Cognitive Loss in Dementia With Lewy Bodies and Alzheimer Disease

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Background: Dementia with Lewy bodies (DLB) is emerging as a common cause of degenerative dementia. Some preliminary evidence exists that the pattern of cognitive impairment in DLB is different from that in Alzheimer disease (AD).

Objective: To delineate features of cognitive impairment of DLB on standardized neuropsychological tests.

Methods: We performed neuropsychological assessments of 26 patients with probable DLB (based on criteria of the consortium on DLB international workshop) and of 52 patients with probable AD (based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke [now the National Institute of Neurological Disorders and Stroke]–Alzheimer’s Disease and Related Disorders Association) who were matched to the patients with DLB 2:1 by age, sex, education, and Mini-Mental State Examination score.

Results: Compared with the group with probable AD, the group with probable DLB scored significantly lower on the picture arrangement, block design, object assembly, and digit symbol substitution subtests of the Wechsler Adult Intelligence Scale–Revised and on the Raven Colored Progressive Matrices test and significantly higher on the Mini-Mental State Examination locational orientation subtest and the Alzheimer’s Disease Assessment Scale word recall subtest. A discriminant analysis revealed that the word recall score on the Alzheimer’s Disease Assessment Scale and the block design score on the Wechsler Adult Intelligence Scale–Revised were the best discriminant factors.

Conclusions: The disproportionately severe visuoconstructive, visuospatial dysfunc-

tion and the disproportionately mild memory impairment in DLB compared with AD, which likely reflect the distribution of the pathologic changes in DLB, can help to differentiate DLB from AD.

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DEGENERATIVE dementia characterized by the presence of Lewy bodies in cortical and brainstem structures has been variously referred to as “diffuse Lewy body disease,”1,2 “senile dementia of the Lewy body type,”3 or “the Lewy body variant of Alzheimer disease [AD].”4 In 1996, an international workshop5 recommended “dementia with Lewy bodies [DLB].” This disorder is increasingly being recognized as a common cause of dementia in elderly people and is probably the second most common type after AD in postmortem studies.5 Clinically, DLB is characterized by progressive dementia and often occurs with a fluctuating course, extrapyramidal signs, hallucinations, and increased sensitivity to neuroleptic drugs.3

When the initial presentation of DLB is impaired cognition, DLB is difficult to differentiate from AD at the onset of the illness.4 Histopathological features of AD, usually coexisting with Lewy bodies probably contribute to the symptoms associated with DLB, likely making the clinical differentiation between DLB and AD difficult. Retrospective studies of a limited number of patients whose diagnoses have been pathologically verified have indicated that the pattern of cognitive impairment in DLB is different from that in AD.4,7-9 Preliminary studies of patients clinically diagnosed as having DLB also have suggested a possible usefulness of cognitive assessment in differentiating the 2 diseases.10-12 However, studies based on a large number of patients and comprehensive neuropsychological assessments are lacking. In the present study, to delineate distinctive features of cognitive impairment between DLB and AD, we assessed the performance of patients with probable DLB and those with probable AD on standardized neuropsychological tests.

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SUBJECTS AND METHODS

SUBJECTS

Patients with probable DLB or AD were recruited from those who were admitted from July 1, 1993, to April 30, 1997, to the infirmary of the Hyogo Institute for Aging Brain and Cognitive Disorders, Himeji, Japan, a research-oriented hospital for dementia, for investigation. All patients were examined comprehensively by both neurologists and psychiatrists and were given standard neuropsychological examinations, routine laboratory tests, electroencephalography, cranial magnetic resonance imaging, and nuclear neuroimaging studies. Staff physicians closely monitored the fluctuation of cognitive functions during 1-month hospital stays in terms of Mini-Mental State Examination (MMSE) performance, activities of daily living, and episodic confusion. The clinical and investigative data that were collected prospectively in a standardized manner were entered into the institute’s dementia registry. The whole procedure followed the Clinical Study Guidelines of the Ethics Committee of the institute and was approved by the Internal Review Board in 1993. Informed written consent was obtained from the subjects and their relatives.

