Table 2 Characteristics of controls, moderate and severe hypertensives

	Controls n=*65*	*Moderate hypertensives* n=*43*	*Severe hypertensives* n=*10*	P-*value*
Clinical background				
Age (years)	84.2±5.8	85.5±4.8	83.5±5.2	0.356
Male: female	36: 29	18: 25	4: 6	0.329
Type of ischemic stroke				
Large-artery atherosclerosis: *n* (%)	34 (52.3)	24 (55.8)	4 (40.0)	0.671
Small-vessel occlusion: *n* (%)	13 (20.0)	17 (16.3)	2 (20.0)	0.885
Cardiac embolism: *n* (%)	18 (27.7)	12 (27.9)	4 (40.0)	0.722
Clinical findings on admission				
BMI ($kg\,m^{-2}$)	19.9±3.1	20.0±3.2	18.1±3.4	0.625
SBP (mm Hg)	133.5±18.4	175.0±9.3***	210.3±13.9^{***++}	<0.001
DBP (mm Hg)	73.9±14.6	90.6±14.9***	106.7±17.7^{***++}	<0.001
Pulse pressure (mm Hg)	60.5±15.2	83.8±16.5***	103.4±12.1^{***++}	<0.001
Glasgow Coma Scale	13.9±3.6	11.9±3.6**	12.2±2.3**	0.002
WBC ($\times 10^{12}\,l^{-1}$)	6.47±1.81	6.72±2.18	8.59±2.59^{**+}	0.010
Serum C-reactive protein ($mg\,l^{-1}$)	3.6 (0.8–15.1)	3.1 (1.0–10.2)	5.5 (1.9–15.8)	0.471
Serum albumin ($g\,l^{-1}$)	35.4±4.5	35.2±3.9	36.3±6.2	0.784
Dysphagia (%)	13.6	39.5**	30.0	0.009
Underlying chronic conditions				
Past history of stroke (%)	40.0	32.6	50.0	0.540
Ischemic heart disease (%)	6.2	14.0	20.0	0.242
Congestive heart failure (%)	16.9	20.9	30.0	0.603
Chronic kidney disease (%)	6.2	9.3	20.0#	0.339
Diabetes mellitus (%)	15.5	20.9	30.0	0.490
Hypertension treatment (%)	18.5	34.9*	20.0	0.146
ARB alone (%)	3.1	2.3	10.0	0.479
ACEI alone (%)	0	2.3	0	0.422
CaB alone (%)	4.6	11.6	10.0	0.394
Thiazide alone (%)	0	2.3	0	0.422
Two or more antihypertensives (%)	10.8	16.3	0	0.335
ARB with/without others (%)	10.8	14.0	0	0.452
ACEI with/without others (%)	1.5	7.0	10.0	0.254
CAB with/without others (%)	9.2	20.9	10.0	0.212
Thiazide with/without others (%)	6.2	9.3	0	0.555
SAP+ (%)	21.5	39.5#	70.0**	0.004
SAP death (%)	3.1	7.0	30.0*!	0.007

Abbreviations: ACEI, angiotensin I-converting enzyme inhibitor; ARB, angiotensin II-receptor blocker; CaB, dihydropiridine calcium-channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.
Results for continuous variables are expressed as mean (95% CI) (range) and compared using one-way ANOVA with Tukey's *post-hoc* analysis. Discrete variables are reported as percentages and compared by χ^2 analysis. Keys as in Table 1. #$P<0.10$, *$P<0.05$, **$P<0.01$ and ***$P<0.001$ *vs.* controls. !$P<0.10$, +$P<0.05$, ++$P<0.01$ and +++$P<0.001$ *vs.* moderate hypertensives.

due to pneumonia is also greater in these patients.[28] Indeed, univariate analysis revealed that elderly SAP+ patients had a significantly lower mean Glasgow Coma Scale score and a higher incidence of dysphagia, as well as higher WBC count and log(serum C-reactive protein) on admission, compared with SAP− patients.

In the present study, however, the most notable finding was the significant association of severe hypertension, defined as 200/120 mm Hg or higher, on admission with the occurrence of SAP. Univariate analysis revealed that elderly SAP+ patients had significantly higher SBP and pulse pressure on admission compared with SAP− patients (Table 1). There were significant differences in Glasgow Coma Scale score, WBC count and incidence of dysphagia among the three BP groups (Table 2). However, even after adjustment for these known confounding factors, severe hypertension on admission was significantly and independently associated with SAP, with OR 2.83 and CI 1.14–7.05, with control BP level as the reference group (Table 3).

The precise mechanism of this association is not known. SAP is most likely to develop in patients who are seriously ill, and aspiration due to dysphagia may be one of the most important causes of this complication. Hypertension in the elderly is a well-known risk factor for silent cerebral infarction, which is a predictor of not only overt stroke[29] but also aspiration pneumonia due to dysphagia.[29,30] On the other hand, known hypertension before stroke was significantly associated with elevated post-stroke BP.[15] In the present study, the incidence of both dysphagia and known hypertension under treatment with antihypertensive agents was significantly higher in patients with moderate hypertension on admission compared with normotensive and/or mildly hypertensive controls (Table 2). Although patients with

Table 3 Association of SAP with hypertensive state on admission after adjustment for potential confounders

Hypertensive state	*Number of cases*	*Relative risk estimate (95% CI)*[a]	*P-value*
Controls[b]	14	1.0	
Moderate hypertensives	17	2.36 (0.76–7.29)	0.136
Severe hypertensives	7	2.83 (1.14–7.05)	0.025

Abbreviation: CI, confidence interval.
[a]Adjusted for age, sex, Glasgow Coma Scale score, WBC, log(serum C-reactive protein) and dysphagia.
[b]Reference group.

Table 4 Association of SAP death with hypertensive state on admission after adjustment for potential confounders

Hypertensive state	*Number of cases*	*Relative risk estimate (95% CI)*[a]	*P-value*
Controls[b]	2	1.0	
Moderate hypertensives	3	2.57 (0.24–27.3)	0.434
Severe hypertensives	3	5.20 (1.01–26.8)	0.049

Abbreviation: CI, confidence interval.
[a]Adjusted for age, sex, Glasgow Coma Scale score, WBC, log(serum C-reactive protein) and dysphagia.
[b]Reference group.

Table 5 Association of poor outcome (in-hospital death or artificial feeding at discharge) with hypertensive state on admission after adjustment for potential confounders

Hypertensive state	*Number of cases*	*Relative risk estimate (95% CI)*[a]	*P-value*
Controls[b]	9	1.0	
Moderate hypertensives	14	2.06 (0.26–16.3)	0.491
Severe hypertensives	5	6.84 (1.32–35.4)	0.022

Abbreviation: CI, confidence interval.
[a]Adjusted for age, sex, Glasgow Coma Scale score, white blood cell count, log(serum C-reactive protein) and dysphagia.
[b]Reference group.

a prior history of dysphagia before the index stroke were excluded in the present study, these observations may indicate that known hypertension would influence subclinical swallowing dysfunction through hypertension-induced brain damage such as silent cerebral infarction before overt ischemic stroke. However, there was no significant difference in the incidence of dysphagia and known hypertension between patients with severe hypertension on admission and patients with control BP. Moreover, conditional logistic regression analysis revealed a significant increase in the risk of SAP in those with severe hypertension compared with control BP patients, even after adjustment for dysphagia (Table 3) and known hypertension under antihypertensive treatment as confounding factors.

