5.3 判別結果

被験者 48 名に対するスクリーニングテストの結果を表 3-5 に示す．ここでは，SPCIR による 1 次スクリーニングのカットオフ値を 26~28 の 3 値で設定した場合の結果を考察する．

同表において，NC の判定において，1 次スクリーニングで健常と判別された人数を括弧に内数で示す．2 次スクリーニングの検証方法には Leave-one-out 交差検定を用いた．

表 3 の結果から，カットオフ値を 26 点に設定することで 24 名（50%）の被験者が 1 次スクリーニングのみで判別を終了するため fNIRS 測定のコストが半分に軽減されることがわかる．NC や AD の正答率はそれぞれ 95%，100%と高く，一見して全体正答率も 85.4%と比較的良い性能に見える．しかしながら，6 名（約 32%）の MCI 患者が 1 次スクリーニングにて「健常」と誤判定された．本スクリーニングの役割が専門医療機関への受診誘導であることを考えると，この判定は看過できない．今回の臨床データに関しては，カットオフ値は小さすぎることがわかる．一方で，表 5 の結果から，カットオフ値を 28 点に設定した場合には被験者全員が 2 次スクリーニングへ移行していることがわかり，スクリーニングのコストは全く軽減できない．しかし，判別性能については MCI および AD の正答率も概ね 90%超と良い結果であり，NC の判定的中率が 100% である点も非常に良い．カットオフ値が 27 の場合は，上記結果の中庸の性能を示した．これらの結果から，本システムの 1 次スクリーニングの NC 判定によるコストリダクション効果と MCI を見過ごすリスクとのトレードオフの関係が改めて確認された．

今後は，上記の性質を保持しつつ全体の正答率を向上させる改良を進めたい．特に，音韻特徴の精査と特徴選択手法の高度化，ならびに，NC/MCI の弁別を重視した SPCIR を改良するとともに，表 3 や表 4 で誤判別された MCI 患者がその後 AD へ進行する（converter）患者であるか否かを追跡調査したい．

6. おわりに

本研究では，認知症の早期発見・診断の支援を実現するために，高齢者に対して極めて簡便で非侵襲な認知機能障害のスクリーニングシステムを目指して研究開発を行ってきた．本稿では，高齢者の発話音韻，ならびに，機能的近赤外分光法（fNIRS）を用いた認知課題実行中の脳血流賦活特徴に着目したこれまでの研究を統合し，データマイニング・アプローチに基づく音声と脳血流を用いた認知機能障害のスクリーニングシステムを開発し，健常（NC），軽度認知機能障害（MCI），アルツハイマー型認知症（AD）の臨床診断群を 2 段階のスクリーニングで自動判別する手法を提案した．

48 名の高齢者から採取した音声・fNIRS 同時計測データと臨床診断群に関して，カテゴリ想起の課題実行時の発話音韻特徴ならびに脳血流賦活特徴を用いて専門医療機関への受診誘導を想定した 2 段階スクリーニングの評価実験を行った．今後の課題としては，その他の課題実行時のデータを用いた検証実験，高齢者データを増加することによる分析・推定性能の向上，ならびに，音声韻律情報による 1 次スクリーニング性能改善によるコスト効果の向上，ならびに，fNIRS 判別器の 2 次スクリーニングとしての要求仕様を考慮した判別アルゴリズムの考案などがあげられる．

これらの課題を解決し，次世代の認知症のスクリーニングツールを開発することで，地域社会に生活する高齢者全般に認知機能チェックの機会を与えられるような仕組みを提供したいと考えている．

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Relationship between Atrophy of the Medial Temporal Areas and Cognitive Functions in Elderly Adults with Mild Cognitive Impairment

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Key Words
Entorhinal cortex · VSRAD · Voxel-based morphometry · Wechsler Memory Scale · Stroop test

Abstract
Aim: The current study sought to determine which types of cognitive function are related to atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) in elderly adults. ***Methods:*** The subjects were 96 elderly adults (mean age 75.3 years) with mild cognitive impairment. Subjects underwent Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II), Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backword (DSB), digit symbol-coding (DSC), Stroop Color and Word Test-Interference List (SCWT-IL) as well as magnetic resonance imaging (MRI) and were divided into elderly adults without or with mild to moderate MTA-ERC atrophy, and those with severe atrophy. ***Results:*** In all subjects, MTA-ERC atrophy showed significant relationships with age (r = 0.43), education (r = −0.25), WMS-R, LM I (r = −0.21), DSC (r = −0.32), and SCWT-IL (r = 0.32). The mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and age (r = 0.34), DSC (r = −0.28), and SCWT-IL (r = 0.25). In contrast, in the severe atrophy group, MTA-ERC atrophy was correlated significantly with RCF-3 min (r = −0.70) and RCF-30 min (r = −0.74). The linear regression model included demographic variables and cognitive tests; two variables to survive the step-wise analysis were age (β = 0.374) and SCWT-IL (β = 0.247) in all subjects. Age (β = 0.301), and RCF-30 min (β = −0.521) and age (β = 0.460) remained as a significant variable in the mild to moderate atrophy and severe atrophy groups, respectively. ***Conclusion:*** Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and a decline in the RCF test may suggest severe MTA-ERC atrophy in elderly adults with MCI.

Introduction

There is increasing evidence for baseline structural magnetic resonance imaging (MRI) correlates of cognitive impairment in elderly adults exhibiting mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1–4]. To date, the most reliable and well-documented finding is an association between impaired memory ability

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and medial temporal lobe atrophy, which is particularly robust in the hippocampus and entorhinal cortex (ERC) [5]. Several studies have reported that hippocampal and ERC atrophy can predict conversion to AD [6–9], as well as memory decline in MCI and AD [10, 11]. Although memory deficits constitute the hallmark feature of MCI, many patients exhibit deficits in other cognitive domains, such as mild anomia [12, 13], reductions in semantic fluency [14] and executive dysfunction, characterized by impaired working memory, inhibition, set-shifting, and phonemic fluency [15, 16]. The pathological hallmarks of AD (e.g. neurofibrillary tangles and senile plaques) have been found in the ERC in the earliest phase of disease, leading to an overall neuronal loss of 32% compared with control subjects [17]. An MRI investigation of the ERC reported a 37% decrease in patients who went on to develop AD, in comparison with control subjects [18]. These findings indicate that a strong relationship exists between in vivo measures of ERC atrophy in the early stages of AD.

The region of interest (ROI) method and more automated methods such as voxel-based morphometry (VBM) are the most common MR analysis techniques used for examining brain atrophy. Automated analytical methods such as VBM enable objective examination of anatomical group differences in controls, MCI patients, and AD patients across the whole brain. With this statistical parametric mapping technique, researchers are able to evaluate group differences in gray matter, white matter, and cerebrospinal fluid (CSF) volume with high spatial resolution. Whole-brain VBM has the important advantage of not requiring a priori assumptions about the size, location, or shape of the brain ROI(s). Furthermore, VBM allows the quantification of brain changes that are not easily revealed by visual inspection, such as atrophy that is not fully encompassed by sulcal boundaries between structures.

