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お知らせ

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Editorial

Non-pharmacological intervention for dementia patients

OWING TO THE prolonged average life span of human beings since the 19th century, the ratio of the elderly population in the world has rapidly increased, and it will continue to increase, especially in developing regions, including Asia. One consequence of increased longevity is the growing prevalence of dementia in these regions, especially in Asia.[1] In the year 2005, there were 13.7 million dementia patients in the Asian region (5.5 million in China, 3.2 million in India, and 1.9 million in Japan) and this number is expected to increase to 64.6 million (27.0 million in China, 16.3 million in India, and 4.9 million in Japan) by the year 2050.[1] Reflecting the faster increase of the elderly population in developing countries, more dementia patients will be observed in Asia, and in other developing countries, than in developed countries in the near future.[2]

Donepezil, a choline esterase inhibitor, was developed and approved in Japan in November 1999, and it has been the only drug for Alzheimer's disease available in Japan for 12 years. This year (2011), three new compounds (galantamine, rivastigmine, and memantine) have been approved for Alzheimer's disease by the Japanese Government, which has provided alternatives for patients.[3] Even though all of these drugs, including donepezil, are only symptomatic,[4] the possibility of a choice of drugs is certainly favorably accepted by patients and doctors. These drugs will not cure Alzheimer's disease, leaving a similar or even higher number of patients to be treated.

Recognizing the limited benefits of the symptomatic drugs, the development of the disease-modifying drug for Alzheimer's disease is the urgent target for research laboratories and pharmaceutical companies.[5] There are more than 100 compounds searched for and considered for the disease-modifying drug, and some compounds have successfully undergone pre-clinical studies and have been put forward to clinical trials; however, all compounds tested in clinical trials for Alzheimer's disease have failed to demonstrate clinical usefulness in the past 2 decades.

The list of unsuccessful compounds evaluated in clinical trials for Alzheimer's disease includes AN1792 amyloid vaccine (Elan, 1992), atorvastatin (HMG CoA reductase inhibitor, Pfizer), simvastatin (drug for hyperlipidemia, Banyu), Dimebon (antihistaminergic drug, Pfizer, 2010), Ginko biloba (mitochondrial membrane stabilization, and antioxidant effect), tarenflurbil (non-steroidal anti-inflammatory drug, gamma-secretase modulator, Myriad, 2009), phenserine (choline esterase inhibitor, amyloid-beta production inhibitor), rosiglitazone (anti-diabetes drug, insulin resistance, Glaxo-Smith-Kline), tramiprosate (amyloid-beta aggregation inhibitor, Neurochem, 2007), and xaliproden (5-HT1A agonist for amyotrophic lateral sclerosis).

After paying a huge loss of labor, time, and money, researchers are still struggling to determine the reasons for the consecutive failures in developing the disease-modifying drugs for Alzheimer's disease, discussing the discrepancy between animal studies and human clinical trials, the measure of efficacy evaluation in clinical trials, and the validity of the amyloid cascade hypothesis. Considering the difficulty of developing new drugs for Alzheimer's disease, it might be time to think over the possibility of treatment from broader perspectives.[6–8] In this article, complementary and alternative medicine (CAM) for Alzheimer's disease will be briefly reviewed[9] and the present state of non-pharmacological treatment will be discussed.

SOCIAL ASPECT OF DEMENTIA

Dementia is a syndrome associated with a progressive loss of memory and cognitive functions that is serious enough to interfere with performing the tasks of daily life. The loss of memory and cognitive function is caused by a variety of disorders, most commonly in the elderly by neurodegenerative disorders, including Alzheimer's disease. Dementia can occur to anyone at any age from an injury or from oxygen deprivation, although it is most commonly associated with aging. It is the leading cause of institutionalization of the elderly. Along with the progression of cognitive impairment due to dementia, the capacity of performing the tasks of daily life is deteriorated. As shown in Figure 1, complex social life capacity is

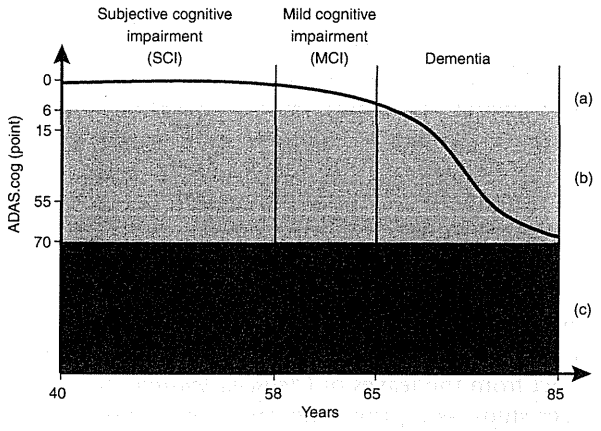

Figure 1. Most people notice memory decline when they become 40 years old on average (subjective cognitive impairment [SCI]), in which the whole capacity including social life, personal life, and biological life are preserved. Some may show mild cognitive impairment (MCI), in which social life capacity is impaired. In dementia stage, social life capacity and personal life capacity are impaired but the biological life capacity is preserved.
(a) Social life capacity. (b) Personal life capacity. (c) Biological life capacity.

gradually deteriorated due to memory impairment during subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) stages, even before the clinical diagnosis of dementia. When the diagnosis of dementia is given, the patient is no more able to function in social life, and their personal capacity will further deteriorate with the progression of the disease; however the biological life capacity will be maintained until the end of life (Fig. 1).

The tasks of daily life are different for each individual, and the timing of diagnosis of dementia may depend on the previous social and occupational complexity of the patient's daily life. If a patient has higher premorbid intellectual function, it is usual that the patient is not diagnosed as having dementia, even though the pathological process in the brain is far advanced, because the patient usually shows a score higher than the cut-off value of a screening test like the Mini Mental State Examination.[9] In this respect, even the diagnosis of dementia is influenced by social factors,[10] including premorbid IQ, level of education, occupation, and complexity of daily life.[6]

The symptoms of Alzheimer's disease differ for each individual patient. At the onset of dementia in some patients, certain personality traits that had been well controlled in the past become accentuated, whereas in others there is a 'loss of personality', where the uniqueness of the patient's personality is lost. Some patients show a more rapid deterioration of cognitive function, whereas others show a slower rate of cognitive decline. Some patients exhibit various types of behavioral and psychological symptoms of dementia (BPSD), whereas others exhibit few abnormal behaviors. Furthermore, the physical, personal, familial, economic, and social environments differ between patients. Thus, each patient should be evaluated as an individual in terms of the needs for intervention, taking into account previous social functioning, family structure, and the patient's living environment in order to deliver the most appropriate care. Interventions for dementia patients need to be individualized further, taking into consideration the different genetic, environmental, and social factors that are specific to each patient.[11–14]

CAM FOR DEMENTIA

Although modern medical science has enabled correct diagnoses to be made and proper treatments to be initiated for acute diseases caused by exogenous pathogenic factors, there are still numerous chronic, incurable diseases caused by endogenous factors, such as dementia, cancer, hypertension, diabetes, chronic pain etc., for which there is no effective treatment, leaving patients with these conditions to suffer. To facilitate the better management of these chronic diseases, recent attention has focused on the use of CAM, together with Oriental and traditional medicines[1,9,14,15] and non-pharmacological intervention.[12] CAM is defined by the American Cancer Society as '. . . supportive methods used to complement evidence-based treatment. Complementary therapies do not replace mainstream treatment and are not promoted to cure disease. Rather, they control symptoms and improve well-being and quality of life.' In contrast, alternative therapies, or alternative medicine, involve non-mainstream treatments that are sometimes used by patients instead of orthodox treatments.

