Ⅱ．研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
Urakami k, Arai H, et al.	Cerebrospinal fluid phosphorylated tau protein at serine 199 is a useful diagnostic biomarker in Alzheimer's disease and mild cognitive impairment	Hanin I, Cacabelos R, Fisher A	Recent Progress in Alzheimer's and Parkinson's Diseases	Taylor & Francis	London &N. Y.	2005	177-182
Urakami K, Taniguchi M, et al.	Studies on diagnostic markers for Alzheimer's disease	Takeda M	Psychogeriatriecs	Blackwell	Australia	2005	99-102

雑誌

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ONISHI J, SUZUKI U, UMEGAKI H, ENDO H, KAWAMURA T, IMAIZUMI M, IGUCHI A	Behavioral, psychological and physical symptoms in group homes for older adults with dementia.	Int Psychogeriatr.			In press
Joji Onishi, Yusuke Suzuki, Hiroyuki Umegaki, Hidetoshi Endo, Takashi Kawamura, Akihisa Iguchi.	A comparison of depressive mood of older adults in a community, nursing homes, and a geriatric hospital: factor analysis of geriatric depression scale.	J Geriatr Psychiatry Neurol.	19(1)	26-31	2006
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Ⅲ. 研究成果の刊行物・別刷

Chapter 23

Cerebrospinal fluid phosphorylated tau protein at serine 199 is a useful diagnostic biomarker in Alzheimer's disease and mild cognitive impairment

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INTRODUCTION

Our recent studies of biological markers in Alzheimer's disease (AD) have focused specifically on analysis of cerebrospinal fluid (CSF) tau protein levels and amyloid β-protein ending at amino acid 42.[1–4] Although CSF total tau (t-tau) level in AD was significantly higher than in controls, there were overlaps between AD and non-AD dementias.[1–3] One possible explanation is that the enzyme-linked immunosorbent assay (ELISA) kit we used detects not only phosphorylated but also normal tau. Therefore, we developed the sandwich ELISA system for phosphorylated tau at serine 199 (p-tau 199) in CSF[5] and examined 236 cases with AD, 206 cases with non-AD demented and non-demented disease controls, and 95 age-matched normal controls.[6]

SUBJECTS AND METHODS

Table 23.1 shows a summary of the patients' demographic data. We surveyed a total of 537 CSF samples. We also examined CSF p-tau 199

Table 23.1 Summary of patients' demographic data

	No. of patients	*Age* (years)	*Gender* (M/F)
Alzheimer's disease (AD)	235*	71 ± 9	66/172
Normal control	95	57 ± 16	51/44
Neurological disease control	122	59 ± 13	70/52
Frontotemporal dementia (FTD)	16*	63 ± 12	9/7
Progressive supranuclear palsy	21	63 ± 7	10/11
Corticobasal degeneration	15	64 ± 4	8/7
Dementia with Lewy body (DLB)	13*	63 ± 10	8/5
Vascular dementia	23	71 ± 6	16/7
Meningoencephalitis	18	51 ± 21	7/11
Creutzfeldt–Jakob disease (CJD)	11*	71 ± 6	6/5

* Two patients with AD, one patient with FTD, one patient with DLB and four patients with CJD were confirmed by autopsy

levels in a population with mild cognitive impairment (MCI). The MCI group was later subdivided into two different categories. One category was that which eventually later progressed to AD (progressive MCI). The other category was that which later did not progress to AD (non-progressive MCI). Memory complainers were patients who complained about memory disturbance, but were not demented. These constituted the control group. CSF samples were taken into polypropylene tubes by lumbar puncture after informed consent was obtained from each patient and/or family members. Bloody or traumatic CSF samples were excluded from this study. After centrifugation at 1500 rpm for 10 min, the aliquots were stored at −80°C until analysis. CSF levels of p-tau 199 were measured by a sensitive sandwich ELISA.[5,6] CSF level of t-tau protein was measured using the sandwich ELISA assay provided by the Innogenetics Company, Belgium.[7]

RESULTS

CSF p-tau 199 levels in the AD group were significantly elevated ($p < 0.001$) compared to those in all the other non-AD groups, including patients with acute neurological conditions such as meningoencephalitis and Creutzfeldt–Jakob disease (CJD) (Figure 23.1). On the other hand, CSF t-tau levels were occasionally very high in the meningoencephalitis and CJD groups,