Recent research has led to the development of a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which enables the examination of atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) using VBM [19–21]. The VSRAD has been shown to achieve high accuracy (87.8%) in discriminating patients in the very early stages of AD with MCI from normal control subjects using Z-scores [21]. Atrophy of the MTA-ERC was indicated by VSRAD to exhibit a clear functional relationship with blood flow changes in the hippocampus, thalamus and temporal lobe, which were suggested to be closely related to interregional anatomical and physiological connections [22]. In cognitive function, Nagata et al. [23] reported that Z-scores of the VSRAD was associated with executive function, although there was no relationship between Z-scores and memory function which was assessed by the Mini-Mental State Examination (MMSE) in the amnestic MCI and early AD patients. These authors suggested that detailed examination such as the Wechsler Memory Scale was required to reveal the relationship between MTA atrophy and memory function. Moreover, it is currently unclear which aspects of cognitive function including memory and executive function are related to the atrophy of the MTA-ERC identified by VSRAD in elderly adults with MCI.

In the current study, we measured volumetric MRI and performance in a range of cognitive domains, including logical memory, visual memory, working memory, processing speed, and executive function in elderly adults with MCI. Overall, we sought to determine which aspects of cognitive performance were associated with MTA-ERC atrophy in elderly adults with MCI.

Methods

Subjects

Subjects in this study were recruited from two volunteer databases (n = 1,543), which included elderly individuals (65 years and over) selected either by random sampling, or when they attended a medical check-up in Obu, Japan. 528 prospective subjects with a Clinical Dementia Rating (CDR) of 0.5, or who complained of memory impairment, were recruited in the first eligibility assessments. 165 subjects responded to the second eligibility assessments, and 125 out of 165 subjects completed the neuropsychological tests which included language and memory tests, attention and executive function tests, clinical diagnosis, activities of daily living (ADL), educational level, and MRI scanning. Out of 125 subjects, 25 were excluded and the remaining 100 subjects met definition of MCI using Petersen criteria [24]. All MCI subjects had objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. Final classification of subjects was based on the above factors and consensus of a team of neuroscientists. Exclusion criteria included CDR 0, or 1–3, a history of neurological, psychiatric, and cardiac disorders or other severe health issues, use of donepezil, impairments in basic ADL, and participation in other research projects. 96 elderly adults remained after these exclusions (mean age 75.3 ± 6.8 years, range 65–93, men n = 48, 50%), and were included in the final analysis. Table 1 shows the characteristics of the subjects.

The purpose, nature, and potential risks of the experiments were fully explained to subjects. All subjects gave written, informed consent before participating in the study. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology.

Table 1. Characteristics of subjects (mean ± SD)

Age, years	75.3 ± 6.8
Male, %	50
Education, years	10.6 ± 2.5
Body mass index	23.0 ± 3.1
Cognitive functions	
MMSE, points	26.5 ± 2.5
WMS-R, LM I, points	14.4 ± 7.1
WMS-R, LM II, points	10.0 ± 7.4
RCF-3 min, points	15.5 ± 6.3
RCF-30 min, points	14.9 ± 6.7
DSB, points	5.2 ± 1.6
DSC, points	46.1 ± 15.9
SCWT-IL, s	21.1 ± 17.2
Medication, yes, %	
Hypertension	44.8
Heart disease	5.2
Diabetes mellitus or hyperlipidemia	20.9
Total number ± SD	2.3 ± 2.1

WMS-R, LM = Wechsler Memory Scale-Revised, Logical Memory; RCF = Rey complex figure retention test; DSB = digit span backward; DSC = digit symbol coding; SCWT-IL = Stroop Color and Word Test-Interference List.

MRI

MRI was performed with a 1.5-T system (Magnetom Avanto; Siemens, Germany). Three-dimensional volumetric acquisition with a T_1-weighted gradient echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time 1,700 ms, echo time 4.0 ms, flip angle 15°, acquisition matrix 256 × 256, 1.3 mm slice thickness).

The MRI images acquired from the subjects were formatted to gapless, transaxial images, followed by extraction of the gray matter images using SPM2. Anatomical standardization was used to fit each individual brain to the standard template MRIs in the common coordinate system of the MNI T_1 MRI template [25, 26]. The segmented gray matter images were then subjected to affine and non-linear standardization using a template of prior gray matter.

The anatomically standardized gray matter images were then smoothed again using an isotropic Gaussian kernel 12 mm in full width at half maximum, to determine the partial volume effect and create a spectrum of gray matter intensities. Gray matter intensities were equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensity was considered equivalent to gray matter concentration. We compared the gray matter image of each patient with the mean and standard deviation (SD) of gray matter images of healthy volunteers using voxel-by-voxel Z-score analysis. In the final step, the Z-score was calculated according to the following equation: (Z-score = ((control mean) – (individual value))/control SD). The Z-score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z-scores indicated clearer MTA-ERC atrophy.

Cognitive Tests

Speech therapists conducted all of the memory tests, and a speech therapist recalculated all of the results. The Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II) [27], Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backward (DSB) and digit symbol-coding (DSC) subset of the Wechsler Adult Intelligence Scale III [28], and Stroop Color and Word Test-Interference List (SCWT-IL) [29] were included as cognitive tests.

Modified versions of the logical memory subtest from the WMS-R and RCF were used to assess logical and visual memory ability, respectively. In the WMS-R, two short stories (story a and b) were read aloud to the subject, who was instructed to recall details of the stories immediately (LM I) and after 30 min (LM II) [27]. We calculated the total score, i.e. sum score of story a and b, of WMS-R in LM I and LM II. In the RCF, subjects were requested to copy the RCF figure (construction ability) and reproduce it after 3- and 30-min delays. One rater independently scored the RCF using the system described by Osterrieth and Rey [30] and translated by Corwin and Bylsma [31]. DSB and DSC were used to assess working memory and processing speed, respectively. DSB required subjects to repeat a series of verbally presented digits of increasing length in backward order. In the DSC, subjects copied symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant drew the symbol under the corresponding number. The score of DSC was the number of correct symbols drawn within 120 s. In the SCWT-IL as a test of executive function, subjects were presented with a series of color words. Our test version consisted of two subtasks. The first subtask showed color words in random order (red, blue, yellow, green) printed in black ink. The second subtask contains color words printed in an incongruous ink color, for example, the word *yellow* printed in red ink. The subjects were instructed to read the words and name the ink color of the printed words as quickly and as accurately as possible in the two subsequent subtasks. The score was measured as the total time taken to complete the task with 24 words [32]. The time limit to complete a subtask was set at 120 s. An interference measure was calculated by subtracting the average time needed to complete the first subtask from the time needed to complete the second subtask.

Analysis

The relationships between atrophy of the MTA-ERC and cognitive measurements were examined with Pearson correlations. The independent associations between MTA-ERC atrophy and cognitive ability with each demographic (i.e. sex, age, and educational level) and diagnosis (aMCI and non-aMCI) variables were tested using a linear regression model with a step-wise analysis. To examine differences in MTA-ERC atrophy level, subjects were divided into the following two groups according to the Z-score: (1) mild to moderate atrophy group (Z-score: 0–1.99) and (2) severe atrophy group (Z-score: 2.00 and over) in the MTA-ERC, according to the results of the VSRAD [23]. Pearson correlations and the linear regression model with a step-wise analysis were used to examine the relationships between MTA-ERC atrophy and cognitive tests in each group. SPSS 18.0 software (SPSS Inc., Chicago, Ill., USA) was used for all data management and statistical analysis. The statistical threshold was set at a $p < 0.05$.