Reflecting the lack of effective medicine to cure most of dementia, including Alzheimer's disease, a variety of CAM are applied without supporting evidences.[16] Since the symptoms of dementia (even the diagnosis, as mentioned above) are influenced by the social factors of each patient, the effectiveness of CAM is not guaranteed to all of the patients. Some

CAM are effective for some patients, but the same CAM is not effective for other patients. There are scarce data of the effectiveness of CAM and their usefulness with scientifically verified statistical analysis, which could be one of the reasons why so many different kinds of CAM are tried in public.[17]

CAM for dementia include off-label-use of drugs, Chinese herbal medicine, natural supplements, food, exercise, leisure activities, lifestyle, and non-pharmacological interventions. Examples of off-label use of approved drugs (alternative medicine) for dementia are Ginko biloba, acetyl-L-carnitine, lecithin, piracetam, curcumin, vinpocetine, phosphatidylserine, and others.[18]

In Asian countries, Chinese herbs are traditionally used for dementia and other medical conditions, from which active components are extracted for the treatment of dementia. Due space limitations, only the popular examples are briefly described below. Galantamine is originally extracted from *Galanthus woronowii*, a plant of the Amaryllidaceae family, and is now approved as the drug for Alzheimer's disease, marketed worldwide by Janssen Pharmaceuticals.[19] Ginkgo biloba leaf preparations have been marketed in Germany and France for 30 years for the treatment of cardiovascular disease, cerebrovascular disease and dementia, and are sold as natural supplements in the USA and other countries. Huperzin A is an extract from *Huperzia serrata* (*Qian Ceng Ta*) for its potent acetylcholine esterase inhibitor action. Huperzine A is widely used as an effective cognitive enhancer for dementia patients in China and in other countries.[20] Ginsenosides extracted from Panax ginseng are shown to improve learning and memory function through the mechanism of increasing acetylcholine level and also density of muscarinic receptors.[21] Ursolic acid extracted from *Salvia officinalis* is shown to have neuroprotective effects and inhibit acetylcholine esterase *in vitro*, showing memory improvement in clinical study. Epigallocatenin-3-gallate is the active component of green tea, a popular daily drink for Asian people, which has shown to have neuroprotective and antioxidative activity. Curcumin, an extract from the Curcuma root, is shown to be effective for improving learning and memory, which is also shown to decrease amyloid-beta by gamma-secretase inhibitor activity. Clausenamide, a major component of aqueous extract from the leaves of *Clausena lansium*, has been under study as a promising candidate for dementia treatment. The list of the compounds extracted from Chinese herbs is growing, and these are only some examples of the compounds that can be developed for drugs for dementia. A more complete list is available in the literature.[22]

NON-PHARMACOLOGICAL INTERVENTION FOR ALZHEIMER'S DISEASE

Four drugs (donepezil, rivastigmine, galantamine, and memantine) are now available in Japan and many other countries. The benefits for patients treated with one of these drugs (some are treated with a combination of acetylcholine esterase inhibitor and N-Methyl-D-aspartate antagonist) are not satisfactory. Even though the treated patient may show some cognitive improvement for several months, they show a similar level of cognitive function after 1 year or so, showing the same rate of cognitive decline as untreated patients (Fig. 2).

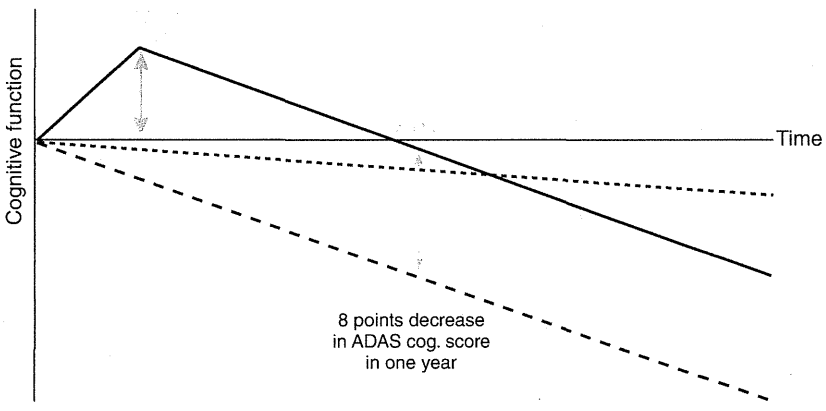

Figure 2. Broken line (– –) shows natural course of cognitive decline with dementia patients. Solid line (——) shows the cognitive function of the patients treated with symptomatic drugs such as AChE inhibitors. Short broken line (- - -) represents the cognitive decline of the patients treated with disease-modifying drugs.

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Table 1. Non-pharmacological intervention to Alzheimer patients

Therapy	Cognitive	ADL	BPSD
Cognitive training	+	+	+
Cognitive rehabilitation	+	+	+
Cognitive stimulation therapy	+	+	+
Snoezelen/multisensory stimulation	+	+	+
Reality orientation	+	+	+
Reminiscence therapy	+	–	+
Validation therapy	+	–	+
Physical activity	+	+	+
Light therapy	+	–	+
Music therapy	+	–	+
Aromatherapy	–	–	+
Animal-assisted therapy	–	–	+

ADL, activities of daily living; BPSD, behavioral and psychological symptoms of dementia.

Patients, caregivers, and medical professionals have been searching for an effective intervention for Alzheimer's disease, and there are a variety of non-pharmacological interventions commonly applied to Alzheimer patients. The limited efficacy of drug therapy and the plasticity of the human brain are the two main reasons that explain this growing interest in non-pharmacological intervention for dementia patients. In Table 1, non-pharmacological interventions are listed with the positive results of published randomized controlled trials (RCT) that have targeted at least one of the symptoms of dementia. The symptoms are grouped under three headings: cognitive function, activities of daily living (ADL), and BPSD. Some popular non-pharmacological interventions are discussed in the frame of two main approaches: cognitive approaches, multi-strategy approaches (reality orientation, reminiscence therapy and validation therapy), and miscellaneous approaches (Table 1).

