Original Research Report

The Development of a Japanese Version of the HIV Dementia Scale to Detect Cognitive Disorders in Patients with HIV, and Its Sensitivity and Specificity

Naotsugu HIRABAYASHI[1], Takeshi SAKAI[2], Tomoko KISO[3], Asako NOBUTO[4], Yukie YAMASHITA[3], Akihiko ISOMOTO[5], Kenichi KOJIMA[6], Tomoyuki HANAOKA[7], Tomoki KIMURA[1] and Katsuyuki FUKUTAKE[3]

[1] National Center Hospital for Mental, Nervous and Muscular Disorders, NCNP (National Center of Neurology and Psychiatry), [2] Department of Psychology, The Faculty of Social and Humanities, Tokyo Metropolitan University, [3] Department of Clinical Pathology, Tokyo Medical University, [4] Department of Psychology, Graduate School of Humanities, Tokyo Metropolitan University, [5] Department of Neuropsychiatry, Kitasato University Hospital, [6] Department of Hematology, Ogikubo Hospital, [7] Epidemiology and Biostatistics Division, National Cancer Center Research Institute East

Objective: The purpose of this study was to develop a new Japanese neuropsychological test to detect cognitive disorders including ADC in patients with HIV infection.

Materials and Methods: The English version of HIV dementia scale (HDS) was translated into Japanese. The subset of timed written alphabets was changed to the subset of timed written Japanese characters (Hiragana), in the Japanese version of the HIV dementia scale (JHDS). After obtaining their informed consent, JHDS was administered to 32 HIV positive patients and 99 seronegative volunteers as controls. Thiry-nine of the 99 HIV negative volunteers were tested with two instruments, the Minimental State Examination (MMSE) and JHDS. To assess the reproducibility of the JHDS, 20 HIV negative volunteers were retested by a different examiner at 4 weeks after the initial assessment.

Results: JHDS was relatively independent from effects of age, sex, years of education, serostate of HIV infection, and the number of CD4 cell counts. It is easier to evaluate the score of JHDS, compared to other neuropsychological tests that are affected by sociodemographic factors, medical factors, etc. Analysis of variance (ANOVA) revealed a significant relationship between the JHDS score and the presence or absence of ADC ($F=29.17$, $p<0.0001$). The score of JHDS only reflected the severity of ADC and decreased with the progression of the stage of ADC. The score of ≤ 10 was the optimal point of JHDS (the sensitivity and specificity were 1.00 and 0.89 respectively) for diagnosing ADC. The correlation coefficient between the initial scores and the second scores was 0.65 ($p=0.0027$). The reproducibility of JHDS was confirmed. The scores of JHDS were significantly correlated to those of the MMSE (standardized regression coefficient $=0.42$, $p=0.009$).

Conclusion: JHDS was a useful device to detect ADC in patients with HIV infection and the score of JHDS was taken into consideration when diagnosing and evaluating the stage of ADC.

Key words: HIV dementia, AIDS Dementia Complex, Neuropsychological Test, JHDS

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Correspondence: Naotsugu HIRABAYASHI, National Center Hospital for Mental, Nervous and Muscular Disorders, NCNP (National Center of Neurology and Psychiatry), Ogawa-higashi-cho 4–1–1, Kodaira city, Tokyo 187–8551, Japan
Fax: +81–42–346–1705 E-mail: hirabaya@ncnpmusashi.gr.jp

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Introduction

Cognitive impairment in human immunodeficiency virus (HIV) infection shows various neurological manifestations in HIV patients, including impairment of concentration, slowing of psychomotor speed, decline of memory recall, and so forth. These neurological

manifestations are thought to be mainly caused by the disturbance of subcortical lesions, and lesions of the frontal lobe. From 7% to 20% of patients with HIV infection have neuropsychological symptoms[1–3]. However, little attention has been paid to this condition in Japan[4–8]. The prevalence of dementia due to HIV infection in HIV positive patients fell to less than 3.4%[5], when associated with the development of an antiretroviral regimen.

The relationship between employment and neurological impairments in patients with HIV infection was reported[9]. Unemployed males showed lower neuropsychological performance than that of employed ones, co-varying for CD4 count, age, and physical limitations. The presence of cognitive impairments is one of the most important factors to determine the quality of life (QOL) for patients with HIV infection.