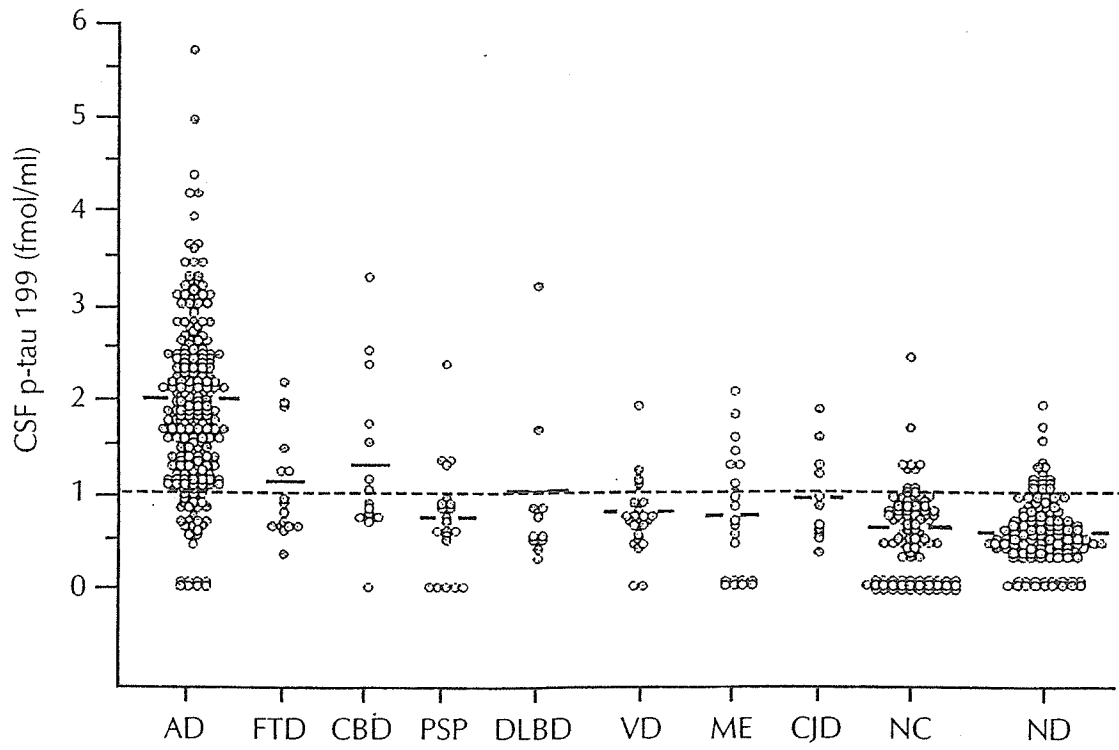

Figure 23.1 The results of cerebrospinal fluid (CSF) phosphorylated tau at serine 199 (p-tau 199) levels, among groups with Alzheimer's disease (AD), frontotemporal dementia (FTD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), dementia with Lewy body disease (DLBD), vascular dementia (VD), meningoencephalitis (ME), Creutzfeldt–Jakob disease (CJD), normal controls (NC) and neurological disease controls (ND)

although most CSF t-tau levels were significantly increased in the AD group compared to normal control groups (Figure 23.2).

A receiver operating characteristics (ROC) curve analysis demonstrated that CSF p-tau 199 was more amenable than CSF t-tau to differentiating between AD and non-AD subjects (Table 23.2).

The results of CSF p-tau 199 levels in the progressive MCI group were significantly

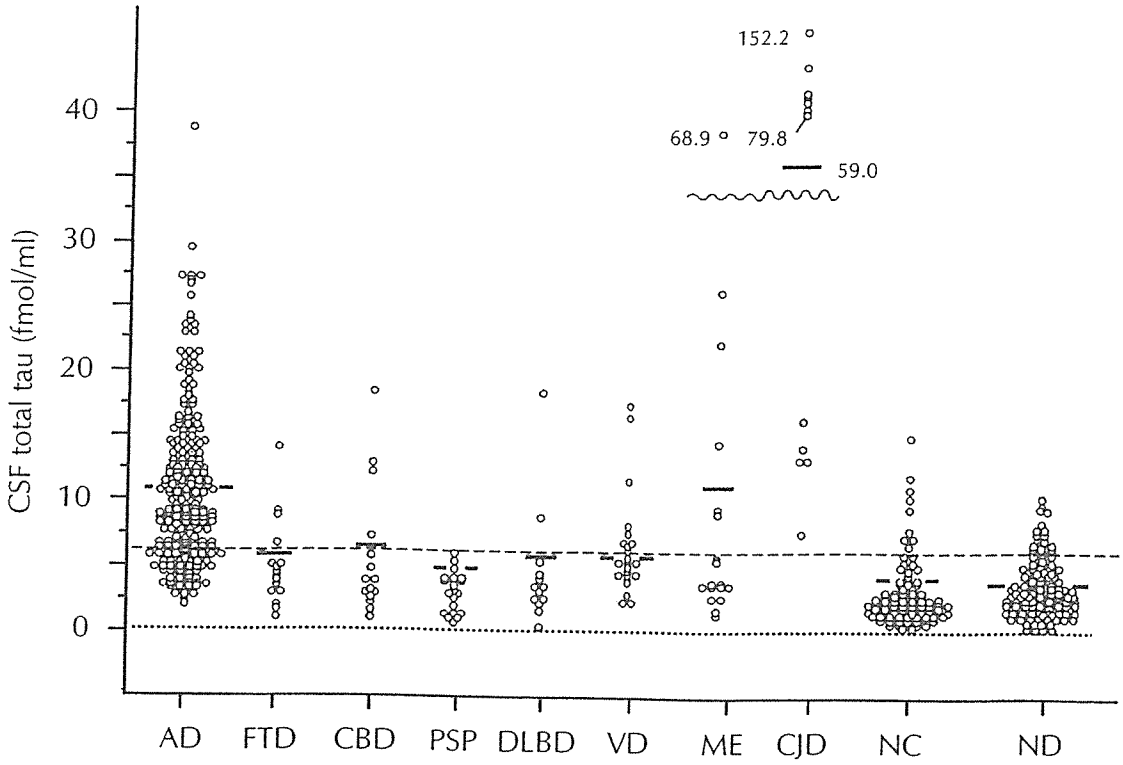

Figure 23.2 The results of cerebrospinal fluid (CSF) total tau levels, among groups with Alzheimer's disease (AD), frontotemporal dementia (FTD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), dementia with Lewy body disease (DLBD), vascular dementia (VD), meningoencephalitis (ME), Creutzfeldt–Jakob disease (CJD), normal controls (NC) and neurological disease controls (ND)

