

nonmortality outcomes averaged over multiple domains (ie, physical, social, and psychological functioning and well-being). Consideration of QOL is essential for the selection of a treatment option, particularly when conditions are noncurative and chronic.¹⁵ Therefore, it is not surprising that physicians who regularly see older patients with multiple chronic conditions consider QOL the most important health care outcome. On the other hand, the term QOL may not be familiar to many health care recipients, and we cannot exclude the possibility that QOL might be confused with other terms, such as standard of living.

Most health care recipients ranked effective treatment of diseases as the most important, suggesting that patients are concerned about their own particular symptoms rather than nonspecific QOL, arguing for efforts to examine the symptoms most concerning to patients. The high importance of effective treatment of diseases ascribed by health care recipients, but not physicians, also implies the significance of the often-neglected aspect of inappropriate prescribing in older adults: underuse of medication likely to be beneficial to older adults. Increased evidence has suggested that failure to prescribe indicated, beneficial medication is common in older adults,^{7,8,16} and recent attempts to provide an explicit list of appropriate, indicated medication for older adults are justified.¹⁰

Interestingly, views on patient satisfaction were also different. All physician groups ranked patient satisfaction as the second top priority, whereas health care recipients considered this to be less important. This tendency has been demonstrated in a prior small study in England more than 15 years ago.¹² Recently, patient satisfaction has been increasingly used to measure health care qualities and compare health plans or physicians.¹⁷ However, our finding may argue against the value of patient satisfaction as a performance measure in geriatric medicine, especially in light of recent evidence suggesting that higher patient satisfaction is accomplished at the sacrifice of increased use of health care resources and may not be directly associated with technical quality of care or improved outcome.^{17,18}

We observed agreement on several items between health care providers and recipients. The importance of physical and mental function, such as maintaining activity or improving physical function, was expressed by both health care providers and recipients. This finding was consistent with prior studies in older adults with multiple chronic conditions^{12,19} or terminal conditions,^{20,21} suggesting that physical and mental function should be an essential factor to consider as a health care outcome in various care settings for older patients.

Reduction in mortality was given the lowest priority by all the groups in health care providers and recipients alike. This view is similar to that observed in previous studies.^{12,19} This finding supports the contention that treatment interventions should be assessed in terms of reduced morbidity and improved QOL in addition to reduced mortality.

In this survey, respondents' characteristics, except age, had limited influence on their views on health outcome prioritization within each group. Geriatricians older than 60 years and community-dwelling adults older than 75 years gave higher priority to effective treatment of diseases compared with their younger counterparts. This suggests that health outcome priorities may not be stable, and can change as respondents age or differ from generation to generation. The cross-sectional design of our survey prevented us from separating the age effect from the secular trend, and further studies will be required to examine the time- or setting-dependent variability of health outcome prioritization.

This study has several limitations. First, although the average response rate was high for a postal survey, it was lower in physician groups than in health care recipient groups (26% to 48% vs 44% to 61%, Table 1). Thus, selection bias cannot be excluded. Second, it was not sure that health care recipients, particularly adult day care participants, correctly understood the study terminology. Third, some of the

items used in the survey were not mutually exclusive. Nevertheless, a similar trend in priorities of outcome measures according to either side of health care providers or recipients suggests that the overall results were not significantly affected by these limitations.

Conclusion

We demonstrated that there was significant agreement and disagreement of health outcome prioritization between health care providers and recipients in geriatric medicine. Health care providers and recipients agreed on high priority for function and low priority for reduction in mortality, but there was obvious disagreement in how they perceived QOL, treatment effect, and patient satisfaction as goals of care. Such disagreement necessitates better communication between providers and recipients to reach goals of care that are mutually understandable and tailored to meet patients' specific needs. The low importance of reduction in mortality and patient satisfaction ascribed by health care recipients may question the value of these outcomes as a way to assess treatment interventions and quality of care. We propose that the priorities of health care outcomes and their differences between providers and recipients demonstrated in this study should be taken into account in the health care of older patients and the design of health care policies and research.

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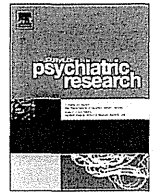


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The high frequency of periodic limb movements in patients with Lewy body dementia

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ABSTRACT

Background: Although dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia after Alzheimer's disease (AD), the clinical diagnosis is frequently difficult. Because both REM sleep behavior disorders and Parkinson's disease also have alpha-synucleinopathy similar to DLB, and show an increase in periodic limb movements (PLM), we evaluated the association between DLB and PLM, which may serve as an additional information to differentiate AD and DLB.

Methods: Overnight polysomnographic recordings were performed for the inpatients in our hospital who were suspected to have dementia. The quality of sleep, oxygen-desaturation index and periodic limb movements were compared among the patients clinically diagnosed with DLB, AD or as having no dementia.

Results: Nine DLB patients, twelve AD patients and ten non-demented patients were enrolled in the study. The number of PLM during sleep per hour of total sleep time (PLMS index) was significantly higher in the DLB patients than the AD patients or the non-demented patients. No significant differences were found between the AD patients and the non-demented patients. To differentiate DLB from AD, a PLMS index of more than 15.0 had a sensitivity of 88.9% and a specificity of 83.3%.

Conclusions: The DLB patients exhibited a higher PLMS index than the AD patients, and this index could be clinically useful for the diagnostic differentiation of DLB from AD.

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1. Introduction

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia after Alzheimer's disease (AD), affecting 15–25% of elderly demented patients (McKeith et al., 1996). DLB is characterized by intracytoplasmic inclusions called Lewy bodies, which consist of filamentous protein granules composed of alpha-synuclein and ubiquitin. Although the pathological diagnosis of DLB can be made based on the observation of Lewy body deposit throughout the cortex and subcortical regions, this is not generally possible except during autopsy.

The clinical diagnostic criteria for DLB were first published in 1996 (McKeith et al., 1996), and were modified in 2005 (McKeith et al., 2005). The central or core symptoms in DLB are progressive cognitive decline, recurrent visual hallucinations, spontaneous features of parkinsonism, and fluctuating cognition. These diagnostic

criteria require a clinical evaluation by a trained neurologist and include few objective markers. Although Single Photon Emission Computed Tomography (SPECT) and ¹²³I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy are useful in the differential diagnosis of DLB (Lobotesis et al., 2001; Colloby et al., 2002; Yoshita et al., 2001; Hanyu et al., 2006), these examinations are too expensive to be generally utilized.

DLB is frequently complicated with REM sleep behavior disorder (RBD) (McKeith et al., 2005; Boeve et al., 2001, 2003, 2007; Gagnon et al., 2006), which is characterized by an increase in periodic limb movements (PLM) (Fantini et al., 2002). Some reports have also indicated that there is an increase of PLM in patients with Parkinson's disease (PD) (Wetter et al., 2000; Lavault et al., 2009). In addition, both RBD and PD are alpha-synucleinopathies, similar to DLB.

The pathophysiology of PLM is not well understood. In addition to RBD and PD, some studies have also shown that advancing age is associated with PLM (Coleman et al., 1981; Ancoli-Israel et al., 1991). Furthermore, Rose et al. have suggested that there is an increase of PLM in severely demented patients (Rose et al., 2011).

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However, these hypotheses have not yet been systematically studied, and no controlled data have been published to date.

We hypothesized that the patients with DLB would exhibit a higher frequency of PLM compared to the demented patients with AD, and evaluated the usefulness of PLM measurement as a novel tool for the differential diagnosis of dementia. As a result, we observed that patients with DLB exhibited a significantly higher PLMS index compared to patients with AD.

2. Methods

2.1. Subjects

The study population was comprised of the consecutive inpatients of the Department of Geriatric Medicine at the University of Tokyo Hospital, who were admitted for the evaluation of progressive cognitive impairment. The patients underwent neuropsychological assessments, including the Mini-Mental State Examination (MMSE), Frontal Assessment Battery and Clock Draw Test. They also underwent blood tests and neuroimaging tests, such as Magnetic Resonance Imaging (MRI) and SPECT. The diagnosis was made at a consensus conference of physicians and neurologists, based on the clinical diagnostic criteria for DLB proposed by McKeith et al. in 2005 (McKeith et al., 2005), and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). The patients with probable DLB and possible DLB were included in the DLB group. The non-demented group comprised the patients who did not fit the criteria for dementia in the medical and neurological examinations. Patients with cognitive impairments other than AD or DLB (e.g., normal pressure hydrocephalus, vascular dementia) were excluded from the study.

From November 2010 to September 2011, 43 patients were enrolled in this study. We excluded the 4 patients whose recorded total sleep time was less than two hours. In addition, we excluded five patients who were taking antipsychotics, antidepressants, levodopa, dopamine-agonists and clonazepam, for those drugs could have some effect on the PLM.

The study was approved by the institutional review board of the Graduate School of Medicine, University of Tokyo, and written informed consent was obtained from all participants before the study.

2.2. Polysomnography

The patients underwent overnight polysomnographic recordings in the inpatient ward. Thirty of the 31 patients underwent polysomnography at least three days after admission. The remaining patient, who was in the non-demented group, underwent polysomnography on an adaptation night. The recordings included two electroencephalogram (EEG) leads (C3–A2 and O2–A1), an electrooculogram (EOG) and submental electromyogram (EMG). Nasal and oral thermistor channels, arterial oxygen saturation (finger oximetry) and an EMG of both anterior tibialis muscles were also monitored (Somnotrac Pro, CareFusion, USA). All sleep recordings were scored visually by an experienced rater according to the standard criteria (Iber et al., 2007).

PLM were scored during sleep in accordance with international scoring rules (Zucconi et al., 2006). PLM were defined as four or more consecutive leg movements, which lasted 0.5–10 s, the interval of which was 5–90 s. Leg movements following apneas or hypopneas were excluded. Respiratory events were scored according to AASM guidelines (Iber et al., 2007). Sleep apneas were defined as complete cessation of airflow >10 s. Hypopneas

were defined as a reduction $\geq 50\%$ in airflow plus $\geq 3\%$ drop in SpO₂ and/or a micro arousal. The apneas-hypopneas index (AHI) was calculated as the number of apneas and hypopneas per sleep hour. In some patients who removed the airflow sensor, oxygen desaturation of 3% or more was substituted to exclude the leg movements associated with breathing disorders and to calculate the AHI. Sleep efficiency, which was defined as the ratio of total sleep time to time in bed, was also calculated.