COGNITIVE TRAINING, COGNITIVE REHABILITATION, COGNITIVE STIMULATION THERAPY

Cognitive training has been frequently mislabeled or conflated with other ill-defined therapies, such as cognitive rehabilitation, and cognitive stimulation therapy. Cognitive training is defined as the structured practice of complex mental activity in order to enhance cognitive function. An operational definition of cognitive training, delineating from other interventions, includes repeated practice, on problem activities, using standardized tasks, and target-specified cognitive domains.[23] Cognitive training can be further distinguished to include training in applied memory strategies versus repetitive cognitive exercises. Training in memory strategies involves the instruction and practice of techniques to minimize memory impairment and enhance performance, and involves learning and practicing strategies, such as the method of loci, mnemonics, and visual imagery. In contrast, cognitive exercise requires the repeated practice of targeted cognitive abilities in a repetitions-sessions format: users typically carry out a number of iterations of a cognitive task in one session, then continue to new tasks in the next session, and eventually return to further train the original task at a harder level in future sessions (i.e., staircase design). Recently, several software applications have been developed that implement cognitive exercises on computer.

There is evidence from a modest number of well-conducted RCT that cognitive training, cognitive rehabilitation, and cognitive stimulation therapy confer modest but significant benefits in the treatment of cognitive symptoms of Alzheimer patients. A meta-analysis of longitudinal RCT of cognitive training in cognitively healthy adults demonstrated efficacy on primary cognitive outcomes.[23]

The systematic review found that cognitive training can produce moderate-to-large beneficial effects to MCI subjects on memory-related outcomes. However, the number of high-quality RCT remains low, and so further trials must be a priority.

Cognitive rehabilitation also appears to result in functional benefits in Alzheimer patients. The modest number of RCT focusing on cognitive training in Alzheimer patients is consistent with the results of larger cognitive training trials in healthy older people.

The best evidence base is for cognitive stimulation therapy, although this approach is labor-intensive, and requires further evaluation of cost-effectiveness. There is currently no evidence that brain-training games provide any significant benefit to people with Alzheimer's disease.[24]

SNOEZELEN/MULTI-SENSORY STIMULATION

The concept of Snoezelen was originally developed in the late 1970s by Dutch therapists, Jan Hulsegge

and Ad Verheul as therapy for children with autism and other learning disabilities. Snoezelen or multisensory stimulation (MSS) is visual, auditory, tactile, and olfactory stimulation offered to people in a specially designed room, which relates to the interdependence of both the space (the physical environment) and the 'client-centered' approach of the practitioner (the human environment). This specially designed sensory physical environment, together with the input of the 'enabling practitioner' initiates changes in arousal by affecting the relaxation process, which aims to maximize a person's potential to focus on his own free will and to engage on a motivational stimulus, and thereby to improve communication and functioning. The clinical application of Snoezelen has been extended from the field of learning disability to dementia care over the past decade. The rationale for its use lies in providing a sensory environment that places fewer demands on intellectual abilities but capitalizes on the residual sensorimotor abilities of people with dementia. Practitioners are keen to use Snoezelen in dementia care, and some encouraging results have been documented in the area of promoting adaptive behaviors. Positive results were reported across a range of behaviors, including a reduction in apathy in people in the later stage of dementia from two RCT. In a Cochrane database review published in 2002, only two trials were reviewed and no firm conclusion was reached, even though both studies examined the short-term values of Snoezelen on people with dementia.[25]

REALITY ORIENTATION

Alzheimer's disease patients may withdraw from contact with others and the environment as they become increasingly disoriented, which results in a lack of sensory stimulation. To prevent this understimulation from sensory inputs, 'reality orientation' was developed. It is based on the belief that continually and repeatedly telling or showing certain reminders to people with mild-to-moderate memory loss will result in an increase in interaction with others and improved orientation. This in turn can improve self-esteem and reduce problem behaviors.

Reality orientation can be taught to caregivers and family members; it can be performed in the home and should be structured around the area in which the patient spends most of his or her time. For example, access to a window is recommended to facilitate orientation to the time of day and the weather. Other than the environmental cues, familiar objects to the patients can be used to stimulate their memory in reality orientation, such as a family scrapbooks, flash cards, Scrabble games, a globe, and large-piece jigsaw puzzles.

The effectiveness of reality orientation in dementia was evaluated by conducting a systematic literature review. This yielded 43 studies, of which, six were RCT meeting the inclusion criteria (containing 125 subjects.) Results were subjected to meta-analysis. Effects on cognition and behavior were significant in favor of treatment. The evidence indicates that reality orientation has benefits on both cognition and behavior for dementia patients. However, a continued program may be needed to sustain potential benefits.[26]

REMINISCENCE THERAPY

Reminiscence therapy is frequently used for patients with impaired memory, paying respect to the life and experiences of the individual with the aim to help the patient maintain good mental health. In one approach, participants are guided by a trained person to reflect on a variety of aspects relating to their lives. This may be themed and centered on one period in time or it may be wider and reflect a guided discussion through an issue. The therapist may use music, photographs, replica documents, drama and sensory gardens to stimulate debate and discussion for the participants. Reminiscence therapy is believed to be useful in supporting confused patients to integrate into new living arrangements by acknowledging and respecting their life history. Reminiscence therapy is believed to promote a sense of security by reviewing comforting memories.

The effect of reality orientation was compared with reminiscence therapy for elderly people in a large residential home, using a controlled cross-over design. Both kinds of therapy group were enjoyed by both staff and residents, and enabled staff to get to know moderately and severely confused residents. The group that received reality orientation followed by reminiscence therapy showed improvement in cognitive and behavioral measures, which was not found in the other two groups. It may be important to use reality orientation techniques with dementia residents before involving them in a reminiscence group.[27]

VALIDATION THERAPY

The validation therapy was developed by Naomi Feil in an attempt to address the shortcomings of other approaches, such as reality orientation, used with individuals who have more advanced dementia. Feil developed a model that sought to classify the stage of dementia that an individual has reached according to cognitive and behavioral signs. Its development was the result of an attempt to provide practical solutions for difficulties experienced by patients and caregivers. Important features of validation therapy include: a means of classifying behaviors; provision of simple, practical techniques that help restore dignity; prevention of deterioration into a vegetative state; provision of an empathic listener; respect and empathy for older adults with Alzheimer's disease, who are struggling to resolve unfinished business before they die; and acceptance of the person's reality.[28]

The way in which these values are applied to provide specific interventions depends on the severity of dementia in each individual case classified into four stages: Mal orientation, Time Confusion, Repetitive Motion and Vegetation. Each stage is identified by specific cognitive and behavioral characteristics, and specific validation therapy interventions address the different cognitive and behavioral features manifested by people with dementia at each of these stages, relying upon the central 14 techniques.[28]

Various observational studies have indicated that there are positive effects in using validation therapy in terms of the amount and duration of interactions that participants are able to make during validation groups.[29,30] However, other studies have found no significant effects of validation therapy.[31]

OTHER NON-PHARMACOLOGICAL INTERVENTIONS

There are many other non-pharmacological interventions applied to Alzheimer patients. Physical activity, especially aerobic exercise, is believed beneficial to cognitive function, improving ADL and ameliorating some forms of BPSD. Light therapy is sometimes used to keep the circadian rhythm of dementia patients in daily life, and there are RCT reporting beneficial effects to cognitive function and BPSD. Music therapy is one of the most popular day care programs in residential care as well as day care institutions. Listening to music, singing and playing music is a popular leisure activity for dementia patients, through which some small benefit to cognitive function is also reported. Aroma oils often gives pleasant feelings and calming effect to patients showing BPSD, especially agitation and aggression. Animal-assisted therapy is reportedly effective to reduce the BPSD of dementia patients.