In Western countries, the neurological performances were evaluated, using standard instruments, including the Grooved Pegboard Test, the Minimental State Examination (MMSE), and the Executive Interview. In addition to these standard instruments, the HIV Dementia Scale (HDS) was developed and validated as a reliable brief screening device to detect HIV dementia[10]. HDS proved superior to other widely used bedside tests such as the MMSE for identifying

HDS 日本語版(JHDS)

氏名 _____(M, F)　　施行日 _____／

項目	質問	(得点)
0	記銘 「これから4つの単語を言いますので、言ってください」 (犬, 帽子, 緑, リンゴ) →完全に言えるようになるまで繰り返す。	
1	注意 左右の指で練習を行った後、動かす指を左右交互にして、本テストを行う。 回数を数える。 →20回連続して行う。 (　　回)	7以上 (0) 6 (1) 5 (2) 4 (3) 3以下 (4)
2	精神運動速度 「"あ・い・う・え・お"と五十音を順番に言って下さい。」 (言えたら) 「テスト用紙の裏に横書きでひらがなを書いてください。」 (言えなかったら) 「1から26までの数字を順番に言って下さい。」 (言えたら) 「横書きで順番にテスト用紙の裏に書いて下さい。」 (言えなかったら) そこでこの項目は終了する。 あ・い・う・え・お　か・き・く・け・こ さ・し・す・せ・そ　た・ち・つ・て・と な・に・ぬ・ね・の　は・ひ・ふ・へ・ほ ま・み・む・め・も　や・い・ゆ・え・よ ら・り・る・れ・ろ　わ・い・う・え・を ん 1・2・3・4・5・6・7・8・9・10 11・12・13・14・15 16・17・18・19・20 21・22・23・24・25・26 →時間を計ること。 (　　秒)	36.1秒以上 (0) 33.1秒-36秒 (1) 30.1秒-33秒 (2) 27.1秒-30秒 (3) 24.1秒-27秒 (4) 21.1秒-24秒 (5) 21秒以下 (6)
3	再生 「最初に言っていただいた言葉を思い出して言って下さい。」 →言えなかった場合はヒントを出すこと。 a. 犬→動物です b. 帽子→身につけるものです c. 緑→色です d. リンゴ→果物です	a (1)→(0.5) b (1)→(0.5) c (1)→(0.5) d (1)→(0.5)
4	構成 「これから図形を見せますので、できるだけ早く正確に書いてください。」 →時間を計ること。 (　　秒)	35.1秒以上 (0) 25.1秒-35秒 (1) 25秒以下 (2)

合計得点:____／16

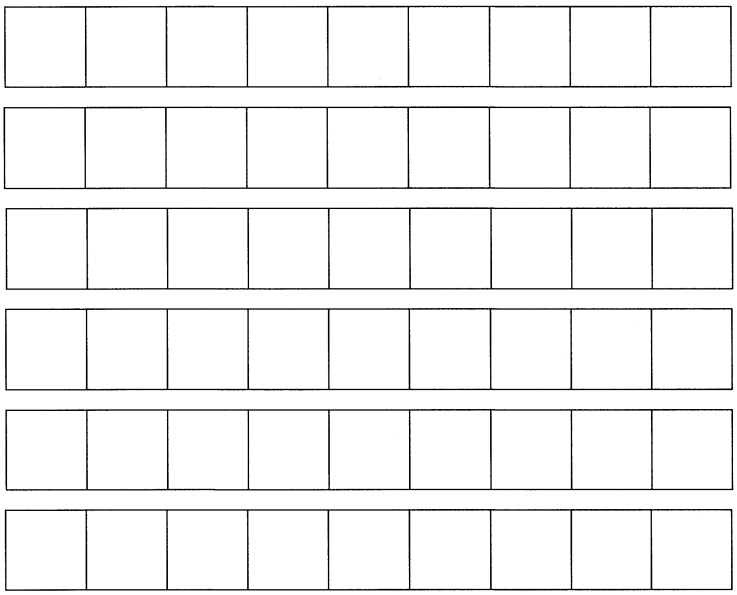
Figure 1

HIV dementia. It takes approximately 10 minutes to administer, and the practice of HDS is easier for health care providers. The effect of highly active antiretroviral therapy (HAART) on HIV-1 associated neurocognitive impairment was surveyed, using these neuropsychological tests. However, health care providers in Japan had little concern about cognitive impairments. No neurological test was developed to evaluate the extent of cognitive impairments due to HIV infection in Japan. It is necessary to develop a new neuropsychological test to detect HIV dementia and evaluate its severity. The purpose of this study was to develop such a new neuropsychological test in Japanese and confirm its reproducibility and validity, and to decide the optimal cut off point to detect ADC.