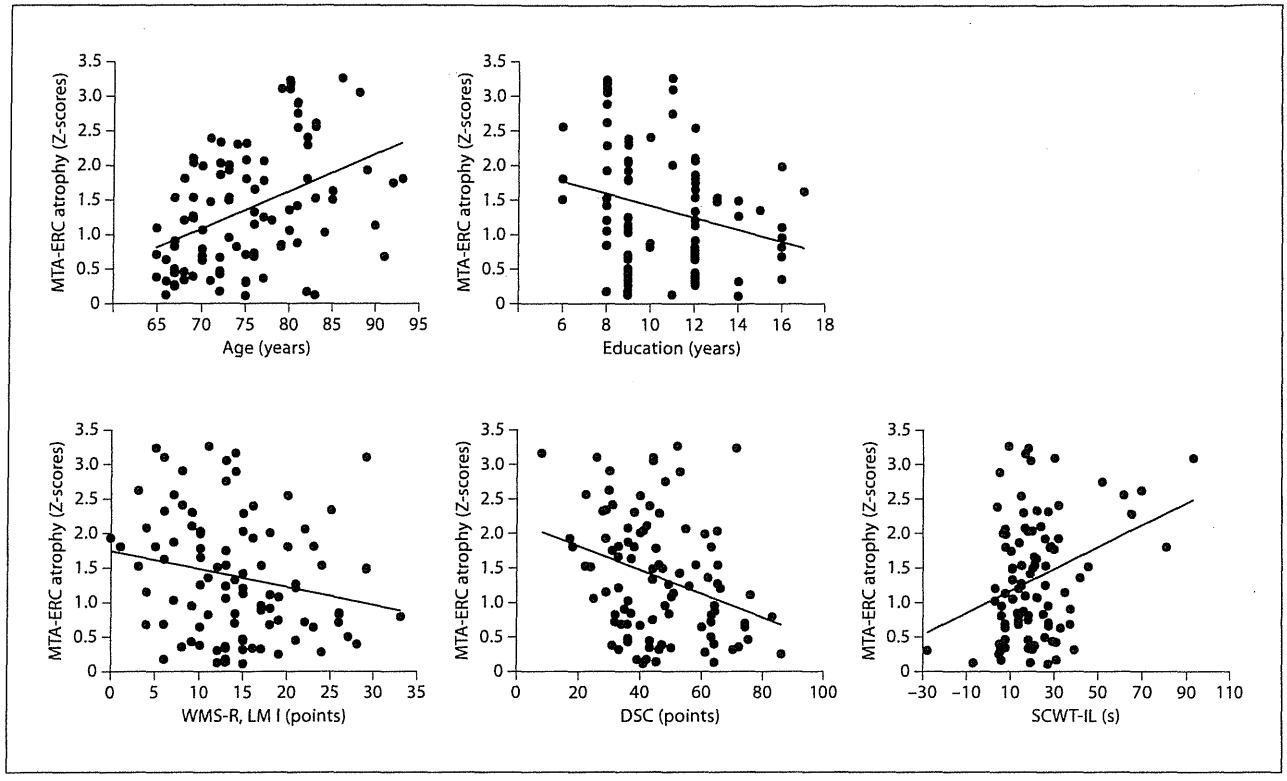

Fig. 1. Relationship between the Z-score of MTA-ERC and age, education, and cognitive test scores. MTA-ERC atrophy was correlated significantly with age ($r = 0.43$, $p < 0.001$), educational level ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$).

Table 2. Pearson correlation coefficients between MTA-ERC atrophy and age, educational level, and cognitive measurements

	All subjects (n = 96)		Mild to moderate atrophy group (n = 72)		Severe atrophy group (n = 24)	
	r	p value	r	p value	r	p value
Age	0.43	**<0.001**	0.34	**0.003**	0.71	**<0.001**
Education	−0.25	**0.012**	0.01	0.921	−0.26	0.224
WMS-R, LM I	−0.21	**0.040**	−0.17	0.155	−0.06	0.774
WMS-R, LM II	−0.09	0.370	0.03	0.812	−0.22	0.308
RCF-3 min	−0.16	0.119	−0.10	0.396	−0.70	**<0.001**
RCF-30 min	−0.13	0.201	−0.11	0.386	−0.74	**<0.001**
DSB	−0.15	0.134	−0.12	0.298	−0.14	0.511
DSC	−0.32	**0.002**	−0.28	**0.016**	−0.05	0.825
SCWT-IL	0.32	**0.002**	0.25	**0.031**	0.18	0.404

For abbreviations, see table 1.

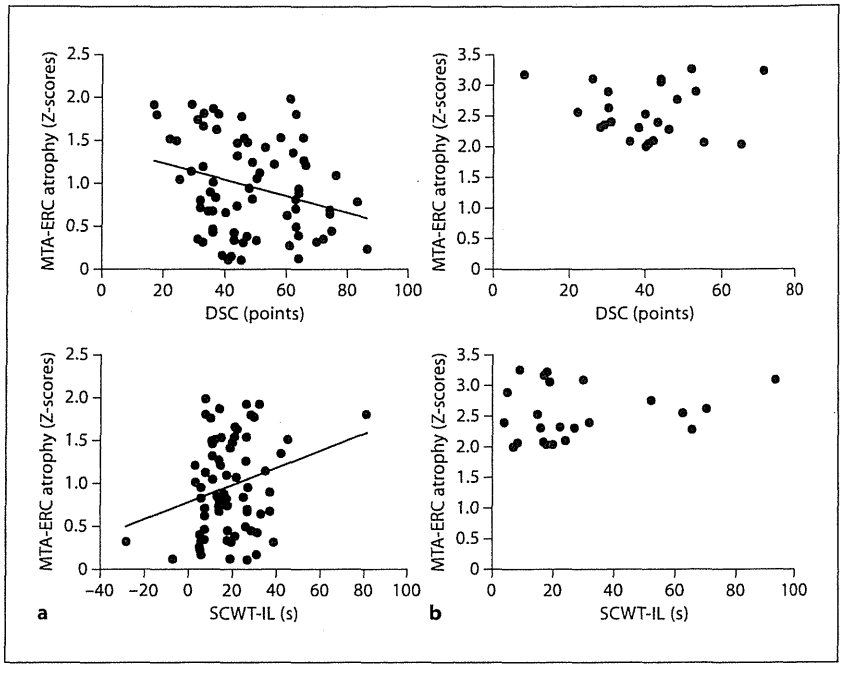

Fig. 2. Relationship between the Z-score of MTA-ERC and processing speed and executive function in the mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and DSC and the lower panel shows scatter plots between MTA-ERC atrophy and SCWT-IL. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with DSC ($r = -0.28$, $p = 0.016$) and SCWT-IL ($r = 0.25$, $p = 0.031$) in the mild and moderate atrophy group.

Table 3. Multivariate regression analysis between MTA-ERC atrophy and age, educational level, and cognitive measurements

	β	t value	p value	R^2
All subjects				
Age	0.374	4.0	<0.001	0.236
SCWT-IL	0.247	2.6	0.01	
Mild to moderate atrophy group				
Age	0.301	2.6	0.011	0.091
Severe atrophy group				
RCF-30 min	−0.521	−3.8	0.001	0.706
Age	0.460	3.4	0.003	

For abbreviations, see table 1.

Results

In all subjects, Z-score showed significant relationships with age ($r = 0.43$, $p < 0.001$), education ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$) (fig. 1; table 2). There were no significant relationships between Z-score and WMS-R, LM II, RCF-3 min, RCF-30 min, and DSB (table 2). In linear regression model, two variables to survive the step-wise analysis were age ($\beta = 0.374$, $p < 0.001$) and SCWT-IL ($\beta = 0.247$, $p < 0.010$) (table 3).

