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ORIGINAL ARTICLE

Dental status and mortality in institutionalized elderly people

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Background: Inadequate dentition for mastication is one of the major issues associated with systemic health for institutionalized elderly people, but its prognostic value and related deaths have not been fully examined.

Methods: Four hundred and three patients aged 65 and older were recruited from nine nursing homes and were prospectively followed up for morbidity and mortality for 5 years in Japan. These patients were classified into three groups according to dental status: patients who had adequate dentition with natural teeth only or natural teeth with partial dentures (Group A); those who were edentulous but wearing full dentures (Group B); and those who had inadequate dentition without dentures (Group C).

Results: Dental status was strongly related to age, cognitive function and activities of daily living. After allowing for confounding effects, the 2-year risk of mortality among those in Group C was 1.84 times that of Group A (95% confidence interval 1.01–3.36, $P = 0.047$). Furthermore, the 5-year mortality rate in Group C was higher than that in Group A, whereas that was not significant with a hazard ratio of 1.30 (0.90–1.88, $P = 0.168$). The main causes of death were respiratory infections, which explained 14.1% of all causes of death in Group A, 14.3% in Group B and 18.3% in Group C. Any associations between a specific cause of death and the different dental status did not reach a significant level.

Conclusion: Inadequate dental status is associated with high overall mortality. Our findings suggest that systemic attention to dental status should be recommended in institutionalized elderly people.

Keywords: activities of daily living, dental status, mortality, respiratory infections.

Introduction

The loss of teeth is an irreversible process that peaks in old age and seriously influences oral function including mastication, deglutition and phonation.[1] A common cause of teeth loss in elderly people is alveolar pyorrhea, which can be prevented by intensive oral care.[2] Although elderly populations are retaining their teeth due to recent heightened concern about oral hygiene,[3] institutionalized elderly people still have poor oral health.[4,5] Simons reported that elderly people in residential homes had a high proportion of edentulousness of 57.4%, and high plaque and gingival indices of 2.3 and 1.7, respectively.[6] Moreover, in Japan, even though many institutionalized elderly people have lost many teeth, they do not use dentures to keep their masticatory capacity.[7] Such poor oral status of the institutionalized elderly may contribute to eating problems, low nutrition and an increase in intraoral bacteria.[8–12] Because many institutionalized elderly people are chronically infirm, these results may cause weight loss, disability and respiratory infections.[13,14]

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Little is known about the effect of inadequate dental status for mastication on mortality in the institutionalized elderly. Shimazaki *et al.* demonstrated that institutionalized elderly people being edentulous without dentures were 1.8 times more prone to death during the 6-year follow up as compared with those with 20 or more teeth.[15] However, they did not determine the underlying and immediate cause of death. Therefore, we conducted a study of elderly Japanese people to analyze recent dental status in nursing homes, poor dental status as a risk factor for mortality, and a relationship between dental status and specific causes of death. During the entire 5-year follow-up period, these patients were examined. We also analyzed cognitive function and activities of daily living (ADL), which might be potentially related to mortality.

Methods

Study population

Subjects were members of the Oral Care Study cohort.[16] A total of 403 patients consisting of 86 men and 317 women, aged 65 years or older (82.8 ± 7.7 [mean ± SD] years) were recruited at nine nursing homes in Japan in September 1999. Each nursing home had 50–100 beds and served as long-term care facilities for older patients who were physically handicapped and/or suffering from mental deterioration.

The criterion for patient selection was that physical symptoms were stable for the preceding month. All patients had no acute disorders, for example, pulmonary diseases with dyspnea, infection, heart failure, or stroke requiring special treatment and intensive care. In addition, patients with immunocompromised disorders such as active malignant disease, renal dialysis, hypogammaglobulinemia or HIV-1 infection, were excluded from the study. Our study protocol was approved by the ethical review committee at Tohoku University School of Medicine, and all patients or their families provided written informed consent.

Dental and clinical examination

At baseline, we evaluated the patients' dental status for mastication. Patients were grouped into one of the following three categories according to different levels of dental status: Group A consisted of patients whose dental status was functionally adequate for mastication by natural teeth only or natural teeth with partial denture(s); Group B consisted of patients who were edentulous but kept their masticatory capacity by dentures in both jaws; and Group C consisted of patients with a functionally inadequate dental status without dentures. There was no significant difference in the percentage of the basic clinical conditions among the groups, of which information was given on admission by patients' family member and/or other reliable collateral source such as cardiac diseases, cerebrovascular diseases, hypercholesterolemia, diabetes mellitus and cardiac arrhythmias, and the use of medications for these diseases (Table 1). During follow up, tooth brushing was performed by the patients themselves or by caregivers at least once a day. If patients were using dentures, nurses cleaned the dentures with a denture brush every day and with denture cleanser once a week.

Because of the potential effects on mortality, cognitive function and ADL were evaluated in all the patients. Cognitive function was examined using the Mini-Mental State Examination (MMSE).[17] ADL was evaluated using the modified Barthel Index.[18] Both MMSE and the modified Barthel Index have a 30-point scale for healthy older people, with a score of 0 indicating complete loss of cognition and dependence. If the MMSE score was 22 points or less, patients were considered as cognitively demented. If the modified Barthel Index was 20 points or less, patients were considered as physically disabled.

Following up the patients

These patients were followed up for mortality until September 2004. If the patients were discharged from the nursing home, mortality was ascertained by contact with their families. When the patients died, the underlying and immediate causes of death were determined by medical doctors. Their death certificates and medical records were reviewed (by M.Y., T.M. and T.O.) and the only medical events leading directly to death were coded according to the ninth version of the International Classification of Diseases (ICD-9).[19] Any other records about other significant conditions contributing to death but not related to cause were not considered here.

Statistical analysis

Statistical analyses were carried out with statistical software package SPSS version 10.0 (SPSS, Chicago, IL, USA). Baseline characteristics among age groups and different levels of dental status were compared by one-way ANOVA for continuous variables and by χ^2 tests for categorical variables. When significant differences between groups were found, a post hoc analysis was performed to test by Fisher's test on the groups significantly differing from each other.