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Masatoshi Takeda, MD, PhD,
Toshihisa Tanaka, MD, PhD,
Masayasu Okochi, MD, PhD and
Hiromitsu Kazui, MD, PhD
Department of Psychiatry, Osaka University Graduate School of Medicine
Suita, Japan

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Original Research Article

Different Characteristics of Cognitive Impairment in Elderly Schizophrenia and Alzheimer's Disease in the Mild Cognitive Impairment Stage

Hiroaki Kazui[a] Tetsuhiko Yoshida[a, b] Masahiko Takaya[a] Hiromichi Sugiyama[a] Daisuke Yamamoto[a] Yumiko Kito[a, c] Tamiki Wada[a] Keiko Nomura[a] Yuka Yasuda[a] Hidenaga Yamamori[a] Kazutaka Ohi[a] Motoyuki Fukumoto[a] Naomi Iike[a] Masao Iwase[a] Takashi Morihara[a] Shinji Tagami[a] Eku Shimosegawa[d] Jun Hatazawa[d] Yoshiyuki Ikeda[e] Eiichi Uchida[e] Toshihisa Tanaka[a] Takashi Kudo[a] Ryota Hashimoto[a, f] Masatoshi Takeda[a]

[a]Psychiatry, Department of Integrated Medicine, Division of Internal Medicine, Osaka University Graduate School of Medicine, [b]Department of Psychiatry, National Hospital Organization Osaka National Hospital, [c]Department of Psychiatry, Nissay Hospital, [d]Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine, [e]Department of Radiology, Uchida Clinic, and [f]Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Kanazawa University and Hamamatsu University School of Medicine, Osaka, Japan

Key Words
Alzheimer's disease · Attention deficit · Delayed recall · Executive function · Recent memory · Three-dimensional stereotactic surface projections · Voxel-based specific region analysis · Working memory

Abstract
We compared indices of the revised version of the Wechsler Memory Scale (WMS-R) and scaled scores of the five subtests of the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) in 30 elderly schizophrenia (ES) patients and 25 Alzheimer's disease (AD) patients in the amnestic mild cognitive impairment (aMCI) stage (AD-aMCI). In the WMS-R, attention/concentration was rated lower and delayed recall was rated higher in ES than in AD-aMCI, although general memory was comparable in the two groups. In WAIS-R, digit symbol substitution, similarity, picture completion, and block design scores were significantly lower in ES than in AD-aMCI, but the information scores were comparable between the two groups. Delayed recall and

Hiroaki Kazui, MD, PhD

Psychiatry, Department of Integrated Medicine, Division of Internal Medicine
Osaka University Graduate School of Medicine, D3 2-2 Yamadaoka, Suita-City
Osaka 565-0871 (Japan)
Tel. +81 66 879 3051, Fax +81 66 879 3059, E-Mail kazui@psy.med.osaka-u.ac.jp

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forgetfulness were less impaired, and attention, working memory and executive function were more impaired in ES than in AD-aMCI. These results should help clinicians to distinguish ES combined with AD-aMCI from ES alone.

Introduction

Schizophrenia is a common psychiatric disease with onset usually occurring during adolescence or early adulthood. Recently, new atypical antipsychotic drugs for schizophrenia have been developed, and social systems to support schizophrenia patients have been established. As a result, schizophrenia patients are now living longer than they used to [1], and the number of elderly schizophrenia (ES) patients is increasing. The number of Alzheimer's disease (AD) patients has also increased due to the rapid aging of society. Although the incidence of AD rises with age, AD also occurs in younger patients; the prevalence rate of AD in people aged ≤64 years is 0.12 cases per 1,000 people (http://www.mhlw.go.jp/houdou/2009/03/h0319–2.html; Japanese Ministry of Health, Labor and Welfare). Therefore, there are many ES patients who also have AD, and their number is supposed to be increasing. In clinical settings, there is a growing need to differentiate between age-related and AD-related cognitive impairment in patients who have developed schizophrenia in adolescence or middle age.

Because some clinical characteristics of schizophrenia and AD are similar, differentiation between ES and AD can be difficult. Neuropsychiatric symptoms, such as apathy, poverty of speech, and delusional thinking, are common in both types of patients. Neuroimaging studies have shown volume loss in the hippocampus [2] and in the frontal lobe [3] in schizophrenia, and similar losses have been observed in AD [4]. Furthermore, patients with schizophrenia are impaired in various domains of cognition, such as memory, working memory, and executive function [5]. These symptoms are also observed in patients with AD.

Acetylcholine esterase inhibitors have been developed for the treatment of AD. Although administration of these agents does not result in a radical improvement of symptoms, their early administration can improve the prognosis of AD patients [6]. In addition, disease-modifying drugs for AD are now being developed. Thus, early diagnosis and early initiation of treatment are important in AD patients. One method to identify early AD with a high probability is the measurement of amnestic mild cognitive impairment (aMCI), which is a syndrome characterized by memory performance below the age norm, while intellectual functioning and activities of daily living are otherwise unimpaired [7]. A substantial proportion of patients with aMCI later develop clinically diagnosable AD [7]. In order to treat early-stage ES patients who have AD in the aMCI stage (AD-aMCI) for AD, it is necessary to differentiate between ES combined with AD, and ES alone. As a first step toward this goal, in this study, we clarified the degree of cognitive impairment in patients with ES compared to patients with AD-aMCI.