Of the 96 MCI elderly adults tested, the mild to moderate atrophy and severe atrophy groups included 72 (75%) and 24 (25%) subjects, respectively. In the Pearson correlation analysis, the mild to moderate atrophy group showed significant relationships between Z-score and age ($r = 0.34$, $p = 0.003$), DSC ($r = -0.28$, $p = 0.016$), and SCWT-IL ($r = 0.25$, $p = 0.031$) (fig. 2; table 2). In contrast, Z-scores were correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group (fig. 3; table 2).

A multivariate regression model indicated that age ($\beta = 0.301$, $p = 0.011$) remained as the only significant variable in the mild to moderate atrophy group (table 3). DSC and SCWT-IL did not reach significance in this group. In the severe atrophy group, two variables to survive the step-wise analysis were RCF-30 min ($\beta = -0.521$, $p = 0.001$) and age ($\beta = 0.460$, $p = 0.003$) (table 3).

Discussion

It is well established that structures in the medial temporal lobe, particularly the hippocampus and ERC, are essential for normal memory function [33]. There is evi-

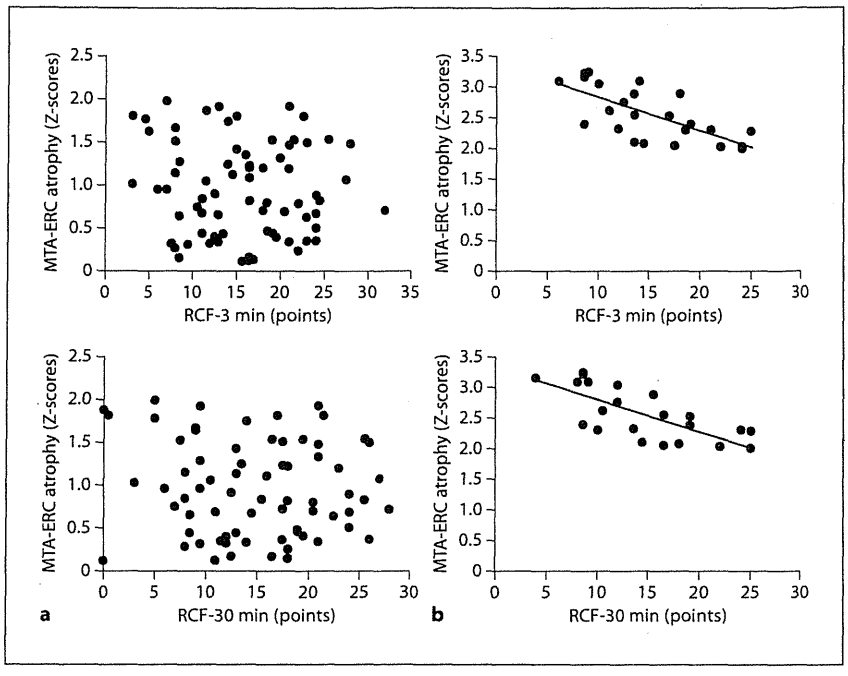

Fig. 3. Relationship between the Z-score of MTA-ERC and Rey complex figure retention test in mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and RCF-3 min and the lower panel shows scatter plots between MTA-ERC atrophy and RCF-30 min. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group.

dence that these brain regions are substantially affected by disease in the early stages of AD [34, 35], in accord with the finding that memory impairment is the earliest symptom of disease in most AD patients. The ERC is part of a critical pathway in the neural system underlying memory. Zola-Morgan et al. [36] reported that this area receives afferents from widespread association and limbic areas, projects to the dentate gyrus of the hippocampal formation, receives afferents from the hippocampus, and sends afferents back to association neocortex. An epidemiological study reported that ERC atrophy was greater than hippocampal atrophy in patients suffering from MCI [35]. However, the two measures were found not to differ in AD, suggesting that the ERC atrophies before the hippocampus in incipient AD [37]. An autopsy study of early AD patients reported neurofibrillary tangles in the ERC before evidence of hippocampal involvement [35]. Thus, volumetric MRI analysis of the MTA included ERC may be a sensitive predictor to identify AD conversion and decline of neuropsychological performances in MCI elderly adults.

In the current study, 25% of elderly adults with MCI exhibited severe atrophy in the MTA-ERC. The VSRAD analysis revealed that Z-scores indicating probable AD and amnestic MCI patients averaged 1.94 ± 1.24 (ranging from 0 to 4.69) [22]. Subjects exhibiting MTA-ERC atrophy as well as probable AD were included in the present MCI study. Numerous imaging studies have reported a correlation between increasing age and decreasing brain volume [38–42]. This decline in brain volume may be due to a non-linear acceleration in rates of atrophy after 70 years of age [43]. In the current study, 72 subjects (75%) were 70 years and over. Thus, the brain volume of our sample may have been affected by advancing age. In fact, we found significant relationships between age and MTA-ERC atrophy in MCI elderly adults. Similar findings were revealed in the relationship between MTA-ERC atrophy and educational level. Educational level was also a potential confounding factor of the prevalence and risk of dementia [44–46]. Educational level is thought to construct cognitive reserve, which modifies the relationship between brain atrophy and cognitive decline [47].

In the cognitive tests, WMS-R, LM I, DSC, and SCWT-IL showed significant correlations with MTA-ERC atrophy in univariate regression analysis. However, a multivariate regression model that included age and educational level revealed that MTA-ERC atrophy, i.e. high Z-score of VSRAD, was related only to SCWT-IL score in all subjects. Functional neuroimaging studies during executive tasks suggest that dorsolateral prefrontal cortex is responsible for maintenance of task demands and preparatory deployment of attention, and anterior cingulate

cortex is responsible for monitoring performance in order to detect cognitive and behavioral conditions with potential negative outcomes, and triggering dorsolateral prefrontal cortex to increase attention or change behavior [48–52]. A volumetric MRI study showed that there was an association between left hemisphere dorsolateral prefrontal cortex and anterior cingulate cortex atrophy and poorer attentional control accuracy. In the right hemisphere, atrophy of the temporal-parietal junction and ventrolateral and dorsolateral prefrontal cortices were associated with slower response times during attentional control on accurate trials [53]. This evidence from neuroimaging studies suggests that an executive deficit was caused by brain disorders in widespread regions that included prefrontal cortex, parietal lobe, and cingulate cortex. Neuropathological studies have shown that axonal pathology is strongly associated with cognitive impairment [54], and MCI patients may have increased white matter diffusivity in frontal and temporal regions [55]. The disruption of neural networks between the anterior and posterior cerebral areas, known as disconnection syndrome, during the initial stage of AD and MCI causes executive dysfunction, including changes in inhibition control [56–58]. Atrophy of the MTA is correlated with the degree of dementia and also with the extent of temporoparietal hypometabolism; both results are assumed to reflect changes in cerebral connectivity, especially between the MTA and the neocortex [59–61]. AD patients, as well as older adults with MCI, have shown selective disruption of default network intrinsic connectivity, most prominently in connectivity between the precuneus/posterior cingulate and medial temporal lobe regions [58, 61–64]. In diffusion tensor imaging study, the cingulum fibers, which connect the posterior cingulate gyrus and the hippocampus, may be compromised in the early stage of AD [65]. In recent years, Grambaite et al. [66] reported that frontal and temporal white matter diffusivity changes in the posterior cingulate region as well as the anterior cingulate region in MCI patients who had attention and executive dysfunctions. Reciprocal connections between the dorsolateral frontal cortex and anterior cingulate cortex [67–70] are part of a frontolimbic network [71, 72]. In the present study, MCI subjects showed a relationship between Z-score of the VSRAD and cognitive tests, especially tests of executive function. This relationship may be affected by not only MTA-ERC atrophy but also disconnectivity among MTA, temporoparietal, anterior cingulate, and prefrontal regions.

