HIV Dementia Scale and Psychomotor Slowing—The Best Methods in Screening for Neuro-AIDS

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The authors examined the correlation between Human Immunodeficiency Virus (HIV) Dementia Scale (HDS) and psychomotor tests, evaluating basal ganglia function in 266 HIV-seropositive, Caucasian, homosexual men. Fifty-five HIV-positive, patients with mild dementia (HDS score ≤10) showed significant slowing of most rapid alternating movements (MRAM) and significantly prolonged contraction times compared to 211 HIV-positive nondemented patients (HDS score >10). Motor performance correlated significantly with the time-dependent HDS subscores for psychomotor speed and construction and HDS sum score. In contrast to contraction times and MRAM, HDS scores also showed significant correlations to age, premorbid and actual intelligence, and duration of HIV seropositivity.

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Human immunodeficiency virus type 1 (HIV) associated dementia is the predominant clinical manifestation of HIV in the brain. Human immunodeficiency virus associated dementia is defined by a clinical triad of 1) cognitive deficits, 2) disturbed motor function, and 3) emotional deficits.[1] The HIV Dementia Scale (HDS)[2] was originally designed explicitly to serve as a valid screening tool to identify HIV dementia and to monitor therapeutic effects[3] on the central nervous system (CNS). Initially, the HDS was shown as superior to other widely used rapid screening tests (Mini-Mental State Examination [MMSE], Grooved Pegboard) and to be especially effective in asymptomatic and acquired immune deficiency syndrome (AIDS) defined, but nondemented patients. The HDS is comprised of four tasks that evaluate the domains of memory (recall of four items at 5 minutes), attention (antisaccadic errors), psychomotor speed (timed written alphabet), and construction (cube copy time). A subscore and sum score are calculated for each domain. For more details, see Power et al.[2] Today it is common knowledge that psychomotor slowing (i.e., minor motor deficits) predicts dementia, AIDS, and death.[4,5] Screening for early deficits and care-

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ful evaluation of psychomotor function are therefore essential. Psychomotor slowing can be quantified in various manners: with refined neuropsychological test batteries[5–7] or by an electrophysiological motor test battery that describes basal ganglia motor function in HIV-1 infection[8] and in other well defined basal ganglia diseases such as Parkinson's disease,[9] Wilson's disease,[10] and Huntington's chorea.[11] We, therefore, decided to explore the relation between HDS scores and psychomotor performance as assessed by our test battery.

METHOD

Patients

Between 1988 and September 30, 2002, a total of 2,436 HIV-seropositive patients were recruited consecutively. Assessment with the HDS was introduced in our department on February 2, 1999. We retrospectively selected all patients who were examined parallel to the HDS and the above mentioned electrophysiological test battery.[8] Among patients who received regular follow up, only the first parallel evaluation of HDS and motor performance was analyzed. Only patients with sexually acquired HIV infection were included. Patients who acquired HIV by intravenous drug use were excluded in order to avoid any interference between past or ongoing drug use and test results. Patients with a migration background were also excluded to avoid any influence of different mother languages on the timed written alphabet section of the HDS. To control for potential gender differences, only male patients, who represent the majority of patients in our department, were included. Patients with clinically severe forms of HIV associated dementia were excluded as well as patients with CNS opportunistic infections, CNS lymphoma, or vacuolar myelopathy. Demographical data for all N = 266 patients are presented in Table 1. Six men have died meanwhile. Stages of HIV-1 infection were grouped according to the current Centers for Disease Control (CDC) classification[12] into non-AIDS or AIDS stages. On the basis of an HDS score ≤10, the HDS between AIDS patients with and without mild dementia is distinguishable in the original scale,[2] and we divided patients into two groups accordingly. To assess premorbid verbal intelligence and actual nonverbal intelligence, the *Mehrfachwortauswahltest* (MWT-b)[13] and Raven[14] tests were performed in all patients.

Central Motor Testing

In 1987, central motor testing was established for HIV-1 (positive) patients in our department and includes analysis of the following:

1. postural tremor of the outstretched hands [tremor peak frequency (TPF)];
2. most rapid alternating movement (MRAM) of index finger;
3. most rapid isometric contraction (extension) of index finger (MRC), including
   a. simple reaction time (RT); and
   b. contraction time

Methodological details were published earlier[8,15]: a lightweight accelerometer taped to the nail of each subject's index finger was used for recording the TPF and the MRAM. To determine TPF, subjects were requested to hold their arms in a horizontal position, with their forearms fully pronated and fingers completely outstretched. Spectrum analysis was performed off-line, and the frequency of the dominant peak of the average spectrum was defined as TPF. To determine MRAM, subjects were requested to flex and extend their index finger at the metacarpophalangeal joint as rapidly as possible. For MRC recordings, the index finger was firmly attached to a force transducer. Subjects were asked to extend the finger immediately after hearing a "go" signal. The simple reaction time (RT) and the time between the onset of the contraction and the point at which it reached its maximum (contraction time) were recorded.

Statistical Analysis

Statistics were performed using the commercially available software package Statview for Windows, Version 5.0.1 (SAS Institutes Inc., Cary, N.C., 1998). Descriptive statistics were used to describe subjects and parameters. Unpaired t tests and contingency tables were used to test for differences between groups. Correlation analyses were used to describe the relationship between variables.

RESULTS

Table 1 provides the demographic data of each patient. Following the original HDS,[2] patients were separated into those with an HDS score >10, considered to be asymptomatic, and those with an HDS score ≤10,

considered mildly demented. Asymptomatic patients were significantly younger than patients with mild dementia. Both groups did not differ with regard to the mode of infection, duration of HIV seropositivity, CDC stages at the time of first examination, type of antiretroviral therapy, CD 4+ cell counts, and HIV plasma viral load. Patients scoring ≤10 showed a significantly lower premorbid verbal IQ (MWT-b) and actual nonverbal IQ (Raven).

In a second step, we compared the results of electrophysiological motor tests in both groups (Table 2). Patients considered mildly demented showed highly significantly prolonged contraction time for both hands and significant slowing of MRAM for both hands. Reaction time was prolonged only for the right hand, whereas there were no differences in tremor peak frequency.

In a third step, we sought to determine which subtest of the HDS correlated best with psychomotor performance, as described by our test battery. We focused on the two parameters significantly altered: contraction time and MRAM. The significance of correlations is presented in Table 3. We found significant correlations between contraction time and MRAM for the HDS sum

TABLE 1. Demographic Data of All (N = 266) Male Patients

	Mildly Demented (N = 55)[a]		Not Demented (N = 211)[b]		
Measure	**Mean**	**SD**	**Mean**	**SD**	**p[c]**
Age (years)	45.2	10.4	41.2	8.8	0.0043
Duration of HIV seropositivity (months)	63.3	48.4	77.2	56.2	n.s.
	N	%	N	%	
Mode of infection					
Homosexual	42	76	186	88	n.s.
Bisexual	6	11	15	7	
Heterosexual	7	13	10	5	
Non AIDS stages			n.s.		
A1	2	4	19		
A2	7	13	42		
B1	1	2	4		
B2	14	25	22		
AIDS stages					
A3	6	11	16	8	
B3	7	13	32	15	
C2	4	7	8	4	
C3	14	25	68	32	
Antiretroviral therapy					
None	9	16	21	10	n.s.
Two nucleoside reverse transcriptase inhibitors	3	6	8	4	
Highly active	43	78	182	86	
CD4+ cell count (cells/μl)					
	Mean	SD	Mean	SD	
	404	249	461	262	n.s.
	N	%	N	%	
500 ≤n	11	20	32	15	n.s.
201 ≤n <500	27	49	95	45	
n <200	17	31	84	40	
HIV plasma viral load (log [copies/ml])					
	Mean	SD	Mean	SD	
	1.97	1.99	1.98	2.02	n.s.
	N	%	N	%	
Viral load x ≤2	26	47	105	50	n.s.
Viral load 2 <x ≤4	19	35	55	26	
Viral load 4 <x	9	16	44	21	
Not available	1	2	7	3	
	Mean	SD	Mean	SD	
Premorbid verbal IQ (*Mehrfachwortauswahl test*)	105	14	116	14	<0.0001
Actual nonverbal IQ (Raven test)	104	14	117	14	<0.0001

[a]HIV Dementia Scale score ≤10
[b]HIV Dementia Scale socre >10
[c]Unpaired t test (contingency table)
HIV = human immunodeficiency virus; AIDS = acquired immune deficiency virus; SD = standard deviation; IQ = intelligence quotient

TABLE 2. Results of Electrophysiological Motor Tests in Both Groups of Male Patients

Measure	Mildly Demented (N = 55)[a] Mean	SD	Not Demented (N = 211)[b] Mean	SD	p[c]
Tremor peak frequency (Hz)					
Right hand	8.29	1.13	8.43	1.30	n.s.
Left hand	8.13	1.78	8.43	1.32	n.s.
Most rapid alternating movement (Hz)					
Right hand	5.3	1.0	5.8	1.1	0.0057
Left hand	5.0	1.2	5.4	1.1	0.0101
Simple reaction time (msec)					
Right hand	182.7	81.0	163.6	44.9	0.0210
Left hand	174.7	65.2	160.6	47.2	n.s.
Contraction time (msec)					
Right hand	161.3	60.9	131.5	40.8	<0.0001
Left hand	179.2	86.6	144.9	46.2	<0.0001

[a]HIV Dementia Scale score ≤10
[b]HIV Dementia Scale score >10
[c]Unpaired t test
SD = standard deviation; HIV = human immunodeficiency virus

score as well as for HDS psychomotor speed and HDS construction subtests but not for HDS memory and HDS attention.

Finally, we aimed to find which potential confounding factors might interfere with both HDS and psychomotor testing. We, therefore, correlated HDS scores (sum, psychomotor speed, construction) and contraction time and MRAM as dependent variables, with age, premorbid verbal IQ, actual nonverbal IQ, CD4+ cell counts, HawaiiV-1 plasma viral burden, and duration of HIV seropositivity as independent variables. Results are given in Table 4. There was no correlation between both tests and the markers of the immune status. Neither the contraction time nor the MRAM showed significant correlation with duration of HIV seropositivity, and no consistent correlation with premorbid or actual intelligence or age was observed. HIV Dementia Scale scores (both sum score and time dependent subscores) showed a consistent and highly significant correlation to premorbid and actual intelligence and, less markedly, to age and duration of HIV seropositivity.

TABLE 3. Correlation Analyses (Significant p Values Are Given)

Independent and Dependent Variables	p
HIV Dementia Scale (HDS) sum score	
Contraction time right	<0.0001
Contraction time left	0.0004
Most rapid alternating movement (MRAM) right	0.0045
MRAM left	n.s.
HDS memory (recall of four items)	
Contraction time right	n.s.
Contraction time left	0.0268
MRAM right	n.s.
MRAM left	n.s.
HDS Attention (antisaccadic errors)	
Contraction time right	n.s.
Contraction time left	n.s.
MRAM right	n.s.
MRAM left	n.s.
HDS psychomotor speed (timed written alphabet)	
Contraction time right	<0.0001
Contraction time left	<0.0001
MRAM right	0.0073
MRAM left	0.0134
HDS construction (cube copy time)	
Contraction time right	<0.0001
Contraction time left	0.0047
MRAM right	0.0228
MRAM left	0.0205

DISCUSSION

The clinical manifestation of HIV-associated dementia carries a poor prognosis for the individual HIV-positive patient.[4,5,16] However, if detected early in the course of the disease, it may be amenable to antiretroviral therapy.[16–21] Effective screening for and adequate quantification of HIV-associated psychomotor slowing are therefore essential to patients, treating physicians, and researching scientists. The ideal screening tool should not be expensive; it should be universally available (ideally bedside), brief, sensitive and reliable in detecting "subcortical" dementia, and it should allow for the selection of patients for more extensive neuropsychological/electrophysiological testing and clinical trials. The HDS was explicitly designed to fulfill these criteria and