Another potential confounder may be drug therapy. ACEI may decrease the prevalence of aspiration pneumonia in elderly subjects, probably due to stimulation of the cough reflex.[31,32] Moreover, several other antihypertensive agents are reported to modify the risk of community-acquired pneumonia.[33] In the present study, the rate of antihypertensive treatment prior to ischemic stroke was significantly higher in the moderate hypertension group than in the control group. However, there was no significant difference in the rate of single or combination use of particular antihypertensive agents between the severe hypertensive group and either the control group or moderate hypertensive group. Moreover, there was no significant difference in the rate of single or combined use of particular antihypertensive agents between SAP+ and SAP− patients. These results indicate that the effect(s) of any antihypertensive treatment prior to ischemic stroke on SAP is minimal.

Another possible explanation may be overactivation of the sympathetic nervous system. Acute severe hypertension in the early phase of acute ischemic stroke is related to stroke-induced changes in sympathoadrenergic activity.[12,15,34] Dysphagia and subsequent aspiration are considered to account for the high incidence of bacterial pneumonia after stroke. However, aspiration alone cannot explain the high incidence of SAP,[35] because aspiration occurs in healthy adults during sleep without inducing pneumonia.[36] The high incidence of pneumonia in patients with acute ischemic stroke may be due to stroke-induced immunodeficiency primarily caused by overactivation of the sympathetic nervous system, which was described in mouse models of cerebral ischemia.[37,38] In these animal models, experimental stroke propagated bacterial aspiration ranging from harmless intranasal colonization to harmful pneumonia, which was exacerbated by immunodepression due to sympathetic hyperactivity. Moreover, immediately after admission, chest X-ray infiltrate was noted only in 4 normotensive and/or mildly hypertensive control subjects, but not in the 7 subjects with severe hypertension on admission, out of the 38 SAP patients in the present study (data not shown). This evidence may suggest that severe hypertension preceded SAP, at least in the seven patients, in our study. Although we did not determine sympathetic activity including circulating levels of catecolamines in the present study, overactivation of the sympathetic nervous system could induce both severe hypertension and immunodepression, resulting in SAP in our elderly ischemic stroke patients. Further, studies are required to elucidate the precise mechanism of the association of severe hypertension with SAP.

In the present study, severe hypertension on admission was an independent predictor not only of SAP but also of SAP death (Table 4), and of poor outcome associated with in-hospital mortality and artificial feeding at discharge (Table 5). Severe hypertension in the early phase of acute ischemic stroke is a predictor of a poor outcome, with higher mortality and a poor functional outcome.[18–20] Because SAP is an important cause of death[1,3,4] and a worse long-term clinical outcome,[4] the association of severe hypertension with poor outcome would, at least in part, be explained by higher SAP death and poor functional outcome in those with severe hypertension revealed in the present study. However, in view of the small sample size, care must be taken when these results are interpreted and further evaluation in larger trials is needed. Moreover, four patients suffered from SAP already on admission, but remaining 34 patients with SAP were diagnosed as nosocomial, hospital-acquired pneumonia occurring during hospitalization. Microbiological examination of tracheal specimens and/or blood cultures did not detected atypical pathogens, such as *Chlamydia pneumoniae, Mycoplasma pneumoniae* or *Legionella pneumophila* (data not shown), suggesting aspiration pneumonia as predominant type in these 38 SAP patients. However, we previously reported association between human metapneumovirus seroprevalence and hypertension in elderly subjects.[39] Further, studies including examination of pathogen(s) are also needed to elucidate precise mechanism for the association of severe hypertension and SAP.

ACKNOWLEDGEMENTS

This work was supported by Research Funding for Longevity Sciences (20A-02) from the National Center for Geriatrics and Gerontology (NCGG) Japan, Comprehensive Research on Aging and Health, the Ministry of Health, Labour and Welfare, and grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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The Journal of International Medical Research
2012; 40: 601 – 611 [first published online as 40(2) 7]

Sleep Apnoea Syndrome as a Risk for Mortality in Elderly Inpatients

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OBJECTIVE: The characteristics of sleep apnoea syndrome (SAS) in the elderly, including subtype classification and association with mortality, have not been fully elucidated. This study examined these factors in an elderly Japanese inpatient population. METHODS: Overnight polysomnography was used to diagnose and classify SAS in 145 elderly inpatients (mean ± age 81 ± 8 years). Clinical data, including brain computerized tomography findings, were recorded. The study population included nine inpatients with obstructive SAS, 12 with central SAS, 25 with mixed SAS and 99 controls (no SAS). RESULTS: Increased body mass index and grade of aortic arch calcification independently contributed to risk of all subtypes of SAS combined. There was an independent association between SAS and increased risk of mortality from all causes as well as from pneumonia and from cardiovascular disease. Only mixed SAS was independently and positively associated with increased risk of death from pneumonia. CONCLUSIONS: Obstructive, central and mixed SAS were associated with increased risk of cardiovascular-related and all-cause mortality. Mixed SAS was associated with an increase in mortality from pneumonia. There was no relationship between mortality and severity of SAS.

KEY WORDS: SLEEP APNOEA–HYPOPNOEA SYNDROME; CHEYNE–STOKES BREATHING SYNDROME; ELDERLY; MORTALITY; PNEUMONIA; CARDIOVASCULAR DISEASE

Introduction

Sleep apnoea syndrome (SAS) is estimated to affect 2 – 4% of middle-aged adults in the USA,[1] with a higher prevalence (7.5%) reported in Japanese industrial workers.[2] Obstructive SAS, the predominant subtype in middle-aged populations, is an independent risk factor for hypertension[3] and stroke,[4] and is associated with increased cardiovascular disease mortality.[5] Central SAS is often accompanied by congestive heart failure and is associated with increased mortality.[6] The clinical characteristics and mortality risks of other subtypes of SAS, such as mixed SAS,[7] have not, however, been studied.

Studies indicate a relatively high prevalence of SAS in the elderly,[8,9] and increased SAS-related mortality was reported

in a cohort of noninstitutionalized elderly individuals.[10] Detailed characteristics of SAS in the elderly, including subtype classification, clinical contributing factors for each subtype, and association with mortality (especially pneumonia and cardiovascular disease which are two major causes of death in disabled elderly subjects[11]) have not been fully elucidated. The present study examined these factors in an elderly inpatient population.

Patients and methods

STUDY POPULATION

This study was conducted at Sengi Hospital, Kanazawa, Japan – a 540-bed hospital and long-term care facility for elderly persons, which is a common combination in Japan of medical and care services.[12] Consecutive Japanese inpatients aged ≥ 65 years with an admission period of at least 6 months and who were hospital inpatients at the time of the study were enrolled. Exclusion criteria were: (i) immunocompromised state; (ii) hypothyroidism; (iii) receiving oxygen administration; (iv) pneumonia within the past 3 months; and (v) renal failure (serum creatinine > 265 μmol/l).

The research protocol was approved by the Ethics Committee of Sengi Hospital. All in patients who gave written informed consent (or whose family members gave consent) were enrolled.