A Cox proportional-hazards model was used to estimate mortality risk by levels of dental status, with adjustments for other potential covariates: age, gender, basic clinical conditions, cognitive function and ADL.[20] Because mortality, cognitive function and dental status are all strongly linked with age, all models were validated using graphical and analytical techniques to

Table 1 Distribution of clinical characteristics and 2-year and 5-year mortality according to dental status

Variables	Total	Oral status			*P*-value*
		Group A	Group B	Group C	
Number of patients	403	99	98	206	
Age, year	82.8 ± 7.7	79.5 ± 6.9**	84.3 ± 6.8	83.7 ± 8.0	< 0.001
Gender (male/female)	86/317	25/74	13/85	48/158	0.075
Dentition					
Natural teeth	5.1 ± 7.4	12.7 ± 8.9	0	3.9 ± 5.3	< 0.001
Edentulousness, n/N (%)	192/403 (47.6%)	0/99 (0%)	98/98 (100%)	112/206 (54.4%)	< 0.001
Clinical basic conditions					
Cardiac disease, n/N (%)	68/403 (16.9%)	17/99 (17.2%)	18/98 (18.4%)	33/206 (16.0%)	0.874
Cerebrovascular disease, n/N (%)	117/403 (29.0%)	21/99 (21.2%)	26/98 (26.5%)	70/206 (34.0%)	0.061
Diabetes mellitus, n/N (%)	31/403 (7.7%)	11/99 (11.1%)	5/98 (5.1%)	15/206 (8.3%)	0.275
Arrythmia, n/N (%)	39/403 (9.7%)	8/99 (8.1%)	12/98 (12.2%)	19/206 (9.2%)	0.581
Medications, n/N (%)	166/403 (41.2%)	36/99 (36.4%)	42/98 (42.9%)	88/206 (42.7%)	0.533
Cognitive function					
MMSE (points)	10.6 ± 9.5	15.4 ± 9.4**	13.4 ± 8.9**	7.6 ± 8.3	< 0.001
Dementia, n/N (%)	346/403 (85.9%)	72/99 (72.7%)	81/98 (82.7%)	193/206 (93.7%)	< 0.001
ADL					
Barthel Index (points)	15.8 ± 7.1	19.2 ± 6.3**	18.8 ± 6.0**	12.8 ± 6.7	< 0.001
Disability, n/N (%)	283/403 (70.2%)	51/99 (51.5%)	57/98 (58.2%)	175/206 (85%)	< 0.001
Mortality					
2 years, n/N (%)	112/403 (27.8%)	14/99 (14.1%)	21/98 (21.4%)	77/206 (37.4%)	< 0.001
5 years, n/N (%)	235/403 (58.3%)	45/99 (45.5%)	54/98 (55.1%)	136/206 (66.0%)	0.002

*One-way ANOVA for different dental status. **The post hoc significant differences from corresponding values in Group C are indicated by $P < 0.0001$. Group A, adequate dentition with natural teeth only or natural teeth and partial dentures; Group B, edentulous and denture wearers; Group C, inadequate dentition without dentures. Mean ± SD for continuous variables and number (%) for categorical variables. ADL, activities of daily living; MMSE, Mini-Mental State Examination.

check for possible non-linearity and interactions. Kaplan–Meier curves were used to display the results. All tests were two-sided and statistical significance was set at $P < 0.05$.

Results

Dental status and other variables

Of the 403 patients who were evaluated at baseline, 192 (47.7%) were edentulous. The prevalence of edentulousness and number of natural teeth strongly correlated with age (Table 2). The prevalence of edentulousness for patients 65–74 years of age was 24.6%; this significantly increased to 40.4% for those 75–84 and to 63.4% for those 85 and older ($P < 0.001$). The number of natural teeth for patients 65–74 years of age was 9.4 ± 8.9; this significantly decreased to 5.6 ± 7.4 for those 75–84 and to 3.0 ± 5.8 for those 85 and older ($P < 0.001$). Ninety-eight of the 192 edentulous patients (51.0%) were denture wearers and the prevalence significantly decreased in patients 85 and older ($P = 0.008$).

When each patient was categorized into one of the groups according to levels of dental status, 99 patients met the criteria for Group A, which consisted of patients who had adequate dentition with natural teeth only or natural teeth with partial dentures; 98 patients were in Group B, which consisted of patients who were edentulous but wearing full dentures; and 296 patients were in Group C, which consisted of patients who had inadequate dentition without dentures. In univariate analysis, these different levels of dental status were significantly associated with age ($P < 0.001$), MMSE score ($P < 0.001$) and Barthel Index ($P < 0.001$) (Table 1).

Dental status and overall mortality

During the first 2-year follow up, 112 patients died. There were 14 (12.5%) deaths in Group A, 21 (18.8%) in Group B and 77 (68.8%) in Group C ($P < 0.001$) (Table 1). By the end of the 5-year follow up there were another 123 deaths (total 235): 45 (19.1%) of the death were in Group A, 54 (23.0%) were in Group B, and 136 (57.9%) were in Group C ($P = 0.002$) (Table 1) (Fig. 1).

Table 2 Demographic variables among different age groups

Variables	65–74 years	75–84 years	85 ≤ years	*P*-value*
Number of patients	65	166	172	
Gender (male/female)	27/38	32/134	27/145	< 0.001
Dentition				
Natural teeth*, N	9.4 ± 8.9**	5.6 ± 7.4**	3.0 ± 5.8	< 0.001
Edentulousness, n/N (%)	16/65 (24.6%)	67/166 (40.4%)	109/172 (63.4%)	< 0.001
Denture wearers in edentulous, n/N	11/16 (68.8%)	42/67 (62.7%)	45/109 (41.3%)	0.008
Cognitive function				
MMSE (points)	13.7 ± 9.5**	11.5 ± 9.9**	8.7 ± 8.7	< 0.001
Dementia, n/N (%)	51/65 (78.5%)	139/166 (83.7%)	156/172 (90.7%)	0.032
ADL				
Barthel Index (points)	16.7 ± 6.8	16.5 ± 6.9	14.9 ± 7.4	0.059
Dependence, n/N (%)	44/65 (67.7%)	114/166 (68.7%)	125/172 (72.7%)	0.643

*One-way ANOVA for different dental status. **The posthoc significant differences from corresponding values in Group C are indicated by $P < 0.0001$. Mean ± SD for continuous variables and number (%) for categorical variables.

