NEUROCOGNITIVE IMPAIRMENTS IN HIV INFECTION

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ABSTRACT

Neuropsychological impairments punctuate the early neurological involvement among HIV-1 infected patients. Three groups of patients, twenty in each were selected. The first group consisted of seronegative local controls, the second being a group of asymptomatic seropositive patients and the third a group of seropositive symptomatic individuals. All these three groups were tested using standard neuropsychological tests. Results indicate that a broad spectrum of impairments occur in the seropositive patients and that the impairments of various functions occur at different phases of the illness. The importance of these findings in prediction of early neurological disturbance is highlighted and their significance in the total management and rehabilitation is discussed.

Key Words: AIDS, neurocognitive impairments, early detection, cerebral reserve

Following the early occurrence of HIV infection in India during the last decade and its pandemic spread across the nation with consummate rapidity, vast numbers of patients have graduated into late complications, particularly of the central nervous system. The annual rate of HIV related dementia is reported at seven to fourteen percent and psychopathology due to milder forms of cognitive deficits is evident in about one half of persons with frank AIDS (Atkinson and Grant, 1994). Primary damage to the central nervous system is characterised by destruction of subcortical regions and also of significant synaptic pathology of the neocortex. Post dendritic spines appear swollen and vacuolated, signifying disruption of complex neural activities (Wiley, 1994). A broad spectrum of neurocognitive disturbances in information processing, attentional deficits, memory, visuospatial functions, verbal fluency, abstraction and others have been described among these patients. Though most impairments have been mild, they exert a summated decline in the individual’s behavioural adaptation, vocational efficiency and quality of life.

Studies have shown that cognitive disturbances including dementia might be preventable and could even be improved with psychopharmacological measures (Angrist et al., 1992; Portegies et al., 1993). This emphasises the need for early detection and professional management of neuropsychological rehabilitation. Moreover, many of these changes occur at different phases of the illness and detection of early changes might help in prognosticating the consequences (Lunn et al., 1991).

Measurement of neuropsychological impairments using standard scales is beset with the problem of absence of standardised normative data (Stem, 1994). Most of these tests have been standardised on middle class, urban population and may not be applicable to a population characterised by illiteracy, naivete and a varied cognitive style (Sinha, 1985). The design of a neuropsychological evaluation under these conditions would thus necessitate the
The present study aims to assess the nature and extent of neuropsychological impairments among the HIV patients in India, in different stages of the illness using equivalent controls.

MATERIAL AND METHOD

The study was performed in the Department of Sexually Transmitted Diseases, Government Rajaji Hospital, Madurai from January 1997 to August 1997. Subjects were chosen by the Venereologist on the basis of the following criteria:

1. Age of the subjects should be between 20 years and 45 years.
2. History of alcohol or drug dependency should be absent.
3. VDRL test should be non-reactive.
4. No history of neurological complications such as sequelae due to head injury or seizure disorder should be present.
5. Subjects should not evince features of delirium, HIV associated dementia or secondary neurological complication such as tuberculous meningitis or opportunistic infections.
6. Those who were unwilling to perform the tests and those who were unable to perform the tests on reasons other than disability (e.g. severe depression) were excluded.

Subjects were assigned by the Venereologist according to clinical and serological data into three groups (CDC, 1993). Group I consisted of individuals who were serologically negative for HIV infection. Group II included subjects who were asymptomatic, but serologically positive (category A of CDC, 1993). Group III subjects who were serologically positive, clinically symptomatic, with AIDS related conditions but, did not manifest features of AIDS defining illness or infections (category B of CDC, 1993). Twenty subjects were assigned to each group on the basis of comparability in age and literacy.

The following tools were used to collect data.

I. Proforma for sociodemographic details.
II. Details of relevant clinical history and present clinical status, including venereological, neurological and psychiatric aspects.
III. Neuropsychological tests which covered a wide range of cognitive functioning and which were simple enough for application to the local population. The tests were chosen after pilot trials with naive subjects and included the following.