OBSERVATION OF PATIENTS

Baseline data were collected between 1 January and 31 March 2003. Follow-up observation began on 1 April 2003 and ended on 31 March 2006. No distinct outbreaks of nosocomial pneumonia occurred during the observation period. Data on death due to acute stroke,[13] coronary artery disease,[13] deterioration of congestive heart failure, pneumonia and other causes were collected daily. Pneumonia was not listed as a cause of death in patients with pneumonia who died during the acute or critical phase of any of the other listed illnesses; rather, the cause of death was determined to be the underlying disease. None of the inpatients received treatment for SAS.

Known contributing factors for SAS were recorded. These included: body mass index (BMI);[14] serum levels of albumin and total cholesterol; hypertension (systolic and/or diastolic blood pressure ≥ 140/90 mmHg, or drug treatment);[3] chronic cardiovascular disease (previous myocardial infarction or angina pectoris);[4] chronic heart failure (left ventricular ejection fraction < 40%); chronic phase of stroke (motor deficit and evidence of cerebral deficit on computerized tomography [CT]);[15] diabetes mellitus (fasting blood glucose ≥ 7 mmol/l, or drug treatment); dementia (Mini-Mental State Examination score ≤ 23);[16] past history of lung disease (chronic bronchitis, emphysema, bronchiectasis, interstitial lung disease or sequelae of tuberculosis); atrial fibrillation; and bedridden state. Severity of aortic arch calcification (AAC) on the chest X-ray was graded as previously determined:[17] grade 0, no visible calcification; grade 1, small spots of calcification or single thin calcification of the aortic bulb; grade 2, one or more areas of thick calcification; and grade 3, circumferential calcification of the aortic bulb. Data were retrieved from medical records before the start of the examination (i.e. before SAS screening and brain CT). Personal physicians made the diagnoses, which were further evaluated by a committee of expert physicians convened for the purposes of this study. Routinely collected medical information (patients' previous history of illnesses, current complications,

current medications, and the family histories of illnesses) was used to improve diagnostic accuracy.

DIAGNOSIS AND CLASSIFICATION OF SAS

Screening for SAS was performed using a pulse oximeter (Pulsox-24M; Teijin, Osaka, Japan) according to the method by Raymond *et al.*[18] Oximetric arterial oxygen saturation (SaO_2) was assessed from 21.00 h to 07.00 h whilst patients were in bed. Pulse oximetry was measured 12 times per minute, with each data point representing the lowest saturation level in a 5-s interval. Inpatients with at least five desaturation events per hour (defined as a ≥ 3% decrease in SaO_2) were selected as candidates for SAS. All patients underwent overnight polysomnography with a cardiorespiratory monitoring device (Morpheus®; Teijin) to diagnose and classify SAS types.[19] Apnoea was defined as complete cessation of airflow for ≥ 10 s, and hypopnoea as a ≥ 50% reduction in oronasal airflow for ≥ 10 s or a decrease in SaO_2 of ≥ 3% for ≥ 10 s. The apnoea–hypopnoea index (AHI) was defined as the frequency of these events per hour during overnight recording.[19] SAS severity was classified as mild (AHI 5 – < 15 events/h), moderate (AHI 15 – < 30 events/h), or severe (AHI ≥ 30 events/h).[7] Apnoea events were classified as obstructive, central, or mixed SAS.[7] Obstructive SAS was defined as the need for thoracic effort for continued breathing following complete cessation of air flow. Central SAS was characterized as the complete cessation of both the respiratory system and air flow for ≥ 10 s. Mixed SAS was a mix of obstructive SAS and central SAS, defined as a pause of the respiratory system followed by obstruction of ventilation for a relatively short term.

BRAIN CT EXAMINATION

The CT images of the brain were obtained along the orbitomental line of a 0.5 cm thick slice using X-Force apparatus (Toshiba Electric Co., Tokyo, Japan). Leukoaraiosis (i.e. nonspecific changes in the cerebral white matter that can be detected with high frequency by CT and magnetic resonance imaging in aged individuals) was assessed in seven brain regions and recorded as: absent, 0; mild, 1; or severe, 2.[20] Mean scores across the seven regions were calculated. The presence (1) or absence (0) of lacunar infarctions in the basal ganglia, as well as cortical deficit due to previous cerebral haemorrhage or infarction, were noted.[21]

STATISTICAL ANALYSES

Data were analysed using SPSS® software package version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Data were expressed as mean ± SD for continuous variables and number (percentage) for categorical variables. Comparisons between two groups for association between SAS and clinical variables were examined by the χ^2-test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Comparisons among three or more groups were analysed by the Kruskal–Wallis test and Mann–Whitney *U*-test with *post hoc* Bonferroni correction. Multiple logistic regression analysis was carried out to determine independent contributing factors for SAS using the confounding factors of age, male gender and potential factors (e.g. congestive heart failure) at $P < 0.20$.[22] Conditional multiple logistic regression analysis was performed to determine independently contributing factors between the control group and obstructive, central or mixed SAS.

Patients with no fatal events were censored at the end of the study period and

excluded from the analysis. Cumulative risks of fatal events in the control group and SAS subtypes were plotted using the life table method (Kaplan–Meier analyses). Unadjusted odds ratios (OR) and 95% confidence intervals (95% CI) of fatal events, according to age, gender and SAS risk factors, were estimated by the Cox proportional hazards model. Multivariate models were used to adjust for potential confounding factors at $P < 0.20$.[22] Cases of death due to underlying disease were not included in analysis of death from pneumonia or cardiovascular disease. A two-tailed value of $P < 0.05$ was considered to be statistically significant.

Results

The study recruited 151 elderly inpatients. Six patients (4%) who had no follow-up data because of discharge from hospital were excluded and so the final study population included 145 inpatients (38 males/107 females; mean ± SD age 81 ± 8 years; age range 66 – 96 years). The study population comprised 46 (32%) patients with SAS; nine (6%) with obstructive SAS; 12 (8%) with central SAS and 25 (17%) with mixed SAS.

Demographic and clinical data for the study population are given in Table 1. The prevalence of congestive heart failure was significantly higher in patients with central SAS than in controls (no SAS) ($P = 0.006$). Patients with SAS had a higher BMI than controls, but this did not reach statistical significance. Obstructive SAS was characterized by a significantly lower mean grade of leukoaraiosis compared with central SAS and mixed SAS ($P = 0.001$ for both), and a significantly lower prevalence of lacunar infarction than controls and central SAS ($P < 0.001$ for both). The aortic arch calcification (AAC) grade was significantly higher in patients with obstructive or central SAS patients than in controls ($P < 0.001$ for both). There were no significant differences between the three SAS subtypes in SAS severity or AHI.

Multiple logistic regression analysis revealed that higher AAC grade (OR 2.11 [95% CI 1.48, 2.99]) and higher BMI (OR 1.18 [95% CI 1.03, 1.35]) were independent contributing factors for all subtypes of SAS combined. Conditional logistic regression analysis found that independently contributing factors for obstructive SAS were higher AAC grade (OR 4.43 [95% CI 1.54, 12.8]) and lower prevalence of lacunae (OR 0.12 [95% CI 0.02, 0.86]). Independently contributing factors for central SAS were higher AAC grade (OR 4.73 [95% CI 1.73, 12.9]) and higher leukoaraiosis grade (OR 2.65 [95% CI 1.19, 5.89]). The single independent contributing factor for mixed SAS was higher BMI (OR 1.18 [95% CI 1.01, 1.37]).

