14. Junius-Walker U, Stolberg D, Steinke P, et al. Health and treatment priorities of older patients and their general practitioners: A cross-sectional study. Qual Prim Care 2011;19:67–76.
15. Symonds T, Berzon R, Marquis P, Rummans TA. The clinical significance of quality-of-life results: Practical considerations for specific audiences. Mayo Clin Proc 2002;77:572–583.
16. Gurwitz JH. Polypharmacy: A new paradigm for quality drug therapy in the elderly? Arch Intern Med 2004;164:1957–1959.
17. Fenton JJ, Jerant AF, Bertakis KD, Franks P. The cost of satisfaction: A national study of patient satisfaction, health care utilization, expenditures, and mortality. Arch Intern Med 2012;172:405–411.
18. Chang JT, Hays RD, Shekelle PG, et al. Patients' global ratings of their health care are not associated with the technical quality of their care. Ann Intern Med 2006;144:665–672.
19. Fried TR, Tinetti ME, Iannone L, et al. Health outcome prioritization as a tool for decision making among older persons with multiple chronic conditions. Arch Intern Med 2011;171:1854–1856.
20. Rosenfeld KE, Wenger NS, Kagawa-Singer M. End-of-life decision making: A qualitative study of elderly individuals. J Gen Intern Med 2000;15: 620–625.
21. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med 2002;346:1061–1066.

Journal of Psychiatric Research 46 (2012) 1590–1594

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

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

Shinichiro Hibi [a], Yasuhiro Yamaguchi [a,*], Yumi Umeda-Kameyama [a], Hiroshi Yamamoto [a], Katsuya Iijima [a], Toshimitsu Momose [b], Masahiro Akishita [a], Yasuyoshi Ouchi [a]

[a] Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[b] Department of Radiology, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

ARTICLE INFO

Article history:
Received 12 January 2012
Received in revised form
5 July 2012
Accepted 9 July 2012

Keywords:
Periodic limb movements
Dementia with Lewy bodies
Alzheimer's disease
REM sleep behavior disorder
Polysomnographic recordings

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.

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 ^{123}I-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).

* Corresponding author. Tel.: +81 3 5800 8652; fax: +81 3 5800 6530.
E-mail address: yamayasu-tky@umin.ac.jp (Y. Yamaguchi).

0022-3956/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2012.07.007

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 ≥50% in airflow plus ≥3% drop in SpO_2 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%.

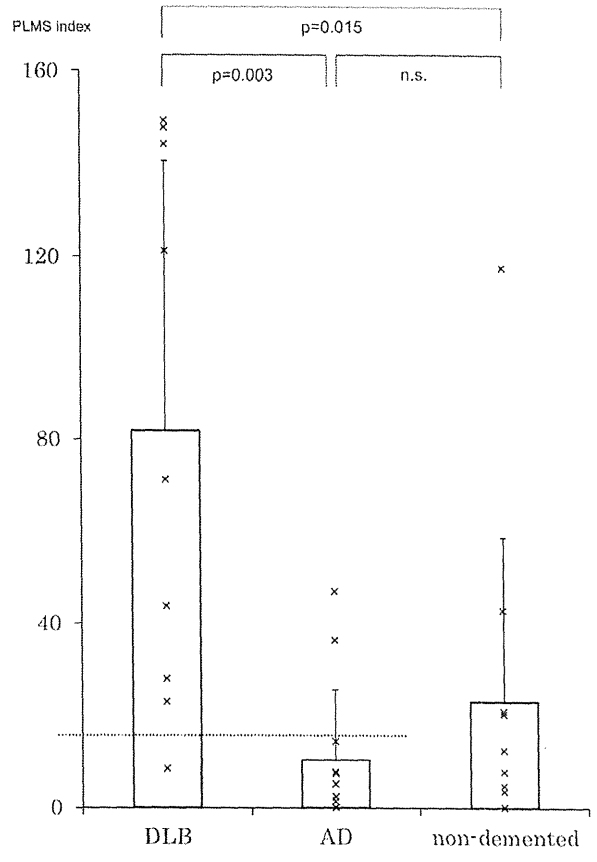

Fig. 1. Individual values for the periodic limb movements during sleep (PLMS) index in DLB patients, AD patients and non-demented patients. The boxes indicate mean and the vertical bars represent standard deviation; DLB = 81.8 ± 58.8, AD = 10.3 ± 15.3, non-demented = 23.0 ± 35.7. Mann–Whitney *U* test 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.

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 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).

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.

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 (Bilwise 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.

Role of funding source

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.

Acknowledgment

This work was supported by grants-in-aid for young scientists and scientific research from the Ministry of Education, Science, Sports and Culture of Japan, and Research Grants from the Mitsui Sumitomo Insurance Welfare Foundation. We thank all participants.