Patients With Probable DLB

The group with probable DLB comprised 26 patients. The inclusion criteria for DLB were the clinical criteria of the consortium on DLB international workshop,5 the absence of any evidence of focal brain lesions on magnetic resonance imaging. Those who fulfilled the criteria for possible DLB of the consortium criteria for DLB international workshop5 (the presence of a cluster of key symptoms (Table 2: the presence of any complication of other neurologic diseases, and the absence of any evidence of focal brain lesions on magnetic resonance imaging. The consortium criteria for DLB include 3 core features—fluctuating cognitive functions, recurrent visual hallucinations, and spontaneous parkinsonism—and 2 of them are necessary for a diagnosis of probable DLB. The mean ± SD age was 73.6 ± 3.1 years for the 16 women and 10 men. The mean ± SD educational attainment was 8.9 ± 2.0 years, and the mean ± SD score (the best performance in repeated measures) of the MMSE13 was 16.4 ± 4.0. Nine patients with probable DLB had fluctuating cognition and visual hallucinations, 7 had fluctuating cognition and parkinsonism, 4 had visual hallucinations and parkinsonism, and 6 had all 3 features. These 4 subgroups of patients with probable DLB did not differ significantly in age, sex, years of education, MMSE score, or duration of illness (Table 1).

Patients With Probable AD

The group with probable AD comprised 52 patients. Patients were sampled from the same cohort as those with probable DLB and were matched to the patients with probable DLB 2:1 on the basis of age, sex, years of education, and MMSE score. The inclusion criteria for AD were those of the National Institute of Neurological and Communicative Disorders and Stroke (now the National Institute of Neurological Disorders and Stroke)—Alzheimer’s Disease and Related Disorders Association for probable AD,14 the absence of any complication of other neurologic diseases, and the absence of any evidence of focal brain lesions on magnetic resonance imaging. Those who fulfilled the criteria for possible DLB of the consortium on DLB international workshop5 (the presence of only 1 of the triad) were not included. The mean ± SD age was 73.7 ± 5.1 years for the 32 women and 20 men. The mean ± SD educational attainment was 9.2 ± 2.1 years, and the mean ± SD MMSE score was 16.5 ± 4.0. Whereas the ADAS construction score; WAIS-R picture arrangement, block design, object assembly, and digit symbol substitution subscale scores; and the Raven Colored Progressive Matrices score were significantly worse in the group with probable DLB than in the group with probable AD. As a result, the performance IQ was lower in the group with probable DLB than in the group with probable AD (62.5 ± 9.1 vs 72.0 ± 13.0; P < .001). No differences were found between the groups in the MMSE temporal orientation score or the ADAS word recognition score. Furthermore, there were no differences in the WAIS-R information, digit span, vocabulary, arithmetic, comprehension, similarities, or picture completion scores or in the verbal IQ (73.0 ± 9.2 vs 75.6 ± 9.4; P = .25).

There were significant differences between the 2 groups (partial r squared = 0.22, F1,75 = 21.53; P < .001) and the ADAS word recall (partial r squared = 0.12, F1,75 = 10.59; P = .002). The discriminant analysis was performed as follows: classification score for DLB = 1.858 × word recall + 0.150 × block design − 4.710; and the classification score for AD = 1.188 × word recall + 0.644 × block design − 3.900. This model correctly predicted 53.8% cases of probable DLB and 88.5% cases of probable AD. The Figure illustrates

RESULTS

The duration of dementing illness was significantly shorter in the group with probable DLB than in the group with probable AD (t135 = 2.83; P = .006); the duration after the onset of cognitive impairments was 26.6 ± 23.9 months in the group with probable DLB and 42.1 ± 24.5 months in the group with probable AD. There was no significant difference in the ADAS scores between the 2 groups (t135 = 0.62; P = .54); the ADAS total score was 26.4 ± 9.4 in the group with probable DLB and 27.9 ± 11.1 in the group with probable AD. The global severity of dementia as demonstrated by the Clinical Dementia Rating Scale was comparable between the 2 groups (U150 = 636; P = .68); the Clinical Dementia Rating Scale scores of 0.5, 1, 2, and 3 were obtained by 0, 16, 7, and 3 patients, respectively, in the group with probable DLB and by 6, 24, 19, and 3 patients, respectively, in the group with probable AD.