(T1) Delayed response ability
(T2) Differences and similarities test
(T3) Ideational fluency
   a. 'wood'
   b. 'round'
(T4) Paired associate word learning test
(T5) Logical memory
(T6) Digit forward
(T7) Digit backward
(T8) Digit Symbol Substitution Test (DSST)
(T9) Bender Gestalt Test (BGT)
   a. major deviations
   b. minor deviations
   c. raw score
   d. configuration score
(T10) Complex figure learning test
(T11) Color cancellation test
   a. 'correct responses'
   b. 'skipped responses'
(T12) Paced Auditory Serial Addition Test (PASAT)
(T13) Koh's block design test
(T14) Trail making test - part A
   a. duration
   b. within two minutes
(T15) Benton Visual Retention Test (BVRT)

The tests were conducted in the department of Sexually Transmitted Diseases, often in more than two sittings, taking into consideration the sustainability of motivation and fatigueability. The performance was scored using standard methods and the raw scores were used in comparing the groups. All three groups were compared using ANOVA and the differences between the groups were determined by
Scheffe's multiple range procedure. The extent of association between impairments in various tests was studied using a correlation matrix and a probability of one percent was considered to mark significant association between the variables.

RESULTS

Each of the three groups contained 18 males and 2 females. None of them were on any psychopharmacological medication. The age ranged from 21 to 45 years and number of years of schooling from 2 to 15 years. All of them were right handed and none had the benefit of antiretroviral therapy either before or during the period of the study. The mean age and literacy statuses were comparable in all group (Table 1).

Fifty one subjects hailed from rural areas and the rest from urban or semi-urban areas. Vocationally, 32 patients were agricultural labourers, 9 were truck drivers and the rest of other occupations. All subjects had a history of venereological disease and were heteropromiscuous. There were no blood or blood products recipients in the sample.

Among the subjects with AIDS related conditions (ARC), sixteen had oral candidiasis infection, four had oral hairy leukoplakia, 12 had lymphadenopathy and four had generalised wasting. Comparison of performance of the three groups was done using ANOVA and the differences between the groups was analysed by Scheffe’s multiple range test (Table 2).

**TABLE 1**

| Group I (N=20) | Group II (N=20) | Group III (N=20) |
|---------------|----------------|-----------------|
| **Mean**     | **SD**         | **Mean**        |
| **Age**      | **31.0**       | **33.8**        | **32.05**       |
| **Literacy** | **8.8**        | **7.8**         | **6.2**         | **2.843** |

Both F-values were not statistically significant

Results showed that statistically significant differences were present between the group in all test. Digit Symbol Substitution Test (DSST), Benton Visual Retention Test (BVRT), and Paced Auditory Serial Addition Test (PASAT) were the only tests in which significant differences were present between the controls and asymptomatic patients, indicating an early decompensation in the course of the illness. PASAT, significant differences occurred with respect to both seropositive groups in comparison to the controls, but no significant difference was noted within the seropositive groups. The differences appeared to stabilize during the early stage of the illness.

Individuals in Group III showed a significant decline in all tests in comparison to controls. Compared to group II cohorts, group III exhibited a poor performance, but the decline was not statistically significant in Verbal Fluency, configuralional score in BGT, Complex figure learning test and Koh's block design test. These results denote that the linguistic and visuospatial functional decline were slower in comparison to other cognitive domains.

As significant differences were noted in all tests among group III subjects, the association between the impairments was further explored through correlation of raw scores (Table 3).

Scores of group III alone were considered, as group II and I did not differ significantly in most tests. The correlation matrix showed that Paired Associate learning, Digit backward, ‘skips’ in Colour Cancellation test, PASAT, Koh’s block design test and BVRT did not display significant correlation with any of the other tests, indicating that the decline in various cognitive domains was not related temporally or in terms of commonality of underlying neuropsychological functions. Significant correlation between Verbal Fluency and Differences - Similarly tests was due to the common linguistic components. Delayed response test was correlated to DSST, ‘correct response’ in colour cancellation tests, and duration in Trail Making test referring to the common time factor in these tests. Digit forward correlated to complex figure recall test and ‘correct responses’ in colour cancellation.
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#### TABLE 2

**COMPARISON OF NEUROPSYCHOLOGICAL TEST PERFORMANCE BETWEEN THREE GROUPS**

| Test                           | Group I mean (SD) | Group II mean (SD) | Group III mean (SD) | F     | Scheffe's test |
|-------------------------------|-------------------|--------------------|---------------------|-------|----------------|
| Delayed response ability      | 15.1 (1.8)        | 14.3 (2.7)         | 6.90 (4.4)          | 4.67* | -              |
| Differences & similarities    | 22.10 (1.8)       | 19.35 (3.6)        | 10.10 (4.6)         | 62.91**| -              |
| Ideational fluency            |                   |                    |                     |       |                |
| 'Wood'                        | 11.90 (4.3)       | 9.75 (2.6)         | 7.10 (3.0)          | 10.05**| -              |
| 'Round'                       | 8.45 (3.8)        | 7.85 (8.5)         | 5.10 (3.5)          | 5.87**| -              |
| Paired associated learning    | 14.60 (4.3)       | 12.45 (3.7)        | 7.85 (4.6)          | 13.31**| -              |
| Logical memory                | 20.80 (5.9)       | 18.00 (6.7)        | 12.10 (6.3)         | 9.84**| -              |
| Digit forward                 | 5.55 (0.9)        | 5.10 (0.4)         | 3.85 (0.8)          | 26.56**| -              |
| Digit backward                | 3.80 (0.6)        | 3.95 (0.8)         | 2.30 (0.6)          | 33.47**| -              |
| Digit symbol substitution     | 57.4 (18.9)       | 40.65 (13.7)       | 22.55 (13.7)        | 25.51**| +              |
| BGT                           |                   |                    |                     |       |                |
| Major                         | 28.4 (21.3)       | 36.40 (24.0)       | 75.20 (20.7)        | 25.79**| -              |
| Minor                         | 23.5 (11.4)       | 28.0 (6.7)         | 50.00 (16.8)        | 26.46**| -              |
| Raw                           | 52.7 (28.9)       | 64.40 (25.0)       | 125.2 (24.0)        | 47.27**| -              |
| Configuration                 | 2.75 (3.0)        | 5.30 (3.6)         | 6.85 (5.0)          | 4.47** | -              |
| Complex figure test           | 6.50 (4.5)        | 6.95 (3.1)         | 5.15 (2.6)          | 4.60** | -              |
| Color cancellation            |                   |                    |                     |       |                |
| 'Correct'                     | 90.45 (19.1)      | 79.85 (15.5)       | 47.85 (22.7)        | 26.32**| -              |
| 'Skip'                        | 7.5 (3.4)         | 3.10 (3.0)         | 7.70 (8.4)          | 5.20** | -              |
| PASAT                         | 7.70 (12.0)       | 1.70 (3.6)         | .90 (2.0)           | 5.17** | *              |
| Koh's block                   | 37.8 (40.0)       | 79.85 (114.6)      | 142.10 (111.7)      | 8.07** | -              |
| Trial making                  |                   |                    |                     |       |                |
| 'Time' in seconds             | 395.50 (143.4)    | 447.75 (111.8)     | 799.4 (243.5)       | 31.35**| -              |
| in 2 min                      | 23.35 (6.6)       | 21.15 (3.7)        | 12.15 (5.8)         | 23.02**| -              |
| BVRT                          | 8.30 (1.5)        | 5.0 (1.5)          | 2.65 (1.8)          | 26.59**| *              |

* p < .05 ** p < .01

* significant difference in Scheffe's test reflecting disturbances in selective attentional processes needed for complex test performance.

DSST correlated on one hand to logical memory indicating a common amnestic components and on the other to 'correct responses' in colour cancellation tests and trail making test, indicating the timed nature of the tests. Complex figure test correlated to digit forward test, 'correct responses' in colour cancellation test and trail making test. The correct responses in colour cancellation apart from other tests mentioned previously correlated to trail making test indicating psychomotor retardation as an underlying factor.