References

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Medicine 2003;4:101–19.

Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Periodic limb movements in sleep in community-dwelling elderly. Sleep 1991;14:496–500.

Bliwise DL, Carskadon MA, Dement WC. Nightly variation of periodic leg movements in sleep in middle aged and elderly individuals. Archives of Gerontology and Geriatrics 1988;7:273–9.

Boeve BF, Silber MH, Ferman TJ, Lucas JA, Parisi JE. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Movement Disorders 2001;16:622–30.

Boeve BF, Silber MH, Parisi JE, Dickson DW, Ferman TJ, Benarroch EE, et al. Synucleinopathy pathology and REM sleep behavior disorder plus dementia or parkinsonism. Neurology 2003;61:40–5.

Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 2007;130:2770–88.

Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. Neurology 2010;75:494–9.

Coleman RM, Miles LE, Guilleminault CC, Zarcone Jr VP, van den Hoed J, Dement WC. Sleep-wake disorders in the elderly: polysomnographic analysis. Journal of the American Geriatrics Society 1981;29:289–96.

Colloby SJ, Fenwick JD, Williams ED, Paling SM, Lobotesis K, Ballard C, et al. A comparison of (99m) Tc-HMPAO SPET changes in dementia with Lewy bodies and Alzheimer's disease using statistical parametric mapping. European Journal of Nuclear Medicine and Molecular Imaging 2002;29:615–22.

Desseilles M, Dang-Vu T, Schabus M, Sterpenich V, Maquet P, Schwartz S. Neuroimaging insights into the pathophysiology of sleep disorders. Sleep 2008;31:777–94.

Fantini ML, Michaud M, Gosselin N, Lavigne G, Montplaisir J. Periodic leg movements in REM sleep behavior disorder and related autonomic and EEG activation. Neurology 2002;59:1889–94.

Gagnon JF, Postuma RB, Mazza S, Doyon J, Montplaisir J. Rapid-eye-movement sleep behaviour disorder and neurodegenerative diseases. Lancet Neurology 2006;5:424–32.

Hanyu H, Shimizu S, Hirao K, Kanetaka H, Iwamoto T, Chikamori T, et al. Comparative value of brain perfusion SPECT and [(123)I]MIBG myocardial scintigraphy in distinguishing between dementia with Lewy bodies and Alzheimer's disease. European Journal of Nuclear Medicine and Molecular Imaging 2006;33:248–53.

Hening WA, Allen RP, Earley CJ, Picchietti DL, Silber MH. Restless legs syndrome task force of the standards of practice committee of the American academy of sleep medicine. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004;27:560–83.

Iber C, Ancoli-Israel S, Chesson A, Quan S, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events; rules, terminology and technical specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.

Lavault S, Bloch F, Houeto JL, Konofal E, Welter ML, Agid Y, et al. Periodic leg movements and REM sleep without atonia in Parkinson's disease with camptocormia. Movement Disorders 2009;24:2419–23.

Lobotesis K, Fenwick JD, Phipps A, Ryman A, Swann A, Ballard C, et al. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. Neurology 2001;56:643–9.

Manconi M, Ferri R, Zucconi M, Fantini ML, Plazzi G, Ferini-Strambi L. Time structure analysis of leg movements during sleep in REM sleep behavior disorder. Sleep 2007;30:1779–85.

McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies: report of the consortium on DLB international workshop. Neurology 1996;47:1113–24.

McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. Neurology 2005;65:1863–72.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.

Rose KM, Beck C, Tsai PF, Liem PH, Davila DG, Kleban M, et al. Sleep disturbances and nocturnal agitation behaviors in older adults with dementia. Sleep 2011;34:779–86.

Sforza E, Johannes M, Claudio B. The PAM-RL ambulatory device for detection of periodic leg movements: a validation study. Sleep Medicine 2005;6:407–13.

Staedt J, Stoppe G, Kogler A, Riemann H, Hajak G, Munz DL, et al. Nocturnal myoclonus syndrome (periodic movements in sleep) related to central dopamine D2-receptor alteration. European Archives of Psychiatry and Clinical Neuroscience 1995;245:8–10.

Walker RW, Walker Z. Dopamine transporter single photon emission computerized tomography in the diagnosis of dementia with Lewy bodies. Movement Disorders 2009;24:S754–9.

Walker Z, Jaros E, Walker RW, Lee L, Costa DC, Livingston G, et al. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. Journal of Neurology, Neurosurgery and Psychiatry 2007;78:1176–81.

Wetter TC, Collado-Seidel V, Pollmächer T, Yassouridis A, Trenkwalder C. Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep 2000;23:361–7.