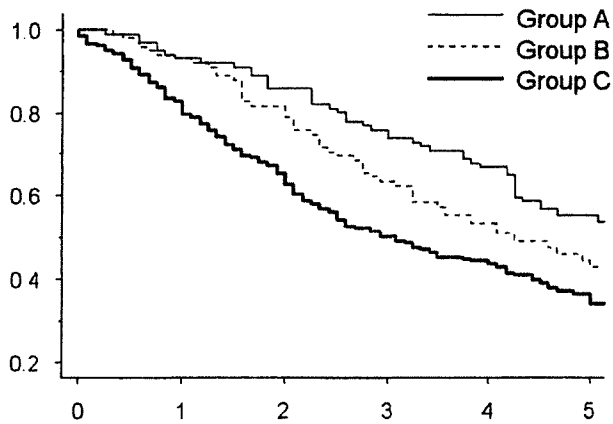

Figure 1 Cumulative event plots according to different dental status were estimated by the Kaplan–Meier method and compared using the log–rank test: survival curves for all causes of death by different levels of dental status. Group A indicates subjects with adequate dentition with natural teeth only or natural teeth and partial dentures. Group B indicates subjects with edentulous and denture wearers. Group C indicates subjects with inadequate dentition without dentures.

In an unadjusted analysis, we examined the effect of dental status on 2-year and 5-year mortality. As compared with Group A, Group C had a relative risk of mortality of 3.09 (2-year: 95% confidence interval [CI] 1.75–5.46, $P < 0.001$) and 1.93 (5-year: 1.38–2.71, $P < 0.001$); Group B did not significantly increase the risk of mortality (Table 3). After allowing for confounding effects of age, gender, basic clinical conditions including cardiac disease, cerebrovascular disease and diabetes mellitus, cognitive function and ADL, the 2-year risk of death among those in Group C was 1.84 times that of Group A (95% CI 1.01–3.36, $P = 0.047$) (Table 3). However, the 5-year mortality among those of Group C was no longer significantly different from that of Group A (hazard ratio: 1.30, 95% CI 0.90–1.88, $P = 0.168$). However, if age or ADL were excluded from the potential confounders, the dental status of Group C independently increased the 5-year mortality (data not shown).

Dental status and specific causes of death

The underlying and immediate causes of deaths are shown in Table 4. Respiratory infections (66 deaths) and senility (52 deaths) were common causes of 5-year mortality. The mortality rate by respiratory infections for patients in Group C was 18.4% (38 deaths/206 patients). This mortality rate was not significantly different as compared with that for patients in Group A (14.1%, 14 deaths/99 patients, $P = 0.079$) and Group B (14.3%, 14 deaths/98 patients, $P = 0.165$). Any other associations between a specific cause of death and the different dental status also failed to reach a significant level (data not shown).

Discussion

Our study had three major findings. First, inadequate dentition for mastication was common in institutionalized elderly patients over the age of 65, and its prevalence is clearly increasing with age and is strongly associated with impaired cognitive function and lower ADL. Second, this poor dental status was associated with approximately a twofold increase in the 2-year risk of death independent of age, gender, basic clinical conditions, cognitive function and ADL. Third, this poor dental status was involved in overall mortality rather than mortality due to specific diseases such as respiratory infections because the number of events may have been too small to permit a detailed, cause-specific analysis.

Table 3 Unadjusted and adjusted 2-year and 5-year mortality ratio

		2-year mortality ratio Unadjusted hazard ratio (95% CI)	*P*-value	Adjusted hazard ratio (95% CI)**	*P*-value	5-year mortality ratio Unadjusted hazard ratio (95% CI)	*P*-value	Adjusted hazard ratio (95% CI)**	*P*-value
Oral status									
	A	1.0		1.0		1.0		1.0	
	B	1.55 (0.79–3.05)	0.202	1.31 (0.66–2.60)	0.472	1.35 (0.91–2.01)	0.134	1.13 (0.75–1.70)	0.554
	C	3.09 (1.75–5.46)	< 0.001	1.84 (1.01–3.36)	0.047	1.93 (1.38–2.71)	< 0.001	1.30 (0.90–1.88)	0.168
Age*									
	65–74	1.0		1.0		1.0		1.0	
	75–84	1.19 (0.60–2.35)	0.614	1.42 (0.71–2.84)	0.321	1.93 (1.17–3.17)	< 0.001	2.29 (1.38–3.81)	0.001
	85–	2.62 (1.39–4.96)	0.003	2.92 (1.51–5.66)	0.002	3.91 (2.41–6.34)	< 0.001	4.51 (2.74–7.44)	< 0.001
Gender	Male	1.0		1.0		1.0		1.0	
	Female	0.55 (0.37–0.81)	0.003	0.46 (0.30–0.70)	< 0.001	0.71 (0.53–0.96)	0.028	0.54 (0.39–0.73)	< 0.001
Cardiac disease	Absent	1.0		1.0		1.0		1.0	
	Present	0.96 (0.58–1.59)	0.865	1.10 (0.65–1.85)	0.718	0.94 (0.66–1.32)	0.705	1.01 (0.71–1.44)	0.961
Cerebrovascular disease	Absent	1.0		1.0		1.0		1.0	
	Present	1.24 (0.84–1.84)	0.280	0.99 (0.66–1.48)	0.942	1.54 (1.18–2.02)	0.002	1.33 (1.00–1.77)	0.038
Diabetes mellitus	Absent	1.0		1.0		1.0		1.0	
	Present	1.02 (0.52–2.02)	0.954	1.20 (0.60–2.42)	0.601	0.92 (0.56–1.51)	0.921	1.14 (0.69–1.89)	0.612
Cognitive function									
Dementia	Absent	1.0		1.0		1.0		1.0	
	Present	4.06 (1.66–9.95)	0.002	2.22 (0.87–5.65)	0.095	2.32 (1.46–3.67)	< 0.001	1.58 (0.97–2.58)	0.067
ADL									
Dependence	Absent	1.0		1.0		1.0		1.0	
	Present	3.32 (1.89–5.81)	< 0.001	2.22 (1.21–4.06)	0.010	1.89 (1.39–2.57)	< 0.001	1.44 (1.02–2.05)	0.040

*Age adjusted odds ratios. Age was fitted 10 years age bands: 65–74; 75–84; 85 or more. **Adjusted model includes the following variables: age; gender and severity of cognitive function and ADL.

Table 4 Underlying and immediate causes of death during 5-year follow up

Causes of death	Group A (n = 99)		Group B (n = 98)		Group C (n = 206)	
	Number of deaths	Mortality rate (n/N,%)	Number of deaths	Mortality rate (n/N,%)	Number of deaths	Mortality rate (n/N,%)
All causes	45	45.5	54	55.1	136	66.0
Respiratory-tract infections	14	14.1	14	14.3	38	18.4
Senility without mention of psychosis	5	5.1	8	8.2	39	18.9
Ischemic heart disease	6	6.1	8	8.2	18	8.7
Cerebrovascular disease	8	8.1	3	3.1	10	4.9
Malignant neoplasms	2	2.0	4	4.1	4	1.9
Other infections*	0	0.0	4	4.1	3	1.5
Gastrointestinal bleeding	0	0.0	0	0.0	5	2.4
Cirrhosis of the liver	0	0.0	1	1.0	1	0.5
Renal failure	0	0.0	0	0.0	1	0.5
External and Unknown causes	10	10.1	12	12.2	17	8.3

*Other infections include septicemia (n = 3) and infections of the kidney and urinary tract (n = 4).