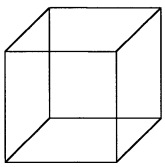
Method and Subjects

The HIV dementia scale was developed by C. Power, and his colleagues, and was used in clinical settings in the USA in order to detect HIV dementia[10]. HDS has the four subsets, including timed written alphabet, recall of four items at 5 min, cub copy time, and anti-saccadic errors. These four assignments are able to evalutate psychomotor speed, memory registration and

2.



4.



recall, construction, and attention. We translated it into Japanes (Figure 1). In the original English version of HDS, psychomotor speed was evaluated through measuring the time to write the 26 letters of the alphabet. The 26 Japanese letters (Hiragana) from "a" to "ha" were used instead of the 26 alphabet letters in the Japanese version of the HIV dementia scale (JHDS). The total score was figured by the sum of four subsets scores and a total JHDS score out of 16 was calculated for each subject.

Thirty-eight HIV positive patients without cognitive disorders due to opportunistic infection sequentially confirmed at three general hospitals in Tokyo and Kanagawa from June 2000 to December 2000, and were encouraged to participate in this study by their physicians. Thirty-two patients voluntarily participated and were examined for their mental state by psychiatrists or psyclologists, using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Six patients were excluded from the analysis because of active psychiatric disorders other than ADC. Thirty-two HIV positive patients remained. Ninety-nine seronegative volunteers were recruited among students in the graduate course of the university and workers in Tokyo and Kanagawa.

The design of this study was explained in writing and informed consents were obtained orally or in written form.

After obtaining their informed consents, JHDS was administered to 32 HIV positive patients and 99 seronegative volunteers as controls. The immunological examination associated with HIV infection was not administered to the 99 controls. Thus, there was a slight possibility that an HIV positive person was included as a control in Japan. Thirty-nine of 99 seronegative volunteers were tested with two instruments, including the MMSE and JHDS. The MMSE was administered after the JHDS. To assess the reproducibility of the JHDS, 20 seronegative volunteers were retested by a different examiner at 4 weeks after the initial assessment.

HIV dementia was called AIDS dementia complex (ADC). ADC was diagnosed in subjects, using the diagnostic criteria of ADC of the American Academy of Neurology AIDS task force[11]. The stage of ADC was decided at the same time, using the Memorial Sloan-Kettering (MSK) classification[12].

The demographic characteristics of the subjects, including gender, age, years of education, occupation, and medical factors such as history of mental disorders, medication of psychotropics, and CD4 cell count were surveyed.

Student's t-test was used to explore the differences in age and years of education between the HIV positive group and the control group. Chi-square test was used to examine the difference in the percentage by gender and employment. Correlation coefficients were calculated identify the relationship between the scores of JHDS, and age, years of education and CD4 cell count. Analysis of variance (ANOVA) was used to examine differences in JHDS score according to two variables, the educational background and the presence of ADC. A p value less than .05 was considered statistically significant. The statistical evaluation was performed using Stat View version 5.0J (SAS Institute Inc., Cary, NC).

The sensitivity and specificity for ADC were calculated and the optimal cut off point of ADC in JHDS was decided to detect ADC.

Results

The demographic characteristics of HIV positive patients and controls are shown in Table 1. There was no significant difference in age and percentage of unemployed people. However, HIV positive patients included significantly more females (88%) than did the controls (51%). There was a significant difference in years of education between the HIV positive patients and controls. Seven of 32 HIV positive patients had ADC. The immune function of HIV positive patients was evaluated, measuring the level of CD4 cell count in their peripheral blood and the results are shown in Table 2. The mean of CD4 cell counts was 396±207/μl.

Table 1 Sociodemographic characteristics.