During 341 person-years of follow-up, 55 (38%) patients died. The incidence of fatal events was 12.6/100 person-years. Causes of death are given in Table 2. These 55 patients were followed-up for a mean ± SD of 15.4 ± 9.9 months (range 1 – 35 months). Overall mortality rate was significantly higher in patients with SAS than in controls ($P = 0.006$) and significantly more SAS patients than controls died of pneumonia ($P = 0.049$) or cardiovascular disease ($P < 0.001$).

Kaplan–Meier analyses of cumulative rates of mortality are shown in Fig. 1. Cox proportional hazards model analysis (using controls and each subtype of SAS as a categorical group) revealed that only mixed SAS was independently and positively associated with mortality from pneumonia ($P = 0.011$). Obstructive, central and mixed SAS were all significantly and positively associated with all-cause mortality ($P = 0.004$, $P = 0.004$ and $P = 0.005$, respectively) and mortality from cardiovascular disease ($P < 0.001$, $P < 0.001$ and $P = 0.037$,

TABLE 1:
Demographic and clinical characteristics of 145 elderly Japanese inpatients according to the absence or presence of different subtypes of sleep apnoea syndrome (SAS)

Characteristic	Control: no SAS ($n = 99$)	Obstructive SAS ($n = 9$)	Central SAS ($n = 12$)	Mixed SAS ($n = 25$)	Statistical significance[b]	Total SAS ($n = 46$)	Statistical significance[a]
Age, years	81 ± 8	79 ± 9	81 ± 11	82 ± 8	NS	81 ± 8	NS
Male/female	26/73	2/7	4/8	6/19	NS	12/34	NS
Body mass index, kg/m^2	18.3 ± 3.7	21.4 ± 2.6	19.2 ± 2.4	19.3 ± 4.4	NS	19.7 ± 3.7	NS
Serum albumin, g/l	34.0 ± 4.4	32.6 ± 4.7	33.9 ± 1.8	33.4 ± 4.6	NS	33.4 ± 4.0	NS
Serum cholesterol, mM	4.3 ± 1.0	4.2 ± 1.2	4.2 ± 1.5	4.1 ± 0.7	NS	4.2 ± 0.8	NS
Major complications							
Hypertension	44 (44)	3 (33)	4 (33)	14 (56)	NS	21 (46)	NS
Ischaemic heart disease	5 (5)	1 (11)	3 (25)	1 (4)	NS	5 (11)	NS
Congestive heart failure	8 (8)	1 (11)	5 (42)[c]	2 (8)	$P = 0.006$	8 (17)	NS
Chronic phase of stroke	62 (63)	7 (78)	11 (92)	11 (44)	NS	29 (63)	NS
Diabetes mellitus	13 (13)	1 (11)	1 (8)	6 (24)	NS	8 (17)	NS
Dementia	83 (84)	6 (67)	12 (100)	23 (92)	NS	41 (89)	NS
Lung disease	9 (9)	1 (11)	2 (17)	4 (16)	NS	4 (9)	NS
Atrial fibrillation	4 (4)	0 (0)	2 (17)	0 (0)	NS	2 (4)	NS
Bedridden state	66 (67)	6 (67)	9 (75)	16 (64)	NS	31 (67)	NS
Brain computerized tomography findings							
Leukoaraiosis, grade (0 – 2)	0.9 ± 0.7	0.3 ± 0.5[d,e]	1.3 ± 0.7	1.3 ± 0.5	$P = 0.001$	1.1 ± 0.7	NS
Lacunae	85 (86)	3 (33)[c,d]	12 (100)	21 (84)	$P < 0.001$	36 (78)	NS
Cortical deficit	40 (40)	4 (44)	5 (42)	7 (28)	NS	16 (35)	NS
Ventricular enlargement	60 (61)	3 (33)	8 (67)	14 (56)	NS	25 (54)	NS
Aortic arch calcification, grade (0 – 3)	1.0 ± 1.2	2.4 ± 0.7[c]	2.6 ± 0.7[c]	1.5 ± 1.2	$P < 0.001$	2.0 ± 1.1	$P < 0.001$

TABLE 1 (continued):
Demographic and clinical characteristics of 145 elderly Japanese inpatients according to the absence or presence of different subtypes of sleep apnoea syndrome (SAS)

Characteristic	Control: no SAS ($n = 99$)	Obstructive SAS ($n = 9$)	Central SAS ($n = 12$)	Mixed SAS ($n = 25$)	Statistical significance[b]	Total SAS ($n = 46$)	Statistical significance[a]
Severity of SAS							
Apnoea–hypopnoea index (events/h)	1.3 ± 1.4	19.3 ± 10.7[c]	24.5 ± 14.4[c]	23.3 ± 14.7[c]	$P < 0.001$	22.8 ± 13.7	$P < 0.001$
Grade (0 – 3)	0	2.1 ± 1.7[c]	2.5 ± 1.0[c]	1.7 ± 1.0[c]	$P < 0.001$	2.0 ± 1.1	$P < 0.001$

Data presented as mean ± SD, *n*, or *n* (%) of patients.
[a]Statistical significance between total SAS and control group calculated by Mann–Whitney *U*-test, with significance set at $P < 0.05$.
[b]Statistical significance between the four groups was analysed by Kruskal–Wallis test and Mann–Whitney *U*-test with *post hoc* Bonferroni corrections, with significance set at $P = 0.008$ (two-group comparisons from four groups gives a statistical significance of $P = 0.008$ [$P = 0.05$ divided by 6]). For analyses between groups: [c]versus control group; [d]versus C-SAS; and [e]versus M-SAS.
NS, not statistically significant ($P \geq 0.05$).

TABLE 2:
Cause of death among 55 elderly Japanese inpatients who died during the 36-month follow-up period, according to the absence or presence of different subtypes of sleep apnoea syndrome (SAS)

Cause of death	Control: no SAS ($n = 99$)	Obstructive SAS ($n = 9$)	Central SAS ($n = 12$)	Mixed SAS ($n = 25$)	Statistical significance[b]	Total SAS ($n = 46$)	Statistical significance[a]	Summary ($n = 145$)
Pneumonia	16 (16)	2 (22)	1 (8)	9 (36)	NS	12 (26)	$P = 0.049$	28 (19)
Cardiovascular disease (total)	5 (5)	2 (22)	7 (58)[c]	3 (12)	$P < 0.001$	12 (26)	$P < 0.001$	17 (12)
Myocardial infarction	2 (2)	1 (11)	3 (25)[c]	2 (8)	$P = 0.002$	6 (13)	$P = 0.007$	8 (6)
Sudden death	1 (1)	0 (0)	0 (0)	1 (4)	NS	1 (2)	NS	2 (1)
Congestive heart failure	2 (1)	1 (11)	4 (33)[c]	0 (0)	$P < 0.001$	5 (11)	$P = 0.006$	7 (5)
Stroke	3 (3)	1 (11)	0 (0)	0 (0)	NS	1 (2)	NS	4 (3)
Other causes	6 (6)	0 (0)	0 (0)	0 (0)	NS	0 (0)	NS	6 (4)
Total	30 (30)	5 (56)	8 (67)	12 (48)	NS	25 (54)	$P = 0.006$	55 (38)

Data presented as *n* (%) of patients.
[a]Statistical significance between total SAS and control group calculated by Mann–Whitney *U*-test, with significance set at $P < 0.05$.
[b]Statistical significance between the four groups was analysed by Kruskal–Wallis test and Mann–Whitney *U*-test with *post hoc* Bonferroni corrections, with significance set at $P = 0.008$ (two-group comparisons from four groups gives a statistical significance of $P = 0.008$ [$P = 0.05$ divided by 6]). For analyses between groups, [c]versus control group.
NS, not statistically significant ($P \geq 0.05$).