Methods

Subjects

All patients in this study were recruited from the Department of Neuropsychiatry of the Osaka University Medical Hospital, which includes Schizophrenia and Neuropsychological Clinics. At both clinics, patients underwent standard neuropsychological examinations as well as routine laboratory tests and cranial magnetic resonance imaging (MRI). Single pho-

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Table 1. Comparison of characteristics of the ES and AD-aMCI groups with and without WAIS-R

Characteristics	ES group			AD-aMCI group		
	with WAIS-R	without WAIS-R	p value	with WAIS-R	without WAIS-R	p value
Sex, male/female	5/9	10/6	0.14	7/6	7/5	0.57
Age, years	56.6 ± 5.5	57.1 ± 5.7	0.79	72.6 ± 6.0	70.2 ± 9.5	0.44
Education, years	13.1 ± 2.6	13.3 ± 2.2	0.79	13.7 ± 3.3	13.4 ± 1.8	0.8
MMSE total score	–	–	–	26.1 ± 1.9	27.0 ± 2.1	0.27
WMS-R GM index	81.3 ± 15.5	79.1 ± 17.0	0.75	80.5 ± 13.1	74.9 ± 6.1	0.19
WMS-R AC index	84.8 ± 10.3	94.8 ± 16.0	0.09	99.8 ± 11.1	97.3 ± 12.7	0.59
WMS-R DR index	75.9 ± 15.9	76.6 ± 18.4	0.92	61.5 ± 9.7	55.8 ± 6.5	0.1

ton emission computed tomography (SPECT) was performed on patients with aMCI at the Neuropsychological Clinic. The clinical and investigative data were collected in a standardized manner and were entered into each registry. In this study, we selected patients with ES and patients with AD-aMCI who met the inclusion criteria mentioned below for each group from the registry. In the Schizophrenia Clinic, we began using the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) in March 2004 and then switched to the third version of the WAIS (WAIS-III) in October 2006. In the Neuropsychological Clinic, we began using five subtests of the WAIS-R in September 2002 and switched to five subtests of the WAIS-III in February 2009. In this study, we selected patients who were evaluated with the WAIS-R, because few patients with AD-aMCI were evaluated with the WAIS-III and then followed up until they reached the dementia stage. The revised version of the Wechsler Memory Scale (WMS-R) has been used in both clinics as a memory test because the third version of the WMS (WMS-III) is not standardized and cannot be used in Japan. In both clinics, the WMS-R was usually used before the WAIS-R. However, in some cases, there was no opportunity to use the WAIS-R.

ES Group

Thirty patients with schizophrenia (15 women and 15 men) were selected from the Schizophrenia Clinic registry. The mean age of the patients was 56.9 ± 5.5 years, and the mean years of education were 13.2 ± 2.3. All subjects in the ES group (1) met the criteria for schizophrenia based on the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR); (2) were aged ≥50 years [8]; (3) showed first symptoms of schizophrenia before 65 years of age; (4) had been evaluated by either the WMS-R or the WAIS-R; (5) had no other neurological disease, and (6) had no evidence of focal brain lesions on MRI. Of the 30 patients, 14 were given the WAIS-R (group with WAIS-R) and the other 16 were not given the WAIS-R (group without WAIS-R). There were no significant differences in gender, age, education, or WMS-R indices between the ES groups with and without WAIS-R (table 1). Other demographic data on the ES group are summarized in table 2. Mean duration of hospitalization was short, although mean duration of disease was long. Many patients received atypical antipsychotic drugs at the time of neuropsychological assessment in this study. There were no significant differences between the groups with and without WAIS-R in any of the items except for the positive/negative symptom scores of the Positive and Negative Syndrome Scale (PANSS). Both PANSS scores were higher in the group without WAIS-R than in the group with WAIS-R. Four of the 30 patients with ES were not given the WMS-R.

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Table 2. Characteristics of the ES group

Characteristics	ES with WAIS-R mean ± SD	ES without WAIS-R mean ± SD	p value	Total mean ± SD (range)
Age of disease onset, years	32.3 ± 12.0	30.1 ± 12.3	0.64	31.1 ± 12.0 (19.0–61.0)
Duration of untreated psychosis, years	3.6 ± 6.5	4.1 ± 8.4	0.87	3.9 ± 7.5 (0–26)
Duration of disease, years	23.8 ± 11.7	27.4 ± 10.7	0.41	25.8 ± 11.1 (1–45)
Total duration of hospitalization, months	14.0 ± 12.2	9.7 ± 19.6	0.56	11.4 ± 16.8 (0–72)
Daily dose of antipsychotic drugs (chlorpromazine equivalent), mg	554.7 ± 283.6	469.1 ± 387.6	0.5	509.0 ± 340.0 (0.0–1,300.0)
Daily dose of atypical antipsychotic drugs (chlorpromazine equivalent), mg	485.7 ± 306.6	318.8 ± 379.9	0.2	396.7 ± 352.0 (0.0–1,300.0)
PANSS score				
Positive symptoms	12.3 ± 4.6	16.3 ± 4.4	0.03	14.5 ± 4.8 (5–28)
Negative symptoms	12.3 ± 3.2	18.3 ± 6.5	0.01	15.5 ± 6.0 (7–30)
Overall severity in the Drug-Induced Extra-Pyramidal Symptoms Scale (n = 21)	0.90 ± 1.9	0.86 ± 0.7	0.94	0.88 ± 1.3 (0–6)

AD-aMCI Group

Twenty-five AD-aMCI patients were selected from the Neuropsychological Clinic registry. The number of males exceeded the number of females (14 males and 11 females). The mean age of the patients was 71.4 ± 7.8 years, the mean years of education were 13.6 ± 2.6, and the mean MMSE score was 26.5 ± 2.0. All subjects in the AD-aMCI group met the criteria for aMCI, which included (1) a memory complaint documented by the patient or another source; (2) a score in the story A recall task in the logical memory II subtest of WMS-R which is less than the age-corrected and education-corrected cutoff score; (3) a score of ≥24 on the MMSE; (4) a total Clinical Dementia Rating (CDR) score of 0.5 and a memory CDR score >0; (5) normal basic and instrumental activities of daily living evaluated with Lawton's Physical Self-Maintenance Scale and Instrumental Activities of Daily Living Scale [9], and (6) no symptoms of dementia based on a clinical examination and an extensive interview with a knowledgeable informant. All subjects in this group also (7) had been evaluated by either the WMS-R or the short form of the Japanese version of the WAIS-R, (8) had no other neurological disease, and (9) had no evidence of focal brain lesions on MRI. To confirm that the aMCI patients had AD in the preclinical stage, at least one of the following three criteria had to be fulfilled: (1) atrophy in the entorhinal cortex on MRI, (2) hypoperfusion in the posterior cingulate cortex (PCC) and precuneus on SPECT, or (3) progression to AD during annual follow-ups. Progression to AD was defined as meeting the criteria of the National Institute of Neurological Disease and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD and a total CDR score of ≥1.0.