It is well documented that many older patients in nursing homes have poor oral status. Other researchers have shown that such poor dental status was strongly associated with age, cognitive function and ADL.[13,21] Nordenram *et al.* reported significant correlations between the ability to chew and cognitive and functional capacity.[22] These findings may be explained in relation to the character of institutionalized elderly patients. For example, they are unlikely to perform personal oral hygiene care sufficient to keep adequate natural dentition because of impaired cognitive function and lower ADL.[5,6] With progression of the disease, demented patients would not keep their dentures on at ease and physically disabled patients may be recommended not to use dentures to prevent inspiration of the dentures.

Further, oral hygiene in long-term-care institutions has been neglected and there are different explanations for this, such as the difficulty of access to professional dental care,[23] little time to share by the staff,[24] and lack of understanding, knowledge, interest by the staff including primary care physicians and geriatricians.[25,26] On the basis of such conditions for oral health and care, many institutionalized elderly may lose their teeth and may be unsatisfactorily treated.

We found that inadequate dentition for mastication significantly increased the risk of 2-year overall mortality in institutionalized elderly patients. A few reports have shown that edentulous people without dentures are significantly prone to death as compared to those with adequate dentition in community-dwelling elderly people[27,28] or institutionalized elderly people.[15] Appollonio *et al.* reported that edentulous people without dentures had a significant risk for death independent of physical–mental health status at baseline and discussed that poor dental status may have negative effects on mortality through malnutrition.[28] In another report they showed that inadequate dental status and micronutrients such as folate were significant and independent predictors of mortality in community-dwelling elderly women.[29] Moreover, a number of studies have shown that poor dental status is associated with malnutrition.[30,31] Although we did not consider estimating nutritional status such as bodyweight and serum albumin, previous studies strongly suggest that inadequate dental status and the susceptibility to death are partly linked by malnutrition.

In contrast, the present study showed that inadequate dental status did not seem to be an independent prognostic variable of 5-year mortality but an associated variable of other strong predictors of mortality, such as increasing age and low ADL. Adjustment for these factors weakened the predictive power of dental status. A possibility is that longer survival rates may be greatly influenced by age and ADL because these older and frail patients might reach the end points sooner apart from dental status.

In our study, death from respiratory infections was scored as a primary cause of death, and no other terminal diseases entered into this group.[32] Therefore, the prevalence of the death from respiratory infections might have been underestimated because people diagnosed as senility were in poorly defined conditions and likely to have underlying disease conditions such as asymptomatic pneumonia.[32] Although a direct and independent relationship between poor dental state and death from respiratory infections remains unclear, it is recognized that respiratory infections can be the result of infection by anaerobic bacteria, and dental plaque would seem to be a logical source of these bacteria, especially in patients with periodontal disease.[12] Poor

dental health may contribute to the development of pneumonia as an independent or associated prognostic variable.[33] We previously demonstrated that intensive oral care lowered the frequency of pneumonia by 50% in the institutionalized elderly.[14] Therefore, intensive oral care should be recommended for patients who cannot keep their teeth clean by themselves to prevent respiratory infections.[34]

A potential weakness of the study is that patients' concurrent illness that would have affected their prognosis was not fully confirmed or followed up because of limited capacity for objective evaluation in the nursing homes and unwillingness for intensive medical care for relatively old patients. Further, lack of patients' subjective compliant due to limited ADL and cognitive function, especially in Group C, might have made it difficult to identify an underlying fatal disease (Table 4). These provide possible reasons why senility was negatively selected as a cause of death without the supportive evidence.

Another limitation of the present study was that the baseline examination of dental status might not reflect their lifetime dental status, and thus not effectively stratify their risk. This might be true especially for elderly people with comorbidity, causing increased mortality and inadequate dental status when close to death. This factor may explain, hypothetically, the association between inadequate dental status and mortality in institutionalized elderly. Although 30 edentulous patients who had dentures but had not used them were included in Group C, their mortality rates were similar to that of the other edentulous patients who did not have dentures (data not shown); therefore, such a distorting mechanism is unlikely.

In summary, our findings highlight a broader concern about inadequate dental status for mastication in institutionalized elderly people and its relation to poor outcomes. Moreover, the present study provides a basis for keeping an adequate dental status in institutionalized elderly patients in order to minimize poor dental status related deaths. Thus, our findings suggest that systemic attention to dental status should be recommended. However, further study about the relationship between poor dental status and specific causes of mortality is necessary to better elucidate the role of poor dental status both as a precursor and as a sequel of disease states to improve methods for its management.

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ELECTRONIC LETTER

Association of susceptibility to the development of pneumonia in the older Japanese population with haem oxygenase-1 gene promoter polymorphism

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Background: Oxidative stresses including cigarette smoking are implicated in the pathogenesis of cerebrovascular diseases, which are associated with pneumonia because of frequent aspiration. Haem oxygenase-1 (HO-1) acts in cytoprotection against oxidants, provides anti-inflammatory effects, and inhibits atherogenesis. A $(GT)_n$ dinucleotide repeat in the human *HO-1* promoter modulates *HO-1* gene expression and shows length polymorphism, which is grouped into three classes: class S (<27 repeats), class M (≥27, <33 repeats), and class L (≥33 repeats) alleles.
Objective: To investigate the correlation between the *HO-1* gene polymorphism and development of pneumonia in elderly Japanese.
Methods: The length of the $(GT)_n$ repeats was analysed in 200 elderly patients with pneumonia and 200 control subjects. The association of the *HO-1* gene polymorphism with risk of pneumonia was estimated by logistic regression.
Results: The proportion of allele frequencies in class L, and the proportion of genotypic frequencies in the L-allele carriers (L/L, L/M, and L/S), was significantly higher in patients with pneumonia than in controls (20% *v* 10% in class L, and 34% *v* 18% in L-allele carriers). After adjustment for potentially confounding factors, both cerebrovascular disorders and *HO-1* gene L-allele carriers were significant and independent risk factors for pneumonia. The adjusted odds ratio for L-allele carriers *v* non-L-allele carrier was 2.1 (95% confidence interval, 1.2 to 3.6).
Conclusions: The large size of a $(GT)_n$ repeat in the *HO-1* gene promoter may be associated with susceptibility to pneumonia in the older Japanese population.

