A Novel Approach to the Determination and Characterization of HIV Dementia

P. Brouwers, E. Mohr, K. Hildebrand, M. Hendricks, J.J. Claus, I.S. Baron, M. Young and P. Pierce

ABSTRACT: Background: Neuropsychological studies of the pattern and extent of cognitive impairment in HIV-infected patients have mostly used deviations from control values and/or cut-off scores as criteria for classification of dementia. There is, however, no agreement as to how to define impairment, and classification is imprecise. Method: The current study used a dementia classification matrix, developed with a step-wise linear discriminant analysis of neuropsychological data from patients with primary neurodegenerative dementias, to classify symptomatic HIV patients as demented or non-demented, and further to differentiate cortical and subcortical dementia patterns. Thirty-two male and 2 female patients (mean age 39 ± 2) with symptomatic HIV disease (mean absolute CD4 count 195 ± 41) participated in the study. Results: Thirty-five per cent of patients were classified as demented. Of these, 83% showed a subcortical pattern and 17% a cortical profile of deficits. Significant differences between patients classified as subcortically demented and those categorized as normal on neuropsychological measures associated with subcortical integrity further validated the classification. Measures of psychiatric status between subgroups were similar. Conclusion: Since certain treatments may delay or reverse cognitive deficits, the use of an objective classification method based on discriminant analysis may help to identify patients who may benefit from therapy.
patients may present with ADC as the first manifestation of symptomatic disease.\textsuperscript{11,12} While many patients show impairments on neuropsychological tests as the disease progresses, type and extent of these deficits in asymptomatic HIV positive patients remains controversial.\textsuperscript{13-15}

Studies of the pattern and extent of cognitive impairment in HIV positive patients have mostly used deviations from control values and/or cut-off scores as their criteria for classification of impairment or dementia (e.g.\textsuperscript{16-19}). These approaches may be insufficient since classification accuracy is imprecise. Moreover, among these studies there is no clear agreement as to what level of cognitive functioning warrants a full diagnosis of dementia with its essential feature of impaired function in work and activities of daily living, as opposed to a finding of neuropsychological deficits that are of insufficient magnitude to significantly interfere with daily life.\textsuperscript{9,19}

Recently we described a new methodology for the objective determination of the incidence and type of both primary and secondary dementia.\textsuperscript{20} The approach used a step-wise discriminant analysis (see Methods for description) for allocation to a diagnostic category using neuropsychological test scores. The method was developed using age-scaled neuropsychological test data from patients with primary neurodegenerative dementias of two different etiologies (Alzheimer’s (AD) and Huntington’s (HD) disease) and normal controls. A classification rule was derived that determined with high sensitivity (100%) and specificity (97%) whether a patient’s functioning was indicative of the presence or absence of dementia. The formula further indicated if an individual’s neuropsychological profile was more suggestive of subcortical (HD-like) or cortical (AD-like) dementia\textsuperscript{21,22} (79% correctly classified). The reliability of this classification formula was demonstrated with a new, independent sample of demented patients which yielded virtually identical results (96% sensitivity for dementia; correct AD/HD classification 78%). Validity was demonstrated in 45 patients with Parkinson’s disease (PD). The proportion of these PD patients classified as demented with the formula (38%) was nearly identical to that reported in another recent study (41%).\textsuperscript{23}

Furthermore, comparisons were made between PD patients classified as demented and as non-demented on neuropsychological measures not included in the discriminant analysis. Significant differences between subgroups were ascertained and differential neuropsychological profiles were found which reflected their type of dementia classification.

The current study uses this methodology to classify patients with symptomatic HIV infection as demented or non-demented, and to determine whether those labelled demented evidence a predominantly subcortical or cortical pattern. To further validate the classifications and assess features of HIV dementia, subgroup differences are compared on additional neuropsychological variables not used in the discriminant function.

**METHODS**

**Patient Selection**

Thirty-four consecutive outpatients with symptomatic HIV infection consented to participate in this study, after full disclosure of potential risks and benefits. Patients with a history of IV drug use or other CNS abnormalities (opportunistic CNS infections, tumors, previous head trauma) were excluded due to the possibility of functional CNS sequelae independent of HIV infection. Assessments were carried out prior to any antiretroviral treatment, which has been shown to alter neuropsychological function.\textsuperscript{24-26} Patients with major psychiatric disorders (DSM-III-R criteria; by history) preceding infection were not eligible to participate. All participants were classified as having AIDS (Class IV) or AIDS Related Complex (ARC; Class III) based on Centers for Disease Control criteria. The mean ± SEM absolute CD4 count was 195.4 ± 41.0 cells/mm\textsuperscript{3}. Subjects included 32 males and 2 females whose mean age was 39.1 years (range 22-65 years), with an average educational level of 15.3 years (range 11-19 years). Fifty-six per cent could be classified as visible minorities or women; 17 males and 1 female were non-caucasian, 15 males and 1 female were caucasian.

