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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-

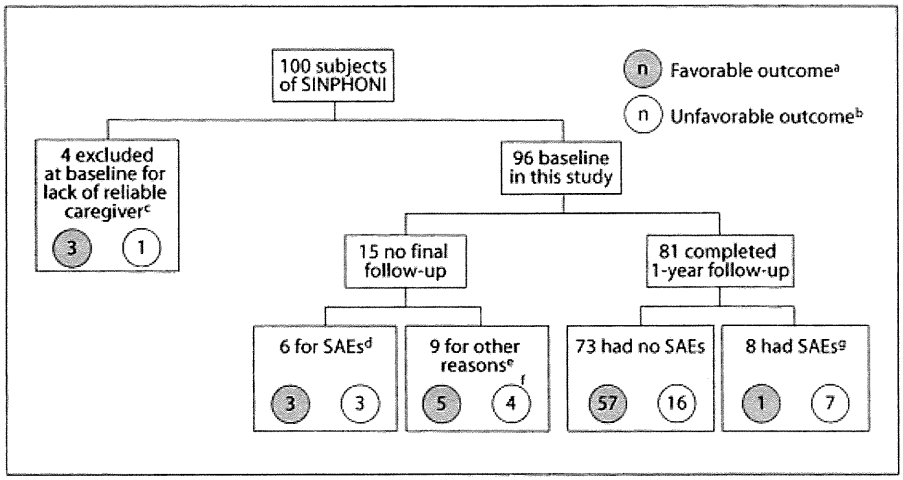

Fig. 1. Flow diagram of this study. [a] Number of patients with favorable outcomes, defined as showing an improvement of ≥1 level in the modified Rankin Scale (mRS) at 1 year after the shunt operation. [b] Number of patients with unfavorable outcomes, defined as showing no improvement in the mRS 1 year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

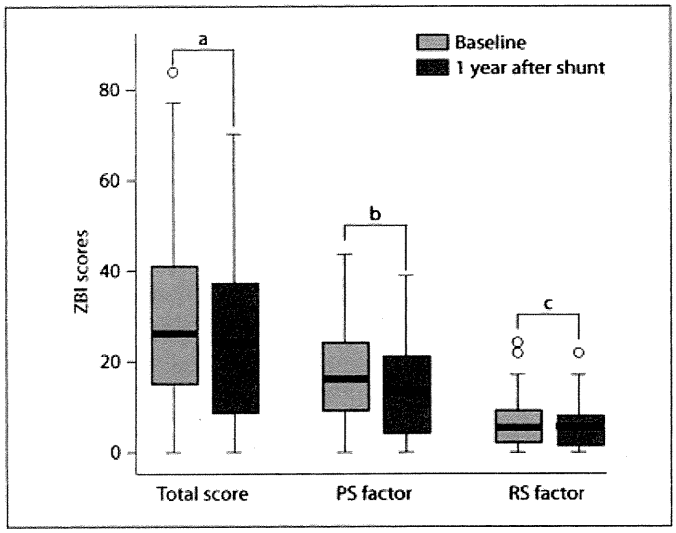

Fig. 2. Box plot of ZBI scores before and 1 year after shunt operation in 81 iNPH patients. Total and PS factor scores of the ZBI significantly decreased after the shunt operation, but the RS factor did not. Bold horizontal lines represent the median values, the boxes represent the interquartile range,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

Protein synthesis in the posterior cingulate cortex in Alzheimer's disease

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Abstract

Background: Neuroimaging studies using ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) have shown that the posterior cingulate cortex (PCC) is the primary and most prominent area of cerebral metabolic and perfusional decrement in early Alzheimer's disease (AD). We carried out the present preliminary study to investigate whether a decline of cerebral blood flow (CBF) in the PCC in early to moderate AD was accompanied with that of cerebral protein synthesis (CPS).

Methods: We carried out both N-isopropyl-p-[123I] iodoamphetamine SPECT (IMP-SPECT) and L-[methyl-11C] methionine positron emission tomography (MET-PET) in eight AD patients with apolipoprotein E epsilon 4 allele in the early to moderate stage. We also carried out IMP-SPECT in eight healthy controls (HC). We located 32 regions of interest (ROI), and values of regional MET or IMP uptakes were averaged in five regions; the frontal lobe (FL), the parietal lobe (PL), the medial temporal lobe (MTL), PCC and the occipital lobe. Furthermore, the values in the FL, PL, MTL and PCC were divided by values in the occipital areas, and normalized values of regional CBF (rCBF) and CPS (rCPS) were calculated. Then, the rCBF in the FL, PL, MTL and PCC were compared between AD and HC. In addition, the rCBF and rCPS were compared in the FL, PL, MTL and PCC of AD.

Results: The rCBF in the PCC, but not in the other three regions, was significantly lower in AD than in HC. The rCBF was significantly lower than rCPS in the PCC, but rCBF and rCPS were comparable in the other three regions in AD.

Conclusions: The CBF reduction in the PCC in AD was partly caused by neuronal loss in the PCC and partly supported the hypothesis that CBF reduction in the PCC was a result of functional deafferentation by neural degeneration in areas other than the PCC.

INTRODUCTION

Neuroimaging studies using ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) have shown that the posterior cingulate cortex (PCC) is the primary and most prominent area of cerebral metabolic and perfusional decrement in early Alzheimer's disease (AD).[1] However, neurofibrillary tangles, a pathological hallmark of AD, and neuronal loss have not been reported in the PCC in early AD.[2] The reasons for the discrepancy between SPECT and FDG-PET abnormalities, and the absence of

neuronal loss and neurofibrillary tangles in the PCC have not been well explained. The discrepancy has often been attributed to functional deafferentation. Functional deafferentation occurs when a pathologically damaged region of the brain causes functional deactivation in other regions that are remote from, but connected to, the damaged region. In AD, the SPECT and FDG-PET abnormalities in the PCC are a result of damage in the entorhinal cortex. The entorhinal cortex is the first area that is pathologically affected in AD and is strongly connected to the PCC.[3] However, recent new neuroimaging techniques have shown the deposition of β-amyloid (Aβ), another pathological hallmark of AD,[4] and cortical atrophy[5,6] in the PCC in early AD patients. These findings might indicate neuronal loss in the PCC of AD.