The number of PLM during sleep per hour of total sleep time (the PLMS index), the apneas-hypopneas index and the number of occasions of oxygen desaturation of 3% or more per hour of total sleep time (3%ODI) were calculated.

The patients who had REM sleep without atonia on polysomnography and had a history of harmful behaviors in sleep were diagnosed with RBD according to the diagnostic criteria (Iber et al., 2007).

2.3. Statistical analysis

The distribution of data was examined using the Shapiro–Wilk test. If data were normally distributed, a one way analysis of variance with Games-Howell post-hoc tests were applied for group comparisons. If the data deviated significantly from normality, the Kruskal–Wallis test was used, followed by evaluation with the Mann–Whitney *U* test for multiple comparisons, with the *p* values being corrected according to the Bonferroni method. The χ^2 test was used to compare categorical variables, such as gender and the number of RBD patients.

The diagnostic cutoff points for the PLMS index to discriminate between DLB and AD were estimated for each outcome by maximizing the Youden index. The discrimination ability was assessed by the area under the curve (AUC). Using this threshold, the sensitivity and specificity were calculated.

All of the statistical analyses were performed using the SPSS software program (version 19.0, SPSS inc., Chicago). Statistical significance was defined as *p* values < 0.05.

3. Results

3.1. Patients

Nine patients with DLB, twelve patients with AD and ten non-demented patients were enrolled in the study. Among the nine patients in the DLB group, five patients had probable DLB and four patients had possible DLB. The diagnoses in the four possible DLB patients were all supported by the typical findings in SPECT; generalized low uptake, reduced occipital activity, and relatively preserved hippocampal blood flow. In addition, three of the four possible DLB patients underwent MIBG myocardial scintigraphy and all showed low uptake. Table 1 shows the characteristics of the subjects. The age, sex distributions, and renal function were not significantly different among the three groups. No significant difference was found between the DLB group and the AD group (*p* = 0.337) in the MMSE. The use of medications for hypertension, hyperlipidemia and diabetes mellitus were similar between the groups. Two patients in the DLB group, two patients in the AD group and no patients in the non-demented group had taken donepezil. None of the patients fit the diagnostic criteria for restless legs syndrome (Allen et al., 2003).

3.2. Findings of polysomnography

The sleep and respiratory measurements are shown in Table 2. There were no significant differences in the percentage of Stage N3 or the percentage of REM sleep among the three groups. As

Table 1
Characteristics of DLB patients, AD patients and non-demented patients.

Characteristics	DLB patients	AD patients	Non-demented	p value
Number of subjects	n = 9	n = 12	n = 10	
Age (years)	82.9 ± 5.9	80.9 ± 6.2	79.1 ± 4.5	n.s.
Sex (men/women)	4/5	3/9	3/7	n.s.
MMSE	22.4 ± 3.5	20.3 ± 3.3	27.8 ± 2.1	<0.001*
Serum creatinine (mg/dl)	0.74 ± 0.27	0.74 ± 0.22	0.67 ± 0.15	n.s.
Hypertension	3 (33.3)	4 (25.0)	5 (50.0)	n.s.
Hyperlipidemia	1 (11.1)	1 (8.3)	1 (10.0)	n.s.
Diabetes mellitus	1 (11.1)	1 (8.3)	3 (30.0)	n.s.

Values expressed as mean ± standard deviation or number (%). * = one way analysis of variance with Games-Howell post-hoc tests: DLB vs AD $p = 0.337$, DLB vs non-demented $p = 0.005$, AD vs non-demented $p < 0.001$. AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; MMSE = Mini-mental State Examination; n.s. = not significant.

expected, the prevalence of RBD was significantly higher in the DLB group compared to the AD group or the non-demented group ($p = 0.004$). The AHI and 3%ODI was slightly higher in the AD group compared to the DLB group and the non-demented group, but the difference was not statistically significant.

The observed PLMS indices are shown in Fig. 1. The patients in the DLB group had a significantly higher PLMS index compared to the patients in the AD group and those in the non-demented group. No significant differences in the PLMS index were found between the AD group and the non-demented group. The PLMS indices of the four DLB patients with RBD were 27.8, 147.8, 43.7 and 149.3, respectively. After the exclusion of these four DLB patients with RBD, there was also a statistically significant difference in the PLMS index between the patients with DLB and AD ($p = 0.025$). To discriminate DLB patients from AD patients using the PLMS index, the most favorable diagnostic threshold was found to be 8.0 (AUC = 0.926). This threshold had a sensitivity of 100% and a specificity of 75.0%. A PLMS index of more than 15.0 had a sensitivity of 88.9% and a specificity of 83.3%.

4. Discussion

In this study, we first observed that patients with DLB exhibited a significantly higher PLMS index compared to patients with AD.

Although the pathophysiology of PLM is not well understood, a decrease in dopaminergic activity is reported to be associated with PLM (Wetter et al., 2000; Desseilles et al., 2008; Staedt et al., 1995; Hening et al., 2004). Because abnormalities of the

Table 2
Sleep measures and respiratory measures of DLB patients, AD patients and non-demented patients.

Polysomnography	DLB patients	AD patients	Non-demented	p value
Total sleep time (min)	283.3 ± 105.8	360.3 ± 89.1	341.8 ± 70.5	n.s.
Stage N1 (%TST)	40.6 ± 12.6	29.9 ± 13.4	29.6 ± 16.5	n.s.
Stage N2 (%TST)	41.0 ± 9.4	50.5 ± 9.5	47.8 ± 12.8	n.s.
Stage N3 (%TST)	3.6 ± 4.9	6.5 ± 4.8	7.4 ± 6.1	n.s.
REM (%TST)	14.8 ± 10.2	13.1 ± 7.8	15.3 ± 8.4	n.s.
Sleep efficiency (%)	75.5 ± 14.3	76.3 ± 8.6	76.5 ± 12.5	n.s.
Sleep onset latency (min)	25.9 ± 23.9	22.2 ± 25.8	21.8 ± 16.5	n.s.
Wake time (min)	96.8 ± 74.4	112.2 ± 44.1	104.1 ± 53.0	n.s.
AHI	11.1 ± 10.5	15.0 ± 12.8	13.8 ± 14.8	n.s.
3%ODI	11.0 ± 11.1	15.2 ± 14.6	13.4 ± 14.3	n.s.
RBD (No. of patients)	4	0	0	0.004*

Values expressed as (mean ± standard deviation). * = Significant differences with the χ^2 test ($p = 0.004$). AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; TST = Total sleep time; REM = Rapid eye movement; AHI = apneas hypopneas index; ODI = oxygen desaturation index; RBD = REM sleep behavior disorder; n.s. = not significant.

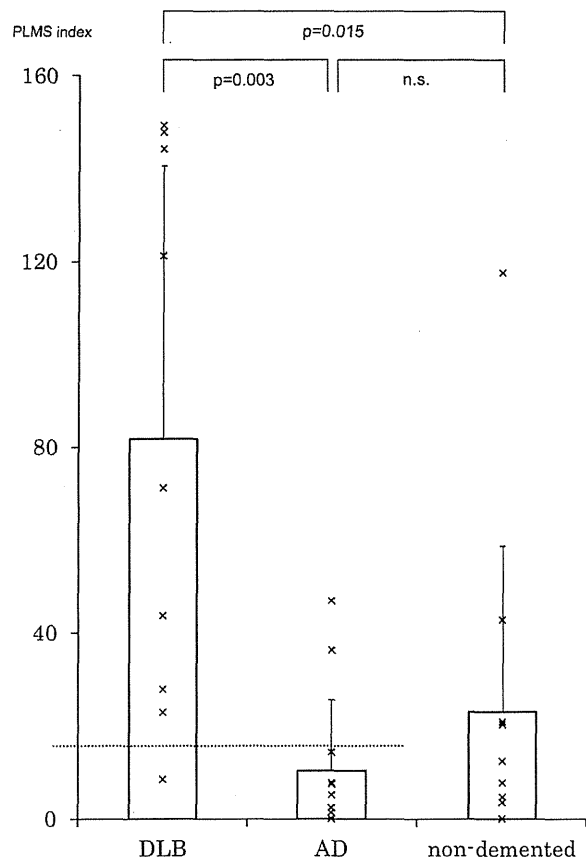


Fig. 1. Individual values for the periodic limb movements during sleep (PLMS) index in DLB patients, AD patients and non-demented patients. The boxes indicate mean and the vertical bars represent standard deviation; DLB = 81.8 ± 58.8, AD = 10.3 ± 15.3, non-demented = 23.0 ± 35.7. Mann-Whitney *U* test for multiple comparisons with the *p* values being corrected according to the Bonferroni method; significant differences in DLB vs AD ($p = 0.003$) and DLB vs Control ($p = 0.015$). The dashed line indicates the diagnostic threshold of the PLMS index of 15.0 between DLB and AD. This threshold had a sensitivity of 88.9% and a specificity of 83.3%. PLMS = periodic limb movements during sleep; AD = Alzheimer's disease; DLB = dementia with Lewy bodies; n.s. = not significant.

nigrostriatal dopaminergic pathway are also present in DLB patients, they would also be expected to exhibit a high frequency of PLM as a result of the decrease in dopaminergic activity (Walker et al., 2007; Walker and Walker, 2009).

We also found a high prevalence of RBD in patients with DLB, as indicated previously (McKeith et al., 2005; Boeve et al., 2001, 2003). RBD is now recognized to be a manifestation of various alpha-synucleinopathies, including DLB (Boeve et al., 2007; Claassen et al., 2010), and is also frequently complicated with an increase in PLM (Fantini et al., 2002; Manconi et al., 2007). These findings suggest the presence of strong pathophysiological associations among the DLB, PD, RBD and PLM through a common central nervous system degenerative process.

Several studies have showed an increase in the PLM frequency with advancing age (Coleman et al., 1981; Ancoli-Israel et al., 1991). Bliwise et al. reported a mean PLMS index during sleep of 20.6 in elderly individuals (Bliwise et al., 1988), which was compatible with our findings in the non-demented group. The clinical use of the PLMS index as a biomarker has not been anticipated, perhaps because of the high frequency of PLM in the elderly. However, our findings indicated that the PLMS index of the DLB patients was still higher than that of elderly patients without dementia, and

furthermore, the distribution of the PLMS index was more clearly separated between the DLB patients and AD patients, likely because the non-specific variability of the PLM frequency would be overcome by the effects of predominantly progressing specific neurodegeneration in these patients.