In a sub-analysis dividing subjects into two groups, the mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and DSC and SCWT-IL. The multivariate analysis on the mild to moderate atrophy group did not sustain the statement that DSC and SCWT-IL performances may be a reliable indicator of MTA-ERC atrophy in MCI patients. Increasing age is related closely with decreasing brain volume [38–42]. In fact, age remains the only significant variable indicating that its relative weight is too high and deletes the association between Z-scores and DSC and SCWT-IL observed in univariate models. In contrast, MTA-ERC atrophy was related closely to RCF-3 min and RCF-30 min in the severe atrophy group. In the multivariate regression model, MTA-ERC was associated independently with visual memory adjusted for age, educational level, and other cognitive functions. For the right temporal lobe there is some evidence that damage specifically in temporomesial structures may be the cause of impairments in nonverbal memory functions. Patients with hippocampal damage showed preoperatively [73] and postoperatively [74] impaired visual memory performance, whereas patients without hippocampal damage exhibited no deficiencies in visual memory. In line with previous operative studies, our results from MCI elderly adults with severe atrophy suggest a special involvement of MTA in visual memory performance. However, the VSRAD system was developed to measure the total atrophy in the bilateral parahippocampal gyrus and ERC. Thus, the association between visual memory and right hippocampal volume reduction should be investigated in the future.

It should be noted that this study may have been limited by a restricted sample. In addition, we did not include an analysis of genetic factors. Because genetic and physical factors such as apolipoprotein E genotype [75] and head size [76] may impact on neurodegenerative disorders and brain volume, analyzing genetic factors may extend the current results. Fitness level may have also acted as a confounding factor. Many studies have reported that physical activity can reduce the likelihood of the development of cognitive decline over time [77, 78]. Higher levels of fitness related to increased physical activity have been associated with enhanced neuronal survival in response to brain insult [79, 80], increased vascularization [81], and elevation of growth factors in areas important for memory [82]. More detailed analysis adjusting for these confounding variables will be required to further elucidate the relationship between MTA-ERC atrophy and memory function.

Overall, the present findings revealed that MTA-ERC atrophy was associated with age, educational level, and executive function, whereas no significant relationship

was found between MTA-ERC atrophy and memory tests in elderly subjects with MCI. This included the adults who had mild to moderate atrophy in MTA-ERC. In contrast, there was a significant relationship between MTA-ERC atrophy and visual memory test scores in elderly adults with severe MTA-ERC atrophy. These results suggest that executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy. A decline of visual memory function suggested severe MTA-ERC atrophy in elderly adults with MCI. Future research needs to determine the relationships between cognitive functions and brain atrophy except MTA-ERC in elderly adults with MCI.

Take Home Message

(1) MTA-ERC atrophy was significantly related to age, educational level, and executive function in elderly subjects with MCI.

(2) The subjects with severe MTA-ERC atrophy showed significant relationships between MTA-ERC atrophy and a decline in visual memory score.

(3) Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and decline in the RCF test suggests severe MTA-ERC atrophy in elderly adults with MCI.

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特集 脳神経外科医が知っておくべき薬物療法の知識

認知疾患治療ガイドライン2010に基づく薬物治療

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Drug Treatments for Alzheimer's Disease based on the Japanese AD Guideline

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There are many cases of dementia in Japan, the number is now over 3,000,000, and this situation is expected to only worsen given Japan's rapidly aging population. Because of this, most neurosurgeons are required to see dementia patients as part of their daily practice. There are four drugs used to treat Alzheimer's disease (AD) in Japan. Clinical registry of an AD drug trial was finished in 2011 in Japan. This trial showed that it is very important to choose the proper drug for each stage of dementia and BPSD. A compact version of the AD guideline was published in 2012. It contains a typical flow chart for the diagnosis and treatment policy in AD. Donepedil, garantamine, rivastigmine, and memantine were all shown to slow the decline in memory and ADL in AD patients, reduce the amount of care time, and also reduce patient care and drug expense. Donepedil which has good effect and few side-effects is a good drug for AD. Galantamine is good for patients with cerebrovascular disease and AD, especially. Rivastigmine is good for improving IADL in early AD. Memantine's strength is its ability to maintain memory function for a long time. Furthermore, good circumstances, proper care and adequate rehabilitation are also important to maintain patients' memory function and QOL.

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Key words : Alzheimer's disease, guideline, drug, treatment

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はじめに

認知症診療は今やすべての脳外科医にとって，避けては通れない状況になっている．現在アルツハイマー型認知症治療薬は4種類存在し，薬剤を適切に選択する時代となった．重症度やBPSD (behavioral and psychological symptoms of dementia)，患者背景に合わせて，適切に選択する必要がある．ドネペジルやガランタミン，リバスチグミン，メマンチンは認知機能の進行遅延のほか，ADLに関わる介護時間の短縮，介護の見守り時間の短縮，入所時期の遅延による医療費・介護費用の削減などの効果が報告されている．さらに認知症に対する良質なケアや脳リハビリが加われば，治療効果も向上する．その結果として，認知症の人や家族へのQOLの向上において重要な意義がある．そのためにも認知症診療において家族の指導，支援が重要となる．現在の治療薬では病気は完治しないが，病状を修飾することができ，病気の進行を遅延させることができる．すなわちこれらの薬剤の利点と欠点を知り，病期，症状に合わせて選択することが重要である．

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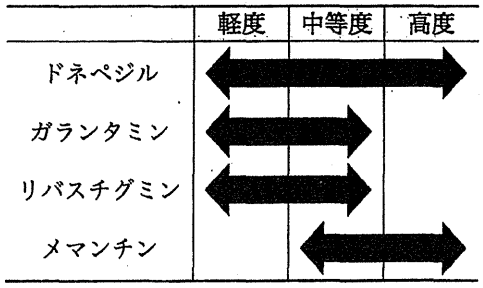
Table 1　New drugs for Alzheimer's disease

一般名	ドネペジル	リバスチグミン	ガランタミン	メマンチン
作用機序	アセチルコリンエステラーゼ阻害	アセチルコリンエステラーゼおよびブチリルコリンエステラーゼ阻害	アセチルコリンエステラーゼ阻害およびニコチン性アセチルコリン受容体へのAPL作用	NMDA受容体チャネル阻害
アルツハイマー型認知症の適応症	軽度～高度	軽度および中等度	軽度および中等度	中等度および高度
剤形	錠，細粒，口腔内崩壊錠，内用ゼリー	パッチ	錠，口腔内崩壊錠，内用液	錠
投与回数	1日1回	1日1回	1日2回	1日1回

（各薬剤の添付文書より）

Table 2　AD stage and drug selection



アルツハイマー型認知症治療における選択肢

アルツハイマー型認知症の4種類の薬が使用可能となり，診断の重要性とともに，ステージに合わせた治療やBPSDの治療が重要であり，薬剤を適切に選択する必要性がある（Table 1）．2010年には認知症疾患治療ガイドラインも発表されている[2]．さらに2012年にはコンパクト版2012が発表されている[3]．認知症の標準的な医療を行ううえで，これに従って診断，治療を行うことが望ましい．薬剤の種類としてはコリンエステラーゼ阻害剤が3種類とNMDA受容体拮抗剤が1種類である．初めに日本において，ドネペジル塩酸塩は，軽度，中等度，高度で投与することが承認されている．これをいわゆる「フルステージ診療」と呼ぶが，実際は予防から終末期医療までを含め，フルステージ診療と呼ぶほうが適切であろう．このことはかかりつけ医が一人の患者を長く，終末期まで連続してフォローする意味でもシームレスケアとも呼ばれている（ガイドライン・グレードA）．