Pneumonia is not only a common infection in older people, it is also the most common cause of death from nosocomial infection in the Japanese population.[1] Disorders of the central nervous system are more likely to develop in the elderly, and pneumonia has been estimated to occur in about one third of patients with stroke.[2] Cerebrovascular disease is associated with a high incidence of pneumonia owing to frequent aspiration.[3] As well as factors including diabetes mellitus, hyperlipidaemia, and hypertension, oxidative stresses such as cigarette smoking are also associated with the pathogenesis of cerebrovascular disease.[4] Genetic factors affecting antioxidants may be involved in the susceptibility to atherosclerosis of the cerebral arteries and the subsequent development of pneumonia in the elderly. Although the antioxidant enzymes inhibit the formation of atherosclerosis,[5] the roles of reduced expression of these enzymes on the development of pneumonia in elderly people are still uncertain.

Haem oxygenase (HO) oxidatively degrades haem to biliverdin, which is subsequently reduced to bilirubin, an efficient scavenger of reactive oxygen species (ROS), by biliverdin reductase.[6] HO-1, an inducible form of HO—and also a constitutive form of HO, including HO-2—provides cellular protection against haem mediated and non-haem-mediated oxidant injury.[6] HO-1 is thought to be an essential component in protection against various ROS.

A $(GT)_n$ repeat in the 5′ flanking region of the human *HO-1* gene is polymorphic,[7] and modulates human *HO-1* gene transcription by thermal stress[8] and hydrogen peroxide.[7] The size of the $(GT)_n$ repeat in the *HO-1* gene is associated with the antiapoptotic effects of HO-1 in lymphoblastoid cell lines.[9] We have shown that the size of the $(GT)_n$ repeat in the *HO-1* gene is associated with susceptibility to chronic pulmonary emphysema (CPE)[7] and lung adenocarcinoma,[10] and with longevity[11] in Japanese populations. This *HO-1* gene polymorphism is also associated with coronary artery disease, one of vascular diseases related to ROS.[12] However, the association between the size of the $(GT)_n$ repeat in the *HO-1* gene and the development of pneumonia in older populations is still uncertain.

In the present study, we screened allelic frequencies of the $(GT)_n$ repeats in the *HO-1* gene promoter in elderly people with and without pneumonia, and examined the association between the risk of senile pneumonia and length of the $(GT)_n$ repeats.

METHODS

Clinical protocol and patient characteristics

We studied 200 elderly patients with pneumonia and 200 elderly control subjects without pneumonia, attending the departments of internal medicine in six hospitals in Miyagi prefecture. The hospitals were a university hospital, a Red Cross hospital, three public general hospitals, and a municipal hospital. All participants were Japanese and aged 65 and older. To evaluate whether *HO-1* genotypes are associated with the development of pneumonia in elderly Japanese people, we selected the subjects with a performance status of 2 or better[13] and in a stable state as potential participants, because those with too low a performance status ran a greater risk of infectious disease, which might mask the preventive effect of any genetic factors. Patients were given a score of 0 if they were fully active and asymptomatic, 1 if they were symptomatic but fully ambulatory, 2 if they were

Abbreviations: COPD, chronic obstructive pulmonary disease; CPE, chronic pulmonary emphysema; HO, haem oxygenase; HO-1, inducible haem oxygenase; ROS, reactive oxygen species; TNF, tumour necrosis factor

Table 1 Characteristics of the study subjects

Characteristics	Control subjects (n=200)	Patients with pneumonia (n=200)	p Value
Age (years)*	73.8 (0.7)	75.4 (1.0)	NS
Sex			
Male	99 (50%)	101 (50%)	NS
Female	101 (50%)	99 (50%)	
Performance status			
0–1	114 (57%)	108 (54%)	NS
2	86 (43%)	92 (46%)	
Smoking history (pack-year)*	18.2 (2.6)	19.3 (2.8)	NS
Cerebrovascular disease			
Yes	14 (7%)	101 (50%)	<0.0001
No	186 (93%)	99 (50%)	
COPD			
Yes	35 (18%)	38 (19%)	NS
No	165 (82%)	162 (81%)	
Congestive heart failure			
Yes	17 (9%)	28 (14%)	NS
No	183 (91%)	172 (86%)	
Hypertension			
Yes	43 (22%)	59 (30%)	NS
No	157 (78%)	141 (70%)	
Diabetes mellitus			
Yes	21 (10%)	34 (17%)	NS
No	179 (90%)	166 (83%)	
Hyperlipidaemia			
Yes	9 (5%)	10 (5%)	NS
No	191 (95%)	190 (95%)	

Values are n (%) or *mean (SD).
COPD, chronic obstructive pulmonary disease.

symptomatic and confined to bed or chair for less than 50% of their waking hour, 3 if they were symptomatic and confined to bed or chair for more than 50% of their waking hours, and 4 if they were completely bedridden. The study was approved by the Tohoku University ethics committee, and informed consent was obtained from each subject. This study was carried out between April 2002 and December 2004.

During the study period, 264 elderly patients with pneumonia were identified. Pneumonia was defined as pulmonary infiltrate on chest radiograph, cough, and a temperature higher than 38.0°C.[3] All patients with pneumonia had the features of pulmonary infiltrate on chest radiographs, cough, and a temperature above 38.0°C. The patients were enrolled consecutively. Among them, we selected for the case group those with a performance status of 2 or better and in a stable state. We excluded patients who were immunocompromised—for example, those with active malignant disease, on renal dialysis, receiving corticosteroid treatment, or with HIV-1 infection. Patients were also excluded if they had obvious swallowing dysfunction, chronic sepsis in pressure sores, venous ulcers, or an indwelling urinary catheter. After these selections and exclusions were applied, 200 elderly patients with pneumonia were enrolled in the case group.

Potential control subjects were 439 elderly patients who continued attending the departments of hospitals over the study period and who had never had pneumonia at any time in their life including the study period. Control subjects were excluded if their past history relating to pneumonia were unclear. After the same selection and exclusion criteria as in the case group were applied, 383 control subjects were available for frequency matching. To carry out a case–control study, we randomly selected 200 control subjects in a frequency matched manner from the control cohort. They were frequency matched on age (±5 years), sex, smoking history, and performance status with the patients with pneumonia. Physical characteristics, smoking history, and complications in patients with pneumonia and control subjects are shown in table 1.

