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Screening for human immunodeficiency virus (HIV) dementia in an HIV clade C–infected population in India

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Although human immunodeficiency virus (HIV) clade C virus infects the largest populations worldwide, to date there are no prospective studies reported thus far to determine the incidence or prevalence of HIV dementia in this population. HIV clade C virus is a CCR5-tropic virus and thus predominantly infects macrophages, which are the key cells implicated in the pathogenesis of HIV dementia. However, HIV dementia has only rarely been reported in these populations. The authors thus used a recently developed International HIV Dementia Scale (IHDS) to screen a well-characterized cohort of HIV-infected discordant couples in Pune, India. 48 HIV+ subjects with CD4 cell count <200 cells/mm^3 and 48 HIV− subjects were studied. The HIV+ subjects had significantly lower IHDS scores compared to the HIV− subjects. 35% of the HIV+ subjects and 15% of the HIV− subjects scored <10 on the IHDS. These observations suggest that the prevalence of HIV dementia may be higher in this population than previously reported. More importantly, it demonstrates that the IHDS can be used as a screening tool in the Indian population. *Journal of NeuroVirology* (2006) **12,** 34–38.

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Introduction

Human immunodeficiency virus (HIV)-associated dementia is characterized as a subcortical dementia with prominent features of cognitive, behavioral, and motor dysfunction. Typical features include memory loss, inability to manipulate acquired knowledge, apathetic personality changes, and generalized slowing of thought processes (McArthur *et al*, 2005).

HIV dementia has been studied primarily in populations in the United States (U.S.) and Europe. It has been estimated to be the AIDS-defining illness in 5% of patients in the U.S. (McArthur *et al*, 2005; Chiesi *et al*, 1996). Since the advent of highly active antiretroviral therapy (HAART), the incidence rates for HIV dementia in the U.S. have been decreasing (Sacktor *et al*, 2001), but with continued survival, the prevalence of this disorder has actually increased (Sacktor, 2002). Given the increased prevalence of HIV dementia and its negative impact on quality of life (Tozzi *et al*, 2004), the morbidity associated with this disorder has the potential to be significant in areas of the world where greater numbers of people are infected with HIV.

The primary genotype of HIV-1 in the U.S. and Europe is clade B, whereas the predominant clade found in India is clade C. Clade B virus can utilize either CCR5 or CXCR4 receptors during its cytopathic course, whereas clade C strongly favors the CCR5 receptor (Albright *et al*, 1999; Spira *et al*, 2003). Given the propensity of clade C for CCR5 and for this receptor's relationship to central nervous system (CNS)-invading macrophages, it has been postulated that patients infected with clade C virus would be at high risk of developing dementia and that dementia may occur earlier in the disease. However, HIV dementia has not been systematically studied in India and scattered reports to the contrary suggest that HIV dementia maybe rare in this region (Teja

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et al, 2005; Wadia *et al*, 2001). Reasons for this could include underdiagnosis, shorter life expectancy, or shorter survival following HIV infection due to opportunistic infections (Shankar *et al*, 2005). The few studies reported thus far from India have included HIV dementia as part of a larger study of neurological complications of HIV and have reported rates ranging from 1% to 8% of study subjects (Teja *et al*, 2005; Wadia *et al*, 2001). However, there remains a lack of means for screening for HIV dementia in this non-English-speaking population.

The purpose of this pilot study was to describe the performance of the International HIV Dementia Scale (IHDS) screening tool in HIV+ subjects in India, and to compare this performance to that seen in HIV− subjects from the same region. To our knowledge, this is the first prospective study screening specifically for HIV dementia in a clade C-infected population. The IHDS is a modification of the HIV Dementia Scale first proposed by Power *et al* (1995) and recently modifiedby Sacktor *et al* (2005). The importance of this modified screening tool is that it is (1) easy to administer; (2) easy to train health professionals to administer, and most importantly; and (3) independent of both language and culture. This tool, if validated, could serve as a tool to identify patients at risk for HIV dementia without the need to do extensive, hours-long neurologic and psychologic evaluations by highly trained testers on every patient.

Results

Between October 2004 and July, 2005, 97 patients were enrolled in this pilot study. One control was excluded due to a score of 0 on the psychomotor testing section of the IHDS. The study thus consisted of 48 subjects each with and without HIV infection.

