prevalence of HAND in Singapore. This study adds another compelling reason for early diagnosis of HIV infection and linkage to care and treatment.

Previous studies have used specially developed neuropsychological batteries to detect and diagnose HAND. To the authors’ knowledge, this present study is the first to use a standardised mental status examination (an acceptable option in the updated research nosology for HAND considering resource-limited contexts) in a novel way of using domain-specific performance in addition to recommended cut-off scores, as well as using a combination of standardised mental status examinations to provide for an assessment of a broad and comprehensive range of cognitive functions. In most South Asian countries, neuropsychological testing is available but mostly in non-integrated settings. Hence, even though resources are not limited, access to it is hindered by many cultural and patient factors. Making clinical diagnoses of cognitive impairment using a combination of clinical judgement and brief bedside tools is the local practice. Thus, the method of detection used in this study was chosen because of its potential clinical utility. The authors acknowledge that this methodology though novel severely limits the study’s comparability with previous studies. Yet it is commendable and worth commenting that the results obtained are strikingly similar to data previously published.

| Cognitive domain                  | Regression coefficient | 95% CI          | p Value |
|----------------------------------|------------------------|-----------------|---------|
| MoCA (visuospatial)              | 3.013                  | 1.954 to 4.073  | <0.001  |
| MoCA (attention)                 | 2.205                  | 1.043 to 3.767  | <0.001  |
| MoCA (language)                  | 1.989                  | 1.247 to 2.731  | <0.001  |
| MoCA (abstraction)               | 1.637                  | 0.895 to 2.379  | <0.001  |
| MoCA (executive function)        | 1.586                  | 0.888 to 2.283  | <0.001  |
| MoCA (total)                     | 1.065                  | 0.671 to 1.458  | <0.001  |
| IHDS (psychomotor speed)         | 0.937                  | 0.500 to 1.373  | <0.001  |
| IHDS (total)                     | 0.802                  | 0.467 to 1.138  | <0.001  |
| IHDS (motor speed)               | 0.791                  | 0.378 to 1.205  | <0.001  |
| MoCA (recall)                    | 0.791                  | 0.384 to 1.200  | <0.001  |

IHDS, International HIV Dementia Scale; MoCA, Montreal Cognitive Assessment.
Further research is essential in order to understand the clinical importance of HAND and the profile of its longitudinal history in HIV-positive patients in South Asia. Validation of the test instruments specifically using HIV negative controls would add to the evidence base of the clinical utility of such tools. Such tools are potentially of immense use even in settings that are not resource limited.

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