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Effect of Shunt Operation on Idiopathic Normal Pressure Hydrocephalus Patients in Reducing Caregiver Burden: Evidence from SINPHONI

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Key Words
Dementia · Multicenter prospective cohort study · Cognitive impairment · Gait disturbance · Urinary disturbance · Zarit burden interview

Abstract
Background/Aims: Patients with idiopathic normal pressure hydrocephalus (iNPH) are often given shunt operations to reduce the triad symptoms (cognitive impairment, gait disturbance and urinary disturbance). We examined whether they also reduce caregiver burden. ***Methods:*** The personal strain (PS) and role strain (RS) factors, which are related to the stress and constraints, respectively, on the caregivers of 81 iNPH patients were evaluated with the Zarit burden interview (ZBI) and each of the triad symptoms was evaluated with the iNPH grading scale (iNPHGS) before and 1 year after the shunt operation. ***Results:*** Each of the iNPHGS scores, the total ZBI score and PS factor significantly improved after the shunt operation, but the RS factor did not. The improvement of cognitive impairment was the major factor in reducing caregiver burden. ***Conclusion:*** Shunt operations reduced the caregiver burden of iNPH patients.

Introduction

The number of people with dementia has recently been increasing as a result of the rising proportion of aged people in the population. Normal pressure hydrocephalus (NPH), one of the causal diseases of dementia, is well known as a syndrome of the classical triad of cognitive impairment, gait disturbance, and urinary disturbance with enlarged ventricles and absence of raised intracranial pressure [1]. Idiopathic NPH (iNPH), which develops with no identifiable causative antecedent disease, has recently attracted much attention for three reasons. First, recent findings of prevalences of 0.51% [2] and 1.4% [3] in community-dwelling elderly people suggest that iNPH is more common than previously thought. Second, its diagnosis has become more accurate, because the characteristics of its symptoms [4, 5] and neuroimaging findings [6–8] have been clarified and can be used to distinguish iNPH from disorders that display similar symptoms, such as Alzheimer's disease and Parkinson's disease. Third, there are now different adjustable valve systems on the market that allow non-invasive handling of complications such as over- and underdrainage, and thus treatment is more safe and effective than many years ago [9].

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As much as 80% of iNPH patients can show sustained (5–7 years) clinical improvement, when revision operations are appropriately performed [10]. Following publication of Japanese [11, 12] and international [13] medical treatment guidelines for the diagnosis and management of iNPH, the diagnostic and treatment methods for iNPH have been standardized.

Caring for patients with dementia is extremely stressful [14]. Caregivers for dementia patients experience feelings of depression, anger, chronic fatigue, sacrifice, perplexity and overexertion. Additionally, caregivers live under many constraints. For example, they have little free time and cannot invite friends to their home. They can also suffer economic difficulties. The prognosis for the patient can worsen due to the emotional stress of the caregiver [15]. For these reasons, caregiver burden has been a topic of intensive research for over a decade and clinical trials recently use caregiver burden as one of the outcome measures [16–18]. In the case of iNPH, shunt operations appeared to reduce caregiver burden, and caregiver burden seemed to decrease with improving cognitive function [19], although these effects were not statistically evaluated. A more rigorous evaluation of the effect of shunt operations on caregiver burden is needed. The effects of shunt operations on symptoms in iNPH are highly variable: 29–80% of the patients showed improvement in cognitive impairment, 58–90% showed improvement in gait disturbance and 20–78% showed improvement in urinary disturbance [11, 12]. For some iNPH patients, symptoms do not improve after shunt operations. In addition, even in patients where improvements are observed, the symptoms do not always disappear completely. Regarding gait disturbance, length of strides and walking speed often improve after shunt operations, but stability rarely improves [20, 21]. Also regarding cognitive impairment, memory function and psychomotor speed often improve after shunt operations, but executive function rarely improves [22]. These findings indicate that shunt operations may not improve the burden of caregivers. Moreover, for some iNPH patients, shunt operations can increase caregiver burden. For example, a shunt operation can reduce apathy, which is often observed in iNPH patients [23], but not necessarily reduce cognitive impairment or gait disturbance. Such patients could have an increased risk of falling, leading to an increase of caregiver burden.

A multicenter prospective cohort study, called the study of idiopathic normal pressure hydrocephalus on neurological improvement (SINPHONI) (ClinicalTrials.gov,NCT00221091, http://www.clinicaltrials.gov/ct/show/NCT00221091?order=1), was conducted in Japan between 2004 and 2006 to examine the therapeutic outcome of installing a shunt with a programmable valve in iNPH patients [24]. The study was limited to patients with specific magnetic resonance (MR) imaging features of iNPH, including ventriculomegaly with narrowing of high-convexity and medial subarachnoid spaces. In that study, the caregiver burden was evaluated before and 1 year after the shunt operation. In this paper, we analyzed the caregiver burden data of SINPHONI to answer two questions: whether shunt operations lessen caregiver burden in general, and how changes of the triad symptoms after the shunt operation contribute to the change in caregiver burden.

Methods

SINPHONI

SINPHONI was conducted in compliance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki (2002) of the World Medical Association. The study protocol was approved by the institutional review boards of each of the 26 centers involved in the study. In SINPHONI, 100 patients with iNPH were recruited according to the criteria described below, and all received a ventriculoperitoneal (VP) shunt with programmable valve. The primary endpoint was improvement of ≥1 level in the modified Rankin Scale (mRS) [25] at 1 year after the operation (favorable outcome). The secondary outcome measures included the iNPH grading scale (iNPHGS) [26], timed 3 m up-and-go test (TUG) [27], and the Mini-Mental State Examination (MMSE) [28]. The iNPHGS is a clinician-rated scale to separately rate the severity of each of the triad symptoms of iNPH. The score of each domain ranges from 0 to 4. Zero indicates normal and higher scores indicate worse symptoms. The TUG is a test of functional mobility that measures the time it takes a subject sitting in an armchair to stand up, walk forward 3 m, and return to the seated position. These measures were repeated before and at 3, 6 and 12 months after the shunt operation. The main results of SINPHONI were reported elsewhere [24]. In summary, the improvement rate, defined as the percent of patients that showed a favorable outcome, was 69.0%, and the response rate, defined as the percent of patients that showed more than one-point improvement on mRS at any evaluation points, was 80.0%. Fifteen patients experienced serious adverse events (SAEs) that were of three types directly related to surgery or VP shunt.

Subjects

Written informed consent was obtained from all subjects, or from their representatives when applicable. The consenting patients were pre-registered and received lumbar puncture. The inclusion criteria of SINPHONI were (1) age between 60 and 85 years, (2) presence of symptom(s) of the iNPH triad which are measurable on the iNPHGS, (3) presence of MR imaging features of iNPH, i.e. both ventriculomegaly of Evans Index >0.3 and tight high-convexity and medial subarachnoid spaces on coronal T1-

weighted MRI [6], (4) absence of known disorders causing ventriculomegaly, and (5) normal cerebrospinal fluid (CSF) content (protein ≤50 mg/dl and cell count ≤3 μm^3) and pressure (≤20 cm H_2O). In this study, the criterion of (6) the presence of reliable caregivers was added. Exclusion criteria of SINPHONI were (1) presence of musculoskeletal, cardiopulmonary, renal, hepatic, or mental disorders that would make it difficult to evaluate changes of symptoms, (2) obstacles to 1-year follow-up, and (3) hemorrhagic diathesis or anticoagulant medication.

Zarit Burden Interview

The Zarit burden interview (ZBI) [29, 30] was used to evaluate family caregiver burden before and 1 year after the shunt operation in SINPHONI. The ZBI is a standardized, validated, reliable tool for assessment of the burden of caregivers for dementia patients, and has been widely used in many studies. It is a 22-item self-rating inventory that examines the burden associated with behavioral/financial impairments in the home care situation. Each item is rated on a 5-point scale, with the total score ranging from 0 to 88. The ZBI has two subscales: the personal strain (PS) and role strain (RS) factors. The PS factor indicates how personally stressful the experience is. The RS factor indicates the constraints on everyday life that occur due to being a caregiver. A primary caregiver was selected for each iNPH patient, that person being the individual who had primary responsibility for care supervision of each patient in SINPHONI and he/she answered the ZBI.

Statistical Analysis

The total score, and PS and RS factors of the ZBI were compared between before and 1 year after the shunt operation using the Wilcoxon signed-rank test. The iNPHGS, TUG, MMSE and mRS scores before and after the shunt operation were also compared in the same way.

In the preliminary analyses, the relationships between changes in the ZBI total score 1 year after shunt operation and changes of the iNPHGS scores 1 year after shunt operation were quantified with Spearman's rank correlation coefficients. In the primary statistical analysis, the specific effects of change in the triad symptoms 1 year after shunt operation on change of caregivers' burden 1 year after the shunt operation were examined by using categorical regression analysis. Categorical regression is useful when analyzing data containing nominal, ordinal, and interval-level independent variables. In categorical regression analysis with SPSS (SPSS Inc., Chicago, Ill., USA), an optimal scaling method is adopted that quantifies categorical variables and then treats them as numerical variables, applying nonlinear transformations to find the best-fitting model. For nominal variables, the order of the categories is not retained, but values that maximize the goodness of fit are created for each category. For ordinal variables, order is retained and values that maximize the goodness of fit are created. For interval variables, order is retained, as are equal distances between values. Categorical regression analysis was performed using change of total score of ZBI as a dependent variable. Independent variables were the change of each of the score of iNPHGS, age and sex. The similar analyses were subordinately repeated with the PS factor or RS factor of the ZBI instead of the total score. All statistical analyses were carried out with SPSS version 11.01 software. The statistical significance level was set at $p < 0.05$.

Results

Subjects

The number of subjects in the study was reduced to 81 after excluding 19 subjects for whom satisfactory ZBI data were not available (fig. 1). Four of these 19 patients did not have reliable caregivers at the time of initial evaluation before the shunt operation and 15 patients did not receive 1-year ZBI follow-ups. Six of these 15 patients were due to SAEs, 2 had withdrawn consent and 7 had incomplete or missing ZBI data. Of the 81 remaining subjects, 8 had SAEs. No significant differences in demographic data, preshunt severity of the symptoms, or the numbers of patients with and without favorable outcomes were observed between the 81 patients and 19 excluded patients (table 1). Additionally, in the three preoperative ZBI scores, no significant differences were observed between the 81 patients and 15 patients that could not be evaluated 1 year after the shunt operation (table 2).

Changes of Symptoms One Year after Shunt Operation

Many of the 81 patients in this study showed improvements of one or more levels in each evaluation at 1 year after the shunt operation: 58 (71.6%) of the patients showed improvement in the mRS, and in the iNPHGS, 47 (58.0%) showed improvement in the cognitive domain, 57 (70.3%) showed improvement in the gait domain and 48 (59.2%) showed improvement in the urinary domain. Twenty-five (30.9%) of the patients had mRS scores of 3 or more, indicating that they were dependent (i.e. required a caregiver), at 1 year after the shunt operation. At 1 year after the shunt operation, the numbers of patients with iNPHGS score of 2 or more (indicating the presence of an objective symptom) in the cognitive, gait and urinary domains were 36 (44.4%), 36 (44.4%) and 23 (28.3%), respectively.

In the 81 patients with iNPH, the three iNPHGS scores, and the mRS, MMSE and TUG scores significantly improved 1 year after the shunt operation (table 1). The total score and PS factor of the ZBI significantly improved after the shunt operation, but the RS factor did not (table 2; fig. 2).

Correlation between Improvement of ZBI and Improvements of Triad Symptoms

Spearman's rank correlation analyses revealed that improvements 1 year after the shunt operation in each of the ZBI scores significantly correlated with improvements in each of the iNPHGS scores, except for urinary disturbance and ZBI RS factor (table 3). Categorical re-

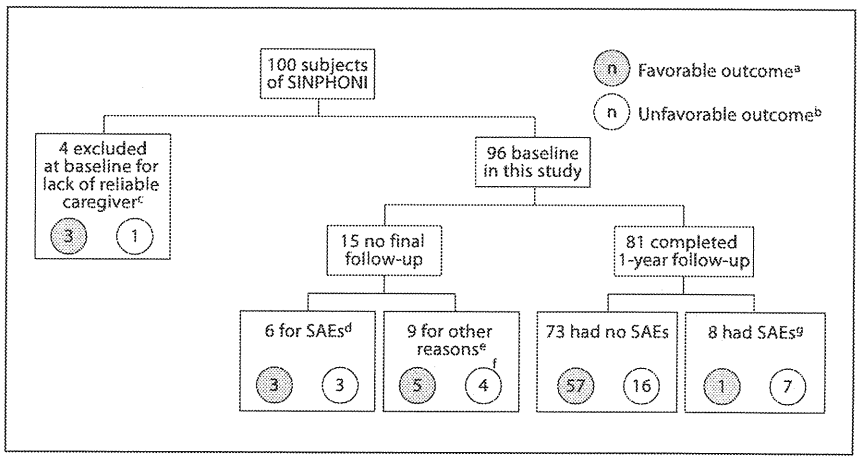

Fig. 1. Flow diagram of this study. [a] Number of patients with favorable outcomes, defined as showing an improvement of ≥1 level in the modified Rankin Scale (mRS) at 1 year after the shunt operation. [b] Number of patients with unfavorable outcomes, defined as showing no improvement in the mRS 1 year after the shunt operation. [c] Four patients who did not have reliable caregivers at the time of the initial evaluation before the shunt operation were excluded. [d] The serious adverse events (SAEs) of the 6 patients who were not included in this study were death by lung cancer in 1 patient, death by pneumonia in 1, cerebral infarction in 2, myocardial infarction in 1, and femoral fracture in 1. [e] Nine patients were excluded during a 1-year follow-up after the shunt operation. The causes included withdrawal of consent (2 patients), loss of Zarit burden interview (ZBI) data (6 patients), and incomplete ZBI record (1 patient). [f] One patient experienced a SAE (cerebral infarction) which was not the reason for lack of follow-up. [g] The 8 patients with SAEs who were included in this study consisted of 2 with pneumonia, and 1 each with laryngeal cancer, chronic subdural hematoma, femoral fracture, bowel perforation, shunt obstruction, and fall with severe bruising.

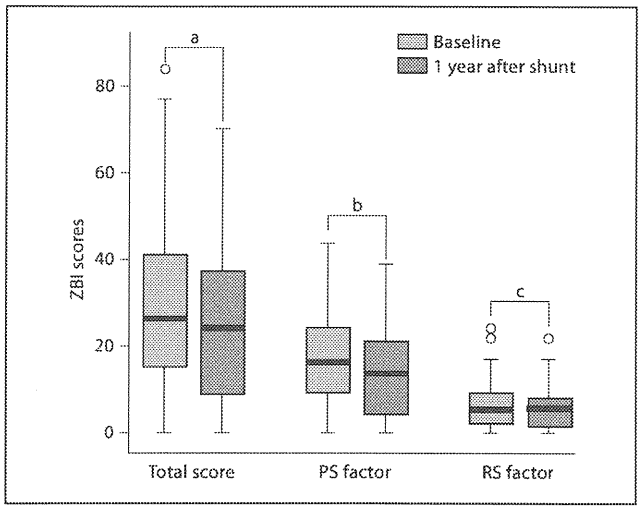

Fig. 2. Box plot of ZBI scores before and 1 year after shunt operation in 81 iNPH patients. Total and PS factor scores of the ZBI significantly decreased after the shunt operation, but the RS factor did not. Bold horizontal lines represent the median values, the boxes represent the interquartile range, the whiskers represent the range, and the circles represent outliers. Wilcoxon signed rank test ([a] T = 923.5, Z = 2.79, p = 0.0052; [b] T = 882.5, Z = 3.01, p = 0.0027; [c] T = 894.5, Z = 1.35, p = 0.18). ZBI = Zarit burden interview; PS = personal strain; RS = role strain.

gression analysis demonstrated that the improvement in each of the iNPHGS scores significantly contributed to the improvement of the ZBI total score and PS factor independently. The improvements of cognitive impairment and urinary disturbance also contributed to the improvement of ZBI RS factor. The improvement of cognitive impairment was the major factor contributing to the improvement of caregiver burden.

Discussion

In the present study, a subset of the SINPHONI cohort was analyzed for changes of caregiver burden after a shunt operation. The ZBI total scores and PS factors for these patients improved after the shunt operation. We found that the shunt operations reduced the burden on caregivers of iNPH patients. Caregiver burden of patients with iNPH before shunt operation in this study was normal when compared to the caregiver burden in the average case of dementia. More specifically, the median score of the total score of the ZBI before shunt operation was 26 in this study. This score is almost identical to the score of 28 in our previous study which had 117 patients with

Table 1. Background characteristics and changes of outcome measures

	19 patients excluded before shunt	81 patients in this study		p values	
		before shunt	1 year after shunt	before shunt 81 vs. 19 patients	81 patients in this study before vs. after shunt
Male/female	9/10	49/32		0.30[a]	
Mean age ± SD, years	74.5 ± 5.1	74.5 ± 5.1		1.00[b]	
iNPHGS					
Cognitive impairment	2 (2–3)	2 (2–3)	1 (0–3)	0.64[c]	<0.0001[d]
Gait disturbance	2 (2–3)	2 (2–3)	1 (0–2)	0.86[c]	<0.0001[d]
Urinary disturbance	2 (1–3)	2 (1–3)	1 (0–2)	0.83[c]	<0.0001[d]
mRS	3 (2–4)	3 (2–4)	2 (1–3)	0.67[c]	<0.0001[d]
MMSE	25 (14–27)	23 (17–25)	25 (21–28)	0.80[c]	<0.0001[d]
TUG	20 (15.0–22.0) [n = 17]	20 (16.0–28.5) [n = 76]	13 (10.0–19.0) [n = 75]	0.77[c]	<0.0001[d]
Outcome (favorable/unfavorable)	11/8	58/23		0.24[a]	

Descriptive statistics are expressed as the mean and SD or the median and 25th–75th percentile interval, shown in parentheses; n = number of patients who performed TUG. Favorable outcome was defined as improvement of ≥1 level in the modified Rankin scale (mRS) at 1 year after the shunt operation, and unfavorable outcome was defined as no improvement in the mRS 1 year after the shunt operation. iNPHGS = Idiopathic normal pressure hydrocephalus grading scale; mRS = modified Rankin scale; MMSE = mini-mental state examination; TUG = timed 3 m up-and-go test.

[a] χ^2 test. [b] t test. [c] Mann-Whitney U test. [d] Wilcoxon signed rank test.

Table 2. ZBI scores before and after shunt operation

ZBI	15 patients excluded before shunt	81 patients in this study		p values	
		before shunt	1 year after shunt	before shunt 81 vs. 15 patients	81 patients in this study before vs. after shunt
Total score	24 (16–37)	26 (15–41)	24 (9–37)	0.74[a]	0.0052[b]
PS factor	14 (9–23)	16 (9–24)	13 (4–21)	0.78[a]	0.0027[b]
RS factor	3 (0–6)	5 (2–9)	5 (1–8)	0.23[a]	0.18[b]

Descriptive statistics are expressed as the median and 25th–75th percentile interval, shown in parentheses. ZBI = Zarit burden interview; PS = personal strain; RS = role strain.

[a] Mann-Whitney U test. [b] Wilcoxon signed rank test.

various diseases causing dementia [30]. The pre-shunt PS and RS factors in this study were also almost identical to those in the previous study (16 and 6, respectively). Therefore, the caregiver burden in this study was high in absolute terms but normal for caregivers dealing with dementia.

No significant improvement was observed in the RS factors after the shunt operation, although the ZBI total scores and PS factors improved. The PS factor, which is a measure of how personally stressful an experience is, was likely improved as a result of improved symptoms due to the shunt operation. If the patient's disability, specifically any part of the iNPH triad, is reduced, the caregiver's assistance to the patients will be reduced, leading to a reduction of the caregiver's burden. The RS factor, on the other hand, is the constraints on everyday life that occur due to being a caregiver. Role strain was reported to be associated with dependence in activity of daily living (ADL) in elderly people [31]. Unless the patient's ADL improves to the level of being able to live independently, the caregiver has to play the role of the caregiver, and eventually the RS factor does not improve. The improvements

Table 3. Correlation among changes in scores after the shunt operation

a Spearman's rank correlation analyses

	Total score		PS factor		RS factor	
	rs	p value	rs	p value	rs	p value
Change of ZBI score						
Age	−0.09	0.42	−0.06	0.61	−0.04	0.69
Sex	−0.19	0.09	−0.18	0.11	−0.16	0.17
Change of iNPHGS score						
Cognitive impairment	0.41	0.00013	0.4	0.00024	0.35	0.002
Gait disturbance	0.42	0.00012	0.41	0.00012	0.25	0.026
Urinary disturbance	0.25	0.025	0.27	0.016	0.18	0.11

b Categorical regression analyses

	Total score		PS factor		RS factor	
	β	p value	β	p value	β	p value
Change of iNPHGS score						
Cognitive impairment	0.40	<0.0001	0.38	<0.0001	0.32	<0.0001
Gait disturbance	0.23	0.012	0.25	0.008	0.15	0.166
Urinary disturbance	0.28	0.0002	0.23	0.006	0.35	<0.0001

ZBI = Zarit burden interview; iNPHGS = idiopathic normal pressure hydrocephalus grading scale; PS = personal strain; RS = role strain.

in the triad were not observed in all patients in this study. Moreover, 30.9% of the patients were dependent based on the mRS score 1 year after the shunt operation. In addition, some patients had obvious triad symptoms 1 year after the shunt operation: 44.4% for cognitive impairment, 44.4% for gait disturbance and 28.3% for urinary disturbance. Namely, not all patients reached the independent level or objectively asymptomatic status 1 year after the shunt operation.

In patients with dementia, cognitive impairment [32, 33], motor dysfunction [34], and urinary incontinence [35] were shown to affect caregiver burden. The present study revealed that improvement in each of the triad symptoms of iNPH, especially the improvement in cognitive function, significantly decreased caregiver burden, in agreement with previous casual observations [19]. Even if the patient has gait and urinary disturbances but does not have cognitive impairment, then the patient can likely handle the problems by him/herself and avoid danger, and thus there may be less effect on the burden of the caregiver. Cognitive impairment is a symptom that is known to be difficult to improve after the shunt operation in patients with iNPH [12], and also in this study it had the lowest frequency of improvement among the iNPH triad. The present results pointed to the need to develop methods for improving the efficacy of treatments for triad symptoms, especially cognitive impairment, in patients with iNPH.

Our finding that the shunt operation reduced the caregiver burden depended on the high efficacy of the shunt operation in SINPHONI; the ratios of patients who improved by one or more levels in the mRS at 1 year following the operation was 69% of all patients of SINPHONI and 71.6% of the present study group. Many studies with iNPH groups have shown highly variable response rates to the shunt operation, ranging from 14 to 89%, but the improvement ratios of most of them were less than 50% with a follow-up typically of 1 year or less [36]. Because it is necessary for the shunt operation to be highly effective in order to decrease the caregiver burden, it might have been difficult to improve the caregiver burden of the patients in these previous studies with the low improvement ratio by the shunt operation. The Dutch NPH Study [37] enrolled 96 iNPH patients with tight convexity subarach-

noid spaces on computed tomography and followed them for 1 year. They observed a 70% rate of improvement with one or more levels in the mRS. McGirt et al. [36] enrolled 132 iNPH patients with A- or B-waves in CSF pressure monitoring and clinical improvement during a 3-day CSF drainage trial, and their improvement rate after VP shunt operation using adjust valves was 75%. Thus, we can increase the efficacy of shunt operation due to refinements in the patient selection criteria and in the shunt surgical technique. Thus, the shunt operation can also improve the caregiver burden.

Nineteen patients of the original 100-patient cohort were excluded from this study. The main reasons for exclusion were drop-out due to lack of ZBI data, SAEs, lack of reliable caregiver, and withdrawal of consent. Although the rate of patients with SAEs was higher in the excluded patient group than in the included patients, more than half of those with SAEs could be analyzed in this study. Moreover, other factors such as demographic data, preshunt severity of the symptoms and preshunt ZBI data were comparable between the included and excluded groups. In addition, the rate of those with favorable outcome after 1 year in the present study group (71.6%) was not significantly different from that of patients excluded from this study (57.9%) and was also quite similar to that in the SINPHONI full set (69%) [24]. Therefore, the subjects in this study were considered to be representative of the full set of SINPHONI.