Yoshita M, Taki J, Yamada M. A clinical role for [(123)I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer's-type and dementia with Lewy bodies. Journal of Neurology, Neurosurgery and Psychiatry 2001;71:583–8.

Zucconi M, Ferri R, Allen R, Baier PC, Bruni O, Chokroverty S, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). Sleep Medicine 2006;7:175–83.

Geriatr Gerontol Int 2012; **12:** *643–651*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

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

Mihoko Ogita,[1] Hiroko Utsunomiya,[2] Masahiro Akishita[3] and Hidenori Arai[1]

[1]*Department of Human Health Sciences, Kyoto University Graduate School of Medicine,* [2]*Department of Community Network and Collaborative Medicine, Kyoto University Hospital, Kyoto, and* [3]*Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*

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, 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

Accepted for publication 2011 December 25.

Correspondence: Professor Hidenori Arai MD PhD, Department of Human Health Sciences, Kyoto University Graduate School of Medicine, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Email: harai@kuhp.kyoto-u.ac.jp

doi: 10.1111/j.1447-0594.2011.00831.x

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								Total
	Place of employment					Clinical experience			
	Hospital $n = 360$	Clinic $n = 166$	Long-term care $n = 20$	Other† $n = 9$	*P*-value	<30 years $n = 317$	≧30 years $n = 238$	*P*-value	$n = 555$
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 comorbidites" 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								Total
	Place of employment					Clinical experience			
	Hospital $n = 360$	Clinic $n = 166$	Long-term care $n = 20$	Other† $n = 9$	*P*-value	<30 years $n = 317$	≧30 years $n = 238$	*P*-value	$n = 555$
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 (64.8)	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 finding 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.

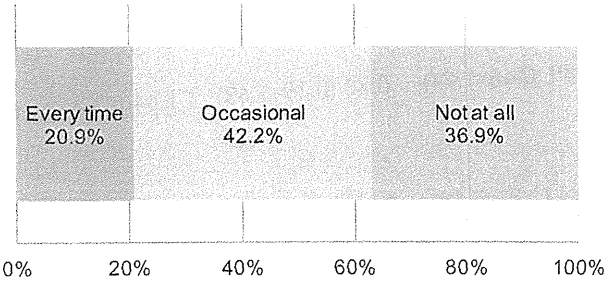

Figure 1 Do you organize a multidisciplinary conference before introducing tube feeding?

"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

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

	Place of employment of geriatricians					Total
	Hospital $n = 249$	Clinic $n = 80$	Long-term care $n = 17$	Other† $n = 3$	*P*-value	$n = 350$
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				
	Non	Occasional		Every time	
		Participating occupation		Participating occupation	
		Few	Multidisciplinary	Few	Multidisciplinary
		OR (95% CI)	OR (95% CI)	OR (95% CI)	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 oropharynegeal 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.

Acknowledgments

We thank all geriatricians in Japan for their kind help and advice during the present research. We also thank Priscila Yukari Sewo Sampaio for critical reading of our manuscript. This study was supported by a Grant-in-Aid (H22-Tyojyu-009) from the Ministry of Health, Labour and Welfare, Japan.

References

1 Dwolatzky T, Berezovski S, Friedmann R *et al.* A prospective comparison of the use of nasogastric and percutaneous endoscopic gastrostomy tubes for long-term enteral feeding in older people. *Clin Nutr.* 2001; **20**: 535–540.