治療戦略について

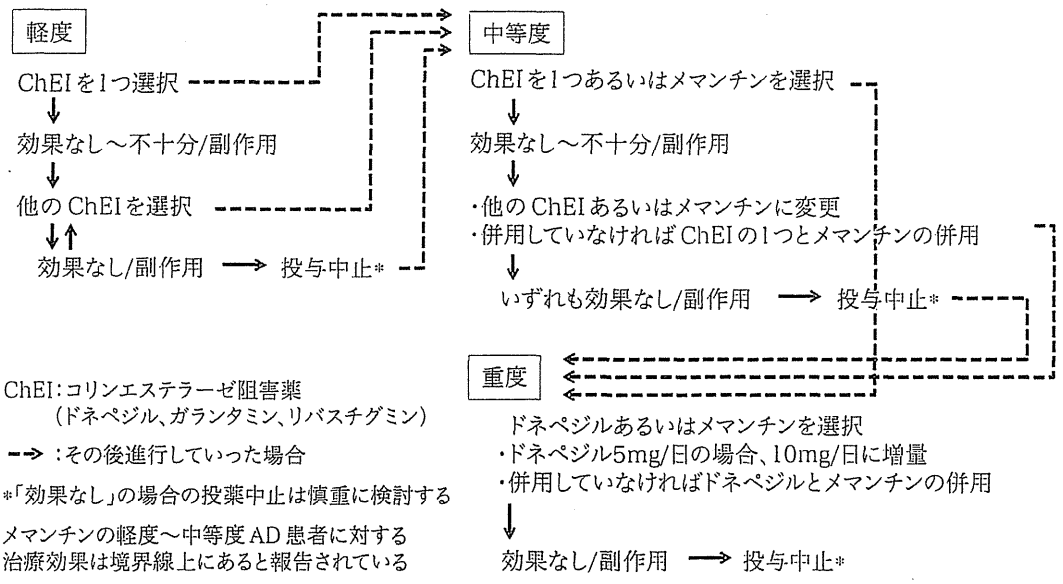
アルツハイマー型認知症治療薬にはそれぞれ適応の時期がある（Table 2）．承認された重症度に応じて薬剤を選択する必要があり，副作用や作用を適切に評価して，無効であれば，他の薬剤に変更したり，併用を検討する．また薬剤は認知症になってから始めるか，認知症の早期に治療を開始するのか，さらにMCIレベルから開始するのかはまだ十分なエビデンスはない．しかしながら薬剤の基礎的データからみれば，なるべく早期に治療を開始することが望ましいといえる．

治療薬の実際

アルツハイマー型認知症になると，脳内の神経伝達物質のアセチルコリンが減少し，記憶障害などの認知機能障害が現れる．コリンエステラーゼ阻害薬は，脳内のアセチルコリンを分解するコリンエステラーゼを選択的に阻害することで脳内のアセチルコリンを増加させる効果作用がある．

1 ドネペジル（アリセプト®）

ドネペジルは軽度，中等度であれば5 mgの投与を行うが，高度であれば10 mgへと増量する．アリセプトは認知機能の進行遅延のほか，ADLに関わる介護時間の短縮，介護の見守り時間の短縮，入所時期の遅延による医療費・介護費用の削減などの効果が報告されている．臨床家にとってドネペジル塩酸塩は長く使用経験があり，安心して用いることができる薬剤である．しかしながら実際には早期発見し，早期治療を開始することでより効果が高いことは知られており，さらに薬剤療法に留まら



(日本神経学会監修：認知症疾患治療ガイドライン 2010 コンパクト版 2012, 医学書院, 2012, p.139.)

Fig. 1 Algorism of AD drug selection

ず，なじみの環境を整えることや，よいケアの提供，さらには効果的な回想療法などの脳リハを併用することで効果が高まることはいうまでもない．ドネペジルは国内においてすでに 30 種類を超える後発品が出てきているが，品質の悪い製剤もあるため慎重に選択すべきである．たとえ後発品であっても，院外薬局サイドが決めるのではなく，医師が自ら後発品の種類を選定すべきである．

ガイドラインに従った一般的な治療のアルゴリズムを Fig. 1 に示した．すなわち軽度アルツハイマー型認知症の場合，初期の投与薬をまずコリンエステラーゼ阻害剤から 1 剤を選択し，2 カ月～3 カ月ごとに効果を観察し，6 カ月程度みても効果がみられない場合には他の薬剤に変更する．その際には薬剤の特徴を考慮する．中等度の場合にはメマンチンの単独のみならず，他のコリンエステラーゼ阻害剤との併用も選択肢として考慮する，また攻撃や興奮などの BPSD がある場合にはメマンチンを初期から投与することも考慮する．重度であればアリセプト 10 mg かメマンチン 20 mg を投与するか，または併用する．

最後に薬剤の中止時期については，嚥下障害などで食事がとれなくなった時，介護施設に入所した場合，病状が悪化した時などである．また重度化し，薬剤の効果が期待できないと判断された場合である．

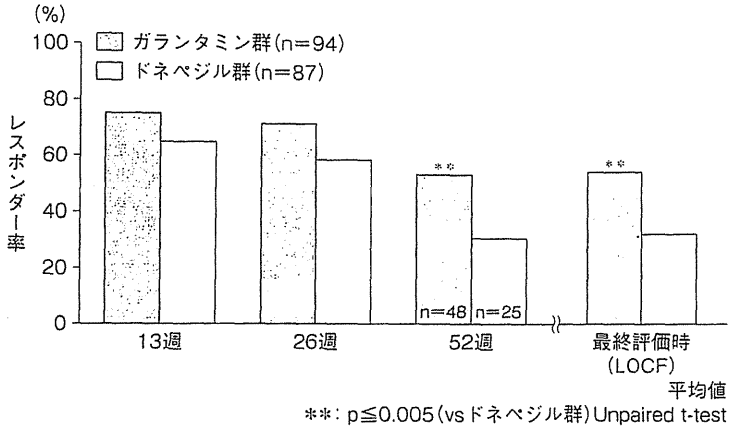
2 ガランタミン（レミニール®）

ガランタミンは軽度および中等度のアルツハイマー型認知症における認知症症状の進行抑制に適応が認められている[4)5)]．少量である 1 日 8 mg から開始し，4 週間経過観察後に順次 16 mg，24 mg へと増量する．本剤は朝夕 2 回に分けて服用する．本剤はコリンエステラーゼ阻害作用だけでなく，APL 作用や神経細胞保護などの他の薬剤にはない神経代謝改善作用があるために，中長期に使用した場合に他の薬剤より高い効果が得られる．APL 作用を加えることで，dual action と呼び，ガランタミンの長期使用時の有用性の高さについての根拠となる仮説である（Fig. 2）．つまりガランタミンは他のコリンエステラーゼ阻害剤より，長期に効果を示すことが報告されている[1)]．さらに神経細胞保護作用やアミロイドの蓄積に対する毒性に対して緩和する作用も報告されている．主な有害事象は嘔気等の消化器症状である．ガランタミンの投与にあたっては，低用量から導入し患者の状態を観察しながら，ゆっくりと増量することで忍容性を高め，治療を継続することが可能である．