L-[methyl-11C] methionine PET (MET-PET), which can visualize cerebral protein synthesis (CPS), is commonly used for detecting brain tumours, because tumours are associated with increased CPS. However, MET-PET can also be used to evaluate the decreased CPS *in vivo*, which could indicate neuronal loss.[7] The neuronal loss in the brain evaluated by MET-PET would mainly indicate loss of neurons, but not glial cells, because neurons synthesize protein at a higher rate than glial cells in the brain.[8] Crossed cerebellar diaschisis (CCD), which is shown in SPECT and FDG-PET images, is a depression of blood flow and oxidative metabolism of glucose in the cerebellum contralateral to a supratentorial brain lesion and is a typical phenomenon of the neural deactivation caused by the remote lesion.[9,10] However, we recently confirmed that CCD was not observed in MET-PET.[10] Thus, MET-PET could evaluate the neuronal loss *in vivo* without being influenced by neural deactivation in other affected regions. This characteristic of MET-PET is useful for evaluating neuronal loss of AD, because AD is a multilesional brain disease.

MET-PET has previously been used to show decreases of CPS in the frontal lobe[11] and temporoparietal area in patients with AD.[12] However, the characteristics of patients with AD in these studies were not well described. Furthermore, these studies set the regions of interest (ROI) directly on the patient's MET-PET images, which inevitably reduced reproducibility as a result of differences in human expertise and intraobserver variations. In addition, the ROI was not set at the PCC in these studies.

In the present study, we carried out both N-isopropyl-p-[123I] iodoamphetamine (IMP)-SPECT and MET-PET in eight patients with mild to moderate AD to assess whether the hypoperfusion was accompanied by the loss of CPS. The apolipoprotein E (ApoE) epsilon 4 allele is associated with a higher risk of AD and hypometabolism in the PCC.[13] In the present study, to increase the number of AD patients who have dysfunction in the PCC, we recruited only AD patients with the ApoE epsilon 4 allele.

SUBJECTS AND METHODS

Patients group

We recruited eight patients (4 females and 4 males) from consecutive outpatients who visited the neuropsychological clinic in the Department of Neuropsychiatry of Osaka University Medical Hospital between April and July in 2006. The inclusion criteria were: (i) a clinical diagnosis of probable AD based on National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria;[14] (ii) scores of less than 24 in the Mini-Mental State Examination (MMSE),[15] and >10 in the Alzheimer's Disease Assessment Scale-Cognitive Component-Japanese version (ADAS J-cog);[16] (iii) a score of 1 or 2 in the Clinical Dementia Ratings (CDR)[17] for the assessment of severity of the disease; (iv) no abnormal findings that caused dementia in the neurological examination and blood chemistry; (v) having the ApoE epsilon 4 allele; and (vi) no other abnormal findings than cerebral atrophy on magnetic resonance imaging (MRI) or computed tomography. The eight patients had a mean age of 73.0 years (SD = 5.4), a mean age of onset 67.8 years (SD = 5.0), a mean duration of illness of 5.3 years (SD = 2.3), and a mean level of education of 10.9 years (SD = 1.5). Their mean MMSE score was 19.3 (SD = 3.3) and their mean ADAS-Jcog. score was 21.3 (SD = 6.5). The scores of the CDR were 1 for three patients and 2 for five patients. The ApoE status was four homozygotes and four heterozygotes.

Healthy control group

Eight healthy control (HC) subjects (6 female and 2 male) were recruited from the community and were comparable to AD subjects on age and educational attainment. They had normal cognitive functions (MMSE score >25), normal findings in the physical and

neurological examinations, no history of psychiatric disorders and head trauma with loss of consciousness, no abnormal findings on MRI other than insignificant leucoaraiosis, and no risk factors for cerebrovascular disease (hypertension, heart disease and diabetes mellitus). Their mean age was 72.5 years (SD = 5.8), their mean level of education was 11.0 years (SD = 1.4) and their mean MMSE score was 28.6 (SD = 1.4).

The AD and HC groups did not significantly differ in age, education ($t = 0.18$, $P = 0.86$; $t = 0.17$, $P = 0.86$, respectively, Student's t-test) or sex ($P = 0.30$, Fisher's exact probability test). However, the AD group had significantly lower MMSE scores than the HC group ($t = 7.42$, $P < 0.001$, Student's t-test).

The present study was approved by the Ethics Committee of Osaka University Hospital. Before their enrollment, the subjects were given detailed explanations of the purpose of the study and all the procedures used. Written informed consent was obtained from all subjects.

PET and SPECT procedures

All AD patients underwent both MET-PET and IMP-SPECT scans with an interval period ranging from 24 to 97 days (59 ± 21 days); there were no clinical changes in any of the patients during this interval period. The HC subjects underwent only IMP-SPECT scans.

MET-PET images were carried out using a Headtome V PET scanner (Shimadzu, Kyoto, Japan) with retractable septa. Scans of all subjects was carried out in the stationary mode with septa in, which allowed acquisition of 63 contiguous transverse slices with a spatial resolution of 3.7 mm full width at half-maximum (FWHM) in the transaxial direction and 5 mm in the axial direction. The patient's head was fixed in place with a head holder and was positioned with light beams to obtain transaxial slices parallel to the orbitomeatal line. The images were acquired with the patient resting in the supine position, with their eye closed. Corrections for absorption were carried out with attenuation measured in a transmission scan using a retractable rotating rod source. MET were given intravenously at the dose of 555–740 MBq. Regional emission images of the brain were obtained for 10 min, beginning 20 min after the MET injection. Scan data were reconstructed with an ordered-subset expectation maximization algorithm (12 iterations with 4 ordered subsets).