In this study, we also compared the PLMS index between the AD group and non-demented group. No significant differences were found, but the PLMS index in the AD patients tended to be lower than that in the non-demented group. These findings might also be a characteristic feature of AD, otherwise it can not be ruled out whether the small sample size may account for a random bias with quite low PLMS indices in the AD group. Therefore, the relevance and phenomenology of PLMS especially in AD, but also in DLB has to be addressed in further studies.

Currently, DLB and AD are diagnosed according to their respective clinical diagnostic criteria (McKeith et al., 2005; McKhann et al., 1984), and their differentiation are frequently difficult. Our findings suggested the usefulness of the PLMS index to discriminate patients with DLB from those with AD. While the utilization of SPECT and MIBG myocardial scintigraphy are limited to well-equipped hospitals, simplified mobile device for the measurement of PLM (Sforza et al., 2005) is expected to perform the examination for more outpatients with dementia in clinical practice.

There are several limitations to the present study. First, we included the patients with possible DLB and probable DLB in the same DLB group. And we also did not make a pathological diagnosis of DLB or AD, which remains to be reported even in MIBG myocardial scintigraphy for the diagnosis of DLB. A prospective investigation on the course of the PLM index and cognitive impairment, including the eventual pathological diagnosis, should be examined in a future study. Second, the number of patients in each group was relatively small. However, our data indicate that there is a significant correlation between DLB and PLMS, and the data may provide a first hint for a difference between AD and DLB on the PLMS index. Third, the data for this study did not include objective or subjective measures of daytime sleepiness or day–night schedule. In the future study, an additional investigation involving a larger number of subjects should be performed.

In conclusion, we found that DLB patients exhibit a higher PLMS index than AD patients, and this index may be clinically useful in the diagnostic differentiation of DLB from AD.

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The funding source had no involvement in the study, design, analysis, interpretation or decision to submit this work.

Contributors

Shinichiro Hibi was involved in design, analysis, interpretation, and drafting of article. Yasuhiro Yamaguchi was responsible for conception, design, analysis, interpretation, and drafting of article. Yumi Umeda-Kameyama and Katsuya Iijima were involved in design. Toshimitsu Momose was involved in analysis. Hiroshi Yamamoto, Masahiro Akishita, and Yasuyoshi Ouchi were involved in design and interpretation. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Indications and practice for tube feeding in Japanese geriatricians: Implications of multidisciplinary team approach

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Aim: The aim of this study was to examine how geriatricians decide the indication of tube feeding in the elderly with eating difficulty as a result of several disorders, and to determine the factors associated with their decision making and interventions for dysphagia.

Methods: The design was a cross-sectional study. All board-certified geriatricians in the Japan Geriatrics Society were recruited to this study in September 2010. We sent questionnaires to 1469 geriatricians. Among them, 629 agreed to participate. The survey consisted of self-administered questionnaires regarding demographic information, indications of tube feeding and interventions for dysphagia before tube feeding.

Results: We analyzed the remaining 555 questionnaires after excluding incomplete ones. Over 90% of geriatricians answered that “neurological disorder” and “stroke” are indications, whereas 46.8% of them answered that “dementia” is an indication for tube feeding. Geriatricians who organize a multidisciplinary team conference tended to carry out more “interventions for dysphagia before the prescription of tube feeding” compared with the reference group (odds ratio 2.1–8.7) after multivariate adjustment.

Conclusions: The results show that approximately half of the geriatricians prescribe tube feeding when the patient has dementia with loss of appetite or apraxia for eating. There is no consensus among Japanese geriatricians about the indication of tube feeding for demented people. We suggest that guidelines for tube feeding in the elderly should be established. Furthermore, a multidisciplinary approach would be desirable for decision making for tube feeding. *Geriatr Gerontol Int* 2012; 12: 643–651.

Keywords: elderly, geriatrician, multidisciplinary team, percutaneous endoscopic gastrostomy, tube feeding.

Introduction

Many older patients have nutritional problems caused by eating difficulties as a result of stroke, cancer,

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dementia and other conditions. When the patients have a functional gastrointestinal tract and they cannot take sufficient nutrition orally, tube feeding is an option. Percutaneous endoscopic gastrostomy (PEG) is the preferential route when enteral nutrition is expected to last for a longer period of time, because it is associated with better nutritional status and a lower incidence of aspiration than nasogastric tube (NGT).¹ PEG was originally developed for pediatric use by Gauderer in 1980.² However, thereafter PEG has become the most

common way to supply artificial enteral nutrition in the elderly, including dementia patients. The number of people on PEG is increasing because of the improved simplicity and safety. Approximately 5–30% of the advanced dementia patients in nursing homes are on tube feeding in Europe and the USA; whereas, in Japan, approximately 50% of those are on tube feeding.^{3–6} Thus, the percentage of tube feeding including PEG for dementia patients is higher in Japan than that in Western countries. However, recent studies have questioned the appropriateness of tube feeding in these patients. The decision of the practice or the withholding of tube feeding in patients with dementia is a difficult challenge among geriatricians and many other health-care professionals, as they need to make a decision with clinical ethical dilemmas. Furthermore, the quality of life (QOL) in the elderly with tube feeding and its effect on long-term survival have not yet been clarified,^{7–13} and neither has a guideline for tube feeding in the elderly, especially in dementia patients. Accordingly, tube feeding is the focus of some extremely complex legal and ethical questions. Therefore, it is important to study the current situation of tube feeding for the elderly in Japan.

When we make a decision on tube feeding, comprehensive assessment of the patient, such as nutrition, cognition and swallowing function, is important and the assessment should be based on a multidisciplinary team approach. Previous studies showed the effectiveness of inpatient geriatric evaluation and management; that is, comprehensive geriatric assessment (CGA).¹⁴ A multidisciplinary approach might be required for medical and nursing care of elderly patients, especially when we need to make a complicated decision, such as that of tube feeding. However, it is unknown whether the team approach can affect the decision making for tube feeding and interventions for dysphagia.

Therefore, the aim of the present study was to examine how geriatricians decide on the indication of tube feeding in the elderly with eating difficulty as a result of various disorders, and to determine whether the team approach can affect their decision making and interventions for dysphagia.

Methods

The design was a cross-sectional study. All board-certified geriatricians in the Japan Geriatrics Society were recruited to the present study in September 2010. We separately sent self-administered questionnaires to 1469 geriatricians by post and collected them from October to December 2010. These geriatricians were chosen because of their experience in taking care of patients who require tube feeding, and carry out CGA by organizing multidisciplinary team conferences. The present study was approved by the Ethics Committee

of Kyoto University Graduate School and Faculty of Medicine (no. E984, 2010).

The questionnaires included demographic information, such as age, sex, place of employment, and clinical experience, reference guidelines for tube feeding, aims and indications of tube feeding in geriatrics, interventions for dysphagia before tube feeding, and multidisciplinary team approach if tube feeding is indicated. It was explained in the questionnaires that the term “elderly” was defined as people over the age of 75 years and those who require nursing care, and tube feeding included NGT, PEG and enterostomy tube.

We carried out descriptive analyses for each item in the questionnaire. The χ^2 -test or *t*-test was used to compare the differences of place of employment and clinical experience. Logistic regression analyses were carried out to evaluate the differences of the frequencies and conference members according to the indication for tube feeding, and the interventions for dysphagia before tube feeding. Each item in the indication for tube feeding or interventions for swallowing disorder was adjusted for sex, working place and clinical experience of geriatricians. The frequency and number of members in a multidisciplinary conference were divided into five categories: not at all, occasional and less than five different health-care professionals, occasionally and ≥ 5 different health-care professionals, every time and less than five different health-care professionals, and every time and ≥ 5 different health-care professionals. The Statistical Package for Social Sciences version 18.0J (SPSS Japan, Tokyo, Japan) was used for statistical analysis. All probability values were two-tailed with a significant level of $P < 0.05$, and all confidence intervals were estimated at the 95% level.

Results

We sent a questionnaire to 1469 board-certified geriatricians, and 51 were returned as a result of being undeliverable because of wrong address. Among the rest, 629 agreed to participate in the present study. The response rate was 44.4%. After excluding the questionnaires with missing data, we analyzed the remaining 555 questionnaires. The prevalence of doctors aged over 60 years and male doctors was 34.6% and 89.2%, respectively. We found that 43.8% of the geriatricians had a clinical experience of more than 30 years, and 63.7% were working in acute hospitals, 30.7% in a clinic and 3.9% in long-term care facilities.