Analysis of length variability of $(GT)_n$ repeats in HO-1 gene promoter

Genomic DNAs were extracted from leucocytes in peripheral venous blood by conventional procedures. The 5′-flanking region containing a poly $(GT)_n$ repeat of the *HO-1* gene was amplified by polymerase chain reaction (PCR)[7 10] with a fluorescently labelled primer p1-s (5′-AGAGCCTGCAGC TTCTCAGA-3′) and an unlabeled antisense primer p1-as (5′-ACAAAGTCTGGCCATAGGAC-3′), which were designed

Table 2 Allele and genotypic frequencies of HO-1at polymorphic locus

	Control subjects (n=200)	Patients with pneumonia (n=200)	OR (95% CI) v all other classes or subjects	p Value
Allele class				
L	38 (10%)	79 (20%)	2.3 (1.5 to 3.5)	<0.0001
M	189 (47%)	159 (40%)	0.7 (0.5 to 0.9)	<0.05
S	173 (43%)	162 (40%)	0.9 (0.7 to 1.2)	NS
Genotype group				
L-allele carrier	36 (18%)	68 (34%)	2.3 (1.5 to 3.7)	<0.001
Non-L-allele carrier	164 (82%)	132 (66%)		

CI, confidence interval; OR, odds ratio.

Table 3 Multivariate analysis of risk factors related to pneumonia in older adults

Variable	OR (95% CI)	p Value
Haem oxygenase-1 genotype subgroup		
L-allele carriers v non-L-allele carriers	2.1 (1.2 to 3.6)*	<0.01
Cerebrovascular disease		
Yes v no	28.0 (13.3 to 58.6)†	<0.0001

*OR was calculated with the non-L-allele carriers as the reference group, and adjusted for age, gender, performance status, smoking history, and complications.
†OR was calculated with the patients without cerebrovascular disease as the reference group, and adjusted for age, gender, performance status, smoking history, *HO-1* genotype, and complications other than cerebrovascular disease.
CI, confidence interval; OR, odds ratio.

according to the published sequence.[7 14] The PCR was carried out over 30 cycles of 20 seconds at 94°C, 10 seconds at 60°C, and 20 seconds at 72°C. The PCR products were analysed in a DNA sequencer (ALF express II DNA sequencer version 2.2, Amersham Pharmacia Biotech, Piscataway, New Jersey, USA). Each size of $(GT)_n$ repeat in the PCR product was calculated with ALFwin fragment analysis version 1.03 (Amersham Pharmacia Biotech) using four cloned alleles as size markers, which were already sequenced with the ABI prism dye terminator sequencing kit (Perkin-Elmer Applied Biosystems, Foster City, California, USA).[7] The repeat numbers of these size markers were 16, 23, 29, and 38, respectively. The investigators of genetic analysis were blinded with respect to the status of the subjects.

Carboxyhaemoglobin concentrations in patients with pneumonia

Blood samples were taken from the radial artery in patients with pneumonia on the first day of hospital admission. The patients for the carboxyhaemoglobin analysis were all non-smokers and consisted of five L-allele carriers and five non-L-allele carriers (L/L genotype and S/S genotype, respectively), who showed a similar C reactive protein concentration (15.0 to 20.0 mg/dl) and white blood cell (WBC) count (9500 to 12 500 cells/μl) at the time of analysis. The carboxyhaemoglobin concentrations were measured with a spectrophotometer (ASL System, Radiometer, Copenhagen, Denmark).[15]

Statistical analysis

In the analysis of *HO-1* gene polymorphism in this study, the patient and control groups were frequency matched by age, sex, performance status, and smoking history. For statistical analysis, age and smoking history (pack-year) between the two groups were compared using Student's *t* test, and sex, performance status, and the frequency of the complications between the two groups were compared using χ^2 tests (table 1), as described previously in coronary artery disease.[12] The proportion of allelic frequencies and genotypic frequencies between the two groups were also compared using the χ^2 test (table 2). Factors associated with the presence of senile pneumonia such as age, sex, performance status, smoking status, complications, and *HO-1* gene polymorphism (L-allele carrier) were examined with multivariate analysis by logistic regression analysis (table 3). Odds ratios (OR) and their 95% confidence intervals (CI) were calculated to assess the relative risk conferred by a particular genotype (L-allele carrier), and adjusted for age, sex, performance status, smoking history, and complications using logistic regression as described previously (table 3).[12] All the statistical analyses were undertaken using SYSTAT (version 10.2; SYSTAT Software, Richmond, California, USA). The values for age and smoking history (pack-year) are reported as means (SD). The *HO-1* genotype distributions were in Hardy–Weinberg equilibrium. Significance was accepted at $p<0.05$.

For statistical analysis in the study on the correlation between carboxyhaemoglobin level and *HO-1* genotype in the patients with pneumonia, the mean values for age (year), smoking history (pack-year), WBC number (cells/μl), C reactive protein (mg/dl), and carboxyhaemoglobin concentration (%) between the five L-allele carriers and the five non-L-allele carriers were compared using Student's *t* test and sex using the χ^2 test (table 4).

RESULTS

Allele frequencies of HO-1 gene in control and patients with pneumonia in older adults

There were between 16 and 39 $(GT)_n$ repeats in the human *HO-1* gene in the study subjects (fig 1). The distribution of the number of $(GT)_n$ repeats was trimodal, as previously reported, with two main peaks located at 23 and 30 GT repeats and another peak located at 33 GT repeats.[7 10 11] We therefore divided the alleles into three subclasses, as previously reported[7]: class S (<27 repeats), class M (≥27 and <33 repeats), and class L (≥33 repeats) alleles.