2 Gauderer MW, Ponsky JL, Izant RJ Jr. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg* 1980; **15**: 872–875.
3 Ahronheim JC, Mulvihill M, Sieger C, Park P, Fries BE. State practice variations in the use of tube feeding for nursing home residents with severe cognitive impairment. *J Am Geriatr Soc* 2001; **49**: 148–152.
4 Mitchell SL, Teno JM, Roy J, Kabumoto G, Mor V. Clinical and organizational factors associated with feeding tube use among nursing home residents with advanced cognitive impairment. *JAMA* 2003; **290** (1): 73–80.
5 Hirakawa Y, Masuda Y, Kimata T, Uemura K, Kuzuya M, Iguchi A. Terminal care for elderly patients with dementia in two long-term care hospitals. *Nippon Ronen Igakkai Zasshi, Japanese Journal of Geriatrics*. 2004; **41** (1): 99–104. (In Japanese).
6 Bellelli G, Frisoni GB, Trabucchi M. Feeding tube use in Italian nursing homes: the role of cultural factors. *J Am Med Dir Assoc* 2005; **6** (1): 87–88.
7 Finucane TE, Christmas C, Travis K. Tube feeding in patients with advanced dementia: a review of the evidence. *JAMA* 1999; **282**: 1365–1370.
8 Gillick MR. Rethinking the role of tube feeding in patients with advanced dementia. *N Engl J Med* 2000; **342**: 206–210.
9 Rudberg MA, Egleston BL, Grant MD, Brody JA. Effectiveness of feeding tubes in nursing home residents with swallowing disorders. *JPEN J Parenter Enteral Nutr* 2000; **24**: 97–102.
10 Meier DE, Ahronheim JC, Morris J, Baskin-Lyons S, Morrison RS. High short-term mortality in hospitalized patients with advanced dementia: lack of benefit of tube feeding. *Arch Intern Med* 2001; **161**: 594–599.
11 Tokuda Y, Koketsu H. High mortality in hospitalized elderly patients with feeding tube placement. *Intern Med* 2002; **41**: 613–616.
12 Murphy LM, Lipman TO. Percutaneous endoscopic gastrostomy does not prolong survival in patients with dementia. *Arch Intern Med* 2003; **163**: 1351–1353.
13 Gaines DI, Durkalski V, Patel A, DeLegge MH. Dementia and cognitive impairment are not associated with earlier mortality after percutaneous endoscopic gastrostomy. *JPEN J Parenter Enteral Nutr* 2009; **33** (1): 62–66.
14 Van Craen K, Braes T, Wellens N *et al.* The effectiveness of inpatient geriatric evaluation and management units: a systematic review and meta-analysis. *J Am Geriatr Soc* 2010; **58** (1): 83–92.
15 The Japanese Society for Parenteral and Enteral Nutrition. *Practical Guidelines for Parenteral and Enteral Nutrition*, 2nd edn. Tokyo: Published by Nankodo Co., Ltd., 2006.
16 The Japan Gastroenterological Endoscopy Society. Practical guidelines for gastroenterological endoscopy. In: Suzuki Y, ed. Chapter 27, *Guideline of Percutaneous Endoscopic Gastrostomy*, 3rd edn. Tokyo: Igaku-shoin Co., Ltd., 2006; 310–323.
17 Volkert D, Berner YN, Berry E *et al.* ESPEN guidelines on enteral nutrition: geriatrics. *Clin Nutr* 2006; **25**: 330–360.
18 Sobotka L, Schneider SM, Berner YN *et al.* ESPEN Guidelines on Parenteral Nutrition: geriatrics. *Clin Nutr* 2009; **28**: 461–466.
19 Vitale CA, Hiner T, Ury WA, Berkman CS, Ahronheim JC. Tube feeding in advanced dementia: an exploratory survey of physician knowledge. *Care Manag J* 2006; **7**: 79–85.
20 Sanders DS, Carter MJ, D'Silva J, James G, Bolton RP, Bardhan KD. Survival analysis in percutaneous endoscopic gastrostomy feeding: a worse outcome in patients with dementia. *Am J Gastroenterol* 2000; **95**: 1472–1475.

Geriatr Gerontol Int 2012; **12:** *425–430*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Polypharmacy as a risk for fall occurrence in geriatric outpatients

Taro Kojima,[1] Masahiro Akishita,[1] Tetsuro Nakamura,[2] Kazushi Nomura,[1] Sumito Ogawa,[1] Katsuya Iijima,[1] Masato Eto[1] and Yasuyoshi Ouchi[1]

[1]*Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, and* [2]*Research Institute of Aging Science, Tokyo, Japan*

Objective: To investigate the predictors of falls, such as comorbidity and medication, in geriatric outpatients in a longitudinal observational study.

Methods: A total of 172 outpatients (45 men and 126 women, mean age 76.9 ± 7.0 years) were evaluated. Physical examination, clinical history and medication profile were obtained from each patient at baseline. These patients were followed for up to 2 years and falls were self-reported to their physicians. The factors associated with falls were analyzed statistically.

Results: A total of 32 patients experienced falls within 2 years. On univariate analysis, older age, osteoporosis, number of comorbid conditions and number of drugs were significantly associated with falls within 2 years. On multiple logistic regression analysis, the number of drugs was associated with falls, independent of age, sex, number of comorbid conditions and other factors that were significantly associated in univariate analysis. A receiver–operator curve evaluating the optimal cut-off value for the number of drugs showed that taking five or more drugs was a significant risk.

Conclusion: In geriatric outpatients, polypharmacy is associated with falls. Intervention studies are needed to clarify the causal relationship between polypharmacy, comorbidity and falls. **Geriatr Gerontol Int 2012; 12: 425–430.**

Keywords: bone/musculo-skeletal, elderly, falls, geriatric medicine, internal medicine, polypharmacy.