Table 1 shows the percentage of geriatricians who follow the guidelines and the purpose for tube feeding according to the geriatrician’s place of employment and clinical experience. A total of 68% of geriatricians did not use any guideline for tube feeding. Among geriatricians following guidelines for tube feeding, 137 used “Guideline of Parenteral and Enteral Nutrition (EN) in

Table 1 Use of guidelines and the aims of tube feeding according to place of employment and clinical experience

Questions	Characteristics of geriatricians					Clinical experience			Total n = 555
	Place of employment				P-value	<30 years n = 317	≥30 years n = 238	P-value	
	Hospital n = 360	Clinic n = 166	Long-term care n = 20	Other [†] n = 9					
Do you use any guidelines for TF in geriatrics? [‡]									
Guideline of Parenteral and EN in Japan*1	84 (23.3)	48 (28.9)	4 (20.0)	1 (11.1)	ND	87 (27.4)	50 (21.0)	0.082	137 (24.7)
Guideline of PEG in Japan*2	51 (14.2)	21 (12.7)	4 (20.0)	1 (11.1)	ND	41 (12.9)	36 (15.1)	0.460	77 (13.9)
Guideline of Parenteral and EN in America*3	13 (3.6)	11 (6.6)	0 (0.0)	0 (0.0)	ND	11 (3.5)	13 (5.5)	0.253	24 (4.3)
Guideline of Parenteral and EN for elderly in Europe*4	9 (2.5)	11 (6.6)	0 (0.0)	1 (1.1)	ND	9 (2.8)	12 (5.0)	0.178	21 (3.8)
Not using guideline for TF	253 (70.3)	106 (63.9)	10 (50.0)	7 (77.8)	ND	209 (65.9)	167 (70.2)	0.291	376 (67.7)
What are the aims of TF in geriatrics? [§]									
Improvement of survival	63 (17.5)	29 (17.5)	6 (30.0)	0 (0.0)	ND	54 (17.0)	44 (18.5)	ND	98 (17.7)
Improvement of general condition and prevention of complications	201 (55.8)	93 (56.0)	12 (60.0)	3 (33.3)	–	163 (51.4)	146 (61.3)	–	309 (55.7)
Improvement of activities of daily living	17 (4.7)	9 (5.4)	0 (0.0)	1 (11.1)	–	22 (6.9)	5 (2.1)	–	27 (4.9)
Improvement of quality of life	24 (6.7)	9 (5.4)	2 (10.0)	2 (22.2)	–	24 (7.6)	13 (5.5)	–	37 (6.7)
Satisfaction of patient	15 (4.2)	13 (7.8)	0 (0.0)	2 (22.2)	–	19 (6.0)	11 (4.6)	–	30 (5.4)
Burden of caregiver	5 (1.4)	9 (5.4)	0 (0.0)	0 (0.0)	–	6 (1.9)	8 (3.4)	–	14 (2.5)
Length of hospital stay	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	–	3 (0.9)	0 (0.0)	–	3 (0.5)
Living will	27 (7.5)	3 (1.8)	0 (0.0)	1 (11.1)	–	20 (6.3)	11 (4.6)	–	31 (5.6)
Other	5 (1.4)	1 (0.6)	0 (0.0)	0 (0.0)	–	6 (1.9)	0 (0.0)	–	6 (1.1)

Number (%). *P*-values were tested by χ^2 -test. [†]Other included part-time doctors, retired doctors, researchers and so on. [‡]Multiple answers were allowed. [§]Simple answer was allowed for nine items. *1 From Japanese Society for Parenteral and Enteral Nutrition *2 From Japan Gastroenterological Endoscopy Society *3 From American Society for Parenteral and Enteral Nutrition *4 From European Society for Gastroenterological Endoscopy Society. EN, enteral nutrition; ND, not determined; PEG, percutaneous endoscopic gastrostomy; TF, tube feeding.

Japan" from the Japanese Society for Parenteral and EN. For the purpose for tube feeding, more than half of the geriatricians chose "improvement of general condition or prevention of complications." However, a few geriatricians chose "improvement of QOL," "satisfaction of patient" or "living will." The working place or clinical experience did not affect the aims of tube feeding placement.

Table 2 shows the indication for tube feeding and the interventions for dysphagia before tube feeding according to place of employment and clinical experience. Among the seven target indications for tube feeding in the elderly, over 90% of the geriatricians answered that "neurological disorders other than dementia" and "stroke" are indications for tube feeding. Over 80% of the geriatricians answered that "head injury or facial trauma" and "oropharyngeal malignancy" are also an indication. In contrast, 46.8% of the geriatricians answered that "dementia" is an indication for tube feeding, and 65.9% of the geriatricians answered that "aspiration-prone frail elderly without comorbidities" is an indication. The place of employment was not associated with the judgment for the indication. The percentage of geriatricians who answered that "head injury or facial trauma" and "neurological disorders other than dementia" were an indication for tube feeding was significantly higher in those with less than 30 years of clinical experience than in those with more than 30 years of clinical experience" (head injury or facial trauma; $P = 0.012$, neurological disorder; $P = 0.049$). However, following guideline for tube feeding did not affect the decision making of tube feeding for these disorders (data not shown). We also asked about the life expectancy of the patient after PEG placement, and 79.5% answered that at least more than 12 weeks were expected.

Next, we asked how many interventions they carried out for swallowing disorder before tube feeding. The mean number of interventions was 6.22, and geriatricians with less than 30 years of experience carried out significantly more interventions than those with more than 30 years (6.49 ± 3.2 vs 5.86 ± 2.8 , $P = 0.015$). The number of interventions was not significantly different between geriatricians working in an acute hospital and those working in a clinic. Among 15 items of interventions for swallowing disorder, over 70% of geriatricians answered that "thickening agent" and "using semi-solid and liquid foods" were afforded to patients with swallowing disorder.

Figure 1 shows the percentage of geriatricians organizing a multidisciplinary conference for tube feeding. A total of 63% of geriatricians discussed with other health-care professionals every time or occasionally. They also answered that physicians including themselves (95.4%), primary nurses (84.9%), dieticians (49.7%) and speech therapists (42.0%) were the

members of the conference. The place of employment was not associated with the number of conference members (Table 3).

Table 4 shows the multiple logistic regression analysis for the frequencies and conference members according to the indication for tube feeding and interventions for dysphagia before tube feeding. More "interventions for dysphagia before introducing tube feeding" were carried out in geriatricians organizing a multidisciplinary team conference than the reference group after multivariate adjustment (odds ratio 2.1–8.7). We also found that geriatricians who always organize a conference with many types of health-care professionals (multidisciplinary) carried out more tests for the assessment of swallowing function and interventions for dysphagia before introducing tube feeding, such as oral ice massage, than the reference group. However, the indications for tube feeding were not affected by a multidisciplinary conference.

Discussion

In the present study, we found that approximately 70 % of board-certified geriatricians did not use any guidelines for tube feeding in their practice. We also noted that the use of guidelines was not associated with the decision making for tube feeding in the elderly, because "Guideline of Parenteral and EN in Japan" or "Guideline of PEG in Japan" does not describe the indications for tube feeding in elderly patients, especially in dementia patients.^{15,16} Furthermore, more than half of the geriatricians consider that the purpose of tube feeding is to improve the general condition or to prevent complications in the elderly with eating problems. In contrast, only a few geriatricians selected living will or patient satisfaction. Decision making of geriatricians for tube feeding did not seem to be related to their working place or clinical experiences. Although the guideline describes that "respecting the wishes of the family or living will of the patient when nutrition therapy is needed for the elderly at the terminal stage or with dementia,"¹⁵ most geriatricians who decide the indication of tube feeding might not have a chance to care for patients' living will. Although there is an ideal description in the guideline, it might be difficult for doctors to obtain a patient's living will beforehand, even if they understand the importance of respecting the living will of the patient. Therefore, comprehensive approaches not only from the field of nutrition and gastroenterology, but also from the experience and know-how from the professionals involved in medicine, nursing and care for the elderly, such as geriatricians, nurses, speech therapists, caregivers and care managers, would be expected to make a new guideline for tube feeding in the elderly.

Several studies have shown that there is no survival benefit in dementia patients who receive artificial

Table 2 Indications for tube feeding and interventions for dysphagia before introducing tube feeding according to place of employment and clinical experiences

Questions	Characteristics of geriatricians Place of employment				P-value	Clinical experience		P-value	Total n = 555
	Hospital n = 360	Clinic n = 166	Long-term care n = 20	Other [†] n = 9		<30 years n = 317	≥30 years n = 238		
Is the following disorder an indication for TF?									
Head injury or facial trauma	313 (86.9)	144 (86.7)	8 (40.0)	7 (77.8)	ND	208 (88.3)	192 (80.7)	0.012	472 (85.0)
Oropharyngeal malignancy	286 (79.4)	143 (86.1)	13 (65.0)	7 (77.8)	ND	258 (81.4)	191 (80.3)	0.736	449 (80.9)
Neurological disorder	328 (91.1)	155 (93.4)	15 (75.0)	7 (77.8)	ND	295 (93.1)	210 (88.2)	0.049	505 (91.0)
Stroke	334 (92.8)	147 (88.6)	18 (90.0)	8 (88.9)	ND	290 (91.5)	217 (91.2)	0.899	507 (91.4)
Dementia	177 (49.2)	66 (39.8)	13 (65.0)	4 (44.4)	ND	1156 (49.2)	104 (43.7)	0.198	260 (46.8)
Aspiration-prone frail elderly without comorbidity	238 (66.1)	108 (65.1)	15 (75.0)	5 (55.6)	ND	216 (68.1)	150 (63.0)	0.208	366 (65.9)
Malnutrition in frail elderly without comorbidity	115 (31.9)	58 (34.9)	9 (45.0)	5 (55.6)	ND	115 (36.3)	72 (30.3)	0.137	187 (33.7)
How long does a patient need to survive after PEG placement? [‡]									
2 weeks	3 (0.8)	2 (1.2)	0 (0.0)	0 (0.0)	ND	3 (0.9)	2 (0.8)	ND	5 (0.9)
4 weeks	19 (5.3)	16 (9.6)	1 (5.0)	2 (22.2)	-	18 (5.7)	20 (8.4)	-	38 (6.8)
6 weeks	4 (1.1)	2 (1.2)	1 (5.0)	1 (11.1)	-	7 (2.2)	1 (0.4)	-	8 (1.4)
8 weeks	39 (10.8)	21 (12.7)	3 (15.0)	0 (0.0)	-	37 (11.7)	26 (10.9)	-	63 (11.4)
12 weeks	295 (81.9)	125 (75.3)	15 (75.0)	6 (66.7)	-	252 (79.5)	189 (79.4)	-	441 (79.5)
Interventions for swallowing disorder before introducing TF									
No. Interventions; mean ± standard deviation (total 15 items)	6.44 ± 3.12 [*]	5.83 ± 2.93	6.70 ± 2.00	3.67 ± 3.32 [*]	0.010 [§]	6.49 ± 3.20	5.86 ± 2.82	0.015	6.22 ± 3.06
No. interventions, ≥6 items [‡] (total 15 items)	211 (58.6)	84 (50.6)	14 (70.0)	2 (22.2)	ND	188 (59.3)	123 (51.7)	0.073	311 (56.0)
Consultation									
To otolaryngologist	131 (36.4)	60 (36.1)	3 (15.0)	4 (44.4)	ND	123 (38.8)	75 (31.5)	0.076	198 (35.7)
To speech therapist	166 (46.1)	31 (16.7)	7 (35.0)	1 (11.1)	ND	131 (41.3)	74 (31.1)	0.013	205 (36.9)
To certified nurse of dysphagia nursing	77 (21.4)	25 (15.1)	4 (20.0)	2 (22.2)	ND	67 (21.1)	41 (17.2)	0.250	108 (19.5)
Test									
Repetitive saliva swallowing test	111 (30.8)	63 (38.0)	4 (20.0)	2 (22.2)	ND	109 (34.4)	71 (29.8)	0.257	180 (32.4)
Water swallowing test	243 (67.5)	104 (62.7)	13 (65.0)	5 (55.6)	ND	210 (66.2)	155 (65.1)	0.783	365 (65.8)
Video endoscopy	55 (15.3)	26 (15.7)	1 (5.0)	0 (0.0)	ND	50 (15.8)	32 (13.4)	0.444	82 (14.8)
Video fluorography	163 (45.3)	47 (28.3)	4 (20.0)	2 (22.2)	ND	140 (44.8)	76 (31.9)	0.003	216 (61.1)
Practice and education									
Oral ice-massage	102 (28.3)	23 (13.9)	5 (25.0)	0 (0.0)	ND	86 (27.1)	44 (18.5)	0.017	130 (23.4)
Swallowing exercise	72 (20.0)	40 (24.1)	5 (25.0)	0 (0.0)	ND	70 (22.1)	47 (19.7)	0.505	117 (21.1)
Vocalization exercise	50 (13.9)	20 (12.0)	1 (5.0)	0 (0.0)	ND	44 (13.9)	27 (11.3)	0.376	71 (12.8)
Using semi-solid and liquid foods	267 (74.2)	120 (72.3)	18 (90.0)	3 (33.3)	ND	236 (74.4)	172 (72.3)	0.565	408 (73.5)
Thickening agent	308 (85.6)	131 (78.9)	20 (100.0)	3 (33.3)	ND	267 (84.2)	195 (81.9)	0.474	462 (83.2)
Positioning	235 (65.3)	106 (63.9)	17 (85.0)	4 (44.4)	ND	215 (67.8)	147 (61.8)	0.138	362 (65.2)
Appropriate approach for swallowing	161 (44.7)	80 (48.2)	12 (60.0)	2 (22.2)	ND	153 (48.3)	102 (42.9)	0.206	255 (45.9)
Ways of coping with aspiration	161 (44.7)	85 (51.2)	17 (85.0)	4 (44.4)	ND	142 (44.8)	125 (52.5)	0.071	267 (48.1)