The demographic and clinical characteristics of the subjects are shown in Table 1. The average age of HIV+ subjects was 36.0 years (range 22–64) and of HIV− subjects was 29.2 years (range 20–42). The majority of HIV+ subjects were male (87%), whereas the majority of HIV− subjects were female (88%). The average number of years of education for HIV+ subjects was 8.4 whereas that of HIV− subjects was 8.2. All HIV+ subjects had a CD4 cell count of <200 cells/mm^3, with an average CD4 count of 118 cells/mm^3. There were 48 episodes of remote opportunistic infections (OIs) diagnosed in 33 HIV+ subjects prior to enrollment in this study (15 HIV+ subjects had no OIs). There were no significant differences between the HIV+ and the HIV− subjects for age and years of education.

Table 1 Demographic and clinical characteristics of study subjects

Variable	*HIV+ (*n = *48)*	*HIV− (*n = *48)*
Mean age (year)	36.0 (22–64)	29.2 (20–42)
Sex, no. (%)		
Male	42 (87)	6 (12)
Female	6 (13)	44 (88)
Education, years	8.4 (0–15)	8.2 (0–16)
Mean CD4 cell count	118 (6–198)	NA

The HIV+ subjects had significantly lower IHDS scores compared to HIV− subjects ($P < .005$) (Figure 1A). Although 17 HIV+ subjects had total scores <10, interestingly 7 HIV− subjects also had total scores <10 on the IHDS. Analysis of the individual components of the IHDS revealed that in the memory recall portion of the IHDS, all HIV− subjects scored ≥3.5, whereas nine HIV+ subjects scored ≤3. The differences between the HIV+ and HIV− subjects were significant ($P < .05$) (Figure 1B). However, no significant differences were present between the two groups on examination of motor speed (Figure 1C). One HIV+ subjects and two HIV− subjects scored a 2 on the motor speed part of the IHDS, but all other subjects in both groups scored ≥3. But examination of psychomotor speed showed clear differences between the two groups ($P < .01$) (Figure 1D). Fourteen HIV+ subjects scored <3, whereas 3 HIV− subjects scored <3. The average scores for each group on the three components of the test are shown in Figure 1. There were no significant differences between the age and years of education between the subjects who scored <10 and ≥10 on the IHDS for both HIV+ and HIV− subjects.

Discussion

In this study the IHDS screening exam for HIV dementia was used to screen for cases of HIV dementia in a non–English-speaking, clade C-infected population. It demonstrates that this rapid screening tool can be used in this population and administered by non-neurologists. It identifies the population at risk with composite scores of <10 who would need further detailed neuropsychological testing to confirm the presence of dementia or cognitive impairment. Although this test does not replace the need for detailed neuropsychological testing, it may help direct limited resources for the diagnosis of dementia to those most at risk for the development of this complication.

On analysis of the components of the IHDS, it was found that the differences between the HIV+ and HIV− subjects were significant for both the memory recall and the psychomotor speed portions of the exam, with psychomotor speed being the most distinguishing test. These portions of the IHDS were the most sensitive for picking up the early changes associated with HIV dementia similar to that found in the previous study (Sacktor *et al*, 2005).

Nearly 35% (17 of 48) HIV+ subjects had low scores on the IHDS screen (i.e., <10) and 15% (7 of 48 patients) had an IHDS scores of <10, which suggests the possibility that HIV dementia may be more prevalent in India than previously recognized. We selected patients with CD4 cell counts of