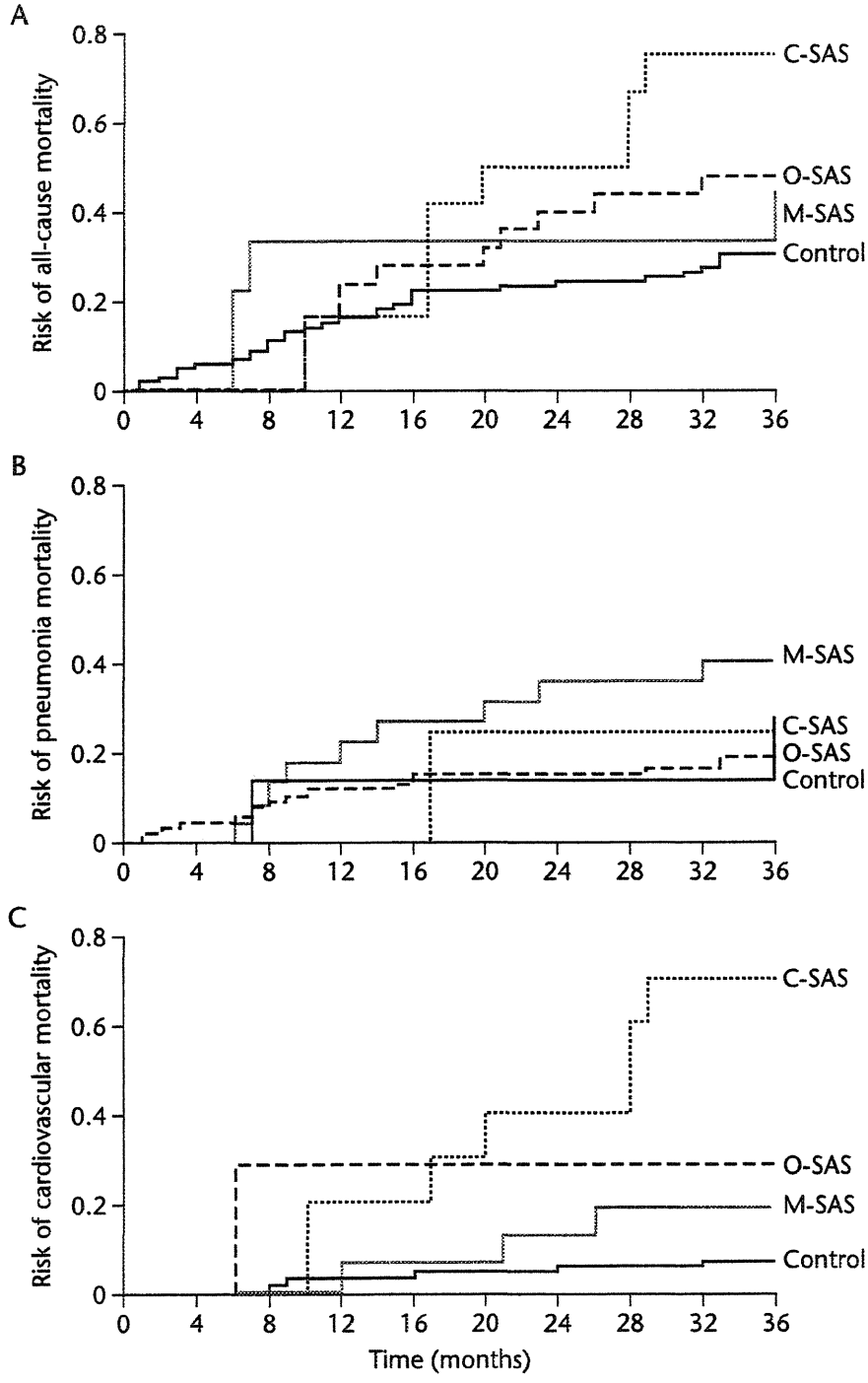

FIGURE 1: Kaplan–Meier plots of cumulative mortality amongst 55 elderly Japanese inpatients during the 36-month follow-up period, according to the absence or presence of different of sleep apnoea syndrome (SAS) subtypes: control, free from SAS (n = 30); C-SAS, central SAS (n = 8); O-SAS, obstructive SAS (n = 5); M-SAS, mixed SAS (n = 12). (A) Risk of all-cause mortality. (B) Risk of pneumonia mortality. (C) Risk of cardiovascular mortality

respectively). There was no association between any cause of death and SAS severity or AHI.

Discussion

The prevalence of SAS in the elderly inpatients in the present study was 32%,

which is much higher than that reported in Japanese industrial workers,[2] but consistent with other reports.[8,9] The present study revealed a predominance of mixed and central SAS among elderly SAS inpatients, in contrast to previous reports in young and middle-aged subjects[3] and in the elderly[9] in which obstructive SAS was the predominant subtype. This difference may be due to the fact that almost all the subjects in the present study were disabled elderly inpatients.

Multiple logistic regression analysis revealed that factors known to be related to SAS in younger subjects[3,23] were not associated with SAS in the elderly, although higher BMI[14] was found to be associated with SAS. The present study revealed that AAC, a known risk for coronary heart disease and ischaemic stroke,[24] was an independent risk factor for obstructive and central SAS in elderly inpatients. The patients with obstructive SAS in the present study were relatively free from ischaemic impairment of the brain, such as lacunae and leukoaraiosis, compared with controls and other SAS subtypes. A higher grade of leukoaraiosis was independently related to the risk of mixed SAS in this population. These observations are in contrast to the findings of Davies *et al.*,[25] who reported no significant difference in the prevalence of either lacunae or leukoaraiosis between obstructive SAS patients and controls aged 30 – 80 years. Mixed SAS is thought to develop in patients with obstructive SAS who also experience episodes of apparent central SAS.[7] Mild hypoxaemia and/or mild hypocapnia due to hypoxaemia induced hyperventilation have been reported to contribute to the shift from obstructive to mixed SAS.[26] In addition, central SAS can be secondary to damage to the respiratory centre of the brain, as seen in cases of ischaemic brain stem infarction.[7] These observations suggest that age-related ischaemic brain damage represented by lacunae and/or leukoaraiosis may result in a decrease in the prevalence of obstructive SAS and instead a predominance of mixed and/or central SAS.

The main cause of death in the present study was pneumonia followed by cardiovascular disease, a finding that is partly in accordance with reports from a disabled elderly population,[11] and elderly patients with SAS.[27] The present study showed SAS to be an independent predictor of reduced survival due to all-cause mortality and also mortality due to pneumonia and cardiovascular disease. In addition, an independent association between mixed SAS and increased mortality due to pneumonia was found. The precise mechanism of this association is not clear but severe leukoaraiosis predicted pneumonia death (with a hazard ratio of 8.3) in a study of patients with neurological deficit.[28] Since leukoaraiosis was associated with increased risk of mixed SAS in the present study, the relationship between mixed SAS and pneumonia mortality may be mediated by leukoaraiosis.