Progression to AD from aMCI during the subsequent follow-ups (up to 8 years) was confirmed in 17 of the 25 patients. Nineteen of the 25 AD-aMCI patients received three-dimensional spoiled gradient echo MRI, which identified atrophy in the entorhinal cortex in 13 of the 19 patients. Twenty-three of the 25 AD-aMCI patients received N-isopropyl-p-[^{123}I]-iodoamphetamine (^{123}I-IMP)-SPECT, and hypoperfusion in either the PCC or precuneus was identified in 12 of the 23 AD-aMCI patients. One patient was recruited due to abnormality on the MRI and 7 patients were recruited due to abnormality on SPECT. Of the 25 patients, 13 were given the five subtests of the WAIS-R (group with WAIS-R) but the other 12 were not (group without WAIS-R). There were no significant differences in gender, age, education,

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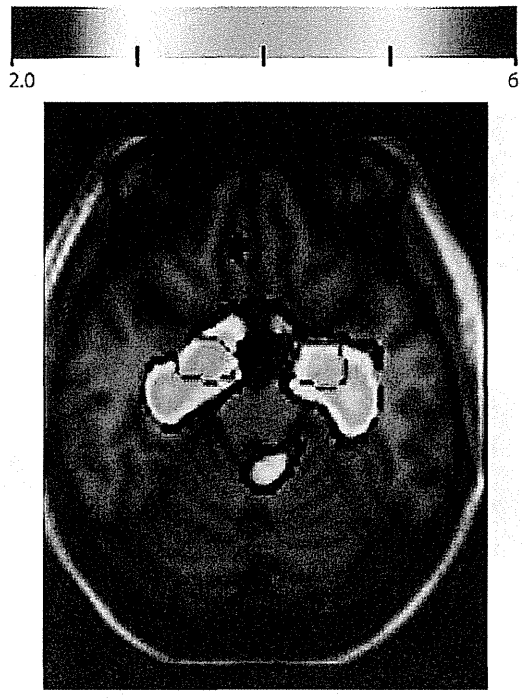

Fig. 1. Z-score map overlaid on an MRI template of a representative patient with AD-aMCI made with VSRAD. This patient was included in the study because of the presence of significant atrophy in the entorhinal cortices on MRI. Parts of the colored areas are in the areas circumscribed by purple lines, indicating significant atrophy in the entorhinal cortices. Purple lines indicate the bilateral entorhinal cortices. Colored areas on MRI are those with a Z-score >2 (significant atrophy). Color bar indicates Z-score.

MMSE score or WMS-R indices between the two groups with and without WAIS-R (table 1). All AD-aMCI patients were administered the WMS-R.

Comparison of Demographic Data in the ES and the AD-aMCI Groups

There was no significant difference between the ES and the AD-aMCI groups in terms of sex ($p = 0.48$, χ^2 test) or education ($p = 0.71$, t test). However, the ES group was significantly younger than the AD-aMCI group ($p < 0.001$, t test).

MRI and SPECT Criteria for the AD-aMCI Group

MRI was performed on a 1.5-tesla system (Signa Excite HD 12x; General Electric Medical Systems, Milwaukee, Wisc., USA). A three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections that covered the whole calvarium. The operating parameters were as follows: field of view = 240 mm, matrix = 256×256, 124×1.40 mm contiguous sections, TR = 12.55 ms, TE = 4.20 ms, and flip angle = 15°. The three-dimensional T1-weighted MRI data of the patients were analyzed with the voxel-based specific region analysis for AD (VSRAD) [10] (fig. 1). VSRAD contained the MRI data of normal control subjects with a wide age range and could automatically compare the gray matter intensities of the MRI data on a voxel-by-voxel basis between an aMCI patient and age-comparable normal control subjects after a series of steps including segmentation, anatomical standardization and smoothing using Statistical Parametric Mapping 2002 (SPM2; Wellcome Department of Imaging Neuroscience, London, UK). The Z-score is calculated on a voxel-by-voxel basis as (Is – Ic)/SD where Is and Ic are the gray matter intensities of an aMCI patient and the mean of normal control subjects, respectively, and SD is the standard deviation of the gray matter intensities of the normal control subjects. The region of interest was set to the entorhinal cortex in the VSRAD software. Atrophy corresponding to a Z-score >2.0 in the entorhinal cortex was used as a criterion for AD in the VSRAD method.

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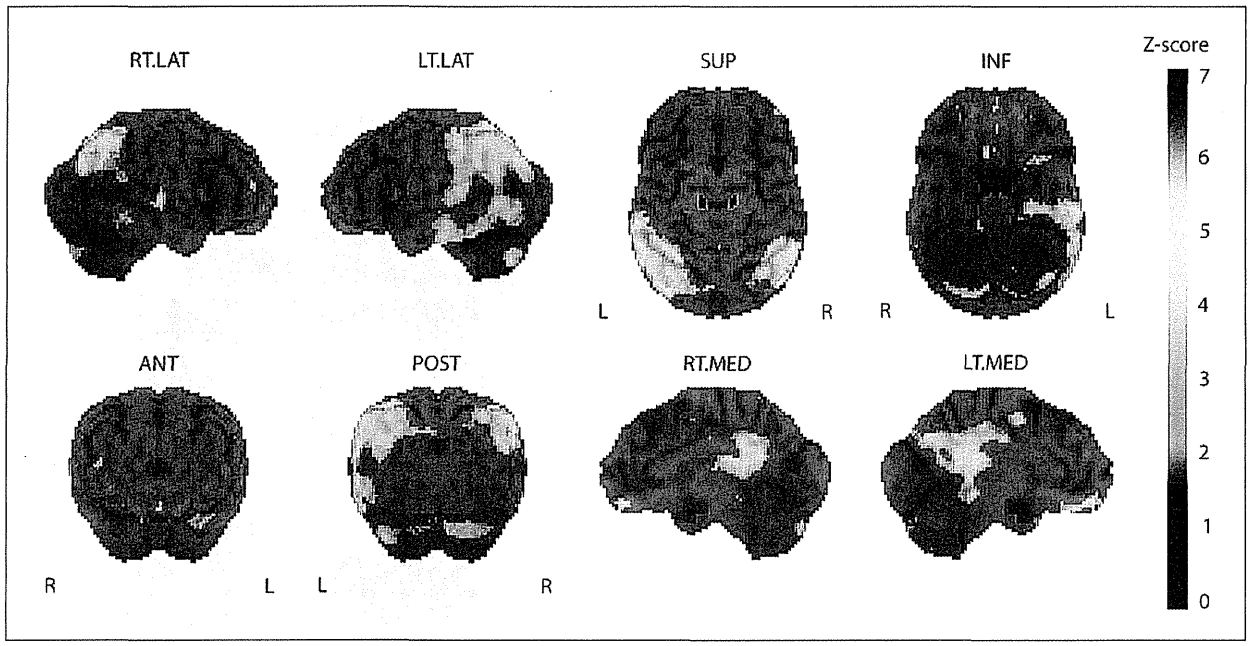

Fig. 2. Z-score map of a representative patient with AD-aMCI made with 3D-SSP. This patient was included in the study because of the presence of hypoperfusion in the PCC and precuneus on SPECT. Colored areas contain PCC and precuneus. Colored areas with significant rCBF reduction with a Z-score of >2.32 were overlaid on original surface images from eight views. Color bar indicates Z-score. RT.LAT = Right lateral; LT.LAT = left lateral; SUP = superior; INF = inferior; ANT = anterior; POST = posterior; RT.MED = right medial; LT.MED = left medial.

