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Short Communication

Sustained cognitive decline in HIV infection: relationship to CD4+ cell count, plasma viremia and p24 antigenemia

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To determine the clinical and virological correlates of neuropsychological test performance decline in HIV infection, we measured viral burden in blood in 272 HIV-seropositive men without dementia in the Baltimore arm of the Multicenter AIDS Cohort Study (MACS). These measures were then related to neuropsychological (NP) decline, defined as a decline relative to prior best performance of 2.0 standard deviations or more on one or more neuropsychological tests. A short battery of NP tests (Mini-Screen Battery) was administered to all 272 men. NP test performance decline was identified in 53/272 (19.5%) of participants on the Mini-Screen Battery. Follow-up NP data were available for 204 participants who had undergone the Mini-Screen. The frequency of sustained NP test performance decline was 7.8% for the Mini-Screen Battery. A lower CD4+ cell count was weakly associated with sustained NP test performance decline. After adjustment for CD4+ cell count, hemoglobin, body mass index, and presence of AIDS, none of the viral burden measures (p24 antigenemia, plasma viremia, quantitative culture) correlated with sustained NP test performance decline. We conclude that these measures of blood HIV viral burden are not markers for NP decline, but that a lower CD4+ cell count is.

Keywords: HIV infection; cognition; neuropsychological tests; viral load

Introduction

Central nervous system (CNS) disorders occur frequently in patients with HIV infection. While opportunistic infections and neoplasms can affect HIV-seropositive individuals (McArthur, 1987), nervous system diseases due to HIV itself can also occur (Janssen *et al*, 1991). HIV dementia, for example, occurs in approximately 20% of AIDS patients (McArthur *et al*, 1993). HIV-associated vacuolar myelopathy (Dal Pan *et al*, 1994) and predominantly sensory neuropathy (Cornblath & McArthur, 1988) are also common.

Studies of the relationship of cerebrospinal (CSF) viral burden (Singer *et al*, 1994; Royal *et al*, 1994; Buffet *et al*, 1991) to neurological disease have suggested that neurological dysfunction is associated with increased CNS HIV burden. Studies of peripheral blood HIV burden have demonstrated that increasing peripheral blood HIV burden is a predictor of subsequent AIDS and portends an overall poor prognosis (Farzadegan *et al*, 1992). Studies of the relationship of blood HIV burden and neurological disease have demonstrated that HIV-seropositive patients with neurological abnormalities have higher blood levels of HIV-1 RNA (Conrad *et al*, 1995) and HIV-1 proviral DNA (Schmid *et al*, 1994), compared to seropositive individuals without neurological abnormalities.

The frequency of cognitive impairment progresses with more advanced systemic disease, and neuropsychological (NP) test decline is rare during the asymptomatic phase of infection (Selnes *et al*, 1990). More subtle forms of cognitive dysfunction may occur prior to AIDS, and subtle, yet detectable, changes in NP performance in HIV-infected persons without dementia indicate a higher risk of subsequent AIDS and death (Mayeux *et al*, 1993). In an

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analysis of the Baltimore arm of the Multicenter AIDS Cohort Study (MACS), we demonstrated that cognitive decline in non-demented HIV-seropositive individuals was associated with a higher risk of subsequent AIDS, dementia, and death (Sacktor *et al*, 1996). In that study, cognitive decline was defined as a persistent decline of 2.0 standard deviations, relative to an individual's prior best performance, on at least one test in a 'mini-screen' battery composed of two brief neuropsychological tests.

In the present study, we have extended this analysis of cognitive decline to explore the influence of peripheral blood HIV burden on this measure of cognitive decline. We examined the relationship of p24 antigenemia, plasma viremia, quantitative lymphocyte microculture, and AZT usage to NP test decline in a cohort of HIV-seropositive homosexual men with serial prospective NP examinations.

Results

Two hundred and seventy-two participants underwent NP testing with the Mini-Screen at the index visit. Fifty-three of these 272 (19.5%) had NP decline at the index visit and 16/204 (7.8%) had sustained NP decline at follow-up. Of the remaining 37 participants who had NP decline at the index visit, 14 did not have NP decline at the follow-up visit and 23 were lost to follow-up. Of the 188 participants examined at both the index visit and at the follow-up visit in whom there was no evidence of sustained NP decline, 22 showed evidence of decline at the follow-up visit only. There were no significant differences between decliners and non-decliners at the index visit in terms of age (decliners 43.0 ± 8.3 years *vs* nondecliners 41.1 ± 7.4 years, P=0.14), education (100.0% of decliners and 89.5% of non-decliners had >12 years of education, P=0.12), hemoglobin (decliners 13.9 ± 1.0 gm/dl *vs* non-decliners 14.2 ± 1.3 gm/dl, P=0.47), proportion with AIDS (4/16 decliners and 25/188 non-decliners had AIDS, P=0.20), or body mass index (decliners 23.2 ± 3.5 kg/m^2 *vs* non-decliners 24.6 ± 2.8 kg/m^2, P=0.33). The pooled median value of the IUPM measurement was 16.0.