Obstructive, central and mixed SAS were all independent risk factors for both all-cause mortality and mortality from cardiovascular disease. Obstructive SAS increases mortality from cardiovascular disease in the general population[5,6] and in the elderly.[29] Central SAS has also been associated with increased mortality from cardiovascular disease in the general population[30] and in an elderly population.[31] The present study also revealed an independent contribution of mixed SAS to mortality from cardiovascular disease, in addition to death from pneumonia.

Neither AHI nor SAS severity were associated with any cause of death in the

present study. Previous studies have found a significant association between severity of obstructive SAS and coronary artery disease,[32] and severity of central SAS and congestive heart failure mortality.[31] Lavie *et al.*[33] found that the association between SAS severity and increased mortality disappeared in older SAS patients. The high mean age of the patients in the present study may be one of the causes of the lack of association between SAS severity and mortality of any cause.

In conclusion, the present study found an increased risk of cardiovascular and all-cause mortality in elderly inpatients with obstructive, central and mixed SAS. Mixed SAS was associated with an increase in mortality from pneumonia. There was no relationship between mortality and severity of SAS. Future trials should be conducted to determine a definite relationship between SAS and mortality using a larger number of patients.

Acknowledgements

This study was supported in part by a grant-in-aid for scientific research from the Ministry of Health, Labour and Welfare of Japan (to S.M.) and a grant for promoted research from Kanazawa Medical University (S2005-5 to T.T.).

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

• Received for publication 3 April 2011 • Accepted subject to revision 10 August 2011
• Revised accepted 14 March 2012

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J Exp Clin Med 2012;4(5):296–297

Contents lists available at SciVerse ScienceDirect

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LETTER TO THE EDITOR

Guidelines for Nonmedical Care Providers to Manage the First Step of Emergency Triage of Elderly Evacuees: Downloaded via Smart Phones in Japan☆

Japan experienced strong earthquakes in 1995,[1] 2004,[2] and 2007.[3] These disasters hit the elderly population of the communities particularly hard. Surviving older adults were largely left to their own devices and were marginalized in shelters. Elderly evacuees tended not to complain about their problems, so their excessive mental and/or physical stress under the altered environment tended to be underestimated. Therefore, it is important for nonmedical care providers (NMCPs) to detect medical conditions quickly in elderly evacuees. The NMCP include volunteers, helpers, and family members who are taking care of the elderly.

The Study Group on "Guidelines for the First Steps and Emergency Triage to Manage Elderly Evacuees" was established with funding from the Ministry of Health, Labor, and Welfare of Japan in April 2010. The study group aimed to complete and revise the guidelines. After the Great East Japan Earthquake of 2011, we quickly published the Japanese guidelines for NMCP, public health nurses (PHN), or certified social workers (CSW) to manage elderly evacuees.[4,5] The guidelines for the elderly have three chapters: (1) features and prevention of critical diseases in evacuation areas, (2) signs of acute diseases, and (3) symptoms of anxiety in shelters. We would like NMCP, PHN, and CSW for their permission to use the guidelines to rapidly detect illnesses in the elderly in shelters or homes. NMCP, PHN, or CSW should immediately inform attending medical staff when those with the signs or symptoms are detected.

We uploaded and started to provide the guidelines for NMCP, PHN, or CSW on the personal digital assistant (PDA) system on May 11, 2011. Figure 1 shows the guidelines downloaded via PDA (i.e., Android and iPhone versions were made by Google and Apple companies, respectively). The guidelines' numbers distributed to the smart phones are increasing, even up to the time of writing this letter (June 2, 2012), suggesting that general interest regarding measures against the natural disasters is continued among Japanese people. International provision of the guidelines written in English is now being promoted on the PDA system. Feedback concerning the guidelines downloaded will need to be collected from the NMCP, PHN, or CSW to evaluate the guidelines' usability. Previous guidelines failed to cover because of the unexpected phenomena following the 2011 Japan quake. We further should investigate the morbidity and mortality from disaster-related illnesses among the elderly to clarify efficacy and limitation of the guidelines.

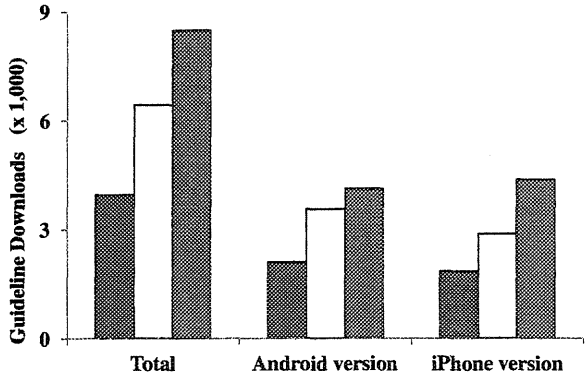

Figure 1 Numbers of the guidelines downloaded via personal digital assistant (Android and iPhone versions were made by Google and Apple companies, respectively) from May 11, 2011 through June 2, 2012 in Japan. The numbers distributed to the smart phones are increasing, even up to the time of writing this letter (June 2, 2012). Black column, September 11, 2011; open column, January 14, 2012; light gray column, June 2, 2012. The Android and iPhone versions can be downloaded from the corresponding sites (https://play.google.com/store/apps/details?id=jp.co.kgc.android.oneswingviewer.WJGSM001G#?t=W251bGwsMSwyLDIxMiwianAuY28ua2djLmFuZHJvaWQub25lc3dpbmd2aWV3ZXIuV0pHU00wMDFHIl0 and http://itunes.apple.com/jp/app/id434573392?mt=8).

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☆ This study was funded, in part, by the research funding for comprehensive research on aging and health, H22-003, from the Ministry of Health, Labor, and Welfare of Japan to Dr. Shigeto Morimoto.

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http://dx.doi.org/10.1016/j.jecm.2012.09.010

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Jul 5, 2012

LETTERS TO THE EDITOR

RESEARCH

DEPOPULATION WITH RAPID AGING IN MINAMISOMA CITY AFTER THE FUKUSHIMA DAIICHI NUCLEAR POWER PLANT ACCIDENT

To the Editor: On March 11, 2011, a strong earthquake (magnitude 9.0) occurred off the Pacific coast and hit the northeast of Japan, followed by devastating tsunamis, which destroyed many coastal cities.[1,2] The three operating reactors at Fukushima Daiichi nuclear power plant shut down automatically just after this earthquake,[3] but 41 minutes later, a massive wall of rolling water burst through the plant's defenses and inundated the reactor buildings. The tsunami flooded emergency generators, leaving the plant without power for cooling systems while radioactive decay kept heating the cores. In the control room, plant workers desperately tried to run crucial instruments, using torches and car batteries scavenged from nearby vehicles, but the last line of emergency systems failed, and the three reactors melted down several days later. This process induced release of hydrogen gas, which caused explosions in the reactor buildings.