**Statistics and Test Battery**

The classification formula developed by Mohr et al.\textsuperscript{20} based on stepwise linear discriminant analysis was applied to the HIV patients to determine the incidence and subtype of dementia. Step-wise linear discriminant analysis allows the simultaneous comparison of several study groups on multiple variables. A subset of variables is combined into a mathematical equation, much like a linear regression equation, to predict group membership. Variables are entered into the equation successively (step-wise) on the basis of greatest discriminating power, until adding another variable does not significantly improve the predictive power of the equation. Age-scaled subtest scores (Block Design; Object Assembly; Digit Span) from the Wechsler Adult Intelligence Scale-Revised\textsuperscript{27} (WAIS-R) and the Memory Quotient and age-scaled Visual Reproduction subtest score from the Wechsler Memory Scale\textsuperscript{28,29} (WMS) were included in the formula.

In addition, a comprehensive neuropsychological test battery covering a wide range of functions including cognition, motor performance and affect was administered. Tests not used for the discriminant function were used to compare HIV patients classified as ‘demented’ with those classified as ‘normal’ in order to assess the validity of the classifications and other features of cognitive function in patients with symptomatic HIV infection. Split-plot repeated measures analysis of variance (ANOVA)\textsuperscript{30} and Mann-Whitney-U tests were calculated to investigate further differentiating characteristics between subgroups.

**RESULTS**

**Classification of the HIV Patients**

Twenty-two of 34 HIV patients (64.7%) were classified as ‘normal’ while 12 (35.3%) were classified as ‘demented’ (Table 1). There was no significant difference between these two groups in disease stage, as reflected by their absolute CD4 counts (mean ± SEM cells/mm\textsuperscript{3} normal HIV 199.5 ± 45.0; demented HIV 188.3 ± 83.5). Of the HIV patients classified as ‘normal’, 64% had CD4 counts below 200, and 29% had counts below 50, while for those classified as ‘demented’, 75% were below 200 and 50% below 50.

Of the patients classified as demented, 10 (83.3%) showed a subcortical (HD-like) and 2 (16.7%) a cortical (AD-like) pattern. This distribution was compared to that of the AD and HD
patients and normal controls used to develop the classification matrix (Table 1).20 The distributions of the HIV (demented) and Alzheimer's patients showed significant differences (χ² = 11.1; \( p < .001 \)). In contrast, the distributions of the HIV (demented) and Huntington's patients were highly similar (χ² = 0.03; \( p > .50 \)), suggesting that the HIV impairment profile is principally 'HD-like'.

Comparison of HIV Patient Subgroups

Further analyses contrasting HIV patients classified as HD-like with those classified as 'normal control-like' (NC-like) were calculated (Table 2). (Since only 2 HIV patients were classified as HD-like, compared to NC-like symptomatic HIV patients and normal controls used to develop the classification matrix (Table 1).20 The distributions of the HIV (demented) and Alzheimer's patients showed significant differences (χ² = 11.1; \( p < .001 \)). In contrast, the distributions of the HIV (demented) and Huntington's patients were highly similar (χ² = 0.03; \( p > .50 \)), suggesting that the HIV impairment profile is principally 'HD-like'.

### Table 1: Classification of HIV patients using discriminant analysis of neuropsychological test scores, compared with the classification of patients with Alzheimer's and Huntington's disease and normal controls.