IMP-SPECT images were obtained with a four-head rotating gamma camera fitted with a low-energy, general purpose, parallel-hole collimator with a spatial resolution of 13.0 mm full-width-at-half-maximum (Gamma View SPECT 2000H, Hitachi Medical, Tokyo, Japan). Data were acquired in a continuous rotating mode in reciprocal directions at 20 s per revolution for 66 min from 96 directions in a 64 × 64 matrix. The SPECT scan was started 15 min after intravenous injection of 167 MBq of 123I-IMP (Perfusamine, Nihon Medi-Physics, Hyogo, Japan). The transaxial images were reconstructed using a filtered back projection algorithm and a Butterworth prefilter.

Data analyses

Image data of individual IMP-SPECT or MET-PET scans were stereotactically standardized with Neurological Statistical Image Analysis Software (NEUROSTAT; University of Michigan. Ann Arbor, MI, USA) on a windows personal computer[18,19] in order to remove the difference of the individual's brain size and to minimize the regional anatomical differences. NEUROSTAT has been shown to be suitable for anatomical standardization of the brain with atrophy in AD.[20]

One investigator (T.Y.), who specializes in neuroimaging and who was blind to the subject's clinical information, placed a total of 32 circular ROI of 12-mm diameter on the five cortical areas on the MRI template image of NEUROSTAT; the frontal lobe (FL), the parietal lobe (PL), the medial temporal lobe (MTL), PCC and the occipital lobe bilaterally. Figure 1 shows the ROI on the templates and the anatomical areas. Subsequently, the same ROI were transferred to the standardized MET-PET and IMP-SPECT images.

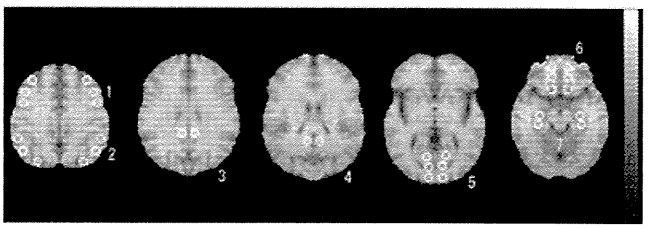

Figure 1 Regions of interest (ROI) on the magnetic resonance imaging (MRI) template images. The ROI shown on the horizontal MRI template images of Neurological Statistical Image Analysis Software (University of Michigan. Ann Arbor, MI, USA)). The anatomical locations of ROI are as follows: 1 and 6, frontal lobe; 2, parietal lobe; 3 and 4, posterior cingulate cortex; 5, occipital lobe; 7, medial temporal lobe.

Table 1 Regional cerebral blood flow and regional cerebral protein synthesis in Alzheimer's disease and regional cerebral blood flow in healthy controls

Region	HC rCBF	AD rCBF	AD rCPS	rCBF in HC *vs* in AD *P*-value	rCBF *vs* rCPS in AD *P*-value
FL	0.80 ± 0.06	0.82 ± 0.09	0.80 ± 0.05	0.999	0.962
PL	0.84 ± 0.08	0.79 ± 0.11	0.80 ± 0.09	0.981	1.000
MTL	0.76 ± 0.03	0.63 ± 0.11†	0.71 ± 0.10	0.442	0.132
PCC	0.84 ± 0.11	0.60 ± 0.11†	0.70 ± 0.08‡	0.026	0.045

†Significantly lower than regional cerebral blood flow (rCBF) in the frontal lobe (FL) and parietal lobe (PL; post-hoc Tukey's HSD test). ‡Significantly lower than regional cerebral protein synthesis (rCPS) in FL and PL (post-hoc Tukey's HSD test). Data are given as mean ± SD. AD, Alzheimer's disease; HC, healthy controls; MTL, medial temporal lobe; PCC, posterior cingulate cortex.

Then, we evaluated the tracer uptake with the semi-quantitative method. We divided the averaged value of each of the four areas (FL, PL, MTL and PCC) out of five ROI areas by the mean values of the bilateral occipital areas; that is, we calculated the cerebral blood flow (CBF) or CPS ratio using the regional-to-occipital cortical ratio, to increase the reliability and to remove the intersubject difference in baseline metabolism or perfusion.[21] The normalized values of the regional MET and IMP uptake ratios (rCBF and rCPS) were relative values, which made it possible to compare them directly.

Statistical analyses

The averaged rCBF or rCPS of the right and left sides were used for the analyses, because averaging both sides would increase the reliability of the measurement. To compare the rCBF between HC and AD, the difference of rCBF was analyzed by using two-way analysis of variance (ANOVA) for repeated measures, with one between-factor (group: HC and AD) and one within-factor (region: FL, PL, MTL and PCC) and post-hoc Tukey's HSD test for comparisons between each pair of regions.

To compare between rCBF and rCPS in AD, the difference of tracer uptakes was analyzed by using two-way ANOVA for repeated measures, with two within-factors (isotope: IMP and MET, and region: 4 regions as aforementioned), and post-hoc Tukey's HSD test. The significance level was set at $P < 0.05$ in all statistical analyses.

RESULTS

As for the comparison of rCBF between HC and AD, two-way ANOVA showed a significant group effect ($F(1,14) = 10.8$, $P = 0.005$), region effect ($F(3, 42) = 11.7$, $P < 0.001$) and a significant group × region interaction ($F(3,42) = 8.8$, $P < 0.001$). The rCBF in the PCC was significantly lower in AD than in HC ($P = 0.026$). In the HC group, the rCBF in the different regions were not significantly different by post-hoc analyses. In the AD group, the rCBF in the MTL and PCC were significantly lower than those in the FL and PL, but there were no significant difference of the rCBF between the MTL and PCC (Table 1).