People in Fukushima mistrust the actions of the government and the Tokyo Electric Power Company because of poor provision of accurate information concerning the plant accident, even 1 year and 4 months after the disaster. Volatile radioactive chemicals including iodine-131 and cesium-137 started to spread into the air and sea. Investigation of radionuclide was conducted on bamboo sampled from six sites within a 25- to 980-km radius of the Fukushima plant in July to August 2011.[4] Strikingly high concentrations of radiocesium-134 and -137 activity were detected in mature leaves from Fukushima city (65 km from the Fukushima plant), in excess of 71 and 79 kBq/kg of dry weight (DW). In Kashiwa city (195 km from the plant), sample concentrations were in excess of 3.4 and 4.3 kBq/kg DW. In Toyohashi city (440 km from the plant), concentrations were below the measurable limits of up to 4.5 Bq/kg DW.

Last summer, a comprehensive public health study was established with a large budget at Fukushima Medical University.[3] This investigation was designed to follow up on the health of some 2 million people in the region for 30 years. According to the latest data (February 20, 2012), 99.3% of 9,747 people living in towns or villages close to the plant received an accumulated effective dose of less than 10 mSv during the first 4 months after the accident. The highest dose was 23 mSv, well below the acute exposure level (100 mSv) related to a slight increase in risk of malignant diseases. In Minamisoma, there were 305 disaster-associated deaths, 298 (97.7%) of which were in elderly adults.

Minamisoma Municipal General Hospital, which is located in the evacuation area 20 km from the plant, has served as a regional core institute for evacuees. Medical care providers have been performing health monitoring and medical care, including vaccination programs, for more than 4,000 victims.

In April 2012, the government released newly revised guidelines regarding the evacuation zones from the plant, but wide-area evacuation still continues in Fukushima. The population of 72,000 in Minamisoma before the accident decreased to approximately 10,000 just after the accident. On March 29, 2012, it had recovered to approximately 45,000. The proportion of those aged 65 and older increased from 25.9% to 32.1% (Figure 1A). In addition, the retention rate of population according to age group has dramatically changed (Figure 1B). Many younger than 40, especially infants, children, and young parents, moved out of the communities because of fear regarding radiation exposure, causing a rapid increase in the proportion of elderly people. In addition, loss of ordinary lifestyle may inhibit activities of daily living of older adults. Elderly adults dislike moving, and many continued to live there, suggesting the breakup of communities and families. The average age of the population in Minamisoma has increased by 14 years because of the nuclear disaster, with younger people leaving, whereas older people have stayed behind, reaching the level that it had been estimated it would reach by 2025. Similar events have been observed in Futaba county and Iitate village near Minamisoma.

Public attention for the nuclear plant workers[5] and people living in Fukushima is fading rapidly. We should continue to pay attention to depopulation with rapid aging, which may make rebuilding populations in stricken areas difficult.

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ACKNOWLEDGMENTS

Conflict of Interest: None of the authors has any financial disclosure to report.

0002-8614/12/$15.00

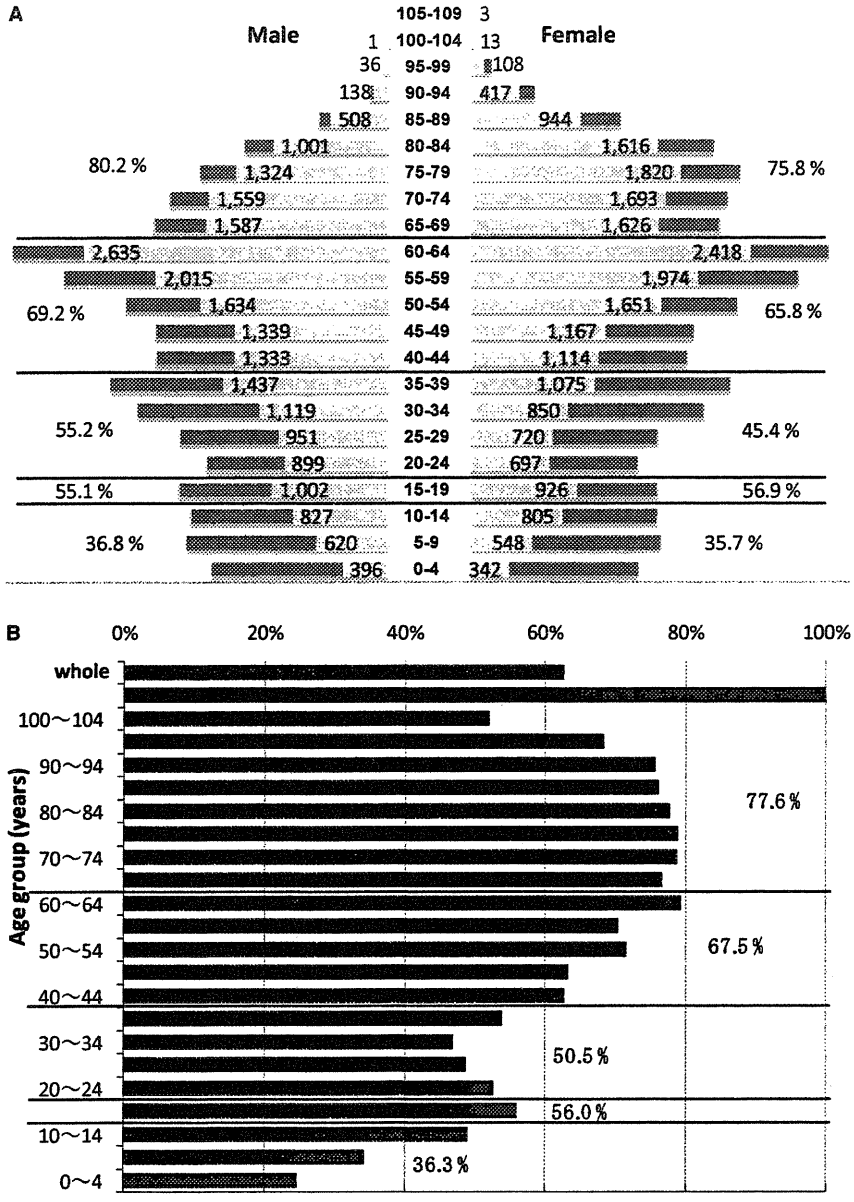

Figure 1. (A) Age-dependent decrease in population in Minamisoma city after the Great East Japan Earthquake and Fukushima Daiichi nuclear power plant accident. (B) Retention rate of population according to age group. Population data in Minamisoma on March 29, 2012 were compared with those on March 1, 2011.

Author Contributions: Ishikawa K. and Morimoto S.: Study concept and design. Kanazawa Y.: Acquisition of data. Ishikawa K.: Analysis and interpretation of data. Ishikawa K. and Takahashi T.: Preparation and writing of the letter.

Sponsor's Role: None.

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ASSOCIATION BETWEEN TEA CONSUMPTION AND DEPRESSIVE SYMPTOMS IN OLDER CHINESE ADULTS

To the Editor: Depression is a common mental illness in elderly adults that is associated with substantial disability,

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RIVASTIGMINE DERMAL PATCH SOLVES EATING PROBLEMS IN AN INDIVIDUAL WITH ADVANCED ALZHEIMER'S DISEASE

To the Editor: Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder and a leading cause of dementia in elderly adults.[1] In 2003, AD was the fifth leading cause of death in individuals aged 65 and older in the United States. The best current estimates indicate that median survival after the onset of symptoms of dementia ranges from 3 to 6 years, shorter than previously estimated.[2] Swallowing dysfunction with or without aspiration pneumonia is a major cause of morbidity and mortality in individuals with end-stage AD.[3,4] Herein is reported an individual with advanced AD with swallowing problems and recurrent pneumonias who was successfully treated with a rivastigmine transdermal patch.