<table>
<thead>
<tr>
<th>Classification</th>
<th>AD-like</th>
<th>HD-like</th>
<th>NC-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's Disease</td>
<td>16 (84%)</td>
<td>3 (16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Huntington's Disease</td>
<td>5 (26%)</td>
<td>14 (74%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Normal Controls</td>
<td>0 (9%)</td>
<td>1 (3%)</td>
<td>28 (97%)</td>
</tr>
<tr>
<td>HIV Disease (AIDS/ARC)</td>
<td>2 (6%)</td>
<td>10 (29%)</td>
<td>22 (65%)</td>
</tr>
</tbody>
</table>

Results for AD and HD patients and normal controls are from a previous study.20

### Table 2: Comparison of HIV patients classified as HD-like with those classified as NC-like.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>HD-like Mean (range)</th>
<th>NC-like Mean (range)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>9/1</td>
<td>21/1</td>
<td>NS</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.1 (11-18)</td>
<td>16.1 (12-19)</td>
<td>&gt;.15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.0 (29-50)</td>
<td>41.9 (22-65)</td>
<td>&gt;.16</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>218.5 (2-847)</td>
<td>199.5 (13-764)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Intellectual Function

<table>
<thead>
<tr>
<th>Test</th>
<th>HD-like</th>
<th>NC-like</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R FSIQ*</td>
<td>86.1 (66-100)</td>
<td>110.0 (88-130)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WAIS-R VIQ*</td>
<td>87.4 (66-98)</td>
<td>111.6 (85-128)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WAIS-R PIQ*</td>
<td>87.0 (70-104)</td>
<td>106.0 (92-125)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ravens Matrices</td>
<td>99.0 (67-116)</td>
<td>121.0 (102-139)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WMS Memory Quotient*</td>
<td>92.0 (72-107)</td>
<td>119.8 (107-137)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Language

<table>
<thead>
<tr>
<th>Test</th>
<th>HD-like</th>
<th>NC-like</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peabody PVT-R</td>
<td>91.2 (64-112)</td>
<td>116.9 (79-143)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WRAT-Reading</td>
<td>86.5 (48-101)</td>
<td>110.9 (81-129)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Word Fluency</td>
<td>32.1 (10-51)</td>
<td>43.0 (24-88)</td>
<td>&lt;.06</td>
</tr>
</tbody>
</table>

### Visuospatial Function

<table>
<thead>
<tr>
<th>Test</th>
<th>HD-like</th>
<th>NC-like</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streetmap Total Errors</td>
<td>6.5 (1-21)</td>
<td>2.5 (0-12)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Streetmap Errors Up-Down</td>
<td>2.7 (1-6)</td>
<td>0.6 (5-4)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

### Attention/Psychomotor Speed

<table>
<thead>
<tr>
<th>Test</th>
<th>HD-like</th>
<th>NC-like</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trail-Making Test A (time)</td>
<td>21.2</td>
<td>17.4</td>
<td>NS</td>
</tr>
<tr>
<td>Trail-Making Test B (time)</td>
<td>153.8</td>
<td>68.9</td>
<td>&gt;.15</td>
</tr>
<tr>
<td>Reaction Time Simple</td>
<td>269.8</td>
<td>259.8</td>
<td>NS</td>
</tr>
<tr>
<td>Reaction Time Choice</td>
<td>413.8</td>
<td>409.0</td>
<td>NS</td>
</tr>
<tr>
<td>Decision Time (CRT-SRT)</td>
<td>144.0</td>
<td>149.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Mood Affect

<table>
<thead>
<tr>
<th>Test</th>
<th>HD-like</th>
<th>NC-like</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression</td>
<td>13.3</td>
<td>11.1</td>
<td>NS</td>
</tr>
<tr>
<td>MAACL -Depression</td>
<td>74.3</td>
<td>66.0</td>
<td>NS</td>
</tr>
<tr>
<td>Anxiety</td>
<td>69.9</td>
<td>66.0</td>
<td>NS</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>71.8</td>
<td>63.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

*WAIS-R subtests Digit Span, Block Design, and Object Assembly and WMS Memory Quotient and Visual Reproduction were used in the discriminant classification matrix.

**Mann-Whitney-U statistic; medians: HD 88.5, NC 68.5.

was 21.2 ± 3.9 (HD) versus 17.4 ± 1.3 (NC), a difference which did not reach statistical significance. Trail Making Test B scores on the other hand were significantly different (Mann-Whitney-U, \( p < .01 \); median completion time (seconds): HD 88.5, NC 68.5; a non-parametric test was used for this variable because scores were not normally distributed). In the Reaction Time Test, differences were not significant between the HD-like and NC-like groups, either in Simple Reaction Time (HD 270 ± 23; NC 260 ± 11), Choice Reaction Time (HD 414 ± 29; NC 409 ± 28) or Decision Time (HD 144 ± 13; NC 149 ± 22).