has proved to be a beneficial screening tool.[2] Human immunodeficiency virus associated dementia is considered a subcortical dementia,[22–24] and its neuropathology focuses on the basal ganglia.[23–31] As the basal ganglia play a pivotal role in movement control,[32] the HDS emphasizes motor skills and timed tasks. Psychomotor speed is assessed with the timed, written alphabet and represents the most important subscore (6 out of 16 points). The construction task (cube copy time) is also a timed task and scores the time needed to correctly copy the cube (another 2 points). Timed motor tasks thus account for 50% of the HDS sum score. With this design, the HDS actually screens for psychomotor slowing. Accordingly, we observed highly significant differences between patients scoring >10 and ≤10 in the HDS for both contraction time and MRAM (Table 2). These parameters have been shown to sensitively describe psychomotor slowing in HIV-positive clinically yet unaffected patients.[8] Analysis revealed significant correlations between contraction time and MRAM on one hand and HDS sum score and HDS subscores for psychomotor speed and construction on the other hand (both timed tasks) (Table 3). Memory and attention do not correlate with contraction time or MRAM. In our population, HDS defines approximately 20% of patients as mildly demented or at risk for HIV dementia. This percentage is comparable to the percentage that we observed in a long-term survey,[20] where the prevalence of pathological contraction time ranged between 12% and 16% for the years since introduction of highly active antiretroviral therapy (HAART) in 1996. In the original study population, the HDS score was relatively independent of age and education. In our patients, we found significant differences between patient groups for age, premorbid verbal intelligence quotient (IQ), and actual nonverbal IQ. We also observed significant correlations between the HDS sum score and the subscores for psychomotor speed and construction and for the premorbid verbal and actual nonverbal IQ (Table 4), which were less marked for age and duration of HIV-seropositivity. These correlations reflect the influence of intelligence on a dementia scale. This is obvious for the premorbid verbal intelligence and a subtest evaluating the written alphabet, as it is for the actual nonverbal intelligence and a dementia scale. In the original HDS, the authors stated accordingly, "The HDS may be insensitive to mild HIV dementia in highly educated patients." Thus, a possible interference has not been excluded. In our cohort, electrophysiological motor testing, as quantified by MRAM and contraction time, was almost completely independent of both premorbid and actual intelligence. This finding is in contrast to other studies[33] and probably reflects that this test battery focuses on motor performance. In this study, we show that electrophysiological motor testing is not influenced by premorbid or actual intelligence, and, in earlier studies, we have demonstrated that it is not influenced by intravenous drug use,[34] concomitant depression,[35] or peripheral nerve damage.[36] Compared to the HDS, this test battery is a simple continuous measure that cannot serve as a simple screening tool for reasons of equipment. However, as a more quantitative method, it is useful in monitoring the course of dementia as well as deterioration and response to antiretroviral therapy.[15,17,21] Furthermore, as it is less subject to potentially interfering factors (see above), electrophysiological motor testing is useful in studies on HIV neuropathogenesis, with a special focus on basal ganglia dysfunction[30,31] In fact, electrophysio-

TABLE 4. Correlation Analyses (significant p-values)

	Independent Variable					
Dependent Variable	**Age (years)**	**Premorbid Verbal Intelligence (MWT-b)**	**Actual Nonverbal Intelligence (Raven)**	**CD 4 Cell Count (cells/µl)**	**HIV-1 Plasma Viral Load (log(copies)/ml)**	**Duration of HIV-1 Seropositivity (months)**
HDS sum score	0.0005	< 0.0001	< 0.0001	not significant	not significant	0.0353
HDS psychomotor speed	0.0019	< 0.0001	< 0.0001	not significant	not significant	not significant
HDS construction	not significant	< 0.0001	< 0.0001	not significant	not significant	0.0098
Contraction times right hand (msec)	0.0121	0.0291	not significant	not significant	not significant	not significant
Contraction times left hand (msec)	not significant	not significant	not significant	not significant	not significant	not significant
MRAM right hand (Hz)	not significant	0.0020	0.0045	not significant	not significant	not significant
MRAM left hand (Hz)	not significant	not significant	not significant	not significant	not significant	not significant

HDS = Human Immunodeficiency Dementia Scale; MRAM = most rapid alternating movements

logical motor testing cannot and should not replace a complete neuropsychological assessment that necessarily covers skills in a variety of domains that are involved in HIV dementia. In conclusion, we view the domain of neuropsychological testing in the description of all deficits observed, the domain of the HDS in rapid screening for psychomotor slowing, and the domain of electrophysiological motor testing as a scientific tool to quantify one pivotal deficit in HIV neuropathogenesis: basal ganglia mediated psychomotor slowing.

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