An 81-year-old woman was diagnosed with AD in 2005, manifesting as gradually progressive short-term memory loss, with a sharper decline during the past 3 years despite vigorous treatment with donepezil. Magnetic resonance imaging revealed brain atrophy, especially in the hippocampus. She had repeated episodes of aspiration pneumonia, malnutrition, dehydration, falls and femoral neck fracture, and sarcopenia. In February 2011, she was hospitalized for recurrent aspiration pneumonia and unresponsiveness. On admission, she was diagnosed as having AD according to the Functional Assessment Staging Scale, spending the entire day in a wheelchair, speaking only several words, and requiring complete support for eating and toileting. She was successfully treated using intravenous antibiotics and hydration. After pneumonia treatment, her oral intake was poor, and she occasionally refused to eat. She was taking just one or two spoonfuls of food or some juice. A bedside swallowing evaluation revealed mild oral dysphagia with delayed swallowing latency (4.2 ± 0.2 seconds).[3,4] Although a mechanically altered diet or nutritional supplements were ordered, her weight declined from 42 to 35 kg, and she developed a pressure ulcer on her hip over the next 3 months. It took a long time to hand feed and deliver oral medications, but her son did not agree to placement of a long-term feeding tube. In June 2011, she was discharged home to be cared for by her son. Her family physician and nurses provided intravenous hydration three times a week. In October 2011, her family physician decided to use a rivastigmine transdermal patch (Rivastach patch) instead of donepezil, and she was titrated from an initial dose (4.5 mg in a 2.5-cm^2 patch per day) to a maintenance dose (18 mg in a 10-cm^2 patch per day) by 2.5 cm^2 at 4-week intervals over 16 weeks. At a dose of 9 mg (5 cm^2) per day, her oral intake improved dramatically, and she gained weight. A bedside test revealed that her swallowing function had improved and that the swallowing latency had shortened (3.1 ± 0.3 seconds).[3,4] Her unresponsiveness was partially resolved, and the pressure ulcer resolved. Her clinical condition has been maintained under treatment with rivastigmine patch until now (May 2012).

DISCUSSION

AD is characterized by progressive cholinergic failure with an extensive loss of cholinergic neurons.[5] It has previously been shown that cholinergic neurons might be involved in the regulation of normal swallowing function,[6] indicating that cholinergic dysfunction might impair swallowing reflex in individuals with advanced AD.[5,6] Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) can regulate the action of acetylcholine in the human brain, and BuChE is capable of compensating for low AChE activity.[7,8] Thus BuChE may become more important as AD progresses, and there is growing evidence that BuChE, as well as AChE, is a clinically relevant treatment target in AD.[7,8] Rivastigmine is the first approved transdermal patch for individuals with AD and has a dual inhibitory action of AChE and BuChE.[7,8] A clinical study demonstrated that rivastigmine dose-dependently inhibited BuChE activity.[7] Rivastigmine might therefore improve swallowing function by slowing the degradation of acetylcholine in the cholinergic nervous system in individuals with advanced AD.

CONCLUSION

In addition to a better tolerability profile than oral rivastigmine, transdermal delivery may allow better delivery for individuals with AD with swallowing disorders. Rivastigmine transdermal patch may enable individuals with advanced AD with eating problems take meals orally.

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ACKNOWLEDGMENTS

Conflict of Interest: Takashi Ohrui is employed at the Division of Geriatric Pharmacotherapy, Tohoku University, which receives research funding support from Ono Pharmaceutical Company, Japan. Ono Pharmaceutical Company manufactures a rivastigmine dermal patch.

Author Contributions: Uwano C, Suzuki M, Aikawa T, Ebihara T, Une K, Tomita N, Kosaka Y, Furukawa K, Arai H, and Ohrui T: Acquisition of subjects and data. Uwano C and Ohrui T: Analysis and interpretation of data and preparation of manuscript.

Sponsor's Role: None.

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RESEARCH STUDIES

POTENTIAL EFFECT OF SCREENING FOR SUBTLE COGNITIVE DEFICITS ON HOSPITAL READMISSION

To the Editor: Several conditions that significantly affect functionality and independence may be subtle and go unrecognized, potentially leading to nonadherence to medical recommendations and readmission. Existing risk-prediction models for hospital readmission have been shown to perform poorly.[1] Studies suggest that unrecognized cognitive deficits may exist after the illness that necessitated the admission was successfully treated, resulting in an unappreciated risk for readmission.

The risk of cognitive impairment increases with age and is amplified with hospitalization resulting in significant morbidity.[2] The frequency of cognitive impairment ranges from 15% to 35% in hospitalized elderly adults on general medicine services but may be even higher.[3] Identifying vulnerable individuals with cognitive deficits at the time of hospital admission is critical to prevent, establish a diagnosis of, and treat delirium.[4] Cognitive impairment is also associated with depression in late life and correlates with poorer quality of life and greater healthcare use.[5] Identification of subtle cognitive deficits can prove to be challenging, because many cognitively impaired individuals with intact language and memory can be perceived to be functionally independent. Executive cognitive functions are cognitive processes that orchestrate complex, goal-directed actions.[6] Impairment of the former undermines an individual's independence by interfering with the direction, planning, execution, and supervision of complex behavior. Screening individuals for obscured cognitive impairment at the time of hospital discharge could be the first step in early identification of mild to moderate cognitive impairment and allow for interventions to reduce related disability and avoidable readmissions.

This study examined subtle cognitive deficits that often go undetected in association with delirium, depression, and executive dysfunction. Individuals aged 65 and older admitted with diagnoses of congestive heart failure, exacerbation of chronic obstructive pulmonary disease, pneumonia, or myocardial infarction regardless of motor deficits were included. Exclusion criteria were admission from a skilled nursing or assisted living facility, medical history of dementia or cognitive impairment, English as a secondary language, and an education level less than high school.

A trained nurse screened older patients on Day 2 or 3 of admission. All individuals were screened for delirium using the Confusion Assessment Method,[7] instrumental activities of daily living using Lawton's scale, executive dysfunction using the Controlled Oral Word Association Test, and the oral version of the Trail-Making Test Part B. Depression screening was performed using the Patient Health Questionnaire. The comparison (control) group consisted of age-matched elective surgical postoperative patients without a diagnosis of dementia or the aforementioned four diagnoses and not admitted from a nursing or assisted living facility.

The study sample consisted of 43 cases and 27 controls. Rates of delirium, depression, and executive dysfunction were 15.2%, 19.6%, and 83.7%, respectively, in the study group and 7.7%, 0%, and 50%, respectively, in the control group. Rate of readmission within 1 calendar year was evaluated; 21 of the 23 (91.3%) readmitted cases and three of the five (60%) readmitted controls tested positive for executive dysfunction ($P < .05$).

It was possible to identify a large prevalence of executive dysfunction in a population at high risk for readmission. Screening older patients, in particular those with underlying diagnoses known to have a high risk for readmission for subtle cognitive deficits, may help to direct interventions and the allocation of limited resources to improve healthcare outcomes, including prevention of readmission.

Institutional review board approval for this quality improvement study was obtained from Greenwich Hospital, Yale New Haven Health.

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