In the control subjects, the distributions of the 400 alleles were 173 (43%) class S, 189 (45%) class M, and 38 (10%) class L (table 2); in the patients with pneumonia, the distributions were 162 (40%) class S, 159 (40%) class M, and 79 (20%) class L. The proportion of allelic frequencies in class L was significantly higher in all patients with pneumonia (n = 79, 20%) than that in all control subjects (n = 38, 10%)

Table 4 Arterial blood carboxyhaemoglobin in patients with pneumonia

Patient	HO-1 genotype	Age (years)*	Sex†	Smoking history (pack-year)*	WBC (cells/μl)*	CRP (mg/dl)*	Arterial blood Hb-CO (%)‡
L-allele carrier 1	LL	71	M	0	12 300	18.3	0.57
L-allele carrier 2	LL	65	F	0	10 500	15.2	0.20
L-allele carrier 3	LL	79	F	0	9 700	15.7	0.80
L-allele carrier 4	LL	73	F	0	9 600	19.0	0.21
L-allele carrier 5	LL	76	F	0	10 020	19.4	1.20
Non-L-allele carrier 1	SS	65	M	0	12 400	18.5	1.50
Non-L-allele carrier 2	SS	77	M	0	11 000	16.3	1.20
Non-L-allele carrier 3	SS	79	F	0	10 500	19.2	1.02
Non-L-allele carrier 4	SS	65	F	0	9 900	15.6	1.10
Non-L-allele carrier 5	SS	75	F	0	9 600	19.5	0.90

*There was no significant difference in the mean value between L-allele carrier and non-L-allele carrier ($p>0.7$).
†There was no significant difference in the ratio between L-allele carrier and non-L-allele carrier ($p>0.5$).
‡There was a significant difference in the mean value between L-allele carrier and non-L-allele carrier ($p<0.04$).
CRP, C reactive protein; F, female; Hb-CO, carboxyhaemoglobin; M, male; WBC, white blood cell count.

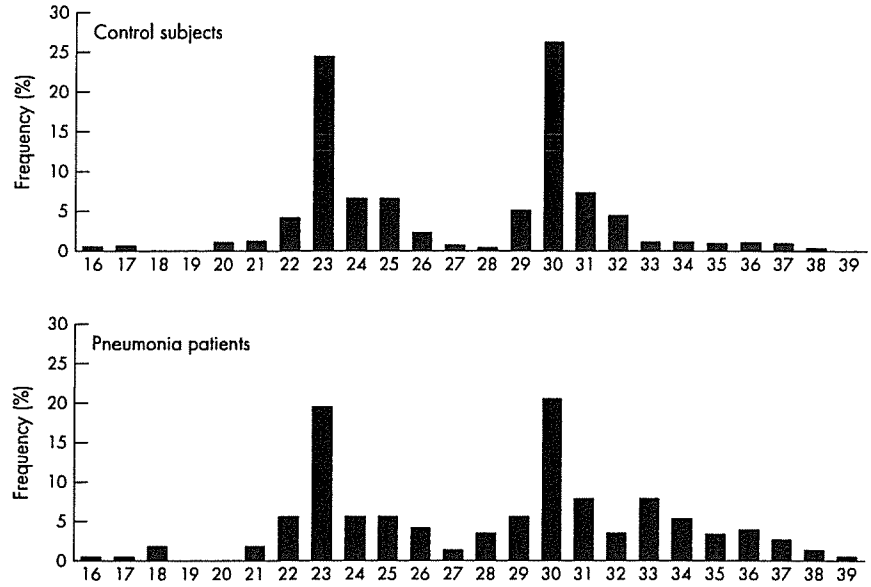

Figure 1 Frequency distribution of the number of $(GT)_n$ repeats in control subjects (n = 400 alleles) and patients with pneumonia (n = 400 alleles).

(p<0.0001). The odds ratio for pneumonia with L alleles *v* non-L alleles (class M allele + class S allele) was 2.3 (95% CI, 1.5 to 3.5) (table 2).

Genotypic frequencies of HO-1 gene in control and patients with pneumonia

Six genotypes (L/L, L/M, L/S, M/M, M/S, and S/S) of $(GT)_n$ repeats in the human *HO-1* gene promoter were divided into two subgroups according to allelic subclasses: L-allele carriers with a class L allele (L/L, L/M, L/S) and non-L-allele carriers without a class L allele (M/M, M/S and S/S).[7] The proportion of genotypic frequencies in L-allele carriers was significantly higher in all patients with pneumonia (n = 68, 34%) than that in all control subjects (n = 36, 18%) (p<0.0001). The odds ratio for patients with pneumonia with L-allele carriers *v* non-L-allele carriers was 2.3 (95% CI, 1.4 to 3.7) (table 2).

Risk factors for pneumonia

On multivariate analysis, cerebrovascular disease (p<0.0001) and *HO-1* genotype (p<0.01) were significantly and independently associated with the development of pneumonia (table 3), when the variables were adjusted by age, sex, performance status, smoking history, and complications including congestive heart failure, COPD, hypertension, diabetes mellitus, and hyperlipidaemia. The adjusted odds ratio (95% CI) was 2.1 (1.2 to 3.6) for *HO-1* genotype and 28.0 (18.3 to 58.6) for cerebrovascular disease (table 3).

Carboxyhaemoglobin concentrations in patients with pneumonia

To show the correlation between *HO-1* genotype and HO-1 activity caused by the inflammation of pneumonia, we examined the carboxyhaemoglobin concentration in several patients with pneumonia on their first day of hospital admission. The subjects for carboxyhaemoglobin analysis were five L-allele carriers and five non-L-allele carriers (L/L genotype and S/S genotype, respectively). There were no significant differences in age, sex, smoking history, WBC count, and C reactive protein concentration level between these two groups. However, the patients without the L-allele showed significantly higher carboxyhaemoglobin levels than those with the L-allele (1.14 (0.23)% *v* 0.5 (0.42)%, respectively; p<0.04) (table 4).

DISCUSSION

In this study we analysed *HO-1* gene polymorphism and showed that the proportion of allele frequencies in class L and the proportion of genotypic frequencies in the L-allele carriers (L/L, L/M, and L/S) were significantly higher in elderly people with pneumonia than in control subjects. The proportion of subjects with cerebrovascular disease in the pneumonia group was significantly higher than in the control group. With multivariate analysis, *HO-1* genotype and the presence of cerebrovascular disease were significant and independent risk factors for pneumonia. These findings suggest that the large size of a $(GT)_n$ repeat in the *HO-1* gene promoter may be associated with the development of pneumonia in older Japanese people with cerebral infarction.

Disorders of the central nervous system are more likely to develop in the elderly, and pneumonia has been estimated to occur in about one third of patients with stroke.[2] Basal ganglia infarction is associated with a high incidence of pneumonia owing to frequent aspiration[3] resulting from the reduction in the cough and swallowing reflexes.[16] In fact, in the present study, half these older patients with pneumonia also had cerebrovascular disease.