Analysis of affective variables with the Beck Depression Scale37 and the Multiple Affect Adjective Checklist (MAACL) indicated that although most patients showed elevated levels of depression and anxiety, there were no statistically significant differences in severity between subgroups. When evaluating the contribution of depression and anxiety to psychometric test
results for all patients, the following correlations were observed with the Beck Depression Inventory: Ravens -.45; Trail Making A .44; Trail Making B .58; Street Map Up Errors .56; Street Map Down Errors .42 (all p’s < .05). MAACL Anxiety showed borderline correlations with Reaction Time (Choice RT -.39, p < .05; Simple RT -.33, p < .10), suggesting that heightened anxiety may result in a quicker response time.

DISCUSSION

Discriminant Analysis

The classification of HIV patients as demented or non-demented on the basis of a discriminant function with neuropsychological variables appears to offer a viable alternative to the use of cut-off scores or deviation from control values on multiple tests. Our approach offers greater precision as it is derived from objective, empirical data from patients with a confirmed diagnosis of primary neurodegenerative dementia, unlike a clinical approach which offers no clear objective criteria. A further advantage of this method is that the step-wise technique requires only limited neuropsychological testing and thus may serve well as a screening method. Dementia can be one of the first manifestations of symptomatic HIV disease\(^1\),\(^2\) and the extent of deficits varies considerably, therefore this strategy may be useful in identifying these patients.

Dementia Classification

Application of this formula to patients with symptomatic HIV disease classified 35% as demented, which falls approximately in the mid-range of previous estimates.\(^1\) The absence of differences in CD4 values between the demented and non-demented HIV patients suggests that ADC is indeed a secondary process, i.e., it does not occur in all patients as the disease progresses.

Further subclassification of those identified as demented indicated that 83% showed a profile of deficits that was more compatible with a subcortical than a cortical dementia. Other studies have also suggested that subcortical structures may be predominantly involved in HIV-induced CNS disease.\(^1\),\(^11\),\(^38\),\(^39\)

Autopsy reports of patients with primary HIV-induced CNS illness suggest that the core brain pathology occurs in the subcortical grey matter (basal ganglia, thalamus) and white matter tracts, with findings of white matter pallor, gliosis and multinucleated giant cells.\(^3\),\(^4\),\(^10\) Quantitative neuroimaging\(^4\) and positron emission tomography (PET) studies of the cerebral metabolic rate of glucose\(^5\),\(^4\) have also tended to implicate subcortical structures in the disease and dementia. We have been able to demonstrate with PET that improvement of neuropsychological status in HIV patients occurred concurrently with increased glucose utilization in subcortical areas.\(^2\),\(^4\) These findings appear to further validate the results of our classification technique, supporting and extending the hypothesis of primarily subcortical involvement in CNS HIV disease.

Subgroup Differences

The validity of the classification approach is further supported by post-classification analysis of subgroup differences on measures not used in the discriminant function, which revealed significant differences between HD-like and NC-like HIV patients in tests of global intellect, language, attention and psychomotor and visuospatial function. The HD-like subgroup scored significantly lower on FSIQ, VIQ, PIQ, WPVT-R, WRAT-Reading, and Ravens Matrices than the NC-like subgroup, but there was also significant overlap between the two groups. This reflects the multidimensionality of the method of dementia classification, which is based on a complex analysis of neuropsychological profile rather than overall level of functioning. The relative deficit of the HD-like group on these tests of global cognitive function is suggestive of the presence of a more global CNS compromise along with subcortical involvement.

The significant visuospatial impairment in the ability to manipulate egocentric space as opposed to extrapersonal space on the Streetmap Test by patients identified with a subcortical-type dementia further validates the classification obtained. In previous studies, we reported that HD patients, unlike AD patients, were impaired to a significantly greater degree when manipulation of egocentric as opposed to extrapersonal space was required.\(^5\),\(^6\) Moreover, these studies showed that this discrepancy correlated with further progression of HD, perhaps in relation to nigrostriatal degeneration.