### DISCUSSION

The study aimed to know the early
neuropsychological decompensation in HIV infected individuals in whom overt neurological involvement was not yet evident. During the selection of cohorts confounding neuropathological variables such as, injuries to the brain (head injury), inherent disorders of brain (seizure disorders), infections of central nervous system, (neurosyphilis, opportunistic infections), chemical interference with functions (alcohol, drug dependence), psychocognitive disturbances (depression) and age related changes which could compromise cognitive performance were sought to be excluded, to enable the collection of a homogenous sample. Influence of age and literacy; was minimized by using comparable group of subjects. As the tests have not been standardized for the local population, the comparison was made against the seronegative local controls.

In all tests, individuals with clinical AIDS related complex (Group III) demonstrated a statistically significant impairment. Though none had evidence of neurological disturbances, the intensity and broad spectrum of impairments signified the decline as precursors and early indicators of neurological decompensation. Similar studies have suggested that subtle cognitive deficits might be apparent during the asymptomatic stage, unassociated to neurologic changes (Lunn et al., 1991; Maj et al., 1994). Radioimaging studies have shown that MRI measures of bicaudal - brain ratio correlated with worsening in certain cognitive functions in asymptomatic HIV-1 infected patients (Hall et al., 1996). These findings validate the usefulness of cognitive testing in the early detection of brain changes in AIDS.

The present study demonstrated the impairment in performance of almost all neuropsychological tests. But, the performance in each test required the integrated functioning of different neuropsychological system and no test reflected only one functional domain. Thus, digit backwards test necessitated the integration of attention, storage of information, mental double tracking, language and internal visual

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**TABLE 3**

CORRELATION MATRIX OF TEST PERFORMANCE OF GROUP 3 PATIENTS

|   | T1   | T2   | T3   | T4   | T5   | T6   | T7   | T8   | T9a  | T9b  | T10  | T11a | T11b | T12  | T13  | T14a | T14b | T15  |
|---|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| T1 | 1.0  |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| T2 | 5.1  | 1.0  |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| T3 | 38.69 | 1.0  |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| T4 | 37.31 | 2.8  | 1.0  |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| T5 | 27.33 | 1.3  | 5.0  | 1.0  |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| T6 | 41.37 | 3.9  | 4.2  | 11.18| 0.2  | 1.0  |      |      |      |      |      |      |      |      |      |      |      |      |
| T7 | 37.35 | 5.5  | 2.6  | 30.32| 1.0  |      |      |      |      |      |      |      |      |      |      |      |      |      |
| T8 | 67.24 | 0.2  | 4.5  | 4.0  | 0.48| 0.1  | 1.0  |      |      |      |      |      |      |      |      |      |      |      |
| T9a| 18.29 | 1.0  | -1.30| -1.36| -1.12| 0.2  | 1.0  |      |      |      |      |      |      |      |      |      |      |      |
| T9b| -48.48| -1.4 | -0.3 | -0.45| -1.14| -0.48| 0.1  | 1.0  |      |      |      |      |      |      |      |      |      |      |
| T10| 37.37 | 4.8  | 3.2  | 5.6  | 5.4  | 4.8  | -1.3 | -5.1 | 1.0  |      |      |      |      |      |      |      |      |      |
| T11a|54.64  | 3.2  | 3.4  | 5.4  | 5.6  | 7.7  | -0.8 | -2.3 | 6.0  | 1.0  |      |      |      |      |      |      |      |      |
| T12a|10.13  | -11  | 3.8  | 0.8  | 0.6  | 2.2  | -2.2 | 0.7  | 2.3  | -0.1 | 1.0  |      |      |      |      |      |      |      |
| T13 | 26.43 | 0.2  | 2.0  | 0.2  | 4.8  | -2.8 | -2.0 | 1.1  | 5.1  | 1.2  | -1.9 | 1.0  |      |      |      |      |      |      |
| T14a|38.37  | -1.4 | 2.4  | 4.2  | 2.5  | 2.9  | -2.9 | 5.5  | -4.9 | -4.5 | -2.0 | -2.0 | 1.0  |      |      |      |      |      |
| T14b|59.47  | 3.0  | 2.2  | 3.4  | 1.1  | 6.7  | -4.4 | -4.3 | 5.1  | 6.3  | -2.8 | -2.8 | -6.7 | 1.0  |      |      |      |      |
| T15 | 20.36 | -1.4 | 3.2  | 2.0  | 0.45| 0.1  | 2.0  | -0.9 | -5.1 | 0.2  | -2.2 | -2.2 | 3.2  | -3.2 | 2.0  |      | 2.4  |