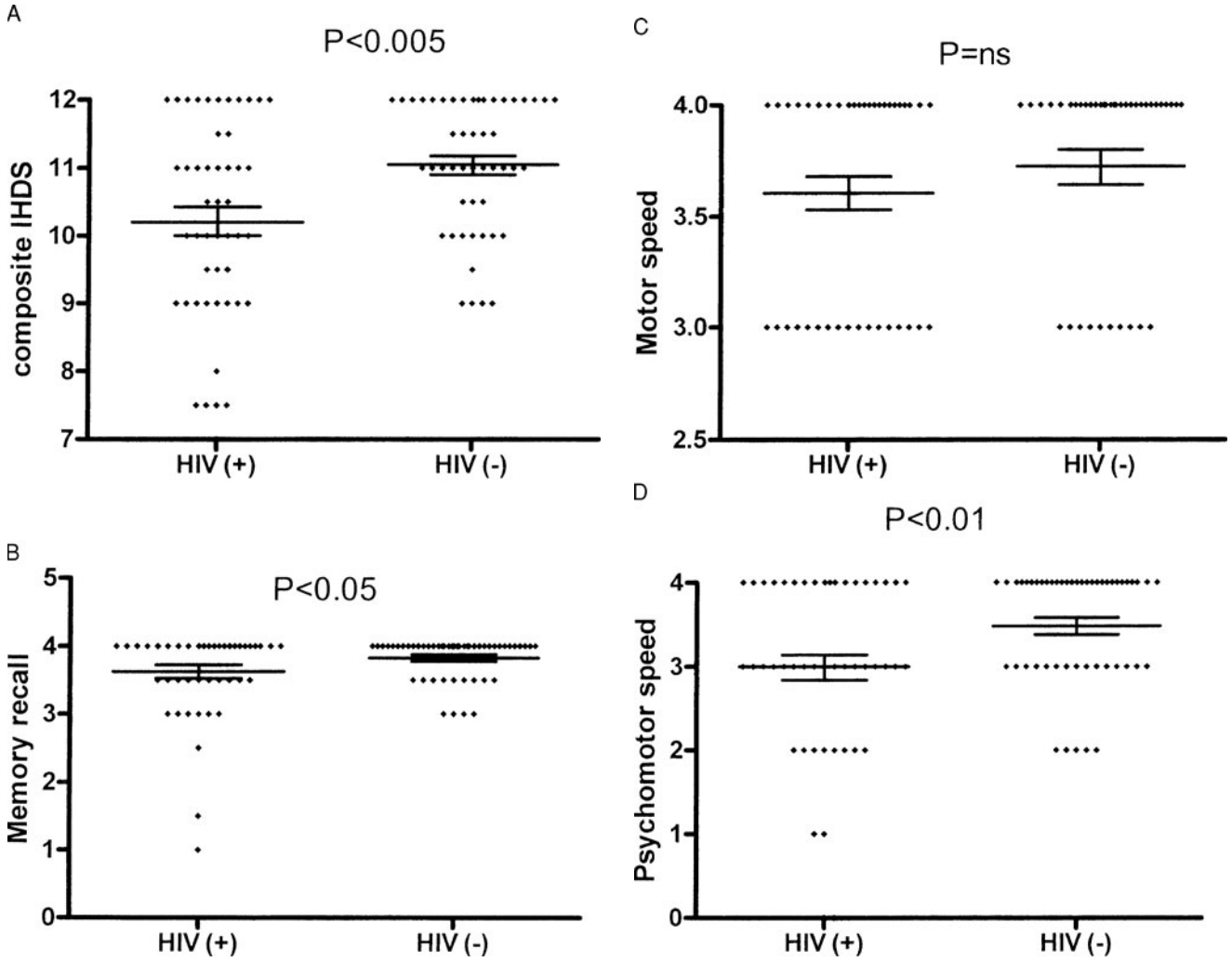

Figure 1 HIV-infected subjects and controls were compared by IHDS testing and are shown as (**A**) composite scores, (**B**) memory recall, (**C**) motor speed, and (**D**) psychomotor speed. Data represents mean ± SEM.

<200 cells/mm^3, hence they were severely immunosuppressed and thus at risk for neurological complications of HIV infection. A previous U.S. study in the pre-HAART era from the DANA cohort that screened patients with CD4 cell count <200 cells/mm^3 had 27.2% patients with HIV dementia. In this study, none of the HIV− subjects with comparable age and education had abnormal IHDS scores (Sacktor *et al*, 2002), which is similar to the proportion of possible HIV dementia cases found in the current study. However, a major difference is the abnormal scores in the HIV− control subjects. This clearly shows the importance of using control subjects from the same population and the challenges faced for developing scales that can be used across various populations in different countries. Nonetheless, this frequency of HIV dementia, if confirmed, would sharply contrast with that found in previous studies in India (Teja *et al*, 2005; Wadia *et al*, 2001) and would be more in line with the prevalence of HIV dementia in the U.S. (i.e., 20% to 30%) (McArthur *et al*, 2003; Sacktor *et al*, 2002). If the prevalence of HIV dementia in severely immunocompromised patients in India were determined to be this high or even nearly so, it would vastly change our understanding of the neuropathology of HIV clade C in HIV patients in India. This in turn would lead to further study of the poorly understood pathogenesis of this process and could lead to significant changes in health policy and timing of initiation of antiretroviral therapy.

The advantages of using the IHDS screening test in India include its utility in patients who do not speak English, its ease and rapidity of administration (usually 2 to 3 min by a trained, non-neurologist), and its requirement only for a watch with a second hand (i.e., no special instrumentation) (Sacktor *et al*, 2005). All of these factors make the IHDS well-suited to an international setting such as India.