Introduction

Previous studies have assessed the risk factors for falls in community-dwelling elderly,[1–3] but not in geriatric outpatients, and history of falls, physical ability and living environment were found to be predictors of falls. Outpatients have different characteristics from community-dwelling elderly, and previous studies have not assessed whether medical comorbidity and therapeutic drugs might be risk factors for falls. Falls in patients on medication are complicated, because some drugs, such as aspirin, can cause serious bleeding when they have injurious falls, and others, such as antihypertensive[4] and hypoglycemic[5,6] agents, can cause falls.

Previously, we reported that polypharmacy was associated with the tendency for falls using four indices of fall tendency in a cross-sectional setting in geriatric outpatients,[7] though that study did not evaluate fall occurrences, and also not in a longitudinal manner. Therefore, we aimed at investigating whether polypharmacy was predictive of fall occurrences in a prospective fashion. For this purpose, we followed geriatric outpatients for up to 2 years, and assessed whether polypharmacy is a risk for fall occurrence, together with other risks.

Accepted for publication 19 October 2011.

Correspondence: Dr Masahiro Akishita MD PhD, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: akishita-tky@umin.ac.jp

doi: 10.1111/j.1447-0594.2011.00783.x

The validity of two novel indices of fall tendency, the 22 items fall risk index[8] and the 13 points simple screening test,[3] which were used in our previous study, have been confirmed in community-dwelling elderly, but not in geriatric outpatients. Therefore, in the present investigation, the association of these two indices with falls was also evaluated to confirm their validity in geriatric outpatients in a longitudinal study.

Methods

Patients

From 2006 to 2007, a total of 190 consecutive patients aged 65 years or older who were receiving treatment for chronic diseases, such as hypertension, dyslipidemia, diabetes and osteoporosis, who were seen every 2–4 weeks at the outpatient clinic of the Research Institute of Aging Science, Tokyo, were enrolled. All the patients were able to walk independently and their condition was stable. Patients who had acute illness or overt dementia were excluded. Anthropometric and medical information including past history of stroke, myocardial infarction, malignancy and prescribed drugs was obtained from each patient at baseline from the medical chart recorded by the physician in charge. However, 18 patients were excluded, because they were lost to follow up soon after enrolment and the medical information was not fully obtained. All prescribed drugs had not been changed in the included patients for at least 2 months before enrolment. The patients were followed up for 2 years.

Occurrence of falls

During the follow-up period, the patients and their family members responded to the annual questionnaire asking about the occurrence of falls within the past year. The questionnaire was repeated for 2 years.

Indices of fall tendency

After enrolment, the patients were examined for two indices to investigate the fall tendency. These were (i) a questionnaire of the 22 items portable fall risk index;[8] and (ii) the 13 points simple screening test to assess the fall tendency.[3]

Ethical consideration

The present study was approved by the Institutional Review Board of the Research Institute of Aging Science. We obtained written consent from all participants and/or their guardians.

Data analysis and statistical methods

Values are expressed as mean ± standard deviation. In order to analyze the relationship between falls and comorbidity or drugs, variables were compared using Student's *t*-test or χ^2-test as appropriate. Significant factors found in univariate analysis were included in multivariate logistic regression analysis to determine the association of falls with other variables. Receiver-operating curve (ROC) analysis was carried out to identify the optimal cut-off value of the number of drugs for predicting falls within 2 years. The value with the highest sum of sensitivity and specificity was used as the optimal cut-off value. Logistic regression analysis was carried out to assess the validity of the two indices of fall tendency, adjusted by age and sex. *P*-values <0.05 were considered statistically significant. Data were analyzed using JMP version 8.0.1 (SAS Institute, Cary, North Carolina, USA).

Results

Baseline medical information and two indices of fall tendency were evaluated in 172 patients (Table 1). Drugs prescribed in less than 5% of the patients are not shown. Because only patients who were in a stable condition and were able to walk independently were included, patients with Parkinson's disease, severe paresis or painful arthralgia were not included. Calcium channel blockers prescribed in the present study were all long-acting agents, and the prescribed aspirin dosage was 100 mg in all cases. Only a few patients were receiving insulin therapy, sulfonylureas, angiotensin converting enzyme inhibitors, β-blockers, α-blockers, non-steroidal anti-inflammatory drugs or anticoagulants. No patients were taking neuroleptics or antiparkinsonian drugs.

After 1 year, all patients, except for one who died of congestive heart failure, were followed up ($n = 171$, follow-up rate 99.4%). Falls occurred in 22 patients. Only a higher age was associated with falls within 1 year on univariate analysis (non-fallers: 76.4 ± 6.8 years, fallers: 81.0 ± 6.9 years, $P = 0.004$).