Table 23.2 Receiver operating curve analysis

	Cut-off level (fmol/ml)	*Sensitivity* (%)	*Specificity* (%)
Alzheimer's disease vs. neurological disease controls and normal controls			
Total tau	4.8	82.7	82.0
p-tau 199	0.96	87.3	87.4
Alzheimer's disease vs. others			
Total tau	6.0	77.1	77.6
p-tau 199	1.05	85.2	85.0

p-tau 199, phosphorylated tau at serine 199

elevated ($p < 0.001$) compared to those in the non-progressive MCI and the control groups (Figure 23.3). We thus propose that CSF p-tau 199 may also be useful for the diagnosis of MCI as it is for AD.

DISCUSSION

In the present study, we examined CSF p-tau 199 levels in a total of 570 living ($n = 562$) or autopsy-confirmed ($n = 8$) subjects with AD and other dementing disorders that resemble AD, as well as normal and neurological diseased controls. A combination of HT-7 (phosphorylation-independent monoclonal antibody; Innogenetics) and the anti-p-tau 199 antibody anti-PS199 allowed us to detect and quantitate CSF levels of the p-tau 199 by a newly constructed sandwich ELISA.[5,6] We reported p-tau 199 to be elevated in AD using different diagnostic antibodies that uniquely recognize specific phosphorylation epitopes of tau. We also monitored the CSF t-tau levels side by side in the same patients to assess and compare the sensitivity and specificity by ROC. Here, it should be noted that CSF p-tau 199 is not only the first biomarker that exceeds (over 85%) both sensitivity and specificity as a sole biomarker of AD, but also meets many other recommended criteria as an ideal biomarker.[8] The improvement of the diagnostic accuracy using CSF p-tau 199 seems to be accomplished not only by enhancing the lowest detection limit but also by eliminating a subset of non-AD patients with high CSF t-tau levels. Indeed, it is noteworthy that a subset of CJD patients with extremely high CSF t-tau levels showed only a mild elevation or an elevation under the cut-off level of CSF p-tau 199.

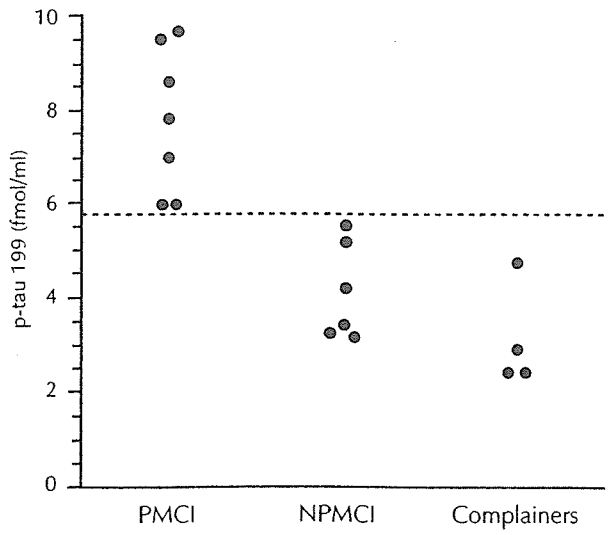

Figure 23.3 The results of cerebrospinal fluid (CSF) phosphorylated tau at serine 199 (p-tau 199) in mild cognitive impairment (MCI). PMCI, progressive MCI (Alzheimer's disease; AD); NPMCI, non-progressive MCI (non-AD). With a cut-off of 5.8 fmol/ml, sensitivity for PMCI 100% (7/7), and specificity for NPMCI 100% (6/6)

Nonetheless, our study suggests that there might be a limitation even in the use of the p-tau assay for a clear-cut distinction to be made between AD and certain tauopathies. In fact, the CSF p-tau 199 levels were over the cut-off value in approximately 30% (16/52) of the non-AD tauopathy group (Figure 23.2). Additional studies reported that pathological tau isoforms purified from tauopathy brains were occasionally hyperphosphorylayed at serine 199.[9,10] Therefore, the CSF p-tau 199 testing may be less accurate in distinguishing AD from other types of degenerative dementia or tauopathies. New and/or modified biomarkers would be necessary to differentiate AD from tauopathies in the future.[11,12]

A substantial proportion of subjects with MCI later developed clinical AD.[13] At autopsy, subjects with MCI showed a broad spectrum of morphological brain changes including typical AD pathological characteristics. Therefore, MCI

partly represents a predementia stage of AD. To maximize the benefit of therapeutic strategies, it is important to identify AD at the stage of MCI. Biochemical markers will be required to establish the diagnosis of MCI.[14] This study showed that CSF p-tau 199 levels in the progressive MCI group were significantly elevated compared to those in the non-progressive MCI and the control groups. We found that CSF p-tau 199 increased in an early stage of AD, the so-called MCI state, and confirmed that CSF p-tau 199 may be useful for the diagnosis of MCI as well as AD.