*p < .01*

T1 Delayed response ability; T2 Differences and similarities; T3 Ideationalfluency; T4 Paired associated learning; T5 Logical memory; T6 Digit forward; T7 Digit backward; T8 Digit symbol substitution test; T9a BGT major; T9b BGT configuration; T10 Complex figure test; T11a Color cancellation 'correct'; T12b Color cancellation 'skips'; T12 PASAT; T13 Koh's block test; T14a Trial making 'time'; T14b Trial making 'within 2 minutes'; T15 BVRT
scanning (Lezak, 1995).

Though impairment was in terms of test performance, the interpretation should be in terms of cognitive functional systems commonality of certain functional system such as speed of information processing visuo-spatial functioning and selective attention was evident in the correlation matrix. Attention, visuospatial perception, constructional ability, abstraction, executive functions and linguistic fluency were the functional systems that were disturbed among these subjects and similar observations were made in other studies (Maj et al., 1994; Hinkin et al., 1995). Functional system have their own neuroanatomical correlates and pathological studies have affirmed the basis for the neuropsychological decompensation (Wiley, 1994).

Results of the study pointed to the disintegration of different system in varying temporal order. Thus, DSST, BVRT and PASAT showed an early impairment, indicating that selective attentional processes involved in complex test performance showed an early decline, evident in the asymptomatic stage itself. Unlike the other two, PASAT was performed by group II and III subjects without much difference, with an inference that the decline was complete early.

Reinvang et al. (1991) suggested that the AIDS population included two subgroups, one with AIDS dementia complex and the other with persistently normal neuropsychological performance. If such a predilection were to exist, the usefulness of these tests in predicting the dichotomy might have enormous preventive and prognostic value. On the same grounds, the late decline in linguistic fluency, or visuospatial functions as predictors of early decline is minimal. Lack of significant correlation between some of the tests (Table 3) indicated that the underlying combination of neuropsychological functions declined disparately. Thus, though the impairment was multidimensional, only certain tests were useful for prediction and prognostication. Low level neuropathological processes in asymptomatic HIV infection could be effectively suppressed by anti-retroviral medication (Pajeau and Roman, 1992). The possibility of such early reversal in the preventive management of neurological complications emphasises the value of early detection.

Though in the present study, asymptomatic patients were found to have neuropsychological deficits, such findings have not been universal (Miller et al., 1991; Selnes et al., 1992). Such interregional differences have been attributed to low 'cerebral reserve' in certain populations of developing countries (Maj et al., 1994; Stern et al., 1996). Redundancies of cerebral networks have been linked to organic and psychosocial factors. Whether such a putative low cerebral reserve is a procedural artifact linked to the sensitivity of the test employed or to the varied cognitive style of the native population not attuned to Western oriented testing needs to be ascertained. Clinically, the multidimensional impairment, prior to the onset of neurological syndromes and the possibility of its early detection with specific tests were of practical significance, particularly if longitudinal studies replicate their prognostic value.

In the context of the rapid and extensive spread of HIV infection in India and the non-availability of anti-retroviral therapy due to its prohibitive cost, the possibility of early detection of HIV patients with cognitive decline by neuropsychological screening would be of practical value in the containment of neurological complications of the illness.