After another year (2 years after enrolment), one patient had died of lung cancer, and five patients were lost to follow up. A total of 165 patients were evaluated (follow-up rate 95.9%), and 10 patients had fallen during the second year; thus a total of 32 patients had fallen within 2 years. As shown in Table 2, higher age, osteoporosis, number of comorbid conditions and number of drugs were significant factors associated with falls. To determine the association of falls with these significant factors, multivariate logistic regression analysis was carried out, and as shown in Table 2, the number of drugs was the only factor that was significantly associated with falls within 2 years.

As polypharmacy was assumed to be a risk for falls within 2 years, the cut-off of the number of the drugs was analyzed. Figure 1 shows the ROC curves to define the optimal cut-off point in relation to falls within

Table 1 Characteristics and univariate analysis of association with fallers and non-fallers within 2 years and risk factors

Total		Non-fallers ($n = 133$)	Fallers ($n = 32$)	P-value (Fallers vs. Non-fallers)
Age (years)	77.0 ± 7.0	76.3 ± 6.9	80.0 ± 6.9	0.007
Body mass index (kg/cm^2)	22.7 ± 3.2	22.7 ± 3.3	22.7 ± 3.1	0.98
No. comorbid conditions	1.9 ± 1.1	1.8 ± 1.1	2.3 ± 0.9	0.009
No. drugs	3.2 ± 2.8	2.8 ± 2.7	4.9 ± 2.5	<0.0001
Female ($n = 122$)	–	72.9%	78.1%	0.66
Hypertension ($n = 106$)	–	62.4%	71.8%	0.41
Dyslipidemia ($n = 76$)	–	47.3%	40.6%	0.56
Diabetes ($n = 23$)	–	12.8%	18.8%	0.40
Osteoporosis ($n = 59$)	–	30.8%	56.3%	0.01
History of stroke ($n = 6$)	–	2.3%	9.4%	0.09
History of myocardial infarction ($n = 3$)	–	0.8%	6.3%	0.10
History of cancer ($n = 8$)	–	5.3%	3.1%	0.99
Calcium channel blocker ($n = 59$)	–	33.3%	46.9%	0.16
Angiotensin II receptor blocker ($n = 56$)	–	33.3%	37.5%	0.68
Statin ($n = 40$)	–	23.5%	28.1%	0.65
Aspirin ($n = 31$)	–	19.0%	24.1%	0.61
Bisphosphonate ($n = 9$)	–	4.6%	9.4%	0.38
H2-blocker ($n = 9$)	–	3.8%	12.1%	0.80
Proton pump inhibitor ($n = 11$)	–	5.3%	12.1%	0.23
Hypnotic ($n = 31$)	–	16.7%	28.1%	0.14

Values are expressed as mean ± SD ($n = 165$).

Table 2 Logistic regression analysis of association of falls within 2 years with age, sex, other significant factors found in univariate analysis, and polypharmacy

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/1 year)	1.08 (1.03–1.13)†	1.06 (0.99–1.13)	1.06 (0.99–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.98 (0.29–3.23)	0.75 (0.23–2.38)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)†	2.76 (0.92–7.38)	3.02 (0.96–6.15)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	0.90 (0.55–1.47)	0.99 (0.62–1.56)
No. drugs (/drug)	1.29 (1.12–1.48)‡	1.30 (1.08–1.57)*	–
Five or more drugs ($n = 0$, Y = 1)	5.04 (2.25–11.3)‡	–	4.50 (1.66–12.2)†

*$P < 0.05$, †$P < 0.005$, ‡$P < 0.0005$. CI, confidence interval.

2 years: the area under the ROC was 0.731, and the optimal cut-off value of the number of drugs was five (sensitivity 0.576, specificity 0.788). Logistic regression analysis showed that taking five or more drugs was significantly associated with an increased risk of falls (odds ratio 4.5, 95% CI 1.7–12.2) after adjustment for age, sex, osteoporosis and number of comorbid conditions (Table 2).

Also, the association between falls and two indices of fall tendency was evaluated to confirm the validity of each index in geriatric outpatients. As both indices included the questionnaire asking whether patients were "taking five or more drugs," the number of drugs was excluded from this analysis because of duplication in the statistical model. As shown in Table 3, the 22 items fall risk index showed a tendency towards an association with falls within 2 years, odds ratio 1.12 (95% CI 1.00–1.26; $P = 0.05$), whereas the 13 points screening test was significantly associated with falls after adjustment for age, sex and other factors significantly associated in the univariate analysis. Therefore, these indices are considered to be good predictors of falls in geriatric outpatients, as has been shown in community-dwelling elderly subjects.