	HIV positive (n=32)	Controls (n=99)	
% female	88	51	$p<0.0002$
Age	33±11	33±9	$p=0.96$
Years of education	14±3	16±3	$p<0.0001$
% unemployed	25	16	$p=0.1952$
AIDS dementia complex	7	0	

The relationship between the JHDS scores, and sociodemographic characteristics and medical factors is shown in Table 3 and Table 4. Simple correlation analysis revealed no significant relationship between the JHDS scores and age or CD4 cell counts. However, the JHDS scores were significantly related to years of education (Table 3). There was no significant difference in the JHDS score according to gender, occupation or HIV infection. The mean score of the JHDS in patients with ADC was significantly lower than those in patients without ADC (Table 4). These results suggested that the JHDS score could be related to the years of education and ADC. When the JHDS score was considered as dependent variable, and years of education (0: 12 yrs or less than 12, 1: 16 yrs or less than 16, 2: more than 16 yrs) and the presence or absence of ADC (0: absence, 1: presence) were considered as independent variables, ANOVA showed a significant difference in the JHDS score according to the presence of ADC ($p<0.0001$), although no difference

Table 2 CD4 cell count of HIV positive patients (n=32).

	n	(%)
$<100/\mu l$	5	(15.6)
<200	19	(59.4)
<500	8	(25.0)

Table 3 The correlation between JHDS scores and, sociodemographic characteristics and CD4 cell counts.

	Correlation coefficients	
Age	−0.15	p=0.093
Years of education	0.35	p<0.0001
CD4 cell count	0.11	p=0.55

Table 4 The relationship between JHDS score and other variables.

		mean	difference of means	(95% confidence interval)
Gender	male	14.1±1.9	−0.82	(−1.7～ 0.05)
	female	13.3±2.9		
Occupation	employed	13.8±3.5	−0.03	(−1.2～ 1.2)
	unemployed	13.7±2.4		
Infection	positive	11.8±3.7	−0.60	(−1.9～ 0.7)
	negative	12.4±3.1		
ADC	presence	7.7±1.8	−6.02	(−7.9～−4.2)
	absence	13.7±2.4		

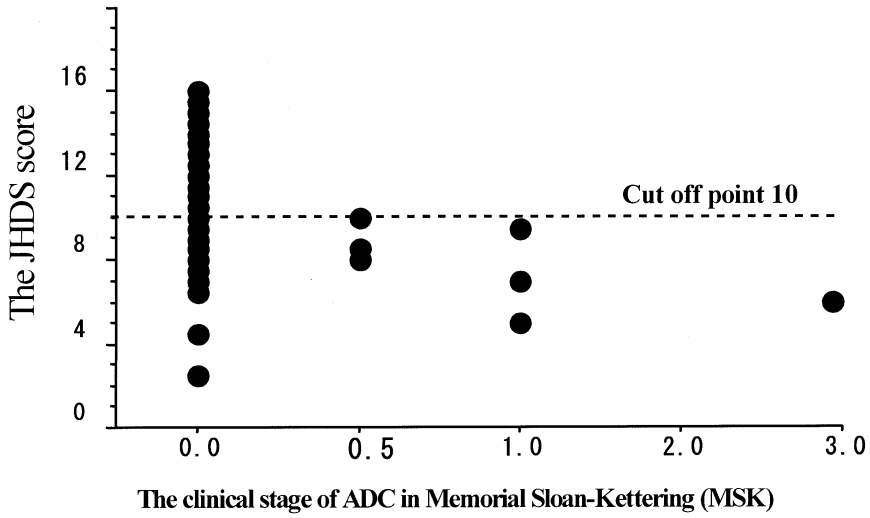


Figure 2 The classification of clinical stage of ADC and the JHDS scores.

Table 5 Screening test's ability to detect ADC.

Cut-off point	8	9	10	11
Sensitivity	0.57	0.71	1.00	1.00
Specificity	0.97	0.96	0.89	0.83
Positive predictive value	0.50	0.50	0.33	0.25
Negative predictive value	0.98	0.98	1.00	1.00

according to years of education was observed ($P=0.54$).

The relationship between the stage of ADC in MSK and the JHDS scores is shown in Figure 2. The JHDS scores decreased when associated with the progress of the stage of ADC. Six patients with ADC and one patient suspected of ADC had less than 10 points in the JHDS score.

Both JHDS and the MMSE were administered to 39 controls in order to identify the relationship between these two instruments. The scores of JHDS were significantly correlated to those of the MMSE (correlation coefficient $=0.42$, $p=0.009$).