A shortcoming of our pilot study was the inability to match HIV+ and HIV− subjects by gender. Due to

the nature of the preexisting discordant couples cohort, matching by gender was not possible. The two groups were, however, automatically matched by socioeconomic background owing to this arrangement, and the average years of education and age was also found to be similar between the two groups. A second drawback of this study was in not comparing the IHDS to a full battery of neuropsychological testing and evaluation to confirm the cases of dementia found by the screening test. Despite the drawbacks of this pilot study, the differences in the cognitive performance between the HIV+ and HIV- subjects suggest that cognitive dysfunction likely occurs in greater proportion in the HIV-infected populations in India than previously appreciated.

Methods

Patients and data collection

The National AIDS Research Institute (NARI) is located in Pune, India. The Institute and its activities are supported by the Indian Council of Medical Research (ICMR) and other agencies. NARI is a member of the National Institute of Health's (NIH) HIV Prevention Trials Network (HPTN) and has participated in multiple HPTN studies. This pilot study utilized the HPTN 034 cohort of patients, which was previously established for ongoing trials.

The HPTN 034 cohort includes 457 HIV-infected discordant couples. Patients have CD4 cell counts checked every 3 months and viral loads every 6 months. The retention rate of this cohort is greater than 90%, and 90% of the population has at least a primary school education. Because the spouse is also regularly screened for HIV infection, the cohort provides a seronegative control population from a similar socioeconomic background.

Each subject had the study explained to them and informed consent was obtained. Consent was obtained by an independent evaluator fluent in the local language of Marathi. This study was approved by the Institutional Review Board (IRB) at Johns Hopkins as well as the Ethics Committee at NARI.

Inclusion criteria were (1) documented HIV infection by enzyme-linked immunosorbent assay (ELISA) (with CD4 count <200); (2) primary language is Marathi (native language of Pune); (3) at least 18 years old; and (4) able to provide informed consent. None of the patients were on antiretroviral drugs. Patients with any of the following were excluded (1) active CNS or other systemic infection; (2) focal neurological signs; (3) physical deficits that would inhibit the ability to participate in testing; or (4) patients abusing alcohol (using the Michigan Alcoholism Screening Test [MAST] >3 points); (5) patients with known learning disability or an unrelated neurological or psychiatric disorder. Patients were evaluated by local physicians trained in the administration of the IHDS between October 2004 and July 2005.

IHDS

The instrument consists of three tasks, each rated on a scale of 0 to 4. For assessment of memory registration, the patients were given four words to recall (Red, Water, Dog, Table), taking about 1 s to say each of the words. (Water and Table replaced Hat and Bean used in the previously published version of the IHDS [Sacktor *et al*, 2005], because Water and Table were words that were more commonly recognized by the general population in India.) The patient was asked to repeat the words. If the patient did not recall all the words immediately the examiner repeated the words. The patient was asked to recall the words after the completion of the motor tasks. For words not recalled a semantic clue was given as follows: color (red), something to drink (water), animal (dog), piece of furniture (table). The patient was given 1 point for each word spontaneously recalled and 0.5 points for each correct answer after prompting. For assessment of motor speed, the patient was asked to tap the first two fingers of the nondominant hand as widely and as quickly as possible. It was scored as follows: 4 = 15 in 5 s; 3 = 11–14 in 5 s; 2 = 7–10 in 5 s; 1 = 3–6 in 5 s; 0 = 0–2 in 5 s. Psychomotor speed was assessed by having the patient perform the following movements in succession with the nondominant hand as quickly as possible: (1) clenching the hand in fist on flat surface, (2) putting hand flat on surface with palm down, and (3) putting the hand perpendicular to flat surface on the side of the 5th digit. After demonstrating the task to the patient, they were asked to perform it twice for practice. The task was scored as follows: 4 = 4 sequences in 10 s; 3 = 3 sequences in 10 s; 2 = 2 sequences in 10 s; 1 = 1 sequence in 10 s; 0 = unable to perform. The total IHDS score was computed. The maximum possible score was 12 points. The sensitivity and specificity for detection of HIV dementia for an IHDS score <10 has been shown to be 71% and 79%, respectively, in a U.S. cohort, and 64% and 71%, respectively, in a Ugandan cohort.

Data analysis

Mean and standard deviations were computed for the IHDS composite score and each of its components for each of the groups. Comparisons between the groups were made by analysis of variance (ANOVA).

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