3 リバスチグミン（リバスタッチパッチ®，イクセロンパッチ®）

リバスチグミンはコリンエステラーゼ阻害剤として，長期に投与した場合の有効性の報告もあり（Fig. 3），図に示すように IADL (instrumental ADL)（DAD [disability assessment of dementia] 尺度による）の改善効果もみられるため，認知症の早期または軽症に使用するとよい可能性がある．またパッチ剤の有用性として 1 日 1 回貼付の簡便な投与方法で効果を示す．さらに食事の有無および食事時間に配慮する必要がなく，他の併用薬剤の服薬

52週直接比較試験におけるレスポンダー率（海外データ：GBR-2）



**：p≦0.005（vsドネペジル群）Unpaired t-test

レスポンダーの定義：MMSEスコアがベースライン（0週）から改善または維持した症例をレスポンダーとした．

対象：アルツハイマー型認知症患者（MMSEスコア：9～18）188例

方法：ガランタミン群，ドネペジル群※に無作為に割り付け，MMSEの経時推移を52週間評価した．投与方法は，ガランタミンは8 mg/日より開始し，4週後に16 mg/日，13週後に医師の判断で24 mg/日とし，ドネペジルは5 mg/日より開始し，4週後に医師の判断で10 mg/日に増量した．

※日本でのドネペジルの用法・用量は，「通常，成人にはドネペジル塩酸塩として1日1回3 mgから開始し，1～2週間後に5 mgに増量し，経口投与する．高度のアルツハイマー型認知症患者には，5 mgで4週間以上経過後，10 mgに増量する．なお，症状により適宜減量する」．

（Wilcock G, et al.：*Drugs Aging* 20：777-789, 2003.）

Fig. 2　Responder rate in long-term galantamine treatment

時間による本剤の投与タイミングを制約する必要がない．介護者等が視覚的に容易に貼付状況（貼付の有無，投与量等）を確認できるため，薬剤アドヒアランスの向上が期待できる．

④ メマンチン（メマリー®）

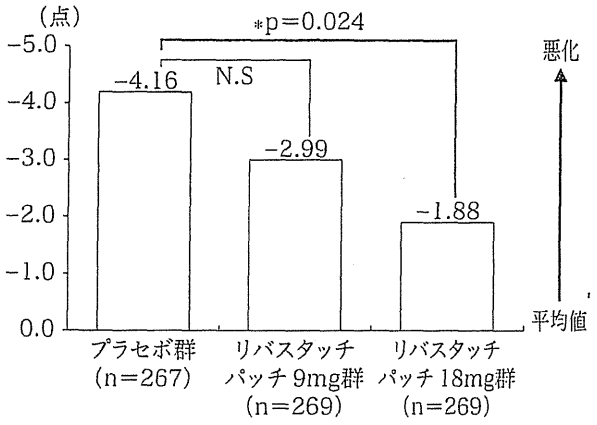
一方メマンチンはアセチルコリンエステラーゼ阻害薬とまったく違った作用機序で認知機能障害の進行を抑制することが確かめられている．アルツハイマー型認知症には，グルタミン酸神経系の機能異常が関与しており，グルタミン酸受容体のサブタイプであるNMDA受容体チャネルの過剰な活性化が原因の一つと考えられている．アルツハイマー型認知症の病態時は，シナプス間隙のグルタミン酸濃度の持続的な上昇によってNMDA受容が活性化され，細胞内へのCaイオンの流入，シナプティックノイズの発生などによって認知機能障害が引き起こされていると考えられている．メマンチンは，NMDA受容体拮抗作用により，神経細胞内への過剰なCaイオンの流入抑制による神経細胞保護効果と，シナプティックノイズの抑制による記憶・学習機能障害抑制作用を有するとされている．さらにメマンチンはコリンエステラーゼ阻害剤と併用するとより認知機能の進行を遅延させることが知られている（Fig. 4）．薬の効果は単独の場合より遅延し，3カ月後にピークがあり，その後比較的長期に持続する可能性がある．さらにメマンチンを長期投与した場合には対象群に比べ脳萎縮の程度が抑制されたとの報告もある．

BPSDの治療とケア

BPSDに対しては薬剤の適応がとれていない薬剤が多い．以前は抗精神病薬が用いられてきたが，最近では漢方薬の抑肝散のほか，リスペリドンやオランザピン，アリピプラゾールなどの非定型抗精神病薬が用いられるようになってきた．しかし米国ではこの種類の薬剤は脳卒中の発生率が高いとして，アルツハイマー型認知症には禁忌となっている．日本では副作用が少なく，有用性があるため，慎重に適応を判断し，使用されている．これらの薬剤では，副作用を軽減するためにも少量から投与することがポイントである．また認知症のBPSDには抑肝散がよく用いられている．副作用としては低カリウム血症に注意する．特にレビー小体病のBPSDには有効性が高いとされている．さらにメマンチンは興奮や攻撃などの周辺症状（BPSD）に有効であることが知られてい

る．頻度は低いが，傾眠傾向が報告されている．BPSDをコントロールすることは医師にとり重要であり，家族や本人の苦痛を取る意味においても重要である．

日常生活動作の評価（DAD）（国内後期第II相/第III相試験）



（承認時申請資料）

Fig. 3 Instrumental ADL improvement by rivastigmine

おわりに

アルツハイマー型認知症を早期に発見し，早期治療した場合に本剤のさらなる有用性に期待している．さらに長期使用時の効果についても一定のエビデンスが存在する．その有用性は確かであろう．しかし日本での効果の検証は今後一定の時間を経て判断する必要がある．ただし新薬に対する認知症の人や家族の期待は大きいが，効果に対する過剰な期待は問題である．

文　献

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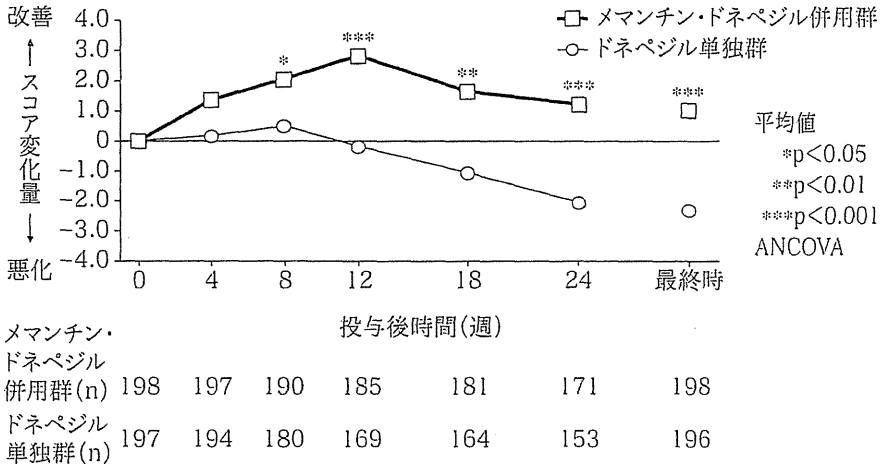

対象：50 歳以上の中等度から高度のアルツハイマー型認知症患者 403 例．
・NINCDS-ADRDA のアルツハイマー型認知症の診断基準を満たす．
・MMSE スコア 5 点以上 14 点以下．
・ドネペジル塩酸塩（以下，ドネペジル）の治療を 6 カ月以上受けている．
方法：ドネペジル（5〜10 mg）の治療を継続し，二重盲検下でメマンチンまたはプラセボを 1 日 2 回 24 週間，朝食後・昼食後に経口投与．メマンチンは 5 mg/日より開始し，1 週間に 5 mg ずつ増量していき，20 mg/日を維持用量とした．
（Tariot PN, et al.：*JAMA* 291：317-324, 2004.）