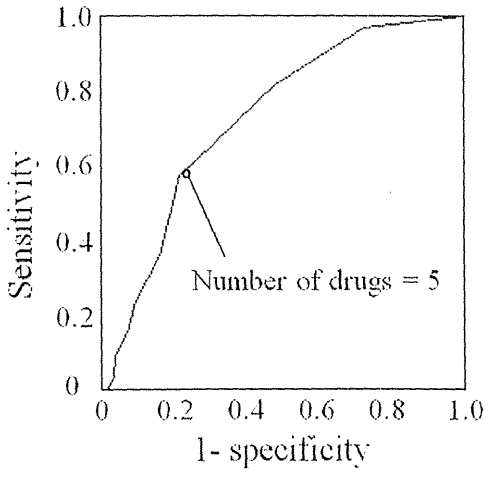

Figure 1 Receiver–operating curves to define optimal cut-off value of number of drugs at baseline in relation to falls within 2 years. Area under the curve was 0.731, optimal cut-off value of the number of drugs was five (sensitivity = 57.6%, specificity = 78.8%).

Discussion

The risk of falls has been assessed in community-dwelling elderly, and history of falls, physical ability and living environment were found to be predictors of falls. Also, in nursing home residents, cognitive function, gait disturbance and urinary incontinence are reported to be risk factors for falls,[9,10] and length of stay, disease condition, surgical procedures and some specific drugs are reported to be risk factors in hospital inpatients.[11,12]

Nevertheless, the risks in geriatric outpatients have not been sufficiently assessed, although assessment of fall risk in geriatric outpatients is important; their medical conditions or drugs might cause falls, and drugs, such as antiplatelet agents or anticoagulants, might cause critical bleeding after a fall. Also, physicians could prevent falls in their patients by giving advice during regular consultations, if risk factors are identified.

In our previous cross-sectional study assessing geriatric outpatients, polypharmacy was significantly correlated with indices of fall tendency, and the present follow-up study of geriatric outpatients showed the impact of polypharmacy on falls within 2 years. Statistical analyses showed that polypharmacy was a risk factor for falls, independent of age, sex and comorbidity.

Besides polypharmacy, several medications and comorbid conditions have been reported as risks for falls.[13–22] Among these, diabetes,[5,6] insomnia,[13] hypnotics,[13–15] antiarrhythmics[22] and antihypertensive agents[14] were not significantly associated with fall risk in the present study. Just 11 patients (45.9% of diabetic patients) were prescribed hypoglycemic agents, such as a sulfonylurea ($n = 8$) or insulin ($n = 3$), and the relatively low rate of prescription of hypoglycemic agents might have affected our result. Neither hypnotics nor antihypertensives were associated with falls. This result might be a result of the small sample size. Anti-arrhythmics were taken by just three patients (digoxin: $n = 2$, class IA anti-arrhythmic drug: $n = 1$). Other drugs, such as major tranquillizers,[14] antidepressants[17,18] and antiparkinsonian agents,[19,22] might increase fall risk; however, no patient used these drugs in the present study. In the present study, most of the patients were in a stable condition throughout the 2 years, though their drugs were changed gradually according to their medical conditions during the observation period. We only used the number of drugs at baseline for statistical analysis; however, the number of drugs increased from 3.2 ± 2.8 to 3.9 ± 3.0 during the 2 years. There were 17 patients whose number of drugs had been decreased, 70 patients not changed and 78 patients increased. The number of drugs after 2 years was also associated with falls ($P < 0.0005$). The optimal cut-off point for the number of drugs was again five (area under ROC curve 0.780, sensitivity 0.576, specificity 0.788). Furthermore, the changes in number of drugs were also associated with falls ($P < 0.05$), and the optimal cut-off point for the change in number of drugs was +1 (area under ROC curve 0.649, sensitivity 0.727, specificity 0.409).

Table 3 Logistic regression analysis of association between 2-year fall occurrences with two indices of fall tendency; 22 items fall risk index and 13 points simple screening test

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/year)	1.08 (1.03–1.15)**	1.06 (0.99–1.13)	1.06 (1.00–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.75 (0.23–2.43)	0.79 (0.24–2.56)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)**	2.56 (0.96–6.82)	2.61 (0.98–6.95)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	1.24 (0.83–1.86)	1.32 (0.88–1.97)
Fall risk index (/item)	1.23 (1.11–1.37)***	1.12 (1.00–1.26)	–
Simple screening test (/point)	1.19 (1.06–1.33)**	–	1.14 (1.01–1.29)*

*$P < 0.05$, **$P < 0.005$, ***$P < 0.0005$. CI, confidence interval.

Consequently, polypharmacy, especially taking five or more drugs, should be considered a risk for falls.