In the comparison between rCBF and rCPS in AD, two-way ANOVA with repeated measures showed a significant region effect ($F(3,21) = 14.1$, $P < 0.001$) and a significant isotope × region interaction ($F(3,21) = 4.3$, $P = 0.016$), but did not show a significant isotope effect ($F(1,7) = 1.8$, $P = 0.22$). rCBF was significantly lower than rCPS in the PCC, but no significant differences were observed in other regions. In the AD group, rCPS was significantly lower in the PCC than in the FL and PL. rCPS in the MTL was lower, but not significantly, than those in the FL and PL ($P = 0.10$ and $P = 0.058$, respectively). rCPS values in the other regions were not significantly different from each other.

DISCUSSION

Both the rCBF and rCPS in the PCC were significantly lower compared with those in the FL and PL in the AD group in the study. The rCBF in the PCC was significantly lower in the AD group than in the HC group in the present study, which was consistent with previous reports of a clear decline of rCBF in PCC in the early to moderate stages of AD.[22] Because we could not carry out MET-PET scans of the HC group, we could not compare the rCPS between HC and AD directly or evaluate whether the rCPS decreased in the PCC of AD in the present study. However, we could approximately calculate the regional-to-occipital cortical ratios of MET-PET in normal subjects from the data of

Coope DJ *et al.*[23] Their study reported that the mean ratios in normal subjects are approximately 0.8–0.9 in all areas examined in the present study. The CPS of the frontal and the temporal cortices in normal subjects measured by Salmon E *et al.*[12] was consistent with those of Coope DJ *et al.*[23] Therefore, we assumed that the rCPS in normal subjects are comparable among the ROI in the four brain areas in the present study and were approximately 0.8–0.9. The rCPS in the PCC appeared to be lower in the AD group in the present study than the normal subjects in the report of Coope DJ *et al.*[23] Thus, protein synthesis in the PCC of the AD patients in the present study appeared to be decreased.

Our finding that rCPS was significantly higher than rCBF in the PCC shows that CBF was more severely decreased than the neuronal loss in PCC. This appears to support the hypothesis that the more severe reduction of the CBF arises from functional deafferentation caused by primary neural degeneration of other brain areas, such as the entorhinal cortex.[24] Thus, the decrease of CBF in the PCC would reflect both the neuronal loss and remote functional hypoperfusion.

The AD patients in the present study had CDR scores of 1 or 2, which are frequently associated with neuropathological Braak stages III and IV.[25] In Braak stages III and IV, MTL is preferably affected with mild neocortical pathology.[25] The neuropathological evidence is consistent with the finding of the present study that the rCPS in the MTL could be lower in the AD group than in the normal subjects in the study of Coope DJ *et al.*[23] The rCBF in the MTL was also lower in the AD group than in the HC group in the present study, although the difference did not reach the significant level. The lack of significant difference might be as a result of a type II error because of the small sample size of the present study. Neuronal loss and neurofibrillary tangles are not common in the PCC in AD patients in Braak stages III and IV.[25] However, recent studies with new neuroimaging techniques showed the presence of pathological changes in the PCC in early AD patients. Neuroimaging studies with [11C] Pittsburgh compound B (PiB)-PET showed Aβ deposition in the PCC[4], which might induce local atrophy of the PCC.[26] MRI studies using voxel-based morphometry (VBM) have shown a regional grey matter loss in the PCC of mild AD.[5,6] Diffusion tensor MRI using the VBM technique showed increased diffusivity in the PCC of AD in the early stage, which might indicate a pathological abnormality.[27] Furthermore, Vogt BA *et al.*[28] reported that neuronal loss in the PCC of AD was accompanied by laminar degeneration. They also found that the ApoE epsilon 4 allele was positively associated with the severity of the pathological change in the PCC, leading to a variable degree of pathological change in PCC among AD patients. In the present study, there was a clear decrease in rCPS in the PCC in AD patients, because the AD patients were limited to those who had the ApoE epsilon 4 allele. Further studies are needed to determine whether the ApoE epsilon 4 allele is associated with neuronal loss in the PCC.

The present study had some limitations. The sample size of this study was small, because we intended to recruit homogenous patients with ApoE epsilon 4 allele. The analyses of the homogenous patients could clarify the significant difference between rCBF and rCPS in the PCC, despite the small sample size of this study. A second limitation is that by limiting the subjects of the present study to AD patients with the ApoE epsilon 4 allele, the results might not apply to AD patients with other ApoE alleles. A possible third limitation is that we used the ROI method rather than a voxel-by-voxel analysis in stereotactic space. The ROI method is not bias-free but could be used in a study with a small sample size. Future studies that use a large number of subjects and a voxel-by-voxel analysis are needed to confirm the present findings.

Our MET-PET results suggest that the hypoperfusion in the PCC observed by SPECT is partially a result of the neuronal loss, which would be indicated by the impairment of CPS, and partially a result of the apparent reduction of CBF. Although the neuronal loss assumed by the MET-PET was not pathologically confirmed, the MET-PET could evaluate the regional neuronal loss in AD *in vivo*.

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特 集 ■ 緩徐進行性高次脳機能障害の病態

意味性認知症

Language Impairment and Semantic Memory Loss of Semantic Dementia

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Abstract

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

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

はじめに

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

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らである。近年，SDに対する症候学的研究に加え，神経画像学的研究，分子生物学的研究が精力的になされ，SDの病態解明が進んできた。本稿では診断に役立つ臨床症状や検査所見の解説に加え，最新の研究で明らかになった知見を紹介する。

Ⅰ．SDの疫学

疾患概念に対する理解がまだ十分に普及していないため，正確に診断がつけられていない可能性があり，国内に限らず海外でも疫学研究は少ない。国内では，hospital-basedの研究で，高次脳機能外来を受診した連続例330例のうち15例（4.5%）であったとの報告がなされている[5]。英国におけるcommunity-basedの研究では，若年発症の認知症患者108例のうち，FTLDが17例，そのうち2例がSDであった[6]。海外では日本に比べ家族発症例のFTLDが多いが，FTLDのサブタイプの中でSDの家族発症は少ないとされている[7]。