There was no significant difference in neuropsychological test scores among subgroups of probable DLB defined by the presence of a cluster of key symptoms (Table 1). The results of each neuropsychological assessment in the groups with probable DLB and AD are presented in Table 2. The MMSE locational orientation score and the ADAS word recall score were significantly better in the group with probable DLB than in that with probable AD, whereas the ADAS construction score; WAIS-R picture arrangement, block design, object assembly, and digit symbol substitution subscale scores; and the Raven Colored Progressive Matrices score were significantly worse in the group with probable DLB than in the group with probable AD. As a result, the performance IQ was lower in the group with probable DLB than in the group with probable AD (62.5 ± 9.1 vs 72.0 ± 13.0; P < .001). No differences were found between the groups in the MMSE temporal orientation score or the ADAS word recognition score. Furthermore, there were no differences in the WAIS-R information, digit span, vocabulary, arithmetic, comprehension, similarities, or picture completion scores or in the verbal IQ (73.0 ± 9.2 vs 75.6 ± 9.4; P = .25).

Those variables that were found to be significantly different between the 2 groups were entered into a stepwise discriminant procedure. Two variables retained significant F values: the WAIS-R block design (partial r squared = 0.22, F1,75 = 21.53; P < .001) and the ADAS word recall (partial r squared = 0.12, F1,75 = 10.59; P = .002). The discriminant analysis was performed as follows: classification score for DLB = 1.858 × word recall + 0.150 × block design − 4.710; and the classification score for AD = 1.188 × word recall + 0.644 × block design − 3.900. This model correctly predicted 53.8% cases of probable DLB and 88.5% cases of probable AD. The Figure illustrates...
METHODS

Duration and Global Severity of Dementia

The “onset of dementia” was defined as the moment of the nearest caregiver’s awareness of the patient’s cognitive abnormality. The “duration of dementia” was the interval from the onset to the assessment and was expressed in months. Global severity of dementia was assessed with the Clinical Dementia Rating Scale. In this scale, functional severity of dementia is graded into 5 classes as 0 (none), 0.5 (very mild), 1 (mild), 2 (moderate), and 3 (severe).

Neuropsychological Assessments

Cognitive functions were assessed with standard neuropsychological tests, including Alzheimer’s Disease Assessment Scale-cognitive part (ADAS), Raven Colored Progressive Matrices, and the Wechsler Adult Intelligence Scale–Revised (WAIS-R). The assessments were performed while the subject was free from neuroleptic and neuromotoric agents and not in a state of confusion or with active hallucinations.

Orientation was assessed by using the temporal and locational orientation subtests of the MMSE. The former includes 5 questions about time (month, date, year, season, and time of day), and the latter includes 5 questions about location (prefecture, city, name of hospital, floor, and number of rooms in the hospital). Verbal memory was assessed by using the ADAS recall and recognition subtests. The ADAS word recall subtest is equivalent to a verbal learning test, in which the retention of a list of 10 written words was measured by free immediate recall after each of 3 learning trials. The score is expressed as the mean number of words recalled in 3 trials. In the ADAS word recognition subtest, the subject was asked to read aloud 12 written high-imagery words and then to select the target words among 24 words randomly mixed with 12 irrelevant words. The score is expressed as the mean number of correct responses on 3 repeated trials. The ADAS construction subtest score (number of correct responses) was also analyzed as an untimed drawing task. The ADAS total score was analyzed as another index of severity of dementia by overall cognitive impairment.

Statistical Analysis

Statistical analyses were carried out with commercially available software (SAS Version 6.10, SAS Institute, Inc, Cary, NC). Group differences were analyzed by using the 2-tailed Student t test, the 2-tailed Mann-Whitney U test, or an analysis of variance as appropriate, with significance set at \( P < .05 \). No correction for multiple comparisons was carried out because of the exploratory nature of the study. To identify the neuropsychological tests most likely to distinguish probable DLB from probable AD, a stepwise discriminant-function analysis was used, with significance set at \( P < .01 \). Data are expressed as means ± SDs.

the relation between the ADAS word recall and WAIS-R block design scores for probable DLB and AD.