^{123}I-IMP-SPECT was performed with a SPECT scanner (SPECT-2000H; Hitachi Medical Co., Tokyo, Japan) and a four-head rotating gamma camera. SPECT data were analyzed using three-dimensional stereotactic surface projection (3D-SSP) software [11] (fig. 2). 3D-SSP contained ^{123}I-IMP-SPECT data of normal control subjects with a wide age range and could automatically compare the regional cerebral blood flow (rCBF) between an aMCI patient and age-comparable normal control subjects. The peak cortical values of the SPECT data were projected back and assigned to the original surface images from eight views on a pixel-by-pixel basis. Z-score was calculated on a pixel-by-pixel basis as (Is – Ic)/SD where Is and Ic are the rCBFs of an aMCI patient and the mean of normal control subjects, respectively, and SD is the standard deviation of the rCBF of the normal control subjects. Areas with a Z-score >2.32 (the significance level of the Z-score) were overlaid on original surface images from eight views. With the computer program Stereotactic Extraction Estimation (SEE) we determined which gyri included the regions with a Z-score >2.32 [12]. In SEE, the percentage of areas with a Z-score >2.32 in each gyrus was calculated and the percentage was called the 'extent'. The presence of areas of hypoperfusion, in which both the Z-score was >2.32 and the extent was >10% [13] in either the PCC or precuneus, was used as the inclusion criteria for AD in the aMCI stage.

Assessment of Cognitive Functions

The attention/concentration (AC) index in the WMS-R was used for measuring attention and working memory, the general memory (GM) index was used for recent memory, and the delayed recall (DR) index for delayed memory. For each index, the normal range is

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Table 3. Cognitive impairment in ES and AD-aMC patients

Test/subtest	ES group	AD-aMCI group	p value
WMS-R			
GM index	80.0 ± 16.2	77.8 ± 10.5	0.58
AC index	91.0 ± 14.7	98.6 ± 11.7	0.046
DR index	76.3 ± 17.2	58.8 ± 8.6	<0.001
GM-DR	3.6 ± 10.7	19.9 ± 8.6	<0.001
WAIS-R			
Information	10.1 ± 3.7	11.2 ± 2.8	0.37
Digit symbol substitution	8.0 ± 2.7	11.6 ± 2.3	<0.001
Similarity	9.9 ± 3.2	12.5 ± 2.2	0.024
Picture completion	8.5 ± 4.0	11.2 ± 1.8	0.037
Block design	8.4 ± 2.7	11.5 ± 1.9	0.0018

between 80 and 120 and the mean index of normal subjects is 100. We also defined a new index equal to the GM index minus the DR index (GM-DR), which is a measure of the degree of forgetfulness.

For the WAIS-R, five test data were used in this study. Four of the five subtests were information, digit symbol substitution, similarities, and picture completion, which were selected according to the manual of the short form of the Japanese version of the WAIS-R [14]. Another was a block design to evaluate visuoconstructive function directly, as this dysfunction is a common symptom in AD patients. In each age-corrected score of the subtest, the normal range is between 7 and 13 and the mean score of normal subjects is 10.

Statistical Analyses

Age-corrected scores of both the WMS-R and the five subtests of the WAIS-R were compared between the two groups using a t test. The significance level was set at $p < 0.05$.

Results

Results of the WMS-R

In this study, the mean GM indices in the two groups were around the lower limit of the normal range, and the mean AC indices in ES and AD-aMCI were normal (table 3). The mean DR index of ES was slightly below the normal range, but the mean DR index of AD-aMCI appeared to be significantly lower. The GM indices of the two groups were comparable. The AC index was significantly lower and the DR index was significantly higher in ES than in AD-aMCI. The difference in the GM and DR scores (GM-DR), which is a measure of the degree of forgetfulness, was significantly lower in ES than in AD-aMCI.

Results of the Five Subtests of the WAIS-R

The mean scores of all the subtests of the WAIS-R in this study in both groups were within the normal range (table 3). The information scores of the two groups were comparable, but scores of the digit symbol substitution, similarity, picture completion, and block design subtests were significantly lower in ES than in AD-aMCI.

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Discussion

We could not confirm that all AD-aMCI patients in this study developed AD to the dementia stage. However, we were able to select aMCI patients that had AD-specific findings on MRI or SPECT in this study. Pathological abnormalities related to AD, neurofibrillary tangles and neuronal loss, were found to be present in the entorhinal cortex of AD in aMCI stage [15], leading to atrophy in the region on MRI [16]. Because the entorhinal cortex is functionally connected to the PCC [17], the reduction of rCBF in the PCC was probably caused by the abnormal pathology in the entorhinal cortex. In addition, atrophy in the entorhinal cortex on MRI [18] and reduction of rCBF in the PCC and precuneus on SPECT [19] predict progression from MCI to AD. We used two reliable and user-independent statistical image-analyzing methods, VSRAD and 3D-SSP, to detect AD-specific abnormalities in the MR and SPECT images.

This is the first report to compare cognitive impairment between ES and AD-aMCI. The WMS-R GM indices of the two groups were comparable, indicating a similarity in the impairment of recent memory between the two groups. Some previous studies compared recent memory in ES and AD at the dementia stage. There is some disagreement on whether recent memory is better [20] or worse [21] in ES than in AD in the dementia stage. aMCI is a relatively homogeneous group with respect to memory impairment, because the definition of aMCI includes the degree of memory impairment. However, the severity of recent memory impairment could vary in patients with ES. The ES patients in this study were mild cases, because they could complete the WMS-R or WAIS-R, which are comprehensive tests, and the mean duration of their hospitalization was short. Thus, the recent memory tests in this study indicated that the recent memory scores of ES patients with mild cognitive impairment were comparable with those of AD-aMCI patients, and, therefore, that recent memory was not useful for distinguishing between ES and AD-aMCI.

The fact that the WMS-R GM indices were comparable in the ES and AD-aMCI groups indicates that the two groups in this study had similar degrees of impairment of recent memory. This narrows down the difference between the two groups to differences in other cognitive impairments, such as forgetfulness, and impairments of DR, attention, working memory and executive function. The WMS-R GM-DR scores were lower and the DR scores were higher in ES than in AD-aMCI, indicating that the degree of forgetfulness was less and DR was better in ES. On the other hand, the AC was lower in ES than in AD-aMCI, indicating that ES patients had more impaired attention and working memory than AD-aMCI patients. DR was found to be better in ES patients than in AD patients in the dementia stage [21], and forgetfulness did not increase in ES patients but increased in AD patients in the dementia stage [20]. The present study confirmed that memory after a short while was retained in ES but not in AD. In addition, we found that the retention in ES patients was better than in AD even at the aMCI stage, which should help to distinguish ES from AD in the very early stage.