Ⅱ．SDの臨床症状

SDの臨床診断は臨床症状の把握と神経画像検査で行われる。まず，最も重要な臨床症状についてまとめる。

1．語義失語

SDでは語義失語と呼ばれる独特の言語障害を呈する。この語義失語の概念は1943年に井村[8]が提唱しており，わが国では欧米と比べても早い時期からその特徴をまとめていた。語義失語の中核症状は，単語に関する情報，特に意味的側面の喪失とでも呼ぶような障害である。他の言語的側面は保たれており，発語は流暢で，音の歪みもない。意味がわからない単語を含め，単語や文章を正確に復唱でき，音韻的側面は保たれる。文法的な誤りもなく，発語量も低下しない。理解面も単語の意味さえわかれば問題なく，いわゆる文レベルの理解は保たれる。書字に関しても音声言語の特徴が反映され，表音文字である仮名操作は保たれる一方，表音文字であると同時に表意文字でもある漢字の操作に障害がみられる。SDでは病初期には障害が言語の側面だけにとどまるため失語の範疇でとらえることもできるが，進行するに従って後述する意味記憶障害ととらえたほうがよい状態となる。以下にSDで認められる言語症状について詳述する。

1）喚語困難・呼称障害

SDの言語症状として最も初期から目立つ症状である。自由会話の中でも適切な単語が円滑に思い出せなくなる。「あれ」，「それ」などの指示代名詞で補うこともある。また物品をみせて，名前を答えるよう指示する呼称課題でも名前を答えられない。認知症患者のスクリーニング検査として行うmini-mental state examination（MMSE）検査で，日常生活はほぼ自立しているにもかかわらず，物品の呼称ができず，SDが疑われることもある。また「豆腐」と答えるべき場面で「納豆」と答えるような語性錯語も認める。語性錯語は意味的に関連のある他の言葉に置き換わる意味性錯語が多いが，「とうふ」を「とうは」というように音が置き換わる音韻性錯語は目立たない。

呼称課題で，患者が答えられない単語に対しては，一般的に，語頭音をヒントとして与え，回答を促す。健忘失語の患者の場合，語頭音ヒントは有効であるが，SD患者では正答に至らないことが多い。例えば，鉛筆を提示して患者に名前を問うが，答えられないときに「『え』で始まりますよ」，次いで「『えん』で始まりますよ」，さらに「『えんぴ』で始まりますよ」というように検者が徐々に長いヒントを出しても最後まで正答に至らない。逆に患者が「これは『えんぴ』というのですね」と理解し，少なくともその診察中は「えんぴつ」という言葉の代わりに「えんぴ」という言葉を使う様子も観察される。このような呼称や喚語できない単語は病初期ではごく少数に限られるが，進行に伴い徐々に増加する。

2）単語の理解障害

いわれた名前に対応する物品を複数の物品の中から選択させる語理解課題でも誤りが生じる。上記の呼称課題とこの語理解課題は表裏をなす課題であるため，1つの単語に対して呼称も理解もできなかった場合，双方向性の障害と表現する。そしてこの双方向性の障害がSDの特徴とされている。また，SD患者では提示された単語（その音の並び）に既知感を感じない。すなわち「えんぴつ」と患者にいっても，その音の並びを聞いたことがないと感じ，しばしば「『えんぴつ』って何ですか」というように逆に質問する。この「○○って何ですか」というフレーズとその言葉を初めて聞くような当惑した様子はSD患者に特徴的であると筆者は感じており，このフレーズを聞くとSDを疑うほどである。呼称障害と同様，疾患の進行に伴い理解できない単語，双方向性の障害を認める単語も徐々に増加していく。

臨床診療場面では，鉛筆，消しゴム，時計，筆，ホッチキス，懐中電灯などの診察室にある日常物品5～10個を用いて呼称と理解を評価することが多い。詳細に調べたいときには失語症語彙検査[9]が有用である。この検査では，カテゴリー（動物，野菜果物，色，身体部位など

10カテゴリー）と親密度（どの程度なじみがあると感じられるかを表した指標で，高と低の2分類されている）が統制された200個の名詞が用意されている。

3）障害されやすい単語

SDでは親密度の低い単語ほど障害されやすい。また単語のカテゴリーによっても障害のされやすさが異なる可能性があり，色や身体部位に関する単語は障害されにくい[10]。また名詞よりも動詞のほうが障害されにくいことも報告されている[11]。

4）障害される単語の一貫性

SD患者に複数回，呼称課題や語理解課題を行うと，呼称障害，語理解障害，双方向性の障害を認める単語，および既知感を有さない単語が一貫する傾向がある[12]。これは失語症患者一般で，障害される単語に浮動性を認めることとは対照的である。しかし，病初期であればSDでも浮動性を認めることもある。経過を観察していくと，全体としては障害を認める単語が増えていく。その中で，障害に浮動性を認める単語が混在しながら，一貫して障害される単語が増えていく。

5）表層性錯読，類音的錯読（surface dyslexia）

欧米の研究で，SD患者では，綴りから予想される発音とは異なる特別な発音をする不規則発音単語を，一般的な規則に従って発音する傾向があることが報告されている。このことから個々の特別な単語をどのように発音するかという知識は障害されるが，一般的な綴りと発音の規則は保たれやすいと考えられる。

わが国の患者においてもこの症状が観察される。ただし，音と文字形態との対応が規則的な仮名では認めにくく，音が複数あり，かつ場合によって意味や読み方が異なる漢字で観察されやすい。例えば，「団子」を「だんし」，「時計」を「じけい」と読む。さらにこの症状は熟字訓と呼ばれる特別な読み方をする熟語で認めやすい。例えば「海老」を「かいろう」，「土産」を「どさん」と読む。文字と線画を対応させるよう指示する課題では，正しく読めなかった物を正しく指示することはまずない。熟語の意味はわからなくても，個々の漢字の意味はわかっていることがあり，例えば「団子」を「だんし」と読んでから，「子」の文字に引きずられるかのように「子供」の線画を指すというような反応はしばしば認められる。この表層性錯読の程度は意味記憶障害の程度とよく相関することが報告されている[13]。