Slowness of response is a major feature of subcortical dementias\(^5\) and has also been a distinguishing characteristic of ADC.\(^3\),\(^4\),\(^7\),\(^8\) Accordingly in our study, performance on Trail-Making Test B, a task of psychomotor speed, was significantly slower in patients classified as demented (HD-like) than in nondemented patients. In Trail-Making A and Reaction Time tests
however, the non-demented and HD-like subgroups, although both slower than established norms, did not differ significantly. These results correspond to other recent studies,49-51 which found that while reaction time was slower in asymptomatic HIV positive patients (early stages) than in HIV negative controls, there was no significant correlation between disease stage (as reflected by CD4 counts) and reaction times in the HIV positive group, suggesting that further disease progression may not lead to further psychomotor slowing. These measures of attentional functioning therefore seem sensitive to HIV-associated CNS compromise in the earlier phases of the disease. However in later stages, such measures may be insensitive to further differentiation between AIDS patients with and without dementia. The discrepancy between the findings on Trail-Making B and Reaction Time tests may also be due to a difference in task requirements. Reaction Time tests are relatively simple externally-paced stimulus-response tasks, while the Trail-Making Test B is a self-paced task requiring more complex response-set shifting behaviors.

Depression can be a behavioral concomitant of subcortical dementia.21 Although most of the HIV patients in the current study showed evidence of depression, there were no significant differences between patients classified as demented (HD-like) or normal on the various depression and anxiety measures. Depression and anxiety can also have significant effects on neurocognitive functioning. The lack of a difference between subgroups again suggests that these behaviors did not significantly influence the dementia classification. Thus deficits in neuropsychological functioning in patients with HIV disease appear to be relatively independent from abnormalities in mood, as other investigators have also found.6,25-54

Cognitive manifestations may become a more critical aspect of HIV disease as advances in anti-retroviral therapy as well as in prophylactic and direct treatment of opportunistic infection lead to longer survival for these patients.55 The detection of significant CNS compromise in patients with symptomatic HIV disease is important for timely commencement of anti-retroviral therapy. Studies have shown that for both pediatric and adult patients, improvements in neurocognitive function can be achieved with anti-retroviral treatments such as zidovudine (ZDV).24,25,55-57 These studies, however, also indicate that CNS efficacy is dependent in part on pharmacological parameters such as dose,25 route of administration,58 absorption59 and CNS penetration.60 Thus the detection of significant CNS compromise in patients with symptomatic HIV disease may require treatment modification. In the absence of established biological markers for dementia, the use of an objective method to determine impaired neuropsychological functioning will be crucial. A method that can enhance diagnostic precision, evaluate progression and assess the effectiveness of pharmacological interventions is especially important given that a number of agents which may alleviate and even reverse neurological dysfunction are currently undergoing clinical trials. The classification approach used here may be one such method.

Acknowledgements

The work reported in this paper was in part supported by a grant (0354) from the American Foundation for AIDS Research. The contributions of Margaret Sampson and Mafalda Urbanyi are gratefully acknowledged.

References

1. Brouwers P, Mohr E, Hendricks M, Baron I. The use of discrimina

tive analysis to differentiate the neuropsychological profile of


vous system HIV-1 infection and AIDS dementia complex.


brains of children and adults with AIDS encephalopathy. Science

1985; 227: 177-182.


virus in macrophages in brain tissue from AIDS patient with


brain barrier synthesis of HTLV-III specific IgG in patients with

neurological symptoms associated with AIDS or AIDS-related


7. Hiv H. Cognition in early human immunodeficiency virus type-1


abnormalities in homosexual men with and without neuropsyc

hological findings. Ann Neurol 1988; 23 (Suppl.): S34-S37.


nomenclature and research case definitions for neurologic mani

festations of human immunodeficiency virus. Neurology 1991; 41:

778-785.


and HIV-1 brain infection: a pathogenetic model of virus-


68: 269-290.


miology of human immunodeficiency virus encephalopa


nervous system involvement in the acquired immunodeficiency

syndrome (AIDS) and other human immunodeficiency virus

(HIV) infections. Studies with neuropsychological testing and

magnetic resonance imaging. Ann Intern Med 1987; 107: 826-

836.


rological and neuropsychological abnormalities in otherwise

healthy HIV-1-infected individuals: results from the Multicenter


dence of cognitive decline during the asymptomatic stages.


ropsychological performance in asymptomatic HIV infection.


17. Wilkie FL, Eisdrof J, Morgan R, Loewenstein DA, Szapocznik J.

Cognition in early human immunodeficiency virus infection.


on the neuropsychological sequelae of Human Immunodeficiency

Virus. Arch Gen Psychiatry 1991; 48: 139-142.

19. Adams KM, Heaton RK. Statement concerning the NIMH neu


960-962.


versity Press, 1990:

22. Tolosa ES, Alvarez R. Differential diagnosis of cortical vs. subcor


investigation of Parkinson's disease with and without dementia: