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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-

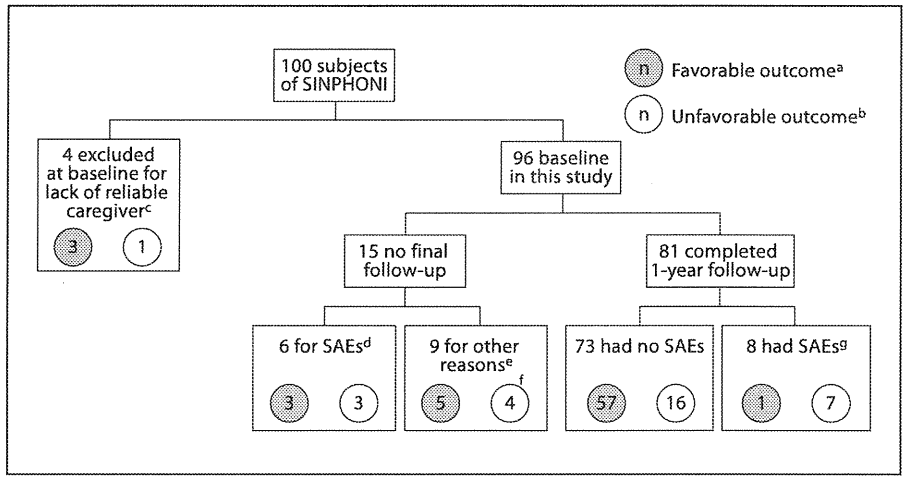

Fig. 1. Flow diagram of this study. [a] Number of patients with favorable outcomes, defined as showing an improvement of ≥1 level in the modified Rankin Scale (mRS) at 1 year after the shunt operation. [b] Number of patients with unfavorable outcomes, defined as showing no improvement in the mRS 1 year 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.

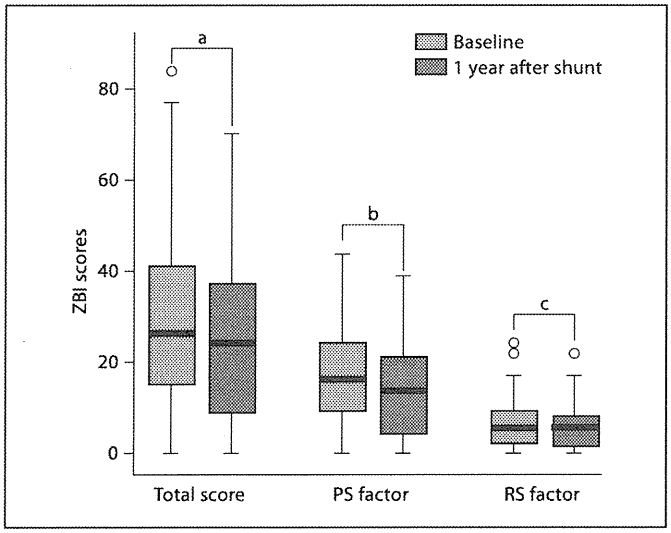

Fig. 2. Box plot of ZBI scores before and 1 year after shunt operation in 81 iNPH patients. Total and PS factor scores of the ZBI significantly decreased after the shunt operation, but the RS factor did not. Bold horizontal lines represent the median values, the boxes represent the interquartile range, 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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RESEARCH ARTICLE

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Association of cerebral small vessel disease with delusions in patients with Alzheimer's disease

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Background: Cerebral small vessel disease (SVD) is frequently observed in patients with Alzheimer's disease (AD). However, the association between SVD and clinical symptoms exhibited by patients with AD remains unclear. This study examined the association of SVD as observed on magnetic resonance imaging (MRI) with behavioural and psychological symptoms of dementia and cognitive function of patients with probable AD.

Methods: A total of 163 consecutive patients (55 men, 108 women) with probable AD were included in this cross-sectional study of a prospective cohort. Patients were divided into two groups based on the presence or absence of cerebral SVD [white matter hyperintensities (WMH) grade 0/1 (Fazekas scale) and no lacunes: SVD absent, WMH grade 2/3 (Fazekas scale) or the number of lacunes ≥1: SVD present]. Cognitive functions were assessed using the Mini mental state examination, word recall and recognition subtests in the Alzheimer's Disease Assessment Scale—Cognitive Subscale, as well as the letter fluency task and the category fluency task. Psychiatric symptoms were rated according to Neuropsychiatric Inventory.

Results: Patients with probable AD with cerebral SVD had significantly more delusions and depression than those without SVD. No significant differences were observed in other neuropsychiatric symptoms, MMSE or word recall and recognition tests between both groups.

Conclusions: Our results suggest that cerebral SVD observed on MRI of patients with AD is associated with delusions and depression.

Key words: Alzheimer's disease; small vessel disease; delusion; depression
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Introduction

Cerebral small vessel disease (SVD), including subcortical lacunar infarcts (lacunes) and white matter hyperintensities (WMH), is commonly observed on brain magnetic resonance imaging (MRI) of older people with and without dementia. Numerous post-mortem studies have shown that WMH correspond to several heterogeneous pathological substrates with a varying extent of demyelination, arteriolosclerosis and gliosis representing not only incomplete infarctions but also tissue degeneration (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001; Fernando and Ince, 2004). Lacunes are small cavities located in the white matter or subcoritical gray matter. They have been considered small ischemic infarcts; however, several pathogenetic mechanisms have been proposed (Wardlaw *et al.*, 2003). Incidence of SVD increases with age and vascular risk factors (Pantoni and Garcia, 1995).

In older people, Alzheimer's disease (AD) is considered the most common cause of dementia, characterised by gradual progressive cognitive impairment (McKhann *et al.*, 1984). In addition to cognitive

impairment, behavioural and psychological symptoms of dementia (BPSD) are important manifestations of AD. These symptoms have been shown to be associated with a reduced quality of life (Shin *et al.*, 2005), a higher cost of care (Beeri *et al.*, 2002), institutionalisation (Steele *et al.*, 1990) and increased caregiver burden (Robert *et al.*, 2005). Vascular risk factors including hypertension (Skoog *et al.*, 1996; Kivipelto *et al.*, 2001), diabetes (Luchsinger *et al.*, 2001), hypercholesterolemia (Kivipelto *et al.*, 2001) and tobacco smoking (Ott *et al.*, 1998) are also associated with increased AD risk and their treatment reduces AD risk (Li *et al.*, 2011). Furthermore, examination of several patients with AD at autopsy has shown a high prevalence of undiagnosed vascular lesions (Lim *et al.*, 1999; Fernando and Ince, 2004).

MRI has revealed that SVD is more prevalent in patients with AD than in older people without dementia (Scheltens *et al.*, 1992; Jellinger and Mitter-Ferstl, 2003). SVD may play a role, at least to some extent, in the clinical symptoms of AD. WMH are known to affect frontal lobe function, resulting in executive dysfunction in patients with AD (Pantel *et al.*, 2004; Tullberg *et al.*, 2004). However, it is still unclear whether SVD is associated with other symptoms such as BPSD in AD. Reports about the roles of SVD and BPSD in AD have been conflicting. Associations among the following conditions have been reported: WMH and depression (O'Brien *et al.*, 2000); apathy (Scheltens *et al.*, 1992); suicidal ideation (Lopez *et al.*, 1997); delusional misidentification (Lee *et al.*, 2006); aberrant motor behaviour (Hirono *et al.*, 2000); and anxiety, aberrant motor behaviour and night-time disturbance (Berlow *et al.*, 2010). However, these studies had relatively small sample sizes, and only few of them could confirm the results of previous studies. Moreover, some studies failed to find any association between WMH and BPSD (Harrell *et al.*, 1991; Lopez *et al.*, 1992; Staekenborg *et al.*, 2008).

In this study, we assessed the relationship of SVD observed on MRI with BPSD and cognitive functions in a relatively large sample of patients with AD attending a memory clinic.

Methods

Subjects

All procedures followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the internal review board. A complete description of all procedures was provided to the patients, and written informed consent was obtained from them or their caregivers.

In this cross-sectional study of a prospective cohort, a total of 163 patients with probable AD were selected from a consecutive series of 1253 patients who underwent a medical examination at the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, from April 2007 to May 2011. All patients were examined comprehensively by two senior neuropsychiatrists (M. I. and M. H.), having sufficient experience in examining patients with dementia. Routine laboratory and standardised neuropsychological tests, such as the Mini mental state examination (MMSE) (Folstein *et al.*, 1975) and Alzheimer's Disease Assessment Scale—Cognitive Subscale Japanese version (ADAS-J cog; Honma *et al.*, 1992) were also conducted. Brain MRI, brain MR angiography and single photon emission computed tomography for cerebral perfusion were also performed. Information on patient demographics including prescribed medications collected from caregivers and investigative data were entered prospectively into the Kumamoto University Dementia Follow-up Registry in a standardised manner. Patients had to meet the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984) for probable AD to be included in this study. Patients under 60 years of age; those who had any evidence suggestive of vascular dementia (VaD), such as focal neurological signs, abrupt deterioration or stepwise progression of cognitive deficits; those with focal vascular lesions except SVD, such as hematomas; significant neurologic antecedents, such as brain trauma, brain tumour, epilepsy or inflammatory disease; those with serious psychiatric diseases, substance abuse or developmental abnormalities; those who had severe behavioural or communication problems that would make clinical or MRI examination difficult or those without a reliable informant were excluded from the study.

The subjects consisted of 108 women and 55 men with a mean age of 76.3 ± 7.2 years and a mean educational attainment of 10.5 ± 2.7 years. The mean duration of symptoms determined through interviews with caregivers was 2.5 ± 1.8 years. Forty-one patients (25.2%) were prescribed cholinesterase inhibitors at examination. The Clinical Dementia Rating scale (CDR; Hughes *et al.*, 1982) revealed a functional severity of very mild in 75 patients, mild in 71, moderate in 16 and severe in 1.

Subjects were divided into two groups based on the presence or absence of SVD, and cognitive functions and BPSD were compared between the two groups.

Assessment of cognitive functions

All patients underwent neuropsychological tests to assess their general cognitive functioning as well as memory and executive functions. General cognitive functioning was assessed using MMSE. Memory function was assessed using ADAS-J cog word recall and recognition subtests. ADAS-J cog word recall subtest is equivalent to a verbal learning test in which the retention of a list of 10 written words was measured using free immediate recall after each of the three learning trials. The score is the mean number of correct responses in three repeated trials. In the ADAS word recognition subtest, the subject was asked to read aloud 12 written high-imagery words and then to select the target words among 24 words randomly mixed with 12 irrelevant words. The score is the mean number of correct responses in three repeated trials. Executive function was assessed using the letter fluency task and the category fluency task. In the letter fluency task, subjects were instructed to say as many words as possible that begin with the letter 'Ka' for 1 min. The score was the number of different words listed. In the category fluency task, the subjects were asked to list as many animals as possible within 1 min. The score was the number of different animals listed.

Assessment of behavioural and psychological symptoms of dementia

We evaluated the comprehensive BPSD semiquantitatively through interviews with their caregivers using the Japanese version of the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994; Hirono *et al.*, 1997). In NPI, the following 10 BPSD were rated on the basis of the patients' condition in the month before interviews: delusions, hallucinations, agitation, depression (dysphoria), anxiety, euphoria, apathy, disinhibition, irritability and lability and aberrant motor behaviour. According to the criteria-based rating scheme, severity of each manifestation was classified into four grades (from 1 to 3; 0 if absent), whereas frequency was classified into five (from 1 to 4; 0 if absent). The NPI score (severity × frequency) was calculated for each manifestation (range of possible scores, 0–12). Thus, the maximum total score for the 10 manifestations is 120.

Assessment of small vessel disease

Scans were made on a 3.0-T MR scanner. Fluid-attenuated inversion recovery (FLAIR), T2-weighted, diffusion-weighted, magnetization-prepared rapid acquisition of gradient echo imaging and susceptibility-weighted imaging were performed. The presence of lacunes and the extent of WMH were determined by a neuroradiologist who was blinded to the clinical data, including cognitive test results and NPI scores. The extent of WMH severity was rated visually on axial FLAIR images using the Fazekas scale as grade 1 (punctate), grade 2 (early confluent) or grade 3 (confluent) (Fazekas *et al.*, 1987). In this study, WMH were considered present if the Fazekas grade was 2 or 3 (Pompili *et al.*, 2008; Staekenborg *et al.*, 2008). Changes in the basal ganglia were rated in the same way and considered as white matter lesions even if they were located in the gray matter nuclei. Lacunes were defined as lesions with diameters of more than 2 mm with hyperintensity on T2-weighted images with central hypointensity on FLAIR images. Seventy-nine patients (48.0%) showed WMH, whereas 54 patients (33.1%) showed with lacunes. Both WMH and lacunes were observed in 40 patients (24.5%). Patients were divided into two groups based on the presence or absence of SVD (WMH grade 0/1 and no lacunes: SVD absent, WMH grade 2/3 or the number of lacunes ≥ 1: SVD present).

Statistical analysis

Group differences were analysed using two-tailed Student t test, two-tailed Mann–Whitney U test or χ^2 test. $p < 0.05$ was considered to be statistically significant. No correction for multiple comparisons was performed because of the exploratory nature of the study. In the present study, patients with SVD were significantly older than those without SVD. Therefore, we also analysed group differences in the neuropsychological tests and NPI scores using analysis of covariance (ANCOVA) with age as the covariate. Furthermore, we performed ANCOVA, with age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR as covariates, as these variables might affect cognition and BPSD. Statistical analysis was performed with SPSS for Windows, version 17.0 (IBM Corporation, Armonk, NY, USA).

Results

Demographic variables of the two groups (patients with SVD and patients without SVD) are shown in Table 1. Patients with SVD were significantly older than those without SVD ($p = 0.005$); however, no significant differences were observed for the male to female ratio, mean level of education, duration of

Table 1 Patient demographics

	Total ($n = 163$)	SVD present ($n = 93$)	SVD absent ($n = 70$)	p
Age (years)	76.3 ± 7.2	77.8 ± 6.1	74.4 ± 8.1	0.005[a,**]
Sex (male/female)	55/108	33/60	22/48	0.588[b]
Education (years)	10.5 ± 2.7	10.3 ± 2.8	10.8 ± 2.5	0.208[a]
Duration of history (years)	2.5 ± 1.8	2.4 ± 1.9	2.6 ± 1.7	0.596[a]
Cholinesterase inhibitor use	41 (25.2)	20 (21.5)	21 (30)	0.216[b]
CDR	0.88 ± 0.47	0.94 ± 0.53	0.80 ± 0.38	0.116[c]
WMH present (Fazekas score ≥2)	79 (48.5)	79	0	
Lacunes present	55 (33.7)	55	0	

Values are presented as mean ± SD, n (%) or n.
SVD, small vessel disease; CDR, Clinical Dementia Rating; WMH, White Matter Hyperintensities
[a]t test; [b]χ^2 test; [c]Mann–Whitney U test; $^{**}p < 0.01$.

symptoms and percentage of patients who were prescribed cholinesterase inhibitors between both groups.

Results of neuropsychological tests are shown in Table 2. No significant differences were observed for MMSE and ADAS-J cog word recall and recognition subtests between both groups. In contrast, patients with SVD were significantly more impaired than those without SVD on the letter fluency task ($p = 0.013$). This difference remained significant after adjustment for age ($p = 0.021$, ANCOVA), but the significance disappeared after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.065$, ANCOVA).

Results of NPI are given in Table 3. In the total cohort of 163 patients, prevalence of any BPSD was 90.8%, with a median NPI score of 7 (range, 0–63). Furthermore, apathy was found to be the most common symptom, whereas euphoria was the rarest (affecting 67% and 1% of the patients, respectively). Delusions were present in 39 patients (23.9%). The total NPI score was significantly higher in patients with SVD than in those without SVD after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.042$, ANCOVA). Patients with SVD had significantly higher scores than those without SVD in the delusion domain ($p = 0.013$), and the difference remained significant even after adjustment for age ($p = 0.036$, ANCOVA), and age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.049$, ANCOVA). In addition, patients with SVD had significantly higher scores than those without SVD in the depression domain after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.044$, ANCOVA).

Discussion

The most remarkable finding of this study was that patients with AD and SVD had significantly more delusions than those without SVD. In the present

Table 2 Neuropsychological performances of subjects

	SVD present ($n = 93$)	SVD absent ($n = 70$)	p	Adjusted $p1$	Adjusted $p2$
MMSE scores	19.7 ± 4.5	20.2 ± 4.1	0.425[a]	0.232	0.633
ADAS-J cog					
Word recall (correct response)	4.1 ± 1.6	3.9 ± 1.4	0.415[a]	0.456	0.166
Word recognition (correct response)	7.7 ± 3.0	8.2 ± 2.8	0.285[a]	0.522	0.888
LFT scores ('Ka')	5.3 ± 3.0	6.5 ± 3.1	0.013[a*]	0.021*	0.065†
CFT scores (animals)	9.0 ± 4.0	9.8 ± 3.3	0.210[a]	0.317	0.571

Values are presented as mean ± SD.
SVD, small vessel disease; MMSE, Mini mental state examination; ADAS-J cog, Alzheimer's Disease Assessment Scale—Cognitive subscale (Japanese version); LFT, letter fluency task; CFT, category fluency task.
[a]t test; age adjustment was performed using analysis of covariance and is represented as adjusted $p1$. Adjustment of age, sex, years of education, disease duration, cholinesterase inhibitor usage and Clinical Dementia Rating scale using analysis of covariance is represented as adjusted $p2$.
$^{*}p < 0.05$; $^{\dagger}p < 0.10$.

Table 3 Prevalence of behavioural and psychological symptoms of dementia and mean composite scores (frequency × severity) of individual Neuropsychiatric Inventory symptoms in patients

	SVD present ($n = 93$)	SVD absent ($n = 70$)	p	Adjusted $p1$	Adjusted $p2$
NPI total scores ≥1	84 (90.3)	64 (91.4)	0.809[b]		
NPI scores					
Total score	11.7 ± 11.4	8.3 ± 9.2	0.036[a]*	0.053†	0.042*
Delusion	1.5 ± 3.0	0.5 ± 1.6	0.013[a]*	0.036*	0.049*
Hallucination	0.3 ± 1.0	0.1 ± 0.6	0.288[a]	0.421	0.839
Agitation/aggression	0.9 ± 1.9	0.9 ± 2.1	0.912[a]	0.938	0.860
Depression/dysphoria	1.5 ± 2.8	0.9 ± 1.6	0.075[a]†	0.062†	0.044*
Anxiety/indifference	0.9 ± 2.6	0.8 ± 2.0	0.726[a]	0.749	0.828
Euphoria	0.0 ± 0.0	0.1 ± 0.5	0.321[a]	0.471	0.358
Apathy	3.9 ± 4.0	3.2 ± 3.2	0.202[a]	0.248	0.332
Disinhibition	0.6 ± 2.0	0.3 ± 1.6	0.373[a]	0.528	0.354
Irritability/lability	1.0 ± 1.8	0.8 ± 1.9	0.521[a]	0.536	0.304
Aberrant motor behaviour	1.2 ± 2.8	0.7 ± 1.9	0.222[a]	0.210	0.478

Values are presented as mean ± SD or n (%).
SVD, small vessel disease; NPI, Neuropsychiatric Inventory.
[a]t test; [b]χ^2 test; age adjustment was performed using analysis of covariance and is represented as adjusted $p1$. Adjustment of age, sex, years of education, disease duration, cholinesterase inhibitor usage and Clinical Dementia Rating scale using analysis of covariance is represented as adjusted $p2$.
*$p < 0.05$; †$p < 0.10$.

study, patients with SVD were significantly older than those without SVD. Both WMH and lacunes have been shown to be associated with aging (Fazekas *et al.*, 1988; Longstreth *et al.*, 1998). Some studies have found a significant association between psychosis in AD and age (Levy *et al.*, 1996; Bassiony *et al.*, 2000) and age at onset of AD (Hwang *et al.*, 1996; Gormley and Rizwan, 1998). However, delusions in patients with AD and SVD were significantly more severe than in those without SVD after adjustment for age in this study. Therefore, the present results cannot be explained by the differences of age between the two groups.

Previous studies have reported relationships between delusions and severity of white matter changes observed on MRI (Lee *et al.*, 2006) and between delusions and lacunar infarcts of white matter observed on computed tomography (Binetti *et al.*, 1995) in patients with AD. Furthermore, one study reported that a history of hypertension increased the risk of delusions in patients with AD (Treiber *et al.*, 2008), and another showed an association between delusions and the use of antihypertensives in patients with AD (Bassiony *et al.*, 2000). Thus, it can be suggested that SVD is a risk factor of delusions in patients with AD.

Mechanisms underlying delusions in patients with AD remain unclear. However, some neuroimaging studies have suggested an association between psychotic symptoms in AD and frontal lobe dysfunction (Sultzer *et al.*, 1995; Mega *et al.*, 2000; Sultzer *et al.*, 2003). Mentis *et al.* (1995) suggested that delusional misidentification in patients with AD are caused because of the abnormal integration of perceptual information from multimodal association cortices with affective information from paralimbic–limbic structures. White matter changes may result in a disruption of the functional connections between the frontal cortex and other related cortices or paralimbic–limbic structures, thus resulting in delusions. Furthermore, white matter changes in basal ganglia may alter connections between the frontal cortex and subcortical regions, resulting in development of delusions (Mentis *et al.*, 1995; McMurtray *et al.*, 2008). Further studies are needed to localise areas on MRI and single-photon emission computed tomography and support this hypothesis.

In this study, there was a trend for patients with SVD to be more impaired on the letter fluency task (for evaluating executive dysfunction) compared with those without SVD. No significant differences were observed in MMSE (for evaluating general cognitive functioning) and ADAS-J cog word recall and recognition subtests (for evaluating memory function) between both groups. In older people, appearance of SVD and incident lacunes on MRI have been reported to be associated with decreases in executive function and processing speed but not in memory or global cognition (Prins *et al.*, 2005; Jokinen *et al.*, 2011). In patients with AD, white matter lesions observed on MRI have been reported to be associated with impaired frontal lobe function, regardless of their

location (Tullberg *et al.*, 2004). These findings were consistent with our results, which suggest that SVD was associated with the impairment of executive function but not to impairments of global cognitive and memory functions. In a study examining the association between cognitive function and BPSD assessed by NPI, the letter fluency task and the category fluency task scores were significantly associated with changes in the psychosis subdomain but not in other subdomains (Tsai *et al.*, 2010). In addition, Swanberg *et al.* (2004) reported that symptoms of psychosis were more frequent in patients with AD with executive dysfunction than in those without. The lesions of the dorsolateral prefrontal circuit mainly involved in executive function are associated with performances of verbal fluency (Duffy and Campbell, 1994; Tekin and Cummings, 2002). In addition, lesions in the dorsolateral prefrontal circuit are associated with psychosis in patients with AD (Sultzer *et al.*, 1995). These previous neuroimaging and cognitive findings and the present result suggest that executive dysfunction due to SVD may be associated with delusions in patients with AD.

In the present study, patients with AD with SVD had significantly more depression than those without SVD after adjustment estimated covariates. Previous study suggests that white matter lesions confer an increased risk for depression in AD (O'Brien *et al.*, 2000). In this study, we did not find evidence to support the previously reported association of WMH with apathy (Scheltens *et al.*, 1992), aberrant motor behaviour (Hirono *et al.*, 2000) as well as anxiety and aberrant motor behaviour (Berlow *et al.*, 2010) in patients with AD. Unlike our study, previous studies failed to find any association between WMH and BPSD (Harrell *et al.*, 1991; Lopez *et al.*, 1992; Staekenborg *et al.*, 2008). Results obtained in our and previous studies may have differed because of the small sample sizes of the previous studies. An advantage of our study is the relatively large study cohort.

This study had some limitations. First, despite the exclusion of patients with any evidence suggestive of VaD, probably a few patients with VaD was included. However, patients with AD have been reported to have more delusions than patients with VaD (Lyketsos *et al.*, 2000; Ikeda *et al.*, 2004), suggesting that a combination of AD pathology and SVD may contribute to delusions. Second, WMH and lacunes are collectively treated as SVD. In this study, 40 patients (43.0% of patients with SVD) had both WMH and lacunes. Because our main aim was to investigate the effect of SVD on clinical symptoms in patients with AD, we analysed the two major representations of SVD together. In the future, WMH and lacunes need to be evaluated separately in order to investigate their independent effect on BPSD of patients with AD in a larger population. Third, in order to measure the extent of WMH, we used a visual rating scale, which may not be as accurate as the MRI volumetric method. However, the Fazekas rating scale, which was used in the present study, is widely accepted and has been shown to provide good global assessments of WMH. In an overview of 26 rating scales used to evaluate WMH on MRI, it was suggested that the simplicity of the Fazekas scale might make it robust, even for images of poorer quality (Scheltens *et al.*, 1998). In addition, simple rating scales, such as the Fazekas scale, have been shown to be comparable with complex measures of WMH in terms of associations with clinical outcome measures (Gouw *et al.*, 2006). Importantly, histopathological analyses have been used to validate this rating scale (Fazekas *et al.*, 1991; Fazekas *et al.*, 1993). Fourth, the study results might be able to be biased because all patients were recruited in only one dementia clinic.

Conclusion

Our results suggest that cerebral SVD observed on MRI is associated with symptoms of delusions and depression in patients with AD.

Key points

- Cerebral SVD in patients with AD is associated with symptoms of delusions and depression.
- No significant differences were observed in other neuropsychiatric symptoms, memory or global cognition between patients with AD with SVD and those without SVD.

Conflict of interest

None declared.

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ORIGINAL ARTICLE

Clinical profiles of late-onset semantic dementia, compared with early-onset semantic dementia and late-onset Alzheimer's disease

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Abstract

Background: Semantic dementia (SD) has been recognized as a representative of dementia with presenile onset; however, recent epidemiological studies have shown that SD also occurs in the elderly. There have been few studies about the differences of clinical profiles between early-onset SD (EO-SD) and late-onset SD (LO-SD). Age-associated changes in the brain might cause some additional cognitive and behavioural profiles of LO-SD in contrast to the typical EO-SD cases. The aim of the present study was to clarify the characteristics of neuropsychological, and behavioural and psychological symptoms of dementia (BPSD) profiles of LO-SD patients observed in screening tests in comparison with EO-SD patients and late-onset Alzheimer's disease (LO-AD) patients as controls.

Methods: Study participants were LO-SD ($n = 10$), EO-SD ($n = 15$) and LO-AD ($n = 47$). We examined the Mini-Mental State Examination (MMSE), the Raven's Coloured Progressive Matrices (RCPM), the Short-Memory Questionnaire (SMQ), the Neuropsychiatric Inventory (NPI) and the Stereotypy Rating Inventory (SRI).

Results: Both SD groups scored significantly lower than the LO-AD patients in 'naming' of the MMSE. In the 'construction' score of the MMSE and the RCPM score, however, the LO-SD patients as well as the LO-AD patients were significantly lower than the EO-SD patients. In the SMQ score, 'euphoria' and 'disinhibition' scores of the NPI, the SRI total and subscale scores, both SD groups were significantly higher, whereas in the 'delusion' score of the NPI, both SD groups were significantly lower than the LO-AD patients.

Conclusions: Visuospatial and constructive skills of LO-SD patients might be mildly deteriorated compared with EO-SD patients, whereas other cognitive and behavioural profiles of LO-SD are similar to EO-SD. Age-associated changes in the brain should be considered when we diagnose SD in elderly patients.

INTRODUCTION

Frontotemporal lobar degeneration (FTLD), the most common form of cortical dementia occurring in the proscenium after Alzheimer's disease (AD),[1] is a disorder characterized by a progressive deterioration of behaviour, personality and cognition in association with prominent frontal and temporal lobar atrophy.[2] FTLD gives rise to three different clinical syndromes determined by the distribution of atrophy within the frontal and temporal lobes; that is, frontotemporal dementia (FTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA).[3] However, FTLD is

not always the disease confined to the proscenium, because recent pathological and clinical studies have reported that the commonest age range at presentation was between 66 and 70 years, and 45% were aged over 65 years in the series of 100 SD cases.[4]

Salient clinical features of SD patients are observed as failures in recall and recognition of amodal semantic representations, whereas they present with relatively preserved function in several cognitive domains including episodic memory, calculation and visuospatial processing. These cognitive features of SD contrast with typical AD characterized by episodic memory loss.

As a family of FTLD, SD patients often show a wide range of behavioural abnormalities, including disinhibition, stereotypical behaviours and changes in eating patterns.[5] These prominent behavioural symptoms are thought to occur as a result of damages across the regions of the frontal lobe, the anterior temporal lobe and the amygdala, intimately connecting with each other and governing human social behaviours.[6]

In degenerative dementia, such as AD and FTD, there have been some reports about the differences of clinical profiles between early-onset and late-onset subgroups. For instance, it has been reported that visuospatial dysfunction[7] occurs more often in early-onset AD (EO-AD) patients. In FTD, it has been reported that late-onset FTD (LO-FTD) patients might have worse memory and visuospatial abilities than early-onset FTD patients.[8] These findings suggest that age at onset as a background factor influences the disease-specific symptoms of dementia. That is the reason why there is a high enough possibility that the differences in age at onset have some influence on the clinical profiles of SD. However, the differences of clinical profiles between early-onset SD (EO-SD) patients and late-onset SD (LO-SD) patients have not been reported yet.

Age-associated changes in the brain might have been reported to develop mild memory and visuospatial deficits in healthy older people.[9] Furthermore, LO-FTD patients have been proven to have more similar neuropsychological profiles to AD patients than previously expected.[8] Therefore, LO-SD patients might also have more common neuropsychological features with AD patients than EO-SD patients.

The aim of the present study was to clarify the characteristics of neuropsychological, and behavioural and psychological symptoms of dementia (BPSD) profiles of LO-SD patients observed in conventional screening tests for dementia in comparison with EO-SD patients and LO-AD patients as controls at the first assessment.

METHODS

Patients

Study participants were consecutive outpatients with a diagnosis of SD or AD between August 1997 and October 2009. All patients were referred for assessment to the Higher Brain Function Clinic for outpatients of the Department of Neuropsychiatry of Ehime University Hospital and the Memory Clinic of Niihama Foundation Hospital. We assessed the severity of dementia using the Clinical Dementia Rating (CDR),[10] cognitive functions using the Mini-Mental State Examination (MMSE),[11] the Raven's Coloured Progressive Matrices (RCPM),[12] the Short-Memory Questionnaire (SMQ),[13] BPSD using the Neuropsychiatric Inventory (NPI)[14] and the Stereotypy Rating Inventory (SRI),[15] which are standardized test batteries, and examined the differences of neuropsychological and BPSD profiles among the three groups (LO-SD, EO-SD and LO-AD groups). Furthermore, physical and neurological examinations and laboratory blood tests including vitamin B12, folic acid and thyroid function were carried out on all patients at the first assessment. All patients underwent brain computed tomography or magnetic resonance imaging, and almost all patients also underwent $^{(99m)}$Tc-hexamethylpropylene amine oxime single photon emission computed tomography (HMPAO-SPECT).

Age at onset and duration of disease were ascertained through interviews with the primary caregivers of all patients. The age at onset was defined as the age of the first appearance of symptoms when their primary caregivers noticed their cognitive impairments or behavioural disturbances, the age at examination was defined as the age at the first assessment, and the duration of disease was defined as the amount of time between the onset and the first assessment.

Three groups of patients were involved in the present study: LO-SD patients ($n = 10$), EO-SD patients ($n = 15$) and LO-AD patients ($n = 47$). In the examination at bedside, we diagnosed the patients presenting with the following symptoms with SD: (i) anomia; (ii) impairment in single-word comprehension; (iii) impoverished semantic knowledge with relative preservation of phonology, syntax, visuospatial pro-

cessing of daily living (e.g. not getting lost behaviour) and day-to-day memory; and (iv) anterior temporal lobe atrophy on structured imaging and anterior temporal lobe hypoperfusion on HMPAO-SPECT. All the SD patients fulfilled the consensus criteria for FTLD, which recognizes the subtypes of FTD, SD and PNFA.[16] As most Japanese cases of FTLD were solitary, all the SD patients were sporadic cases.[17] A total of 47 LO-AD patients, matched for CDR score of the LO-SD patients and the EO-SD patients, and average age at examination of the LO-SD patients, were also selected. The LO-AD patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria for probable AD.[18]

Early-onset dementia was defined as dementia with age at onset <65 years, and late-onset dementia was defined as dementia with age at onset ≥65 years. We examined the differences in age at examination, duration of disease, sex ratio, education, CDR score, MMSE total and subscale scores, RCPM score, SMQ score, NPI total and subscale scores, and SRI total and subscale scores at the first assessment among the three groups.

We excluded patients without reliable caregivers, and patients who had a history of mental disease or substance misuse before onset of dementia. The present study was carried out after obtaining informed consent from all patients or their primary caregivers.

Assessment of cognitive functions

We assessed the differences of cognitive functions among the three groups using the MMSE, the RCPM and the SMQ at the first assessment. The RCPM is an instrument to assess visuospatial ability for reasoning in the visual modality.[9] The RCPM is useful in a patient with aphasia, because verbal instruction is kept to a minimum.[9] The SMQ is an objective tool for the assessment of the memory difficulties. The SMQ consists of 14 questions concerning everyday memory that are directed not to the patient, but to a principal caregiver.

Assessment of BPSD

We assessed the differences of BPSD among the three groups using the NPI and the SRI at the first assessment. The SRI assesses five distinctive stereotypical behavioural disturbances often seen in patients with FTLD: 'eating and cooking behaviours', 'roaming', 'speaking', 'movements' and 'daily rhythm'. 'Eating and cooking behaviours' is to keep eating the same foods or cooking the same dishes. 'Roaming' is to take the same route repeatedly without getting lost. 'Speaking' is to tell the same story repeatedly. 'Movements' is to make the same movements (rubbing knee, clapping hands, etc.) repeatedly. 'Daily rhythm' is to live with a strictly fixed daily rhythm that looks like a timetable. In the SRI, the severity and frequency of each neuropsychiatric symptom are rated on the basis of scripted questions that the patient's primary caregivers are asked. The SRI total scores are calculated, in addition to the scores for the individual symptom domains.