6）類音的錯書

SD患者の漢字の書字で類音的錯書という特徴的な症状を認める。漢字には音と意味とがあるが，漢字の意味は無視し，音のみを使うのである。例えば「汽車」を「寄社」と，「新聞」を「新文」というように漢字の音を借りてあたかも仮名のように使う。

Table　語義失語と意味記憶障害の分類――鉛筆の場合

	語義失語	→	意味記憶障害
呼称（語頭音効果）	×		×
指示	×		×
名前を聞いたことがあるか	×		×
みたことがあるか	○		×
使い方を説明できるか	○		×
使えるか	○		×
関連する物を選択できるか	○		×
一般的知識を有しているか	○		×

この分類は鉛筆のような使用可能な物品に適用可能

7）諺の補完障害と字義的解釈

諺の補完現象とは，例えば，「『ちりも積もれば』の後には何と続きますか」というように，質問したときに，「山となる」と正しく補える現象である。諺の意味を答えることができなくても，よく知られた諺なら重度の失語症患者でも補完は自動的になされることがほとんどで，プライミングの一種と考えられる。しかし，SD患者では「ちりも積もれば山」，次いで「ちりも積もれば山とな」までヒントを出しても補完できない[14]。また諺や比喩の意味を問うたときには字義的解釈にとどまり，諺や比喩の持つ特別の意味は答えられない。例えば，「腹が立つ」の意味を問うたときに，腹を押さえて，次に立つ動作をするというように，「腹」，「立つ」という言葉それぞれの字義的な意味理解にとどまる。

8）語義失語から意味記憶障害へ

縦断的にSD患者の単語の障害を観察していると，当初は語義の障害レベルにとどまっていた単語が，進行に伴い意味記憶障害ととらえられる状態へと進行する。そして，意味記憶障害レベルにある単語が進行に伴い増加する。ここで語義の障害にとどまっているレベルとは，Tableのように鉛筆を例にとると以下のような状態である。Tableの上段3つの項目に障害を認める，すなわち呼称と了解ができない双方向性の障害を認め，かつ名前を聞いたことがないと既知感も有さない。しかし，下段の5つの項目に関しては障害されない。すなわち鉛筆自体はみたことがあるといい，使い方や用途を説明でき，また正しく使える。さらに，ノートや消しゴム，鉛筆削りを関連する物と認識でき，一般的な知識，三菱鉛筆やトンボ鉛筆があり，六角柱をしていることが多いなどを答えることができる。

一方，意味記憶障害レベルとは，その対象物を同定するために一般的に考えることができるモダリティーすべ

てから迫ってもその対象物を同定できない状態で，Tableでは全項目が障害された状態である。当然，鉛筆に関連する一般的な知識をどれくらい詳細に評価するかによって語義の障害レベルか意味記憶障害のレベルかの判断は変わってくるが，臨床的に語義失語のレベルか意味記憶障害のレベルかの区別を厳格にしなければならない場面は少ない。また，同時期に語義失語のレベルにとどまる単語と意味記憶障害のレベルに達している単語が混在することもよくある。また，単語の属性によっても意味記憶障害レベルのとらえ方は異なる。言語情報や視覚情報だけでなく嗅覚情報や触覚情報がその対象物を規定するために有用なこともある。また，「利き手」などの抽象的な言葉もあり，このような単語については語義失語レベルか意味記憶障害レベルかを区別することは困難である。

2．言語以外の意味記憶障害

1）視覚イメージの意味記憶障害

SD患者では両側側頭葉の萎縮が特徴的な所見であるが，通常，萎縮の程度には左右差がある。どちらが優位に萎縮しているかによって左側頭葉優位型と右側頭葉優位型とに分類されるが，臨床的には左側頭葉優位型のほうが多い。どちらの萎縮が優位であっても語義失語と意味記憶障害を呈する。SDでは一般的に視空間認知機能は保たれ無意味図形の模写や弁別に障害はない。しかし，以下のような視覚イメージが喪失されることがあり，この視覚イメージの喪失は，右側頭葉優位型SDのほうが早期から顕著となりやすい。

臨床的にも気づきやすいのは相貌の同定障害である。患者自ら，顔がわからないことを自覚していることもある[15]。有名人，親戚，家族，さらには自分の顔も同定できないし，既知感も有さない。同定できない顔は患者が会っている頻度の影響を受けやすく，毎日会っている家族よりも久しぶりに会う家族の顔のほうがわからなくなりやすい。図形の模写ができるように相貌に関しても，知覚面は保たれ顔写真の異同弁別はできる。また誰の顔であるかはわからなくても「顔」であることはわかっている。

有名な建物や風景の同定障害も認められる。検査としては，絵はがきなどを提示して何であるかを答えさせることが多く，富士山，東京タワー，金閣，国会議事堂などが用いられる。これらの写真に対してもSD患者はみたことがないといい，何であるかわからない。しかし，それぞれ山，タワー，寺であることはわかる。右側頭葉優位型SDの病初期では，有名人や家族の顔を同定することはできなくても，その人の名前から自分との関係やその人の仕事，どんなことをした人かなどその人に関する知識を説明できる場合もある。また，有名な建物や風景をみたことがないといっても，建物の名前からそれがどこにあるのか，どのような建物であるかを答えることができることがある。この段階では視覚失認（連合型）の範疇でとらえることができるが，疾患の進行に伴い，その人，建物についての情報も失っていき，意味記憶障害のレベルへと至る。そのほか，道路標識に関する意味記憶も障害される。

以上のような相貌や有名建物，道路標識のような固有の視覚イメージだけでなく，ホッチキスや懐中電灯のような日常物品に関する視覚イメージも喪失し，みたことがないという。さらにゾウやトラなどの動物の視覚イメージも喪失する。例えば，ライオン，サソリ，クモの写真をみせてもみたことがないと答え，タコの写真をみせたときには，「昔はこんな動物がいたのかな」と発言することもある[15]。右側頭葉優位型SD患者では語義失語による言語情報からの対象物の同定障害に加えて視覚情報からの同定も障害されやすいため，複数モダリティーからの同定障害という意味記憶障害の条件を満たしやすい。