The hippocampus, parahippocampus, and entorhinal cortex have traditionally been thought of as the principal structures responsible for the consolidation of short-term stores into long-term memory. Significant associations between hippocampal size and memory have not been observed in schizophrenia [22], although size reductions in the hippocampus have been reported in schizophrenia [2]. In addition, memory capabilities were similar to general intellectual abilities in ES [23]. Therefore, damage in the medial temporal lobe may not play an important role in memory impairment in schizophrenia. On the other hand, memory impairment in AD is inversely associated with hippocampal volume [24].

The ES group was more impaired on the digit symbol substitution, similarities, picture completion, and block design subtests of WAIS-R than the AD-aMCI group, and each subtest score in the ES group was below the mean of each score of the general population in this study. Although the block design subtest was used to evaluate visuoconstructive function in

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this study, attention and executive function are required to perform the block design subtest [25]. Thus, these findings confirmed that attention, working memory, and executive function are impaired in ES. Previous studies reported that ES patients were impaired in the WAIS-R digit symbol substitution, similarities, picture completion, and block design subtests [21], and in attention, working memory, and executive function [20]. These studies also reported that impairment in these functions were comparable in ES and AD patients in the dementia stage. The differences in cognitive impairment that we found in ES and AD-aMCI deviate from those found in previous studies. This discrepancy may be due to differences in the severity of cognitive impairments in the AD-aMCI patients in this study compared to the AD patients in the dementia stage in previous studies.

Which region of the brain is responsible for the difference in attention, working memory, and executive function in the two groups? Impairments in cognitive function in patients with schizophrenia were found to be related to dysfunction of the prefrontal cortex (PFC) [26]. On the other hand, gray matter loss on MRI [27] and pathological abnormality [28] in the PFC were not observed in AD-aMCI, and gray matter loss on MRI was observed at the time of progression from aMCI to AD [27]. These results suggest that differences in impairment in attention, working memory, and executive function in the two groups probably reflect the difference in impairment in the PFC.

The WAIS-R information scores of the ES and AD-aMCI groups were comparable and within the normal range, being consistent with those of a previous study [29]. Semantic memory may be preserved in ES and AD-aMCI patients because they have less impairment in the inferior and anterior temporal lobe regions, which crucially contribute to semantic cognition [30].

There were some limitations in this study. First, approximately half of the patients in each group were not given the WAIS-R. Second, the ES patients in this study were younger than the AD-aMCI patients, and cognitive function in schizophrenia patients undergoes a marked decline after 65 years of age [8]. Third, we did not control the effects of medication on the cognitive test scores in ES patients. Most ES subjects in this study had received atypical antipsychotic drugs, which might improve cognitive function [31]. These issues should be taken into consideration before the findings are generalized.

In this study, DR and forgetfulness were less impaired in ES than in AD-aMCI, while attention, working memory, and executive function were more impaired in ES than in AD-aMCI. The results of this study should help clinicians to distinguish patients with ES from patients with AD-aMCI and might also give us some clues for distinguishing ES combined with AD-aMCI from ES alone. The next step is to clarify the difference in the characteristics of cognitive impairment in ES combined with AD-aMCI compared to ES alone.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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特 集 ■ 緩徐進行性高次脳機能障害の病態

意味性認知症

Language Impairment and Semantic Memory Loss of Semantic Dementia

数 井 裕 光* 武 田 雅 俊*

Hiromitsu Kazui*, Masatoshi Takeda*

Abstract

Semantic dementia (SD) is a neurodegenerative disease characterized by atrophy of the anterior temporal regions and progressive loss of semantic memory. SD has recently been reported to be associated with a pathologic diagnosis of frontotemporal lobar degeneration (FTLD) with T^{ar} DNA-binding protein of 43 kDa (TDP-43) immunoreactive inclusions (FTLD-TDP) type 2 by Mackenzie. In the first several years of the disease, SD patients, especially those with left hemisphere-dominant temporal atrophy, present with primary progressive aphasia, in which language deterioration is obvious; however, they do not have other cognitive and behavioral impairments. The language impairment in SD is termed as word meaning aphasia, in which patients experience both word finding difficulties and word recognizing difficulties (two-way anomia). Phonemic cues are not effective in improving anomia. In addition, SD patients do not experience a sense of familiarity with words that they cannot find or recognize. While reading and writing Japanese words, SD patients, except those who also have motor neuron disease, exhibit well-preserved kana (phonogram) processing. However, in the case of kanji, they often exhibit surface dyslexia while reading and also exhibit phonetic miswriting. In the aphasic stage, SD patients can explain what the objects are and can use them appropriately; however, they cannot find or recognize the names of the objects. On progressing to the semantic memory impairment stage, the patients do not exhibit any familiarity with the objects whose names they cannot find or recognize and are unable to appropriately use these objects. Semantic memory impairment in SD is attributed to damage of gray matter and of superior and inferior white matter connections in the anterior temporal lobe.

Key words : word meaning aphasia, semantic memory, anterior temporal lobe, motor neuron disease, frontotemporal lobar degeneration with TAR DNA-binding protein of 43 kDa (TDP-43)

はじめに

近年，変性疾患患者の中で他の認知障害と比較して言語障害が目立つ患者が存在することが知られるようになり，原発性進行性失語と総称されるようになった。通常この原発性進行性失語には，本特集の3つの病態，進行性非流暢性失語症，意味性認知症(semantic dementia：SD)，ロゴペニック失語症が含められる。この中でSDの病態像は最も古くから知られており，最初の報告はPick[1]による。その後，1989年にSnowdenら[2]が語の理解や物品・人物に対する知識が障害されている流暢性進行性失語の症例に対し，初めてSDの用語を提唱した。1992年には，Hodgesら[3]が語義の選択的障害について強調し，左右非対称の側頭葉萎縮を伴うことを報告した。しかし，SDの用語が広く用いられるようになったのは，1998年に前頭葉，側頭葉に原発性の変性を有する非Alzheimer病性疾患に対してNearyら[4]が前頭側頭葉変性症（frontotemporal lobar degeneration：FTLD）という包括概念を提唱し，その一型としてSDを分類してか

* 大阪大学大学院医学系研究科内科系臨床医学専攻情報統合医学講座精神医学〔〒565-0871 大阪府吹田市山田丘2-2 D3〕Division of Psychiatry, Course of Internal Medicine, Osaka University Graduate School of Medicine, D3 2-2 Yamada-oka, Suita-shi, Osaka 565-0871, Japan
〔連絡先〕数井裕光

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