Table 1 presents the unadjusted odds ratio for CD4+ cell count, and both unadjusted and adjusted odds ratios for the viral burden measures and for the AZT usage indicators. A lower CD4+ cell count at the index visit was marginally associated with sustained NP decline (P=0.059). The odds ratios were adjusted for CD4+ cell count, hemoglobin, presence of AIDS, and body mass index. In the unadjusted analysis, plasma viremia was significantly associated with sustained NP decline. After adjustment, the association was no longer present. No other odds ratio was statistically different from 1.0, indicating no effect.

Discussion

In this study, we found no association between three measures of HIV burden in the blood and NP test performance decline, after adjustment for baseline illness characteristics. We also did not find a relationship between AZT use and NP test performance decline. Rather, we found that a lower CD4+ cell count was associated with NP test performance decline. These findings suggest that development of cognitive decline is more closely associated with immunodeficiency than with these particular measures of blood viral burden. This study predated the newer PCR-based techniques of measuring viral burden.

Studies of viral burden in blood have largely focused on its impact on transitions to different stages of systemic disease. These studies have demonstrated that increasing systemic HIV burden,

Table 1 Unadjusted and adjusted odds ratios for viral burden measures for subjects receiving the mini-screen battery.

		Sustained Decline		*Unadjusted*		*Adjusted*	
	N	*Present*	*Absent*	*Odds Ratio*[1]	*95% CI*	*Odds Ratio*[2]	*95% CI*
CD4+Cell Count (cells/mm^3, mean, SD)	204	328.6 (364.5)	478.0 (296.6)	0.83	0.68 – 1.01	–	–
IUPM (proportion above pooled group median)	163	9/15 (60.0%)	81/148 (54.7%)	1.34	0.45 – 4.18	1.06	0.32 – 3.49
Plasma Viremia (proportion positive)	148	8/14	40/134	3.13	1.02 – 9.62	1.34	0.34 – 4.08
p24 antigenemia (proportion positive)	165	3/16	26/149	1.07	0.28 – 4.03	0.61	0.17 – 2.16
AZT Usage at Index Visit	204	2/16	58/188	0.32	0.07 – 1.45	0.69	0.27 – 1.77
AZT Usage at Index Visit and Prior Visit	204	1/16	36/188	0.28	0.04 – 2.20	0.67	0.21 – 2.12

[1]Based on univariate logistic regression. [2]Based on multivariate logistic regression.

assessed either by p24 antigenemia (Farzadegan *et al*, 1992) or by plasma viremia (Coombs *et al*, 1989), correlates with increasing stage of HIV infection, is associated with progression to AIDS in HIV-seropositives, and portends a poor prognosis. More recent studies correlating systemic viral burden with neurological disease, using quantitative measures of viral burden including proviral DNA (Schmid *et al*, 1994) and viral RNA (Conrad *et al*, 1995), have demonstrated that increased viral burden is associated with the presence of HIV-associated neurological disease. In those studies, neurological disease was defined as an abnormality on a composite neurological examination.

Several factors may explain the lack of association of these peripheral blood measures of viral burden with NP decline. First, cognitive decline, as defined in this study, may not be due to direct CNS involvement by HIV, but rather may be the result of other factors. In our study we cannot determine definitively whether the mild decline noted is the result of direct CNS involvements by HIV, or whether it can be attributed to confounding causes, such as the nonspecific effects of chronic illness, including fatigue (Miller *et al*, 1991), minor illness (Kewman *et al*, 1991), or depression and anxiety (Hinkin *et al*, 1992). The observation that nearly two-thirds of subjects with cognitive decline at the index visit did not demonstrate sustained decline at the subsequent visit suggests that transient, reversible factors such as these may play a role in decline in NP test performance. However, Sacktor and colleagues (Sacktor *et al*, 1996) showed that sustained NP decline, as defined in this study, predicted the development of HIV dementia. This finding, along with previous findings (Mayeux *et al*, 1993) demonstrating the prognostic significance of NP decline, suggest that nonspecific factors are not solely responsible for its development. The association of a lower CD4+ cell count, a known risk factor for HIV dementia (McArthur *et al*, 1993) with sustained NP decline, reinforces that immunodeficiency is an important determinant of cognitive impairment.