The present study has several limitations. In SINPHONI, information regarding to the caregiver who answered the ZBI was not collected. The effect of caregiver-patient relationships [38] and the age [39] and sex [39] of the primary caregiver on the ZBI score is known, but it is not possible to exclude such effects in the present study. The primary caregiver for some patients might change before and after the shunt operation. The effect of changing primary caregiver on the ZBI score could not be excluded. The effect of the caregiver burden on a patient's neuropsychological symptoms is known [38], but it is also impossible to exclude the effect. Another crucial issue is related to the unblinded design of the SINPHONI: the neurosurgeons, neurologists and psychiatrists in charge of the patients' care and evaluation were aware of the treatment, which represents a possible source of performance and detection bias. These issues should be taken into consideration when the findings are generalized.

In conclusion, shunt operations improved the caregiver burden, as well as the triad symptoms, of patients with iNPH. Among the iNPH triad symptoms, the improvement in cognitive impairment contributed the most to the improvement in the caregiver burden. Future studies are needed to develop methods for selecting iNPH patients who are most likely to show improvements in the triad symptoms, especially cognitive impairment. These methods will lessen the constraints on the everyday life of caregivers. Cooperation among neurosurgeons, neurologists, and psychiatrists will promote the development of such methods.

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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

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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

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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,

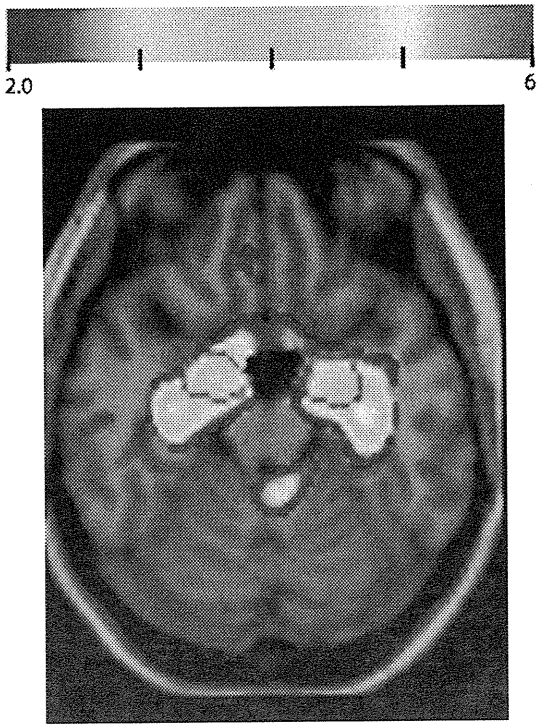

Fig. 1. Z-score map overlaid on an MRI template of a representative patient with AD-aMCI made with VSRAD. This patient was included in the study because of the presence of significant atrophy in the entorhinal cortices on MRI. Parts of the colored areas are in the areas circumscribed by purple lines, 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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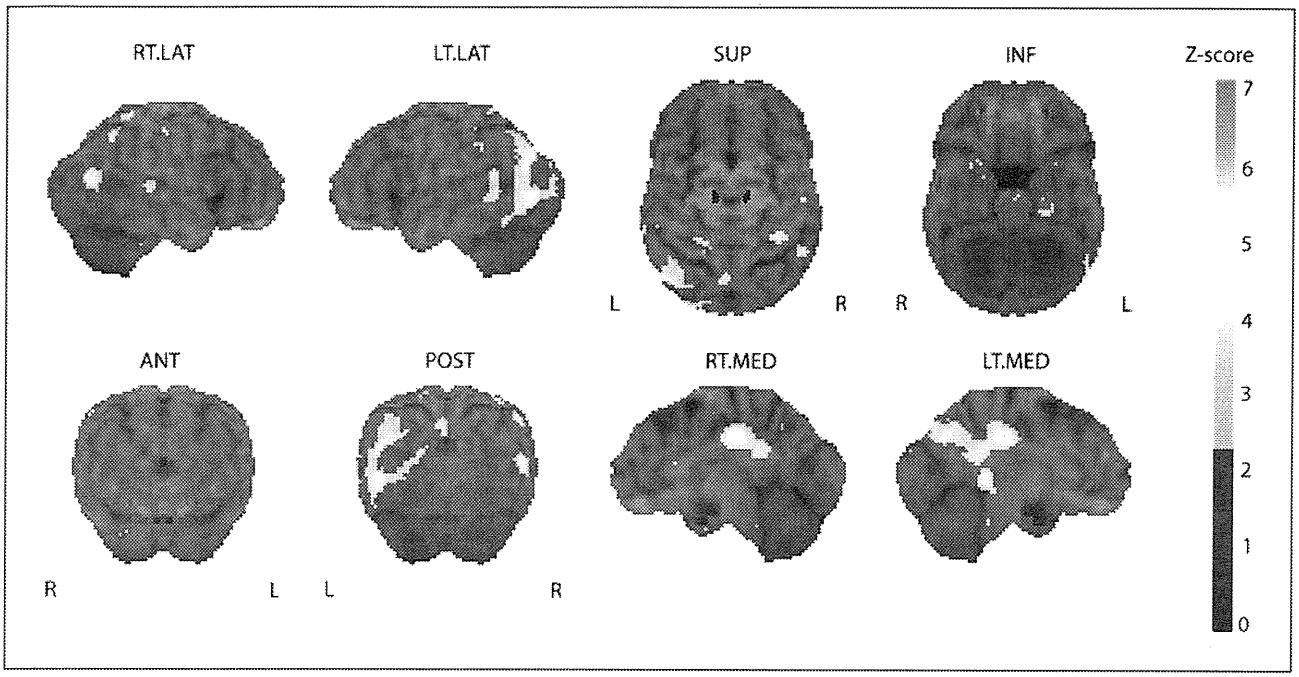