JHDS was repeatedly administered in 20 controls at four weeks after the initial testing. The mean score of the initial performance and the socre of retesting were 14.4 ± 3.6 and 15.2 ± 1.1, respectively. The difference of mean scores was -0.34 (95% confidential interval: $-0.71\sim0.03$). There was no significant difference between the mean score in the initial performance of JHDS and that of the retesting. Correlation coefficient between the initial scores and the second scores was 0.69 ($p<0.0001$).

If the score of ≤9 was set as the cut off point of diagnosing the ADC, the sensitivity and specificity were 0.71 and 0.96, respectively. If the score of ≤10, the sensitivity and specificity were 1.0 and 0.89, respectively (Table 5).

Discussion

The authors developed a new device to detect cognitive disorders in patients with HIV infection, based on the English version of HDS. Such a type of neuropsychological test is necessary for the routine clinical practice to detect cognitive disorders. If cognitive disorders are suspected on JHDS, further examinations are necessary and the choice of effective antiretroviral agents against neuropsychological manifestations could be possible. Some investigators reported that HAART was effective in HIV-associated neurocognitive disorders[13–15]. These reports indicated the necessity and efficiency of development of neuropsychological tests to detect neuropsychological deficits. These tests should be easier for healthy care professionals.

Fortunately, the number of HIV positive patients in Japan is lower than that of most other countries[16]. This study had the limitation of the number of subjects. However, our results proved the effectness of JHDS in detecting ADC. Its validity and reproducibility were confirmed in this study.

JHDS was relatively independent from the effect of age, sex, years of education, the presence or abscence of HIV infection, and the number of CD4 cell count. It is easier to evaluate the score of JHDS, compared to other neuropsychological tests that are affected by sociodemographic factors, medical factors, and so forth. The score of JHDS only reflected the presence of ADC. This is a great advantage when administered to patients with various sociodemographic backgrounds. In addition to this advantage, it takes 10 minutes to administer JHDS. Generally speaking, JHDS does not place an unbearable burden on patients.

The mean age of subjects of this study was 32 ± 10 years old (from 27 to 71). Excluding one subject 71 years old, the range of age was from 27 to 58 years old. This study did not include enough subjects with 65 or more years of age to evaluate the effect of intellectual decline caused by physiological aging. Today, most patients with HIV infection are less than 65 years old in Japan. In clinical settings, JHDS would not be frequently administered to patients 65 or older. However, if JHDS were administered to older patients, we should pay special attention to the decline of intellectual ability caused by physiological aging.

The relationship between the clinical stage of ADC in MSK and the scores of JHDS is shown in Figure 2. It showed that as the clinical stage of ADC advanced, the socres of the JHDS gradually decreased. We tried to decide the optimal point of JHDS for diagnosing ADC. The sensitivity (i.e., the proportion of demented patients who were correctly identified by analysis of the scores of JHDS) on cut off points from 8 to 10, specificity (i.e., the proportion of patients whithout dementia correctly identified by the scores of JHDS), positive predictive value (PPV; i.e., the proportion of patients with impaired test performance correctly diagnosed), and negative predictive value (NPV; i.e., the proportion of patients with normal test performance correctly diagnosed)[17] are shown in Table 5. The dotted line in Figure 2 shows the score 10 points. The original English version of HDS recommended the score of 10 as the cut-off score to detect impaired performance. This cut-off point maximized the sum of sensitivity and specificity[10]. If the score of ≤10 was set as cut-off point of ADC, 6 patients who were clinically diagnosed with ADC and one patient who was clinically suspected of ADC, using the clinical stage of

ADC in MSK, were regarded as exhibiting dementia in JHDS. The sensitivity of JHDS for ADC was 1.0. One hundred twenty-four of 131 subjects were not demented and were classified under stage 0 in MSK. One hundred ten of them showed scores of more than 10 in JHDS, and those were not regarded as demented. Therefore, the specificity of JHDS for ADC was 0.89. The neuropsychological tests used as a screening device for ADC should have high enough sensitivity to detect ADC. Taking this most important function of JHDS into consideration, the score of ≤ 10 was the optimal cut-off point.

As mentioned above, this study has the limitation of a low number of subjects, especially patients with ADC and older patients. Further study is necessary to identify more precise cut-off scores.

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