Number (%), P-values were tested by χ^2 -test and Student's *t*-test, [†]Other included part-time doctors, retired doctors, researchers and so on. [‡]Single answer was allowed for five items, and the other questions were allowed to select more than one. [§]P-values were tested by ANOVA, **P* < 0.05 by Bonferroni. [‡]Number of intervention items were divided into two groups, which used median value (≥6 vs <6). ND, not determined; PEG, percutaneous endoscopic gastrostomy; TF, tube feeding.

feeding by PEG.^{7,8,10,12} In addition, “Guideline of parenteral and EN for elderly in Europe” does not recommend enteral nutrition to persons with severe dementia as a result of more risks than benefits for persons with severe dementia, and occasionally in early and moderate dementia to ensure energy and nutrient supply and to prevent undernutrition.^{17,18} In the present study, we found that approximately 45% of the geriatricians considered that dementia patients with loss of appetite or apraxia for eating should be on tube feeding and that 65% of the geriatricians considered that aspiration-prone frail elderly without comorbidities should also be on tube feeding, which is a relatively high percentage. In a previous study, approximately 60% of

physicians in the USA answered that aspiration pneumonia was the indication for PEG placement, and was the most common medical indication.¹⁹ The present findings are consistent with other results; therefore the medical situation in Japan might be quite similar to that in the USA. Indeed, PEG placement to the elderly with repeating aspiration pneumonia or not eating voluntarily with cerebrovascular disease or dementia is indicated in “Guideline of PEG in Japan.”¹⁶ In the present study, the questions did not specify the stage of disorders or the level of conditions; therefore our results should be interpreted with caution. However, it is certain that there is no consensus among Japanese geriatricians about tube feeding for the elderly with advanced dementia and there is an urgent need to develop guidelines to decide the risk/benefit ratio in the individual patient to optimize the timing and route of nutritional support. Thus, the indication for tube feeding in the elderly should be widely discussed in the future and hence a guideline should be established to describe the indication of tube feeding in more detail.

“Guideline of parenteral and EN for elderly in Europe” indicates PEG placement if EN is anticipated for longer than 4 weeks.^{17,18} In contrast, the present study showed that approximately 80% of the geriatricians consider that survival more than 12 weeks should be expected for PEG placement. PEG is better than NGT for swallowing rehabilitation, and PEG placement

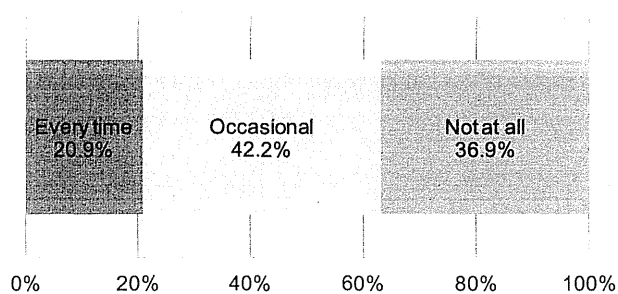


Figure 1 Do you organize a multidisciplinary conference before introducing tube feeding?

Table 3 Conference members for decision making of tube feeding according to place of employment

	Place of employment of geriatricians				P-value	Total n = 350
	Hospital n = 249	Clinic n = 80	Long-term care n = 17	Other [†] n = 3		
No. conference members; mean ± standard deviation (total 12 occupations)	4.4 ± 2.0	4.2 ± 1.8	4.3 ± 1.5	4.8 ± 4.2	0.864	4.31 ± 1.9
Conference members						
Attending physician	238 (95.2)	75 (92.6)	17 (100)	3 (100)	–	334 (95.4)
Primary nurse	224 (89.6)	54 (66.7)	15 (88)	3 (100)	–	297 (94.9)
Otolaryngologist	27 (10.8)	10 (12.3)	0 (0)	0 (0.0)	–	37 (10.6)
Certified nurse of dysphagia nursing	42 (16.8)	18 (22.2)	3 (18)	0 (0.0)	–	63 (18.0)
Physical therapist	55 (22.0)	12 (14.8)	4 (24)	1 (33.3)	–	72 (20.6)
Occupational therapist	37 (14.8)	8 (9.9)	4 (24)	1 (33.3)	–	50 (14.3)
Speech therapist	118 (47.2)	23 (28.4)	5 (29)	1 (33.3)	–	147 (42.0)
Dietician	126 (50.4)	37 (45.7)	9 (53)	2 (66.7)	–	174 (49.7)
Pharmacist	37 (14.8)	12 (14.8)	1 (5.9)	1 (33.3)	–	51 (14.6)
Discharge planning coordinator [‡]	26 (10.4)	14 (17.3)	2 (12)	1 (33.3)	–	43 (12.3)
Medical social worker	89 (35.6)	24 (29.6)	4 (24)	2 (66.7)	–	119 (34.0)
Care manager	46 (18.4)	39 (48.1)	5 (29)	1 (33.3)	–	91 (26.0)

Number (%), P-values were tested by ANOVA, * $P < 0.05$ by Bonferroni. Of the 555 geriatricians, 350 (63.1%) carried out a conference at least once. Respectively, hospital: 249 (69.2%), clinic: 80 (48.2%), long-term care: 17 (85.0%), other: 3 (33.3%). Multiple answers were allowed. [†]Other included part-time doctors, retired doctors, researchers and so on. [‡]They are a registered nurse and work for discharge planning and coordination in the hospital.

Table 4 Multivariate-adjusted odds ratios and 95% confidence intervals for frequency and the conference members according to the indication for tube feeding and interventions for dysphagia before using tube feeding

	Conference		Every time		
	Non Participating Few OR (95% CI)	Occasional occupation Multidisciplinary OR (95% CI)	Participating Few OR (95% CI)	occupation Multidisciplinary OR (95% CI)	
Is the following disorder an indication for TF?					
Head injury or facial trauma	Ref	1.02 (0.55–1.89)	1.15 (0.52–2.57)	0.80 (0.36–1.78)	1.52 (0.62–3.77)
Oropharyngeal malignancy	Ref	0.96 (0.56–1.66)	0.78 (0.41–1.52)	1.05 (0.48–2.31)	1.02 (0.48–2.16)
Neurological disorder	Ref	0.72 (0.34–1.52)	0.56 (0.23–1.34)	1.69 (0.46–6.16)	1.17 (0.39–3.53)
Stroke	Ref	1.41 (0.68–2.90)	1.84 (0.66–5.13)	2.35 (0.68–8.15)	4.03 (0.90–18.05)
Dementia	Ref	0.83 (0.54–1.28)	0.82 (0.48–1.42)	1.86 (1.00–3.44)	1.01 (0.56–1.83)
Aspiration-prone frail elderly without comorbidity	Ref	0.99 (0.63–1.55)	1.23 (0.69–2.19)	1.31 (0.68–2.52)	0.80 (0.44–1.46)
Malnutrition in frail elderly without comorbidity	Ref	0.77 (0.49–1.22)	0.98 (0.56–1.74)	1.30 (0.70–2.42)	1.18 (0.64–2.18)
How long does a patient need to survive after PEG placement? ≥12 weeks [†]	Ref	0.85 (0.50–1.43)	0.89 (0.46–1.74)	0.80 (0.39–1.63)	1.44 (0.64–3.21)
Intervention for swallowing disorder before using TF					
No. intervention items, ≥ 6 items [‡]	Ref	2.07 (1.33–3.20)	3.24 (1.81–5.78)	2.60 (1.39–4.85)	8.71 (3.99–19.00)
Consultation					
To otolaryngologist	Ref	1.13 (0.72–1.77)	1.36 (0.78–2.38)	0.94 (0.49–1.80)	1.48 (0.80–2.72)
To speech therapist	Ref	1.51 (0.93–2.46)	4.57 (2.52–8.29)	2.47 (1.28–4.76)	3.82 (2.01–7.27)
To certified nurse of dysphagia nursing	Ref	1.18 (0.65–2.14)	2.16 (1.11–4.23)	1.65 (0.76–3.61)	4.75 (2.43–9.32)
Test					
Repetitive saliva swallowing test	Ref	1.62 (0.98–2.66)	3.89 (2.16–6.99)	3.91 (2.05–7.44)	4.48 (2.37–8.46)
Water swallowing test	Ref	2.08 (1.32–3.28)	1.63 (0.93–2.87)	1.82 (0.96–3.44)	2.95 (1.49–5.88)
Video endoscopy	Ref	1.53 (0.83–2.82)	1.30 (0.59–2.86)	0.97 (0.37–2.53)	2.89 (1.37–6.09)
Video fluorography	Ref	1.62 (1.03–2.56)	2.08 (1.19–3.66)	3.07 (1.64–5.76)	2.28 (1.23–4.22)
Practice and education					
Oral ice-massage	Ref	1.19 (0.67–2.10)	2.19 (1.16–4.14)	2.34 (1.14–4.79)	3.59 (1.82–7.06)
Swallowing exercise	Ref	1.81 (0.97–3.39)	3.47 (1.74–6.91)	4.86 (2.34–10.09)	6.63 (3.27–13.45)
Vocalization exercise	Ref	1.55 (0.71–3.41)	2.96 (1.28–6.83)	2.70 (1.04–7.00)	6.84 (3.02–15.50)
Using semi-solid and liquid foods	Ref	1.83 (1.13–2.96)	2.12 (1.11–4.06)	1.71 (0.86–3.38)	5.96 (2.24–15.84)
Thickening agent	Ref	1.26 (0.73–2.21)	1.93 (0.85–4.39)	1.18 (0.54–2.59)	4.68 (1.36–16.12)
Positioning	Ref	1.46 (0.94–2.26)	2.36 (1.29–4.31)	1.75 (0.93–3.30)	7.22 (2.94–17.71)
Appropriate approach for swallowing	Ref	2.48 (1.59–3.88)	2.82 (1.62–4.92)	2.13 (1.15–3.95)	5.60 (2.94–10.65)
Ways to coping when the aspiration	Ref	1.48 (0.95–2.29)	2.86 (1.63–5.01)	1.24 (0.67–2.29)	5.31 (2.69–10.48)