2）象徴的動作の意味記憶障害

象徴的動作とは，「敬礼」，「バイバイ」，「おいでおいで」のような特別な社会的意味を有する動作のことである。SD患者では象徴的動作をするよう指示してもできない。逆に象徴的動作をみても何を意味する動作であるかを理解できない[16,17]。しかし，観念運動性失行とは異なり，検者が行う象徴的動作を真似することはできる。以上のことから，SD患者では象徴的動作の意味記憶が障害されていると考えられる。

3）音の意味記憶障害

特別な意味を包含する音があり，環境音と呼ばれる。例えば救急車のサイレンの音，電話の着信音，動物の鳴き声，波の音などである。このような環境音を聞いても，SD患者では何を意味する音かわからなくなることがある[18]。また，SD患者では環境音が同定できるか否かと音に既知感を持つか否かとは関係があり，既知感を持てない環境音は同定困難である。さらに環境音の同定ができない対象については，単語や絵からの同定もできない傾向があり，障害が音の認知に限らず意味記憶障害によると考えるほうが考えやすい。われわれが経験した右側頭葉優位型SD患者では，男性の声か女性の声か，声の主の大まかな年齢を判別できたが，家族の声を聞いても既知感を認めず，誰の声かもわからなかった[15]。

3．SDの意味記憶障害以外の症候

1）精神行動障害

精神行動障害としては脱抑制，考え無精，常同行動，易怒性，意欲低下などを認める。これらは前頭側頭型認知症（frontotemporal dementia：FTD）でも認める症状であるが，脱抑制や意欲低下などの明らかな人格変化はFTDに比べるとやや遅れ，初期には礼節が保たれている場合が多く[19]，日常生活は概ね自立している。SD患者で目立つ症状は常同行動である。同じ話を繰り返す滞続言語，同じ食べ物ばかり食べたがる常同的食行動異常，同じルートを散歩せずにはいられない常同的周遊，自分で決めた時間に決めたことをせずにはおれない時刻表的生活などがしばしば認められる。これらの常同行動を評価する評価尺度としてはStereotypy Rating Inventory（SRI）[20]が有用である。

2）病識

病識については，少なくとも初期には比較的保たれている印象を持つ。患者は言葉が思い出しにくいことを自覚し，思い悩んでいる様子がみられる。そして自ら単語帳を作成する患者もいる。ある患者は，名前がわからなかった物について線画を描き，その横に名前を書いていた。そしてこのような単語がA4用紙数枚にぎっしりと書かれていた。さらにそれらの単語を別の紙にア行，カ行というように行ごとにまとめ直していた。診察のときに物の名前を思い出せないとその用紙を出してきて，答えようとすることもあった。また，顔がわからないことも自覚していることが多く，このことを訴える。自分の顔を鏡でみて自分がこんな顔をしているのかと毎日納得するといっていた患者もいた[15]。

3）芸術的才能の開花

芸術的活動をほとんどしていなかったSD患者が，臨床症状が明らかになった後に素晴らしい絵や写真，彫刻を作成するようになった事実が報告されている[21]。作品は視覚的作品に限られ，その特徴は写実性であり，抽象性，象徴性という要素はなかった。視空間認知機能とエピソード記憶が保たれていたこと，前頭葉の障害が比較的軽度であったことが前提条件であると思われるが，常同行動と疾患に伴う社会との隔絶によるさらなる作品への集中が作品形成を促進したと考えられる。報告者は側頭葉前方部の障害が芸術的才能を，直接，活性化した可能性も示唆している。さらに芸術的才能の開花はFTLD（SD）の診断に役立つとしている。

4．SDの進行に伴う症候の推移

14例の左側頭葉優位型SD患者と5例の右側頭葉優位型SD患者の経過を長期間縦断的に観察した研究[22]では，19例中16例で言語障害が初発症状であった。言語障害の中では，喚語困難・呼称障害が最も早く，発症後平均1.3年の時点で認めた。次いで語理解障害を認め（発症後平均2.1年），その後錯語や読字・書字障害（約2.5年後）を認めた。右側頭葉優位型SD患者では，相貌の同定障害が最も早く出現する症状で発症後平均0.9年の時点であった。これは左側頭葉優位型（4.5年後）と比較して有意に早い時期であった。

常同行動，脱抑制，攻撃性，意欲低下などの精神行動障害は発症後3～5年の時点で認め始めた。その中で最も早期に出現する症状は常同行動であった。易刺激性・攻撃性は右側頭葉優位型患者（平均2.9年後）で左側頭葉優位型患者（平均4.4年後）と比較して有意に早く出現した。

日常生活動作（activities of daily living：ADL）の障害については，平均5年以上の経過で認め始め，道迷い（平均5.4年後），食事の介助（平均6.6年後），尿失禁（平均7.0年後），無言症（平均7.1年後），更衣障害（平均7.1年後），臥床傾向（平均7.4年後）であった。

5．運動ニューロン疾患を伴うSD

FTLDには運動ニューロン疾患（motor neuron disease：MND）を伴う症例が存在することが知られているが，MNDを伴う症例の臨床型はMND with dementia（D-MND）として報告された症例を含めてもほとんどFTD（FTD-MND）である[23,24]。そして，FTD-MNDはMNDを伴わないFTDよりも，生存期間が短く，障害が前頭葉に限局しやすいなど異なる点があることが報告されている[25]。一方，SDにMNDを伴うSD-MNDの報告は日本から3例[26-28]，海外から2例[29,30]にとどまり報告例は少ない。