Fig. 4 Effects of donepedil and memantine combination therapy

要　旨

認知疾患治療ガイドライン 2010 に基づく薬物治療

遠藤　英俊

アルツハイマー型認知症の治療薬は 4 種類存在し，薬剤を適切に選択する時代となった．重症度や BPSD，患者背景に合わせて，適切に選択する必要がある．標準的な診療として認知症疾患治療ガイドラインコンパクト版 2012 が公表されており，ドネペジルやガランタミン，リバスチミン，メマンチンは認知機能の進行遅延のほか，ADL に関わる介護時間の短縮，介護の見守り時間の短縮，入所時期の遅延による医療費・介護費用の削減などの効果が報告されている．さらに認知症に対する良質なケアや環境，脳リハビリが加われば，治療効果も向上する．医師は認知機能だけでなく，本人の気持ちや尊厳，家族の介護負担にも配慮して治療にあたる必要がある．

脳外誌　21：765-770，2012

認知症の薬物療法の実際とその効果

遠藤　英俊

別　刷
日 本 医 師 会 雑 誌
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認知症の薬物療法の実際とその効果

遠藤英俊

キーワード○アルツハイマー病，治療薬，コリンエステラーゼ阻害薬，NMDA 受容体拮抗薬

はじめに

認知症診療は，今やすべての医家にとって避けては通れない状況になっている．現在アルツハイマー病治療薬は4種類存在し，重症度やBPSD（behavioral and psychological symptoms of dementia），患者背景に合わせて，薬剤を適切に選択する時代となった．ドネペジル塩酸塩（以下ドネペジル．アリセプト®）やガランタミン臭化水素酸塩（以下ガランタミン．レミニール®），リバスチグミン（リバスタッチ®，イクセロン®），メマンチン塩酸塩（以下メマンチン．メマリー®）は認知機能障害の進行遅延のほか，ADLにかかわる介護時間の短縮，介護の見守り時間の短縮，入所時期の遅延による医療費・介護費用の削減などの効果が報告されている．さらに，認知症に対する良質なケアや脳リハビリテーションが加われば治療効果も向上し，その結果として，認知症の人や家族へのQOLの向上において重要な意義がある．そのためにも認知症診療においては家族の指導，支援が重要となる．

現在の治療薬では病気は完治しないが，病状を修飾することができ，病気の進行を遅延させることができる．すなわちこれらの薬剤の利点と欠点を知り，病期，症状に合わせて選択することが重要である．

アルツハイマー病治療における選択肢

アルツハイマー病の4種類の薬が使用可能となり，診断の重要性と共に，ステージ診断やBPSDの評価が重要であり，薬剤を適切に選択する必要性がある（表1）．2010年には『認知症疾患治療ガイドライン2010』も発表されており[1]，これに従って診断，治療を行うことが望ましい．すなわち治療に当たり，知識と経験が必要とされる．

薬剤の種類としては，コリンエステラーゼ阻害薬が3種類とNMDA受容体拮抗薬が1種類ある．日本においてはまず，ドネペジルを軽度，中等度，高度で投与することが承認された．これをいわゆる「フルステージ診療」と呼ぶが，実際は予防から終末期医療までを含めてフルステージ診療と呼ぶほうが適切であろう．これはかかりつけ医が1人の患者を長く終末期まで連続してフォローする意味で，シームレスケアとも呼ばれている（推奨グレードA）．

臨床家にとってドネペジルは長く使用経験があり，安心して用いることができる薬剤である．しかしながら実際には，認知症は早期発見し，早期治療を開始することでより効果が高まることが知られており，さらに薬剤療法にとどまらず，なじみの環境を整えることや，良いケアの提供，さらには効果的な回想療法などの脳

The effects of drugs for Alzheimer's disease
Hidetoshi Endo : Department of General Medicine, National Center for Geriatrics and Gerontology
国立長寿医療研究センター内科総合診療部部長

表1　アルツハイマー病の治療薬

一般名 (製品名)	ドネペジル (アリセプト®)	ガランタミン (レミニール®)	リバスチグミン (イクセロン®, リバスタッチ®)	メマンチン (メマリー®)
作用機序	アセチルコリン エステラーゼ阻害	アセチルコリン エステラーゼ阻害 および ニコチン性アセチルコリン 受容体へのAPL作用	アセチルコリン エステラーゼ および ブチリルコリン エステラーゼ阻害	NMDA受容体 チャネル阻害
剤型	錠，細粒，口腔内 崩壊錠，内服ゼリー	錠，口腔内崩壊錠， 内用液	パッチ剤	錠
投与回数	1日1回	1日2回	1日1回	1日1回

(各薬剤の添付文書より作成)

リハビリテーションを併用することで効果が高まることは言うまでもない．

ドネペジルは国内においてすでに30種類を超える後発品が出てきているが，品質の悪い製剤もあるため慎重に選択すべきである．たとえ後発品であっても，院外薬局サイドが決めるのではなく，医師が自ら後発品の種類を選定すべきである．

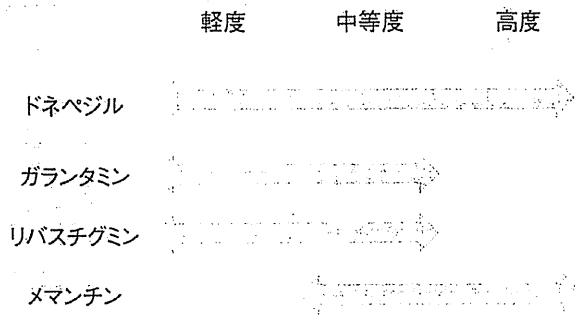

図1　認知症治療薬と適応時期

II 治療戦略について

アルツハイマー病治療薬にはそれぞれ適応の時期がある（図1）．承認された重症度に応じて薬剤を選択する必要があり，副作用や作用を適切に評価して，無効であれば他の薬剤に変更したり，併用を検討する．また，薬剤は認知症になってから始めるか，認知症の早期に治療を開始するのか，さらにMCIレベルから開始するのかについてはまだ十分なエビデンスはない．しかしながら薬剤の基礎的データからみれば，なるべく早期に治療を開始することが望ましいといえる．

III 治療薬の実際

アルツハイマー病になると，脳内の神経伝達物質のアセチルコリンが減少し，記憶障害などの認知機能障害が現れる．コリンエステラーゼ阻害薬は，脳内のアセチルコリンを分解するコリンエステラーゼを選択的に阻害することで脳内のアセチルコリンを増加させる効果作用がある．その点でドネペジル，ガランタミン，リバスチグミンはガイドラインでは推奨グレードAとされている．

1. ガランタミン

ガランタミンは軽度および中等度のアルツハイマー病における認知症症状の進行抑制に適応が認められた新しい薬剤である．1日8mgの少量から開始し，4週間の経過観察後に順次16mg，24mgへと増量する．朝夕2回に分けて服用する．

本剤はコリンエステラーゼ阻害作用だけでなく，APL(allosteric potentiating ligand)作用や神経細胞保護など他の薬剤にはない神経代謝改善作用があるため，中長期に使用した場合に他の薬剤より高い効果が得られる[2,3]．Dual action