Dependent variables: the indication for tube feeding and interventions for dysphagia before introducing tube feeding. Independent variables: frequency and the conference members (ref, non conference; 1, occasional and less than five different health-care professionals; 2, occasional and ≥5 different health care professionals; 3, every time and less than five different health-care professionals; 4, every time and ≥5 different health-care professional. Adjusted for sex, place of employment and clinical experience. [†]The period expected to survive after PEG was divided into two groups. (1: ≥12 weeks, 0: <12 weeks). [‡]Number of intervention items were divided into two groups, which was used median value into 15 items. (1: ≥6 items, 0: <6 items). CI, confidence interval; OR, odds ratio; TF, Tube Feeding.

in patients with stroke and oropharyngeal malignancy was associated with better prognosis; therefore PEG placement is recommended for these disorders by the European guideline.²⁰ We did not investigate how long PEG is placed in each condition. Thus, knowledge of geriatricians for tube feeding or PEG placement was not sufficiently explored in the present study; however, a period of PEG placement should be considered in each condition.

In Japan, requests for PEG to facilitate care are prevalent, because the staff in nursing homes tend to prefer PEG to time-consuming oral feeding. A multicenter study in the USA showed that feeding tube insertion is independently associated with both clinical characteristics of residents and fiscal, organizational and demographic features of nursing homes.⁴ Therefore, these situations might have affected the decision making of geriatricians for tube feeding. Unfortunately, we did not include the question whether or not the request from nursing homes might have affected the decision making for tube feeding in dementia patients. Therefore, we should ask this question next time.

Regarding interventions for swallowing disorder, the mean number of interventions for swallowing disorder before introducing tube feeding was six items, which are not so many. Among the 15 items of interventions before introducing tube feeding, over 70% of the geriatricians answered that "Thickening agent" and "Using semi-solid and liquid foods" were afforded to patients with swallowing disorder. In contrast, consultation with other specialists was not frequently carried out, and care to improve swallowing dysfunction, such as "oral ice-massage," "swallowing exercise" and "vocalization exercise" was not usually carried out either. Therefore, from these data, we think that more interventions would be necessary to care for patients with dysphagia by consulting specialists and multidisciplinary approach.

It is interesting to note the relationship between multidisciplinary conference and knowledge and practice for tube feeding for the elderly. In the present study, we showed that those who have a multidisciplinary team conference for a patient indicated for tube feeding tended to carry out more "interventions for dysphagia before tube feeding" compared with the reference group after multivariate adjustment. Furthermore, the data showed that geriatricians who organize a conference with different health-care professionals carried out more interventions for dysphagia before tube feeding, irrespective of the frequencies of conference. The present study also showed that although there were no differences in the number of conference members and interventions between the geriatricians working in an acute hospital and those in a clinic before introducing tube feeding, the percentage of geriatricians who organized a multidisciplinary conference before introducing tube feeding was higher in the hospital than in the

clinic. Therefore, the characteristics of facilities, not doctors themselves, might have affected this outcome. A previous study reported that multidisciplinary CGA is effective for the care of frail older persons admitted to the hospital, because evaluation and management by a multidisciplinary team during hospitalization documented a lower rate of institutionalization after 1 year.¹⁴ Furthermore, decision making for treatment strategy should be discussed in a multidisciplinary team. The multidisciplinary conference would provide a better answer for each elderly patient who requires tube feeding, because they tend to have a complicated background.

Several potential limitations should be considered when interpreting these results. First, a cross-sectional study does not prove any causal relationship. Second, the practice rate of tube feeding in geriatricians was not clearly determined, because the present study was carried out by self-administered questionnaires. Third, the subjects were limited to geriatricians certified by the Japan Geriatrics Society, and also the response rate was not so high. Therefore, selection bias might have occurred. Finally, we did not investigate the number of beds in their place of employment; therefore these results were not completely adjusted by hospital size.

In conclusion, the present data showed that more than half of the board-certified geriatricians consider that the purpose of tube feeding is to improve the general condition or to prevent complications in the elderly with eating problems. Furthermore, regardless of their clinical experience, approximately 40% of the Japanese geriatricians consider that demented elderly with loss of appetite or apraxia for eating should be on tube feeding. At this moment, there is no consensus among Japanese geriatricians about tube feeding for advanced demented people, and hence the guideline should be established for tube feeding in the elderly. Furthermore, a multidisciplinary team approach is expected to find a better answer for each elderly patient with eating difficulty.

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Testosterone Deficiency Accelerates Neuronal and Vascular Aging of SAMP8 Mice: Protective Role of eNOS and SIRT1

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Abstract

Oxidative stress and atherosclerosis-related vascular disorders are risk factors for cognitive decline with aging. In a small clinical study in men, testosterone improved cognitive function; however, it is unknown how testosterone ameliorates the pathogenesis of cognitive decline with aging. Here, we investigated whether the cognitive decline in senescence-accelerated mouse prone 8 (SAMP8), which exhibits cognitive impairment and hypogonadism, could be reversed by testosterone, and the mechanism by which testosterone inhibits cognitive decline. We found that treatment with testosterone ameliorated cognitive function and inhibited senescence of hippocampal vascular endothelial cells of SAMP8. Notably, SAMP8 showed enhancement of oxidative stress in the hippocampus. We observed that an NAD⁺-dependent deacetylase, SIRT1, played an important role in the protective effect of testosterone against oxidative stress-induced endothelial senescence. Testosterone increased eNOS activity and subsequently induced SIRT1 expression. SIRT1 inhibited endothelial senescence via up-regulation of eNOS. Finally, we showed, using co-culture system, that senescent endothelial cells promoted neuronal senescence through humoral factors. Our results suggest a critical role of testosterone and SIRT1 in the prevention of vascular and neuronal aging.

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Introduction

Advancing age is the most significant risk factor for the development of cognitive impairment [1,2]; however, what age-related changes underlie this effect remains uncertain. With advancing age, men experience a significant decrease in the circulating level of testosterone. Although studies have shown alterations in mood, libido, and cognition resulting from testosterone deficiency [3], the full range of consequences of age-related testosterone loss remains incompletely defined. In a small clinical study of men recently diagnosed with cognitive impairment, testosterone treatment improved performance on cognitive tests [4]. In a prospective longitudinal study using subjects from the Baltimore Longitudinal Study on Aging, men who developed Alzheimer disease (AD) were observed to exhibit low testosterone levels 5–10 years prior to the clinical diagnosis of AD [5]. With a relationship between age-related testosterone decline in men and increased risk for cognitive impairment reasonably well established, a critical issue is how testosterone contributes to the pathogenesis of cognitive decline with aging. The most likely hypothesis is through the regulation of accumulation of amyloid β (A β) peptides, which are widely believed to be the critical initiating step in the pathogenesis of AD. However, it is becoming increasingly clear that not all aspects of cognitive decline can be

explained by A β [6,7]. Findings from such diverse lines of investigations as neuroimaging and clinical trials suggest that non-A β factors also contribute to memory deficit in aged men.

In *S. cerevisiae*, the *Sir2* (silent information regulator-2) family of genes governs budding exhaustion and replicative life span [8,9]. *Sir2* has been identified as an NAD⁺-dependent histone deacetylase and is responsible for maintenance of chromatin silencing and genome stability. Mammalian sirtuin 1 (*Sirt1*), the closest homolog of *Sir2*, regulates the cell cycle, senescence, apoptosis and metabolism, by interacting with a number of molecules such as p53. As recently reported, overexpression of SIRT1 in the brain improved the memory deficit in a mouse model of AD via activation of the transcription of α -secretase [10].

An increasing body of evidence suggests the presence of a link between cognitive decline and vascular dysfunction, especially atherosclerosis [11]. Senescence of endothelial cells is involved in endothelial dysfunction and atherogenesis, and SIRT1 has been recognized as a key regulator of vascular endothelial homeostasis, controlling angiogenesis, endothelial senescence, and dysfunction [12–14].

In the present study, we demonstrated that cognitive impairment in senescence-accelerated mouse prone 8 (SAMP8), a model of cognitive decline with aging, is associated with endothelial senescence in the hippocampus and is ameliorated by testosterone

replacement. SIRT1 plays an important role in prevention of endothelial senescence induced by oxidative stress [13]. We suggest that the protection against endothelial senescence in the hippocampus through up-regulation of testosterone and SIRT1 could contribute to a novel therapeutic strategy against cognitive decline with aging.