CONCLUSION

Our results suggest that CSF p-tau 199 is useful for an early diagnosis of AD.

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REVIEW ARTICLE

Studies on diagnostic markers for Alzheimer's disease

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Received 8 January 2004; accepted 15 January 2005.

Key words: *acetylcholine receptor α7, cerebrospinal fluid, genetic polymorphism, phosphorylated tau protein, touch panel computer.*

Abstract

In recent years, Alzheimer's disease (AD) has increased in incidence in Japan and elsewhere, and the marketing of donepezil hydrochloride (Aricept®) has allowed for the treatment of AD. These circumstances have encouraged the development of and research in markers for the early diagnosis of AD. Currently, the measurement of phosphorylated tau protein in the cerebrospinal fluid is considered to provide the most reliable and useful diagnostic marker for AD. For this purpose, a screening test using a touch panel computer can be recommended. The results of our study also suggest that the analysis of acetylcholine receptor α7 genetic polymorphism may be useful as a marker in the treatment with acetylcholine esterase inhibitors.

INTRODUCTION

In recent years, Alzheimer's disease (AD) has increased in incidence in Japan and elsewhere, and it accounts for about half the dementing diseases.[1,2] The recent marketing of donepezil hydrochloride (Aricept®) has allowed AD to be treated, and researchers have reported its usefulness.[3,4] Thus, the key to the treatment of AD is whether it can be diagnosed early and reliably. Unfortunately, AD is currently diagnosed solely by exclusion, and the development of diagnostic markers that are more easily accessible to everyone is highly desired. Researchers have tried many approaches in the development of diagnostic markers, of which tau protein-related ones have yielded the best results. This paper reports on the studies of tau protein-related markers and other markers.

DIAGNOSTIC MARKERS FOR AD

The Reagan Institute established to eradicate AD specifies that diagnostic biomarkers for AD must have the following characteristics:[5] They must reflect the disease status, be minimally invasive to the patient and have a high diagnostic accuracy in the differentiation between AD and other dementing diseases; that is, have a detection rate (sensitivity) of more than 80% for AD patients and a non-detection rate (specificity) of more than 80% for non-AD patients. We have previously reported that cerebrospinal fluid total tau protein satisfies most of the above requirements fairly well, but it does not have a sensitivity or specificity of over 80%. However, in combination with amyloid β-protein, it achieves a sensitivity and specificity of over 80% (called the AD index or AD unit).[6,7] The use of total tau protein as a biomarker for AD poses particular problems in that meningoencephalitis and Creutzfeldt–Jakob disease are associated with extremely high levels of total tau protein in the cerebrospinal fluid (Fig. 1).[8] To develop a single marker that meets the above requirements, we analyzed phosphorylated tau protein in the cerebrospinal fluid. Since tau protein in the degenerated neurofibrils in the brains of AD patients is hyperphosphorylated, we postulated that the selective measurement of phosphorylated tau protein would yield better results than the measurement of total tau protein. Focusing on phosphorylation at serine 199, our research group developed a sandwich enzyme-linked immunosor-

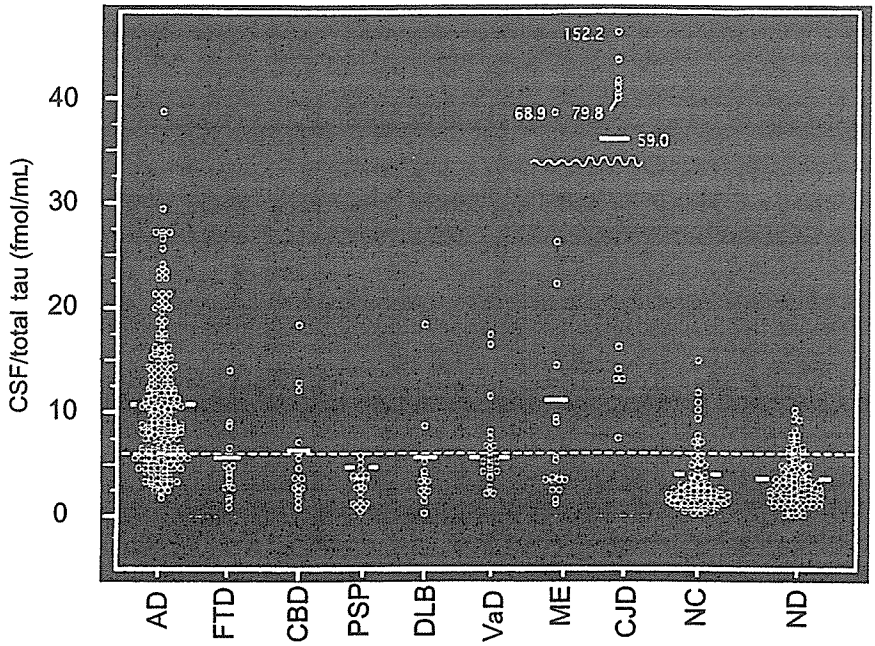

Figure 1 Quantification of total tau in cerebrospinal fluid (CSF). Total tau in CSF was assayed by a sandwich enzyme-linked immunosorbent assay (ELISA) employing anti-tau antibodies. AD, Alzheimer's disease; CBD, corticobasal degeneration; CJD, Creutzfeldt–Jakob disease; DLB, dementia with Lewy body; FTD, frontotemporal dementia; ME, meningoencephalitis; NC, normal controls; ND, non-dementia; PSP, progressive supranuclear palsy; VaD, vascular dementia.