COMMENT

In the present study, the patients with probable DLB and those with probable AD were comparable in the global severity of dementia and the global assessment of cognitive impairment. Nevertheless, the patients with probable DLB had a significantly shorter duration of illness; scored better on the verbal memory subtest of the ADAS; and performed worse on several tests of visuo- perceptual, visuocostructive, and visuospatial functions than the patients with probable AD. Psychomotor slowing accompanying by parkinsonism is unlikely to explain the low performance in visuo- perceptual, visuo- constructive, and visuospatial tests in the patients with probable DLB because they performed worse even on the timed measures, such as the ADAS construction subtest and the Raven Colored Progressive Matrices. No significant difference was noted among the subgroups of probable DLB with each combination of key symptoms, although this is inconclusive because of the small sample size of each subgroup. A discriminant analysis revealed that the ADAS word recall and WAIS-R block design scores were the best discriminant factors. The preferentially affected domains of cognitive function may differ between the 2 diseases.

These findings are consistent with the previous retrospective studies of a limited number of patients with proven disease. Comparing neuropsychological test results among patients with the pathologically proven Lewy body variant of AD, diffuse Lewy body disease, and AD, Galasko et al demonstrated that patients with the Lewy body variant of AD had significantly greater impairment on tests of visuospatial and visuoconstructive abilities. Hansen et al, comparing neuropsychological performance of 9 patients with the Lewy body variant of AD (Lewy body with concomitant AD) and 9 patients with definite AD matched for age, years of education, and overall severity of dementia, suggested that patients with the Lewy body variant displayed disproportionately severe deficits in attention, fluency, and visuospatial processing. In the study by McKeith et al where 21 patients with pathologically verified senile dementia of the Lewy body type and 37 patients with definite AD were examined, performance on the recall subtest of the Blessed Mental Test was better in the patients with senile dementia of the Lewy body type than in the patients with AD. Salmon et al, comparing the neuropsychological deficits of 5 patients with neuropathologically confirmed diffuse Lewy body...
disease with those of 5 patients with neuropathologically confirmed pure AD matched by dementia severity, found a poor visuoconstructive function and relatively preserved memory function in patients with diffuse Lewy body disease.

Poor visuospatial and relatively good memory performances on the Cambridge Cognitive Examination in patients with DLB have been demonstrated also in a prospective study, where 17 patients with probable DLB (satisfying the 1992 McKeith clinical criteria for senile dementia of Lewy body).
The visuoperceptual, visuoconstructive, and visuospatial dysfunctions are disproportionately severe and the verbal memory function is disproportionately mild in patients with probable DLB compared with those with probable AD. These features, which are compatible with neuropathological and neuroimaging findings in DLB, likely reflect the distribution of the pathologic changes in DLB. Neuropsychological assessments may help in differentiating DLB from AD.

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REFERENCES

3. Perry RH, Irving D, Blessed G, Fairbairn A, Perry EK. Senile dementia of Lewy body type and the 1989 Byrne clinical criteria for diffuse Lewy body disease), pointed out the usefulness of the clock-face test, which assesses executive and visuospatial functioning, in differentiating DLB from AD. Patients with AD do well on the “copy” part of the test despite doing poorly on the “draw” part, whereas patients with DLB do equally poorly on both parts of the test. Although it has been claimed that the specificity of this test is not as high as originally reported, the findings of Gnanalingham et al suggested that visuoconstructive ability is more impaired in DLB than in AD.

The distinctive features of neuropsychological impairment between the 2 diseases probably represent the different distributions of pathologic changes. The visuoperceptual, visuoconstructive, and visuospatial dysfunction in probable DLB can be attributed to accentuated damage in the occipital and parietotemporal lobes. Albin et al demonstrated that regional glucose metabolism was decreased in the occipital association cortex and primary visual area in 6 patients with autopsy-proven DLB. In a recent study, using fluoroxyglucose F 18 and positron emission tomography, the glucose metabolic rate in the temporoparieto-occipital association cortices was significantly lower in patients with probable DLB (n = 19) than in controls with probable AD matched by age, sex, disease duration, and MMSE scores. Occipital glucose hypometabolism has been reported in patients with Parkinson disease and dementia. The activity of a cholinergic enzyme—choline acetyltransferase—is reportedly lower in the tempo-