Results

Treatment with dihydrotestosterone ameliorated cognitive function of SAMP8

In order to assess the effects of testosterone on cognitive function, we used an *in vivo* model of aging, SAMP8, and a control counterpart strain, SAMR1. SAMP8 was originally derived from AKR/J strain, litters of which show the characteristic of cognitive decline with aging. These mice exhibit age-related deficits in learning and memory at an early age, and are considered a suitable animal model to study aging and memory deficit. Body weight, appearance, and plasma testosterone level of SAMR1 and SAMP8 at 12 weeks of age were determined. Body weight and appearance did not differ between SAMR1 and SAMP8, but plasma testosterone level in SAMP8 was lower than that in SAMR1 (Figure 1A). By determining the time required to find the platform

(escape latency) as a function of days of training in the Morris water maze, we observed a marked decline in performance in SAMP8 compared with SAMR1 (Figure 1B). Because testosterone acts in part through aromatase-dependent conversion to estradiol, non-aromatizable dihydrotestosterone (DHT) was used to examine a direct role of androgens through androgen receptor (AR). SAMP8 treated with DHT showed significantly reduced escape latency time compared with untreated SAMP8. There was no difference in swim speed between the groups; however, % time in the quadrant was increased in DHT-treated SAMP8 (Figure 1B). These results indicate that DHT treatment ameliorated cognitive dysfunction in SAMP8. The water-maze is appropriate for hippocampal-dependent behavior and how animals respond to different stimuli. Therefore, we performed an open field test to examine locomotion, exploratory behavior, and anxiety. No significant effect of DHT on locomotor performance was observed in SAMR1 and SAMP8, whereas SAMR1 moved significantly more compared with SAMP8 (Figure 1C). The ratio of the distance travelled in the central area to that in the total area in the open-field, an indirect measure of exploratory behavior and anxiety [15], was also observed. In SAMP8, DHT increased this ratio (Figure 1C), suggesting that DHT promoted exploratory behavior and diminished anxiety.

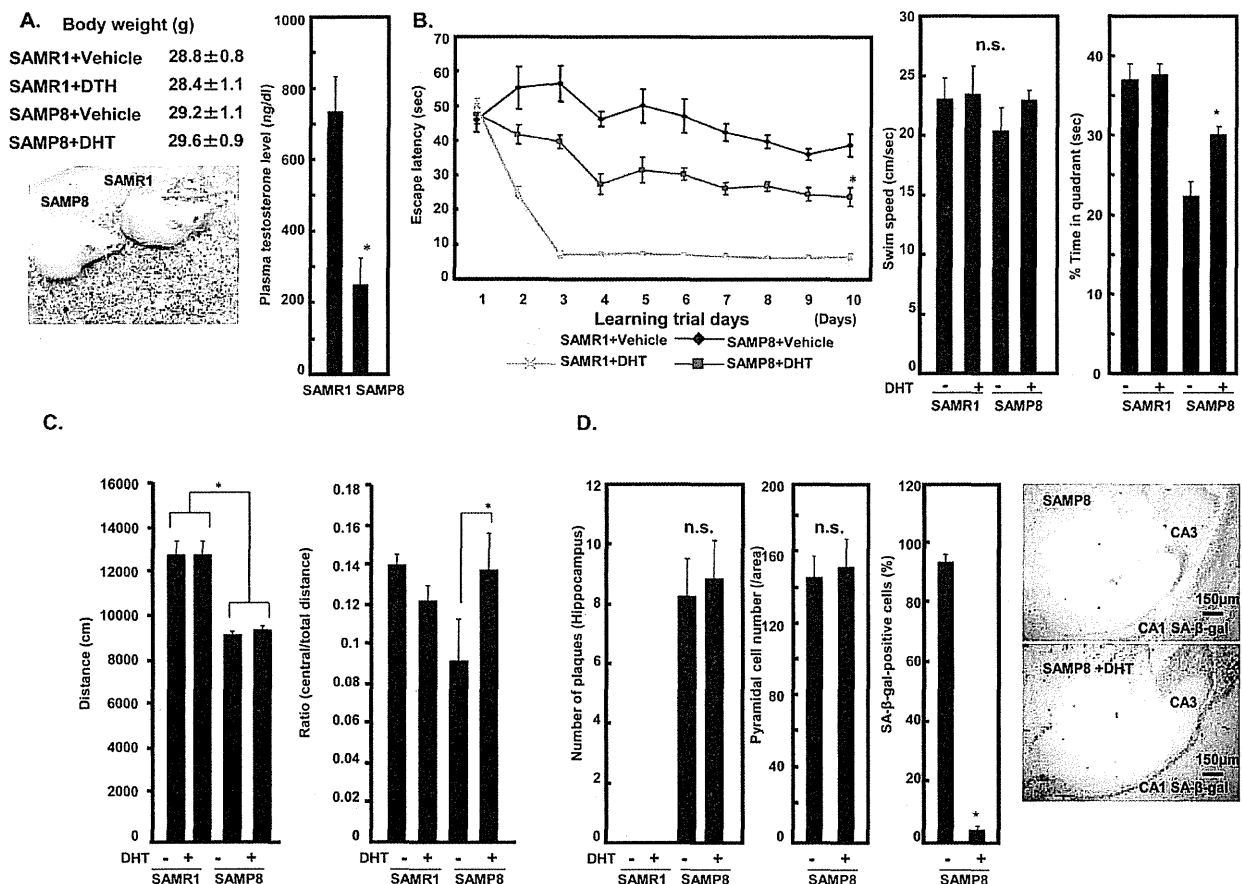


Figure 1. Testosterone deficiency causes senescence of hippocampus and cognitive impairment in SAMP8 mice. **A.** Body weight, appearance, and plasma testosterone level of male SAMR1 and SAMP8 mice at 12 weeks of age. **B.** Escape latency of SAMR1 (N = 10) and SAMP8 mice (N = 10). Male mice were treated daily for 2 weeks with DHT (500 µg s.c.) before trials. Swim speed during quadrant test on day 10. **C.** Total distance and the ratio of central/total distance were measured in open field tests. **D.** Number of amyloid β plaques, pyramidal cells, and SA-βgal-positive cells in CA1 and CA3 areas of hippocampus in SAMR1 and SAMP8. (*p<0.05, n.s: not significant). doi:10.1371/journal.pone.0029598.g001

Next, we assessed the number of amyloid β plaques, pyramidal cells, and SA- β gal-positive cells in CA1 and CA3 areas of the hippocampus in these mice (Figure 1D). The number of plaques was increased in SAMP8 compared with SAMR1, but was unaltered by treatment with DHT. The number of SA- β gal-stained cells was significantly increased in SAMP8 compared with SAMR1, but treatment with DHT prevented this in SAMP8 despite no difference in pyramidal cell number (Figure 1D).

DHT treatment increased protein and mRNA expression of SIRT1 in SAMP8

Furthermore, to estimate the role of testosterone deficiency in SAMP8, we examined the effect of testosterone supplementation on cognitive function in much older SAMR1 and SAMP8. Similarly to young mice, we observed a marked decline in performance in SAMP8 compared with SAMR1 at 18 months of age. SAMP8 implanted with testosterone pellets showed significantly reduced escape latency time compared with placebo-treated SAMP8 (Figure 2A). Plasma testosterone level in SAMP8 at 18 months of age was lower than that in SAMR1, but implanted mice

showed recovery to the level in young mice (Figure 2A). These results indicated that similar to DHT, testosterone also showed the improvement of cognitive function in SAMP8. Next, we examined the cause of low plasma testosterone in SAMP8. SAMP8 showed no testicular atrophy (Figure S1A), but more senescent phenotypes in Leydig cells, which produce testosterone in testes, than SAMR1 (Figure 2B). Moreover, we tried to allotransplant testes from SAMR1 to SAMP8 (Figure S1B). Although performance gradually responded to treatment up to 8-10 weeks, castrated SAMR1 showed a marked decline in performance whereas recipient SAMP8 showed cognitive improvement (Figure 2C).

As recently reported, overexpression or activation of SIRT1 inhibits cellular senescence and protects cellular function in various cell lines [13,16]. Therefore, we examined SIRT1 expression in the hippocampus of SAMP8 with or without DHT treatment, at 12 weeks of age. DHT treatment increased the protein and mRNA expression of SIRT1 in SAMP8 (Figure 2D). To investigate further the involvement of AR, we examined the expression of AR in SAMR1 and SAMP8 brains. The expression of AR was more abundant in the hippocampus than in other brain regions of SAMR1 and SAMP8 (Figure 2E).