しかし，SDの連続剖検18例での検討では，臨床症状の評価時にMNDの症状を呈していた症例はいなかったが，免疫組織学的には18例中13例にMNDに特徴的なタウ陰性ユビキチン陽性封入体を認め，さらにそのうち5例においては運動神経系に病理学的異常所見を認めた[31]。したがって，SDでもMNDを伴う症例が一定数存在すると予想される。報告数が少ないのは，MNDの全経過が短いこと，球麻痺を呈すると言語症状が評価困難であること，SDそのものの頻度が少ないことなどが理由と考えられる。

またSD-MNDでは，仮名の錯書や脱落などの仮名書字障害と色名呼称障害が目立つなど一般的なSDとは異なる症状を有する可能性が報告されている。特に仮名書

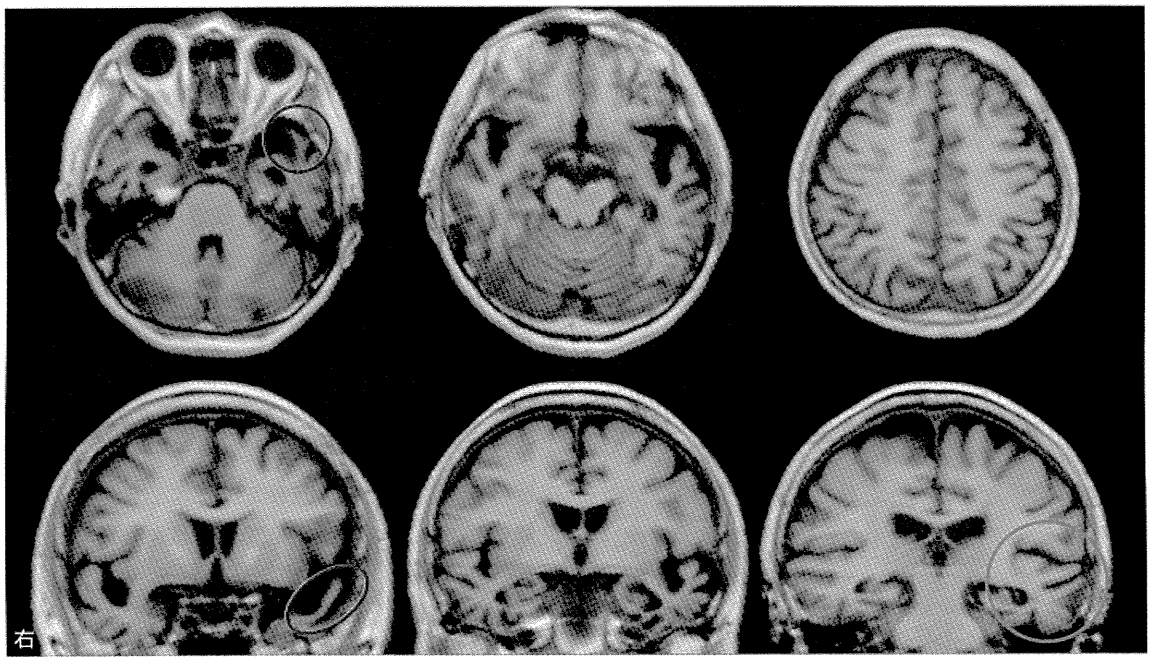

Fig. 1　左側頭葉優位型 SD 患者の MR 画像
左側頭葉前方部に楔形の強い脳萎縮を認める（赤い円）。側頭葉でも後方部になると萎縮は軽度となる（青い円）。また，前頭葉の萎縮は目立たない。

字障害は FTD-MND の特徴的症状とされており，臨床病型によらず D-MND で高率に認める特徴である可能性がある[28]。これらの症状が出現しやすいのは，SD-MND において，仮名書字に関連する左中前頭回と色の呼称に関連する左中・下前頭回を含む前頭葉が一般的な SD よりも早期から障害されるからではないかと考えられている。

Ⅲ. SD の病巣

1．神経画像検査所見

SD の診断には，magnetic resonance imaging（MRI）が有用で，初期には左右非対称性の側頭葉の限局性萎縮を認める（Fig. 1）。特に，側頭極，嗅内皮質，海馬傍回，紡錘状回，下側頭回の皮質の萎縮が顕著である[32]。他に前頭葉眼窩面，島皮質，帯状皮質における萎縮が認められる。進行は当初の障害が目立つのと対側の側頭葉でより速く進行し，末期には側頭葉萎縮の左右差はほとんどなくなることがわかっている[33]。Positron emission tomography（PET）や single photon emission computed tomography（SPECT）といった脳機能画像検査においては，MRI でみられる脳萎縮と同部位に機能低下が認められる[34]（Fig. 2）。

2．意味記憶障害の脳内責任部位

意味記憶は脳内のさまざまな領域に分散して保存され，これらの情報をつなぐ中心が側頭葉前方部にあると考えられている[35]。そして SD 患者では，前方部を含む側頭葉の萎縮のため意味記憶障害を呈すると考えられている。SD 患者に対してトラクトグラフィーを行い白質線維の障害について検討した研究では，SD 患者では側頭葉を通る下縦束，鉤状束，弓状束が障害され，特に側頭極に位置する下縦束の前方部と鉤状束の障害が強い。しかし脳梁膨大部，前頭葉と頭頂葉を結ぶ上縦束の障害は軽度である[36]。この知見から，SD の意味記憶障害は側頭葉前方部と他領域との線維連絡が障害されることによって生じる，すなわち離断症状ととらえることも可能である。例えば視覚野からの視覚情報が下縦束の障害によって側頭葉前方部に至らないという考え方である。一方，上縦束などを介する前頭葉と頭頂葉との線維連絡は相対的に保たれるため，流暢性，文法，語彙と音韻の関連は保たれる。この研究ではさらに単語を読む際の脳活動を機能的 MRI で計測している。その結果，SD 患者では紡錘状回の中央と上側頭回の活動が健常者と比較すると低下していた。

3．表層性錯読時の脳活動

SD 患者に対して表層性錯読の出現メカニズムを調べ