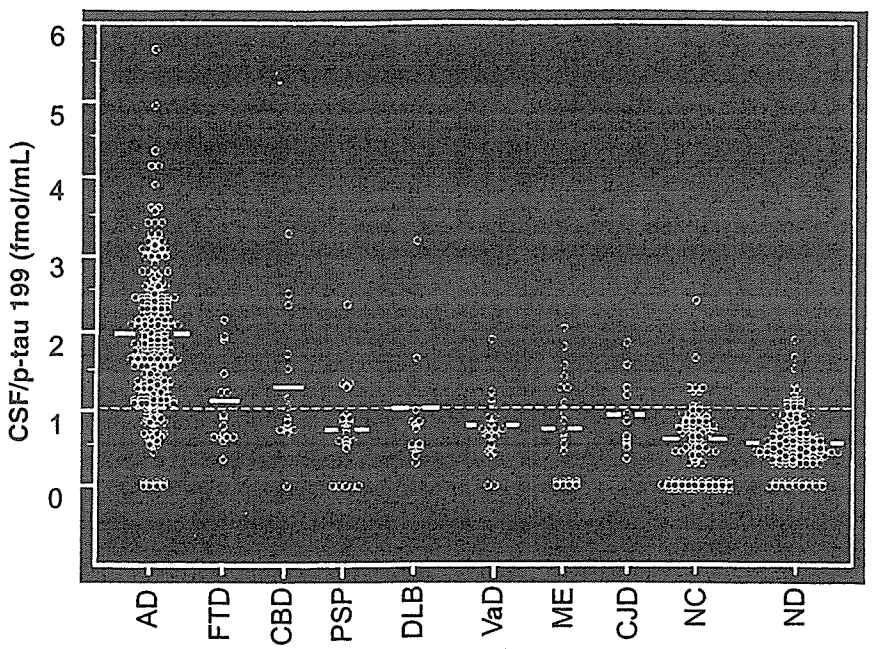

Figure 2 Quantification of phosphorylated tau at Ser 199 in cerebrospinal fluid (CSF). Phosphorylated tau in CSF was assayed by a sandwich enzyme-linked immunosorbent assay (ELISA) employing antiphosphorylated tau antibodies. AD, Alzheimer's disease; CBD, corticobasal degeneration; CJD, Creutzfeldt–Jakob disease; DLB, dementia with Lewy body; FTD, frontotemporal dementia; ME, meningoencephalitis; NC, normal controls; ND, non-dementia; PSP, progressive supranuclear palsy; VaD, vascular dementia.

bent assay (ELISA) to quantify N-terminal fragments of phosphorylated tau protein,[9] which gave better results than total tau protein measurement. In particular, phosphorylated tau protein levels are low in patients with meningoencephalitis and Creutzfeldt–Jakob disease, which are associated with high total tau protein levels (Fig. 2). Thus, the receiver operating characteristic (ROC) analysis also showed improved results, with a sensitivity and specificity of over 80% (Table 1).[10] In addition to our method of quantifying tau protein phosphorylated at serine 199, methods of quantifying tau protein phosphorylated at threonine 181 and threonine 231 have been reported. All these methods have yielded good results, making them the

most reliable diagnostic markers. To further increase the diagnostic accuracy of biomarkers, attempts have been made to increase the ability to differentiate AD from tauopathies typified by corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP),[11,12] such as the method of separately determining the levels of tau isoforms in the cerebrospinal fluid. As tau protein occurs mainly as the 4-repeat isoform in AD, and as the 3-repeat isoform in CBD and PSP, its differentiation is theoretically possible.

SCREENING TEST FOR AD

As described above, the measurement of phosphorylated tau in the cerebrospinal fluid is currently the most reliable marker, but it is not easy to perform a cerebrospinal fluid examination. Therefore, a simple screening test is necessary. One approach is to develop a test that can be performed on blood or urine. Regrettably, no useful markers have been developed so far. Although our group has been measuring blood tau and Aβ levels, we have not achieved satisfactory results. Thus, as another approach, we developed a simple screening method for AD using a touch panel computer.[13] We used questions assessing temporal orientation, delayed recognition and space perception (choosing cubes and triangular prisms), which are sensitive test items. The computer program was developed using Microsoft Visual Basic 6.0, and was made to operate on a PC running a Windows operating system. Hardware with an audio output was used to provide audio information as well as visual information. As elderly individuals are not accustomed to using a mouse, a touch panel was adopted. Incorrect answers were given a mark of 0, and results were graded on a scale of 0 to 15. Tests on 49 AD patients and 30 control subjects showed that almost all the subjects in the control group obtained full marks (with one or two incorrect answers, if any), whereas subjects in the AD group failed to give the correct answer to three or more questions (Fig. 3). Thus, at a cut-off value of 12, the ROC analysis indicated that the screening test has a very high accuracy with a sensitivity of 96% and a specificity of 97%. Because this test can be easily performed anywhere, and is non-invasive, highly sensitive, and highly specific, it is extremely useful.