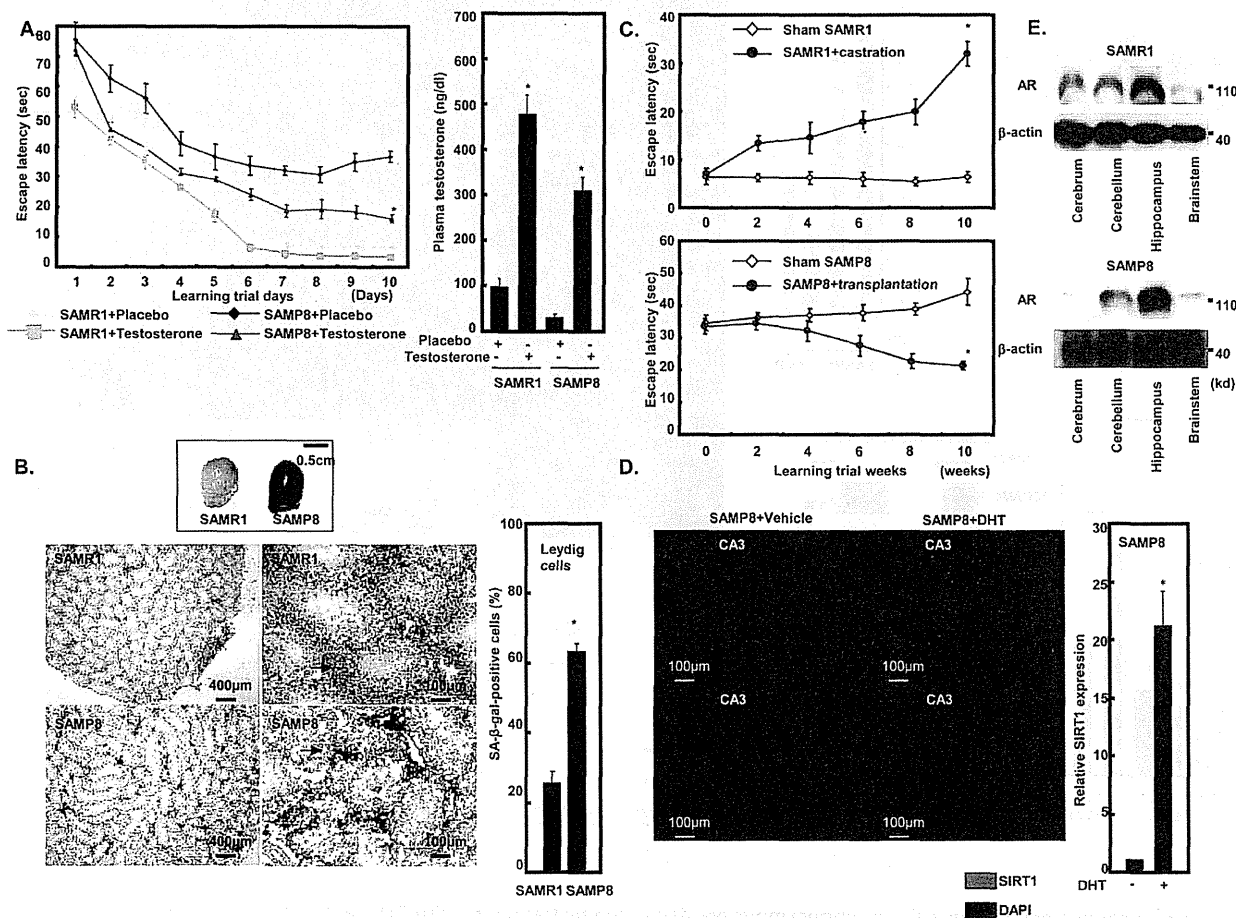


Figure 2. Supplementation of testosterone improves cognitive function in SAMP8 mice. **A.** Escape latency and plasma testosterone level of male SAMR1 (N = 10) and SAMP8 mice (N = 10) at 18 months of age. These mice were implanted subcutaneously with a placebo or a 21-day-release 2.5 mg testosterone pellet in the dorsal neck. **B.** Number of SA- β gal-stained Leydig cells in testes in SAMR1 and SAMP8. Arrows indicate Leydig cells. Representative SA- β gal-stained testes from SAMR1 and SAMP8. **C.** Escape latency of castrated SAMR1 (upper, N = 5) and recipient SAMP8 (lower, N = 5). Observation (0–10 weeks) was started from 3 weeks after operation. **D.** SIRT1 expression in hippocampus of SAMP8 with or without DHT treatment. Immunofluorescent staining for SIRT1 (green) and DAPI (blue). **E.** Expression of AR in SAMR1 and SAMP8 brains. (*p < 0.05). doi:10.1371/journal.pone.0029598.g002

Oxidative stress was increased in hippocampal cells of SAMP8

Oxidative stress may be closely related to senescence and age-related diseases. Also, an increase in oxidative stress has been suggested to be one of the earliest pathological changes in the brain in conditions with cognitive impairment such as AD [17]. Then, we examined the level of oxidative stress, using the SAMR1 and SAMP8 hippocampus at 12 weeks of age. SAMP8 hippocampus showed an increase in the level of oxidative stress compared with SAMR1 as judged by detection of carbonylated proteins. DHT treatment decreased carbonylated proteins in the SAMP8 hippocampus (Figure 3A). In parallel, the concentration of the neurotransmitter acetylcholine in hippocampal lysates was decreased in SAMP8 compared with that in SAMR1, and DHT treatment prevented this (Figure 3B).

Testosterone and DHT acts on vascular endothelial cells and stimulates the PI3K/Akt pathway, leading to eNOS activation through direct interaction of AR [18,19]. The eNOS/SIRT1 axis

is recognized as one of the fundamental determinants of endothelial senescence, and SIRT1 acts as a driver of cellular stress resistance [20]. To examine the influence of DHT treatment on endothelial cells, we determined the degree of senescence and the expression of SIRT1 in endothelial cells around the CA3 area of the hippocampus. DHT-treated SAMP8 showed a reduction of SA- β gal-stained endothelial cells and increased SIRT1 expression compared to untreated SAMP8 (Figure 3C and D). To confirm that these cells were endothelial cells, not neuronal cells, cerebral microvessels were isolated from SAMR1 and SAMP8. In parallel with immunohistological staining, SAMP8 showed a reduction of SIRT1 expression compared to SAMR1, and DTH treatment increased SIRT1 expression compared to that in untreated SAMP8 (Figure 3E). These results suggest that vascular endothelial senescence in the hippocampus may be related to the memory deficit in SAMP8. Since testosterone and DHT activates eNOS, a NOS inhibitor, *N*^G-nitro-L-arginine methyl ester hydrochloride (L-NAME), and *N*⁵-(1-lmino-3-butenyl)-L-ornithine (L-VNIO), a

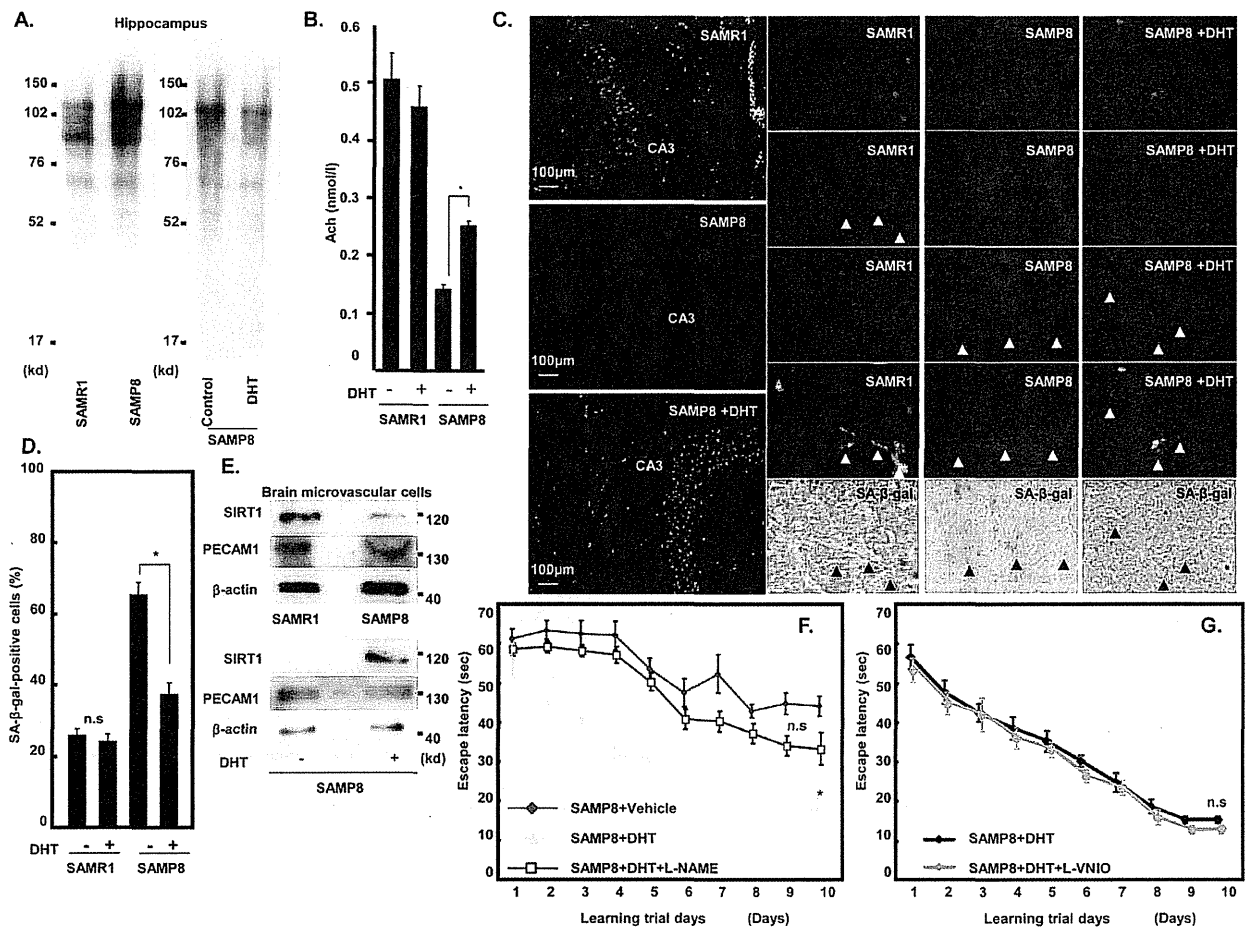


Figure 3. Senescent endothelial cells of hippocampus are decreased by treatment with DHT. **A.** Oxidative stress level was measured by detection of carbonyl groups introduced into proteins. **B.** Acetyl-choline concentration was measured by a colorimetric method. **C.** SA- β gal-stained endothelial cells and SIRT1 expression in CA3 area of hippocampus in SAMR1 and SAMP8 with or without DHT treatment. Immunofluorescent staining for SIRT1 (green), PECAM-1 (red), and DAPI (blue). **D.** Number of SA- β gal-stained endothelial cells in CA3 area of hippocampus in SAMR1 and SAMP8 with or without DHT treatment. **E.** Expression of SIRT1, PECAM-1, and β -actin was analyzed using cerebral micro vascular cells. **F.** Escape latency of SAMR1 (N = 10) and SAMP8 mice (N = 10). Male mice were treated daily for 2 weeks with DHT (500 μ g s.c) and L-NAME (20 mg/kg gavage) before trials. **G.** Escape latency of SAMR1 (N = 5) and SAMP8 mice (N = 5). Male mice were treated daily for 2 weeks with DHT (500 μ g s.c) and L-VNIO (5 mg/kg IP) before trials. (* p <0.05, n.s: not significant). doi:10.1371/journal.pone.0029598.g003