There were several limitations of the present study. First, the falls were self-reported by the patients. Although all the patients had no overt dementia, they might have forgotten the incident of falling. We attempted to count the total fall occurrences in each patient; however, we could not differentiate the repeated falls in the second year from the fall occurrence in the first year. In fact, we asked 22 patients who reported falls in the first year about fall occurrence during the second year, but they did not accurately recall whether they experienced falls in the first or second year. Second, five patients were lost to follow up at 2 years for unknown reasons. The follow-up ratio was acceptable, although some of the patients might have fallen, have been no longer able to come to the clinic and moved to nursing homes. This might have slightly influenced the result. Also, the cause of falls in polypharmacy patients is not explained. Potentially inappropriate medications, which could cause adverse drug reactions, are usually seen in patients with polypharmacy, and falls might be the consequence of adverse drug reactions, such as dizziness, instability and light-headedness. Pathophysiological assessments and drug-reducing interventions are expected to elucidate the causal relationship.

Additionally, we showed that the 22-item fall risk index and its simple screening test were useful to predict falls in geriatric outpatients. Although both indices have been validated in community-dwelling elderly people, the present finding also showed their association with fall risk among geriatric outpatients. The difference of statistical significance between fall risk index and simple screening test might be a result of small sample size or the difference in the contribution of each item to total scores between the two indices. "Taking five or more drugs" accounts for only one item out of the 22-item fall risk index; in contrast, the same questionnaire accounts two points in the 13-point simple screening test. Because polypharmacy was a strong risk factor of falls in elderly outpatients in the present study, the proportion of polypharmacy in the scores might have caused the discrepancy. Taken together, it is likely that 13-point screening test was more suitable to our subjects who were taking several medicines.

In summary, the present study showed that geriatric outpatients with polypharmacy were at a high risk of falls, especially those receiving five or more drugs. Our finding might add new information for pharmacotherapy and geriatric research in elderly patients with chronic diseases. Intervention studies examining the effect of drug reduction for the prevention of falls are required in the future.

Acknowledgment

We thank Ms Fumie Tanaka for her excellent technical assistance. This study was financially supported by grants from the Ministry of Health, Labour and Welfare of Japan (H21-Chouju-Ippan-005, H22-Chouju-Shitei-009).

Disclosure statement

The authors declare no conflict of interest.

References

1 Stel VS, Pluijm SM, Deeg DJ, Smit JH, Bouter LM, Lips P. A classification tree for predicting recurrent falling in community- dwelling older persons. *J Am Geriatr Soc* 2003; **51**: 1356–1364.
2 Kojima S, Furuna T, Ikeda N, Nakamura M, Sawada Y. Falls among community-dwelling elderly people of Hokkaido, Japan. *Geriatr Gerontol Int* 2008; **8**: 272–277.
3 Okochi J, Toba T, Takahashi T *et al.* Simple screening test for risk of falls in the elderly. *Geriatr Gerontol Int* 2006; **6**: 223–227.
4 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999; **47**: 40–50.
5 Berlie HD, Garwood CL. Diabetes medications related to an increased risk of falls and fall-related morbidity in the elderly. *Ann Pharmacother* 2010; **44**: 712–717.
6 Araki A, Ito H. Diabetes mellitus and geriatric syndromes. *Geriatr Gerontol Int* 2009; **9**: 105–114.
7 Kojima T, Akishita M, Nakamura T *et al.* Association of polypharmacy with fall risk among geriatric outpatients. *Geriatr Gerontol Int* 2011; **11**: 438–444.
8 Toba K, Okochi J, Takahashi T *et al.* Development of a portable fall risk index for elderly people living in the community. *Nippon Ronen Igakkai Zasshi* 2005; **42**: 346–352. (In Japanese.)
9 Kron M, Loy S, Sturm E *et al.* Risk indicators for falls in institutionalized frail elderly. *Am J Epidemiol* 2003; **158**: 645–653.
10 van Doorn C, Gruber-Baldini AL, Zimmerman S *et al.* Dementia as a risk factor for falls and fall injuries among nursing home residents. *J Am Geriatr Soc* 2003; **51**: 1213–1218.
11 Halfon P, Eggli Y, Van Melle G, Vagnair A. Risk of falls for hospitalized patients: a predictive model based on routinely available data. *J Clin Epidemiol* 2001; **54**: 1258–1266.
12 Tanaka M, Suemaru K, Ikegawa Y *et al.* Relationship between the risk of falling and drugs in an academic hospital. *Yakugaku Zasshi* 2008; **128**: 1355–1361.
13 Ensrud KE, Blackwell TL, Redline S *et al.* Sleep disturbances and frailty status in older community-dwelling men. *J Am Geriatr Soc* 2009; **57**: 2085–2093.
14 Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999; **47**: 30–39.
15 Woolcott JC, Richardson KJ, Wiens MO *et al.* Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med* 2009; **169**: 1952–1960.