Table 1 Receiver operating characteristic (ROC) analysis of total tau and phosphorylated tau assays

	Cut-off level	Sensitivity	Specificity
AD vs NC + ND			
Total tau	4.8 fmol/mL	82.7%	82.0%
p-tau 199	0.96	87.3	87.4
AD vs others			
Total tau	6.0 fmol/mL	77.1%	77.6%
p-tau 199	1.05	85.2	85.0

ROC analysis also showed an improved sensitivity and specificity of over 80% in the case of phosphorylated tau in the cerebrospinal fluid (CSF) assay.
AD, Alzheimer's disease; NC, normal controls; ND, non-demented controls.

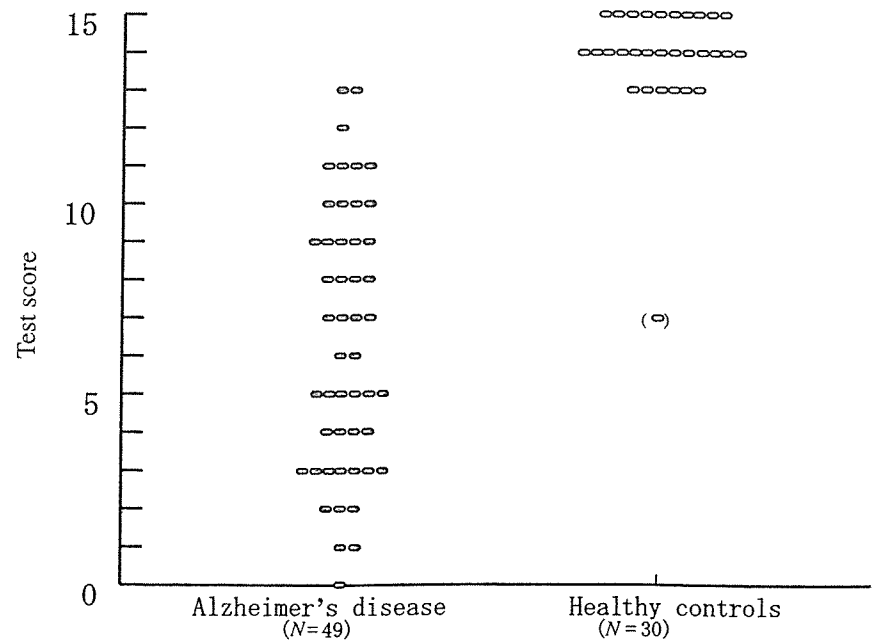

Figure 3 Results of the simple screening test for dementia using a touch panel computer. A simple screening method for Alzheimer's disease (AD) using a touch panel computer was developed. Tests on 49 AD patients and 30 control subjects showed that almost all subjects in the control group obtained full marks.

Table 2 Efficacy of donepezil hydrochloride and acetylcholine receptor (AchR) α7 polymorphism

	No.	Genotype W/W	W/M	M/M	χ^2-test
Responder (improved)	21	10	11	0	$P < 0.05$
Non-responder (not improved)	22	17	5	0	

Donepezil hydrochloride responders were more frequently heterozygous for a 2-base deletion in the AchR α7 gene ($P < 0.05$).

MARKERS FOR THE PREDICTION OF DRUG EFFICACY

With the marketing of donepezil hydrochloride, there is now a treatment for AD. However, responder and non-responder groups exist. Methods to differentiate these groups have also been investigated. As this drug is an acetylcholine esterase inhibitor, we focused our attention on acetylcholine receptor α7 genetic polymorphism, and found that donepezil hydrochloride responders were more frequently heterozygous for a 2-base deletion in the acetylcholine receptor α7 gene ($P < 0.05$, Table 2).[3] This polymorphism requires further analysis not only as a marker for the early detection of AD, but also as a diagnostic marker for predicting the drug efficacy.

CONCLUSION

We consider that the quantification of phosphorylated tau in the cerebrospinal fluid is currently the most reliable and useful biomarker for AD. The method involving the use of a touch panel computer can be recommended as a preliminary screening test. Acetylcholine receptor α7 genetic polymorphism may be a useful marker in the treatment with acetylcholine esterase inhibitors.

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A Comparison of Depressive Mood of Older Adults in a Community, Nursing Homes, and a Geriatric Hospital: Factor Analysis of Geriatric Depression Scale

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ABSTRACT

The Geriatric Depression Scale (GDS)–15 was used in 607 adults aged 65+ years living in a community, nursing homes, and a general hospital to explore characteristics of depressive mood in different care settings. Factor analysis of GDS-15 extracted 4 factors labeled unhappiness, apathy and anxiety, loss of hope and morale, and energy loss. The scale scores labeled unhappiness, apathy and anxiety, and loss of hope and morale were negatively correlated with the Barthel Index and the Mini-Mental State Examination scores. The results classified the depressive patterns into 2 types, one fitting the nursing home residents and the other fitting the hospital patients. The dominant factors of the nursing-home type were unhappiness and loss of hope and morale, and the hospital type was highly related with apathy and anxiety. The results indicate an extended utility of the GDS-15 for a deeper understanding of depressive mood in various care settings. (*J Geriatr Psychiatry Neurol* 2006;19:26-31).