A second possible explanation is that peripheral blood is not the major reservoir for HIV infection, and may account for as little as 2% of the body's HIV burden (Pantaleo *et al*, 1991). In particular, lymphoid viral burden may be substantially higher than peripheral blood viral burden before progression to advanced AIDS (Pantaleo *et al*, 1991), and may be a better reflection of viral burden.

Third, the lack of association between the measures of HIV burden used in this study and NP decline may reflect the insensitivity of the techniques used to measure viral burden. New and more sensitive techniques, including quantitative PCR and branched-DNA assays (Mellors *et al*, 1995; Schooley, 1995), have largely superseded the techniques used in this study. These measures, however, were not available when the data in this study were collected. Further studies with viral burden measures based on quantitative PCR are necessary to more precisely define the relationship between NP decline and viral burden.

The fourth, in this study, we have not included patients with HIV dementia because we specifically focused on patients with a more subtle form of cognitive decline. In doing so, we have intentionally limited the range of cognitive dysfunction under study, and have thus eliminated the possibility of identifying a relationship between blood measures of viral load and cognitive dysfunction over a broad range. Over the relatively narrow range under study, there may be no association with blood viral burden.

In this study, we included two indicators of AZT usage: (1) AZT usage at the index visit, and (2) AZT usage at the index visit and six months prior. Neither measure was associated with the development of cognitive decline. While several studies have shown that AZT can delay the onset of AIDS in HIV-seropositives, reports regarding its specific 'neuro-protective' efficacy have been less consistent. Studies using daily doses of 1000 mg or greater have suggested that AZT may have a protective effect against neurologic disease (Sidtis *et al*, 1993). In our study population, daily doses of AZT are in the 500–600 mg range, suggesting that the efficacy of AZT in preventing neurologic disease may depend on a critical amount of daily AZT intake. The present study is consistent with the findings of McArthur *et al*, 1993), which revealed no specific association between AZT usage and the risk of HIV dementia and expands on those findings to include milder forms of cognitive impairment.

Methods

Patients

Two hundred and seventy-two participants at the Baltimore site of the Multicenter AIDS Cohort Study (MACS) were followed longitudinally for the development of cognitive decline. The MACS is a longitudinal study of the natural history of HIV infection in homosexual and bisexual men, and has been described in detail elsewhere (Kaslow *et al*, 1987). AIDS-defining illnesses (Centers for Disease Control, 1987), CD4+ cell count, hemoglobin level, antiretroviral use, and body mass index were recorded biannually. For each participant, the visit at which HIV burden was determined was identified as the index visit, ie, the visit at which measures of neuropsychological test performance and markers of systemic disease were used in the analysis. Individuals meeting criteria for HIV dementia (Janssen *et al*, 1991) at the index visit, as well as those with opportunistic CNS processes, were excluded from this analysis. Two indices of anti-retrovial use were used: (1) anti-retroviral use at the

index visit and (2) anti-retroviral use at both the index visit and the prior visit.

HIV burden measures
Infectious units of HIV-1 per one million peripheral blood mononuclear cells (IUPM) were determined by serial fivefold dilutions of one million peripheral blood mononuclear cells and co-cultivation with phytohemagglutinin A (PHA) stimulated normal peripheral blood mononuclear cells (Margolick *et al*, 1996). HIV p24 antigen testing and measurement of plasma viremia were performed as previously described (Kelen *et al*, 1993; Margolick *et al*, 1996). These studies were performed before the availability of newer quantitative tests such as the branched-chain DNA test.

Neuropsychological testing
Participants were tested biannually with the following screening tests: Trailmaking Tests A and B and the Symbol Digit Modalities Test, collectively referred to as the Mini-Screen (Selnes & Miller, 1994). NP test performance at the index visit was compared to an individual's prior best performance, and decline at the index visit was defined as a decline of 2.0 or more standard deviations on one or more tests at the index visit, relative to an individual's prior best performance. Sustained NP decline was defined as persistence of the NP decline at the visit subsequent to the index visit.

Statistical methods
Categorical variables were compared using the chi-square test. Group means for continuous data were compared with the Students *t*-test. Adjusted odds ratios were calculated using multivariate logistic regression models. Infectious units of HIV-1 (IUPM) were dichotomized around a pooled (ie, decliners and non-decliners) median value. Adjusted odd ratios were calculated by adjusting for variables that have been shown previously to predict HIV dementia, including CD4+ cell count, hemoglobin, the presence of AIDS and body mass index (McArthur *et al*, 1993). SAS PC Software, Version 6.03 was used (SAS Institute, Cary, NC).

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