REFERENCES

Angrist, B., d'Hollosy, M., Sanfilipo, M., Satriano, J., Diamond, G., Simberkoff, M. & Weinreb, H. (1992) Central nervous system stimulants as symptomatic treatments for AIDS-related neuropsychiatric impairment. Journal of Clinical Psychopharmacology, 12, 268-272.

Atkinson, J.H. & Grant, I. (1994) Natural history of neuropsychiatric manifestation of HIV disease. The Psychiatric Clinics of North America, 17, 17-33.

Centres for Disease Control (1993) Re-
vised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. Morbidity and Mortality Weekly Reports, 41, (suppl.) 44.

Hall, M., Wheley, R., Robertson, K., Hamby, S., Wilkins, J. & Hall, C. (1996) The correlation between neuropsychological and neuroanatomic changes over time in asymptomatic and symptomatic HIV - I infected individuals. *Neurology*, 46, 1697-1702.

Hinkin, C.H., Van Gorp, A.G. & Satz, P. (1995) Neuropsychological and neuropsychiatric aspect of HIV infection in adults. In : *Comprehensive Textbook of Psychiatry*, Vol. 2, Edn. 6, (Eds.) Kaplan, H.L. & Sadock, B.J., pp 1644-1664., Baltimore : Williams and Wilkins.

Lezak, M.D. (1995) *Neuropsychological assessment*, Edn. 3, pp 367-368, Oxford : Oxford University press.

Lunn, S., Skydsbjerg, M., Schulsinger, H., Parnas, J., Pedersen, C. & Mathiesen, I. (1991) A preliminary report on the neuropsychological sequelae of human immunodeficiency virus. *Archives of General Psychiatry*, 48, 139-142.

Maj, M., Satz, P., Janssen, R., Zaudig, M., Strace, F., D’Elia, L., Sugandhabirom, B., Mussa, M., Naber, D., Ndeitei, D., Schulte, G. & Sartorius, N. (1994) WHO neuropsychiatric AIDS study, Cross - sectional phase II. *Archives of General Psychiatry*, 51, 51-61.

Miller, E.N., Satz, P. & Visscher, B. (1991) Computerized and conventional neuropsychological assessment of HIV-1 infected homosexual men. *Neurology*, 41, 1608-1618.

Pajeau, A.K. & Roman, G.C. (1992) HIV encephalopathy and dementia. *The Psychiatric Clinics of North America*, 15, 455-466.

Portegies, P., Enting, R.H., de-Gans, J., Algra, P.R., Derix, M.M., Lange, J.M. & Goudsmit, J. (1993) Presentation and course of AIDS dementia complex : 10 years of follow up in Amsterdam. The Netherlands, AIDS, 7, 669-675.

Reinvang, I., Froland, S.S. & Skripeland, V. (1991) Prevalence of neuropsychological deficit in HIV infection. Incipient signs of AIDS dementia complex in patients with AIDS. *Acta Neurologica Scandinavica*, 83, 289-293.

Selnes, O.A., McArthur, J.C., Royal, W., Updike, M.L., Nance-Spovan, T., Concha, M., Gordon, B., Solomon, L. & Vlahov, D. (1992) HIV-1 infection and intravenous drug use, longitudinal neuropsychological evaluation of asymptomatic subjects. *Neurology*, 42, 1924-1930.

Sinha, D. (1985) Psychology in rural areas : The case of a developing country. In : *Cross cultural and national studies in social psychology*, Vol. 2, (Ed.) Diaz Guerrero, R., pp 431-457. Amsterdam : North Holland.

Stern, Y. (1994) Neuropsychological evaluation of the HIV patients. *The Psychiatric Clinics of North America*, 17, 125-134.

Stern, R.A., Silva, S.G., Chaisson, N. & Evans, D.L. (1996) Influence of cognitive reserve on neuropsychological functioning in asymptomatic human immunodeficiency virus - 1 infection. *Archives of Neurology*, 53, 148-153.

Wiley, C.A. (1994) Pathology of neurologic disease in AIDS. *The Psychiatric Clinics of North America*, 17, 1-15.

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