Keywords: depressive mood; Geriatric Depression Scale; factor analysis

Depression is one of the most common and insidious problems for older adults, including those in long-term care settings. Although nursing home residents and geriatric hospital patients often receive comprehensive assessments involving instruments programmed to evaluate depression, it has been suggested that clinicians tend to underestimate the presence of depression, possibly because depressive symptoms may be assumed to be a part of normal aging, not related to the disease of depression, and therefore are sometimes overlooked.[1] We previously reported on the relationship between functional disabilities and depressive mood in older patients admitted to the geriatric ward of a general hospital using factorial analysis.[2] The results clarified factorial components of the Geriatric Depression Scale (GDS)–15,[3] which consists of 4 major factors. Two of those factors, "loss of morale and hope" and "memory loss and reduction of social activity," were significantly correlated with the presence of functional disabilities; thus, we concluded that depression associated with physical and/or cognitive handicaps could be reflected in patterns of GDS scores. However, as suggested in our report, the features of depression affected by acute medical conditions in hospitalized elderly patients may not always be generalized to older adults living in a community or other long-term care settings.

In this study, we extended this line of research to include a community and several nursing homes, both to apply this new and easy method using factorial analysis and to clarify the differences in patterns of depressive mood among these 3 settings.

Received January 28, 2005. Received revised June 13, 2005. Accepted for publication June 13, 2005.

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This study was supported by Grant-in-Aid for Scientific Research, titled Clinical Research for Evidence Based Medicine from the Ministry of Health, Labour and Welfare. We would like to thank all the staff of the health care center of Tsukude village, where this study was carried out, for their cooperation.

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DOI: 10.1177/0891988705284725

Table 1. Profiles of the Participants in Three Settings

	N	*Age*	*Basic ADL*	*MMSE*	*GDS-15*
Community	184	71.5 ± 7.5	19.7 ± 0.8]**	27.9 ± 0.4[a]	5.1 ± 3.5]**
Nursing homes	178	82.4 ± 6.1	13.8 ± 4.6]**	21.0 ± 4.5]**	8.6 ± 2.1]**
General hospital	245	77.4 ± 6.6	17.7 ± 4.0	25.7 ± 4.2	5.7 ± 3.8
Total	607	79.4 ± 9.6	17.2 ± 4.2	24.7 ± 4.4	6.4 ± 3.6

Note: ADL = activities of daily living; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale.

a. MMSE was measured in 22 randomly sampled older adults in the community. The comparative analysis including residents in the community was not performed.

**$P < .01$

METHODS

Participants and Measurements

We sampled 928 adults aged 65 years or over. Among these, we consecutively enrolled 184 community-dwelling residents in Tsukude village, a rural village in central Japan, 389 residents in 4 nursing homes (mean length of stay, 409 ± 313 days at the survey), and 355 patients admitted to the geriatric ward of a teaching general hospital. In the community, data were collected from physically and cognitively independent volunteers visiting a health care center for an annual health check. All participants were asked to complete the Japanese version of short form GDS-15[4] and the Barthel Index[5] to assess their basic activities of daily living (ADL), with the assistance of attending staff if necessary. The GDS-15 is a well-established assessment scale for depressive mood, consisting of 15 self-administered alternative (yes/no) questions. A higher score indicates a greater degree of depressive mood with a cutoff score set at 6/6+.[6] All nursing home residents and all hospital patients underwent the Mini-Mental State Examination (MMSE),[7] administered by the attending doctors for hospital patients and by nurses for nursing home residents. In the community, because of availability of staff, MMSE was measured in 22 randomly sampled older adults to represent their cognitive status. Participants who were unable to answer the questionnaires because of acute illness and those who declined to cooperate with the study were excluded. Also in accordance with previous reports[8,9] regarding the validity of the GDS, participants who scored below 15 on the MMSE were excluded. As a result, 211 nursing home residents and 110 hospital patients were not included, and the data of remaining 607 participants (female 56.7%; mean age 77.1 ± 8.0 SD) were used for analysis.

Statistical Analysis

Correlation coefficients were calculated by Pearson's method for parametric data and by Spearman's method for nonparametric data. Differences in continuous variables among more than 2 groups were determined by a one-way analysis of variance, and Tukey's test was used for subsequent multiple comparisons. Kruskal–Wallis test was used for categorical comparisons of the nonparametric data. The internal consistency of the GDS-15 was calculated with Cronbach's α. The principal factor analysis for the GDS-15 was performed with an eigenvalue of 1.0 or more as the extraction criterion, and factors were identified after varimax rotation. Scale scores were calculated by counting the number of scored items belonging to the factors extracted from the GDS-15. Values of $P < .05$ were considered to indicate statistical significance, and all tests were 2-tailed. All statistical analyses were performed on a personal computer with the statistical software package SPSS for Windows version 11.0 (SPSS Inc, Chicago, IL).

RESULTS

Table 1 shows the mean age, basic ADL, MMSE, and GDS-15 scores for each group of participants. Basic ADL and MMSE scores were highest in the community and lowest in the nursing homes. The mean GDS-15 score of all the participants was 6.4 ± 3.6 SD, and 49.7% of them scored above 6. The GDS-15 score was significantly higher in the nursing homes than in the other settings, and no fewer than 87.6% of the nursing home residents had a GDS-15 score above 6.