Statistical analyses

Data analyses were carried out using SPSS Version 15.0 (SPSS, Chicago, IL, USA) and KyPlot Version 5.0 (KyensLab, Tokyo, Japan). Age at examination, duration of disease and education among the three groups were analyzed using one-way analysis of variance. If significant differences were found, the post-hoc Tukey–Kramer test for multiple comparison was used. The sex ratio among the three groups was analyzed using Fisher's exact test. CDR score, MMSE total and subscale scores, RCPM score, SMQ score, NPI total and subscale scores, and SRI total and subscale scores among the three groups were analyzed using the Kruskal–Wallis test. If significant differences were found, the post-hoc Steel–Dwass test for multiple comparison was used. The KyPlot Version 5.0 was only used for the Tukey–Kramer test and Steel–Dwass test. *P*-values of less than 0.05 were considered to be statistically significant.

RESULTS

There were a total of 25 SD patients, the mean age at onset was 63.1 ± 8.4 years and 40% of them were over 65 years-of-age at onset. Table 1 shows the comparison of demographic variables among the three groups. There were significant differences in the age at examination and the education among the three groups; the age at examination of LO-SD patients, as well as the LO-AD patients, was significantly higher than that of the EO-SD patients; the LO-SD patients as well as the LO-AD patients were significantly lower than the EO-SD patients in

Table 1 Comparison of demographic variables among the three groups

	LO-SD ($n = 10$) (range)	EO-SD ($n = 15$) (range)	LO-AD ($n = 47$) (range)	*P*-value	*P*-value (post-hoc test) LO-SD *vs* EO-SD	*P*-value (post-hoc test) LO-SD *vs* LO-AD	*P*-value (post-hoc test) EO-SD *vs* LO-AD
Age at onset (years)	71.4 ± 3.7 (66–76)	57.5 ± 5.5 (47–64)	74.4 ± 5.1 (65–86)				
Age at examination (years)	75.1 ± 3.8 (69–82)	60.5 ± 5.4 (50–67)	77.7 ± 4.8 (68–87)	<0.001*	<0.001**	0.264	<0.001**
Duration of disease (years)	3.7 ± 1.6 (2.1–7.0)	3.0 ± 1.4 (1.2–5.6)	4.2 ± 2.7 (0.3–10.7)	0.199	NS	NS	NS
Sex ratio (male/female)	3/7	8/7	15/32	0.337	NS	NS	NS
Education (years)	9.7 ± 2.1 (7–15)	12.0 ± 2.5 (9–16)	9.0 ± 2.3 (5–16)	<0.001*	0.045**	0.673	<0.001**
CDR score (0/0.5/1/2/3)	0/4/1/5/0	1/9/3/2/0	0/17/12/15/3	0.057	NS	NS	NS

*Significant difference was found by one-way analysis of variance ($P < 0.05$). **Significant difference was found by the post-hoc Tukey–Kramer test for multiple comparison ($P < 0.05$). Mean ± standard deviation or *n*. CDR, Clinical Dementia Rating; EO-SD, early-onset semantic dementia; LO-AD, late-onset Alzheimer's disease; LO-SD, late-onset semantic dementia; NS, not significant.

education. No significant differences were found in the duration of disease, sex ratio and the CDR score among the three groups.

Table 2 shows the comparison of cognitive functions among the three groups. There were significant differences in 'naming' and 'construction' scores of the MMSE, the RCPM score and the SMQ score among the three groups; both SD groups scored significantly lower than the LO-AD patients in 'naming' of the MMSE; the LO-SD patients, as well as the LO-AD patients, scored significantly lower than the EO-SD patients in 'construction' of the MMSE and the RCPM, and both SD groups scored significantly higher than the LO-AD patients in the SMQ. No significant differences were found in the MMSE total score, 'orientation in time and place', 'registration', 'serial-7s', 'repetition', 'three-stage command', 'reading', 'recall' and 'writing' scores of the MMSE among the three groups.

Table 3 shows the comparison of neuropsychiatric symptoms among the three groups. There were significant differences in 'delusion', 'euphoria' and 'disinhibition' scores of the NPI among the three groups; both SD groups scored significantly lower than the LO-AD patients in 'delusion' of the NPI, whereas they scored significantly higher than the LO-AD patients in 'euphoria' and 'disinhibition' of the NPI. No significant differences were found in the NPI total score, 'hallucination', 'agitation', 'dysphoria', 'anxiety', 'apathy', 'irritability' and 'aberrant motor behaviour' scores of the NPI among the three groups.

Table 4 shows the comparison of stereotypical behaviours among the three groups. There were significant differences in the SRI total and all subscale scores among the three groups; both SD groups scored significantly higher than the LO-AD patients.

DISCUSSION

We assessed cognitive functions using the MMSE, the RCPM, the SMQ, BPSD using the NPI and the SRI among the three groups. As a result, the LO-SD patients overlapped with the LO-AD patients in some neuropsychological profiles. However, the SMQ and BPSD profiles of the LO-SD patients showed in accordance with the EO-SD patients and they were distinct from the LO-AD patients.

Although SD patients are known to have better memory and visuospatial abilities than AD patients,[16] the LO-SD patients as well as the LO-AD patients