Fig. 2. Z-score map of a representative patient with AD-aMCI made with 3D-SSP. This patient was included in the study because of the presence of hypoperfusion in the PCC and precuneus on SPECT. Colored areas contain PCC and precuneus. Colored areas with significant rCBF reduction with a Z-score of >2.32 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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Risk of progression from mild memory impairment to clinically diagnosable Alzheimer's disease in a Japanese community (from the Nakayama Study)

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ABSTRACT

Background: Memory impairment has been proposed as the most common early sign of Alzheimer's disease (AD). The aims of this work were to evaluate the risk of progression from mild memory impairment / no dementia (MMI/ND) to clinically diagnosable AD in a community-based prospective cohort and to establish the risk factors for progression from MMI/ND to AD in the elderly.

Methods: Elderly subjects aged over 65 years were selected from the participants in the first Nakayama study. MMI/ND was defined as memory deficit on objective memory assessment, without dementia, impairment of general cognitive function, or disability in activities of daily living. A total of 104 MMI/ND subjects selected from 1242 community-dwellers were followed longitudinally for five years.

Results: During the five-year follow-up, 11 (10.6%) subjects were diagnosed with AD, five (4.8%) with vascular dementia (VaD), and six (5.8%) with dementia of other etiology. Logistic regression analysis revealed that diabetes mellitus (DM) and a family history of dementia (within third-degree relatives) were positively associated with progression to AD, while no factor was significantly associated with progression to VaD or all types of dementia.

Conclusions: DM and a family history of dementia were significant risk factors for progression from MMI/ND to clinically diagnosable AD in the elderly in a Japanese community.

Key words: dementia, vascular dementia, mild cognitive impairment

Introduction

Alzheimer's disease (AD) is one of the most common causes of dementia in the elderly. There is increasing evidence that medical, behavioral and social interventions can delay the cognitive and functional decline associated with AD (Burns and O'Brien, 2006). Even though several treatment options are available, treatment is often started too late, i.e. when considerable neuropathological changes have already occurred (Hulette *et al.*, 1998). For early intervention, it is essential to identify subjects who will later develop AD (Heun *et al.*, 2006). This evaluation could be improved by a better knowledge of the early signs of AD, and the presence of mild cognitive impairment (MCI) could be an early sign of AD. MCI was first defined as an isolated memory disorder that can precede dementia, characterized by subjective memory complaints and objective memory impairment on neuropsychological testing in non-demented individuals (Petersen *et al.*, 1999). A substantial number of subjects with MCI progress to dementia. However, not all MCI subjects develop AD, as subjects may remain stable for a long period, revert to a normal state, or progress to another type of dementia (Petersen *et al.*, 2001). Moreover, the clinical diagnosis per se is often uncertain in MCI. To increase the accuracy of detection of MCI and its subtypes, a great

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