Table 2 shows depressive response rate (the rate of respondents who had an alternative choice representing depressive mood) for each GDS-15 item in the 3 groups. Nursing home residents scored significantly higher than the other 2 participant groups on the following 10 of the 15 items: satisfied, dropped activities, emptiness, often bored, in good spirits, feels happy, prefers to stay in, wonderful to be alive, feels worthless, and feels situation is hopeless. "Full of energy" was the only item in which the hospital patients scored highest. The internal consistency of the GDS-15 was high, with Cronbach's α being .778. The factor analysis of GDS-15 extracted 4 factors, whose loading values are shown in Table 3. Factor I represented "unhappiness," which included the items 1, satisfied; 5, in good spirits; 7, feels happy; and 11, wonderful to be alive. Factor II, labeled "apathy and anxiety," was made up of 6 items: 2, dropped activities and interest; 3, emptiness; 4, often bored; 6, afraid something bad will happen; 8, often feels helpless; and 15, most people better off than self. Factor III, labeled "loss of hope and morale," included 4 items: 9, prefers to stay in; 10, more problems with memory than most; 12, feels worthless; and 14, feels situation is

Table 2. Depressive Response per Group to Each Geriatric Depression Scale–15 Item

	Community	*Nursing Homes*	*General Hospital*	*Kruskal–Wallis Test (P)*
1. Satisfied	26.0	**75.1**	*19.8*	<.001
2. Dropped activities and interest	*40.0*	**55.9**	51.3	<.001
3. Emptiness	*18.9*	**41.7**	33.9	<.001
4. Often bored	*15.4*	**46.0**	28.9	<.001
5. In good spirits	33.4	**88.1**	*21.8*	<.001
6. Afraid something bad will happen	*40.2*	50.3	**50.6**	.076
7. Feels happy	28.7	**81.8**	*21.9*	<.001
8. Often feels helpless	*52.6*	**68.6**	63.0	.007
9. Prefers to stay in	43.4	**60.8**	*43.0*	<.001
10. More problems with memory than most	**66.3**	64.4	*54.0*	.021
11. Wonderful to be alive	27.0	**65.9**	*22.2*	<.001
12. Feels worthless	*17.2*	**41.8**	28.9	<.001
13. Full of energy	46.0	*33.5*	**63.1**	<.001
14. Feels situation is hopeless	*30.9*	**52.5**	43.2	<.001
15. Most people better off than self	*29.7*	**33.0**	30.8	.795

Note: Bold indicates highest; italic indicates lowest.

Table 3. Principal Factor Analysis (Varimax) of the Geriatric Depression Scale–15

Item	*Factor I Unhappiness*	*Factor II Apathy and Anxiety*	*Factor III Loss of Hope and Morale*	*Factor IV Energy Loss*
1. Satisfied	0.776			
2. Dropped activities and interest		0.413		
3. Emptiness		0.756		
4. Often bored		0.532		
5. In good spirits	0.746			
6. Afraid something bad will happen		0.421		
7. Feels happy	0.771			
8. Often feels helpless		0.385		
9. Prefers to stay in			0.280	
10. More problems with memory than most			0.247	
11. Wonderful to be alive	0.684			
12. Feels worthless			0.567	
13. Full of energy				0.475
14. Feels situation is hopeless			0.690	
15. Most people better off than self		0.418		
Explained variance	2.3	1.8	1.4	0.5
Cumulative percentage of variance explained	15.3	27.5	36.8	40.3

Note: The factor score was calculated by a regression method, which cumulated factor loadings of all items of Geriatric Depression Scale–15.

hopeless. Factor IV, labeled "energy loss," included the item 13, full of energy. The cumulative percentage of variance explained was 40.3%.

The GDS-15 score had a significant negative correlation with basic ADLs (Pearson's $r = -.304$, $P < .001$) and with MMSE score ($r = -.220$, $P < .001$), but not with age. Table 4 shows the correlations between the scale score of each factor extracted from GDS-15 and age, basic ADL, and MMSE score. The scale scores of factors I, II, and III were negatively correlated with basic ADL and MMSE scores, whereas that of factor IV showed significant positive correlations with basic ADL and MMSE scores.

Based on the results of the scale-score calculations, a radar chart was created to analyze patterns in the GDS-15 scores. Figure 1 illustrates the patterns of 3 care settings. The pattern in nursing homes was wide above and below, indicating large contributions of Factors I (unhappiness) and III (loss of hope and morale) to the participants' depressive mood. On the other hand, the pattern in the general hospital had a sharply pointed shape, which suggested the large contribution of factor II (apathy and anxiety).

DISCUSSION

In the present study, most of the nursing home residents were in a depressive mood. Their average GDS-15 score was 8.6 ± 2.1 SD, higher than in the studies of nursing home residents by Sutcliffe et al,[10] Casarett et al,[11] and Rinaldi et al,[12] which showed averages of 5.4 ± 3.2 SD, 5.6 ± 4.4 SD, and 6.7 ± 3.8 SD, respectively. With an intent to secure the validity of the GDS-15, we excluded participants with moderate and severe cognitive impairment. Rinaldi et al included participants with MMSE scores of 5 or higher (mean MMSE score 20.0 ± 6.1 SD), and Sutcliffe et al had no exclusion criteria based on MMSE score.