Oxidative stress such as cigarette smoking[1] is one of the important risk factors for cerebrovascular diseases, including basal ganglia infarction. Various ROS including superoxide and hydrogen peroxide induce lipid peroxide formation, which is a key process in atherosclerotic plaques in hypercholesterolaemia.[17] ROS are also involved in the brain tissue damage in stroke.[18] On the other hand, antioxidant systems such as glutathione, superoxide dismutase, and HO are suggested to protect the vascular disease caused by ROS.[19] The initial degradation of haem by microsomal HO involves the liberation of iron and CO and the formation of biliverdin, which is subsequently reduced to bilirubin by cytosolic biliverdin reductase.[4] Higher intracellular HO-1 activity may increase the content of bilirubin, which is an efficient scavenger of ROS,[6] and a natural inhibitor of intimal hyperplasia after balloon injury.[20] In fact, Ishikawa *et al.*

reported inhibitory effects of HO-1 on the atherogenesis in hyperlipidaemic rabbits.[21] Enhanced endothelial cell injury caused by oxidative stress was observed in a human case of *HO-1* deficiency.[22] Reduced expression of HO-1 might be partly associated with the development of stroke and subsequent pneumonia.

A $(GT)_n$ dinucleotide repeat in the 5'-flanking region of human *HO-1* gene shows length polymorphism.[7] We previously reported the influence of the number of the $(GT)_n$ repeats on the inducibility of the *HO-1* gene promoter under oxidative stimulus by transient transfection assay in human cell lines. The promoter activity of *HO-1* is modulated by the length variability of the $(GT)_n$ repeats, and large $(GT)_n$ repeats have a potent inhibitory activity on H_2O_2 induced gene expression of HO-1.[7] Furthermore, Epstein-Barr virus transformed lymphoblastoid cell lines were established from smokers with class L alleles (L/L) and with class S (S/S). When treated with H_2O_2, lymphoblastoid cells with the L/L genotype showed lower viability than those with the S/S genotype.[9] The GT dinucleotide repeat polymorphism has emerged as a potent genetic risk factor in various diseases, including vascular diseases such as coronary arteriosclerosis[12] and restenosis after balloon angioplasty.[23] These findings are consistent with the view that tissues of the non-L allele carrier could employ the antioxidant activity of HO-1 to a greater extent than that of the L-allele carrier when exposed to reactive oxygen species.[10] Large $(GT)_n$ repeats may affect the protective function against oxidant induced vascular endothelial injury and arteriosclerosis through the inhibition of HO-1 expression.

The results of our study suggest that the *HO-1* genotype is associated with susceptibility to pneumonia independently of cerebrovascular disease. Senile pneumonia is characterised by a high likelihood of aspiration pneumonia.[16] The severity of aspiration pneumonia is associated with the lung inflammation mediated by cytokines such as tumour necrosis factor α (TNFα).[24] On the other hand, it was reported that overexpression of the *HO-1* gene attenuated inflammation and decreased apoptosis of bronchial epithelial cells in a murine model of lung inflammation induced by *Pseudomonas aeruginosa*.[25] Furthermore, overexpression of the *HO-1* gene could reduce TNFα mediated apoptotic cell death in human endothelial cells.[26] These findings suggest that *HO-1* gene expression could be associated with the progress of aspiration pneumonia, and that reduced expression of the *HO-1* gene in elderly L-allele carriers might allow the development of pneumonia independently of cerebrovascular disease.

To examine the association between *HO-1* genotype and HO-1 activity in the pneumonia, we evaluated the carboxyhaemoglobin level in L-allele carriers and non-L-allele carriers with pneumonia. As a result, even after adjustment for the peripheral WBC count and C reactive protein level, patients without the L-allele showed higher carboxyhaemoglobin levels than those with the L-allele. Carbon monoxide (CO) is produced endogenously by HO and combines haemoglobin to form carboxyhaemoglobin complex. Therefore, the carboxyhaemoglobin concentration in the subject is a good marker of endogenous HO activity.[27] Furthermore, it has been reported that HO-1 is strongly induced in patients with bacterial infection.[28] We have already shown that arterial carboxyhaemoglobin increases at the onset of pneumonia in untreated patients returns to baseline on recovery after treatments.[15] We also showed that an increase in arterial carboxyhaemoglobin in pneumonia would be caused by carbon monoxide production in pulmonary inflammation, and that the arterial carboxyhaemoglobin is significantly correlated with disease severity in patients with bacterial pneumonia.[29] A study of lymphoblastoid cell lines by Hirai *et al* showed that mRNA level and activity of HO-1 were significantly higher in lymphoblastoid cells with the S/S genotype than in those with the L/L genotype after oxidant stimulation.[9] Therefore, analysis of the carboxyhaemoglobin level in pneumonia according to *HO-1* genotype would clarify the association between the *HO-1* genotype and HO-1 activity—that is, the HO-1 protein level, resulting from pneumonia. These findings suggest that HO-1 induction might be associated with the *HO-1* genotype (S>M>L).

In contrast to arterial blood carboxyhaemoglobin concentrations, we did not measure HO-1 activity in patients with pneumonia at the onset. However, we obtained new blood samples from eight people in the control group and seven in the pneumonia group after recovery from pneumonia, and analysed the serum HO-1 protein levels using enzyme linked immunosorbent assay methods as previously described.[10] There was no significant difference between these two groups when they were in good physical condition (2.6 (1.2) *v* 2.4 (1.0) ng/ml, p>0.2). These values were compatible with the results from a previous report.[10] Because the *HO-1* gene is inducible by inflammation or oxidative stress, the baseline expression of the this gene should be low regardless of the *HO-1* genotype, which was demonstrated in lymphoblastoid cell by Hirai *et al*.[9] Further studies are needed to clarify the relation between HO-1 activity and the *HO-1* genotype at the onset of pneumonia.

Conclusions

This is the first study to show that the 5'-flanking polymorphism in the *HO-1* gene is associated with the development of pneumonia in an older Japanese population with basal ganglia infarction. Increased susceptibility to developing pneumonia may be associated with sclerosis in the cerebral arteries.

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ACE inhibitors and protection against pneumonia in elderly patients with stroke

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Pneumonia is the most common cause of death from nosocomial infection in the elderly. The increased incidence of pneumonia and the high mortality are consequences of a number of age-related factors, including coexisting illnesses, therapeutic interventions, and the aging process itself.[1] Pneumonia has been estimated to occur in about one third of patients with stroke.[2] The most important factor contributing to the risk of pneumonia in patients with stroke is suggested to be dysphagia with aspiration.[1]

Angiotensin-converting enzyme (ACE) inhibitors have been shown to improve silent aspiration[3] and prevent pneumonia in elderly patients with stroke.[4] However, little is known about whether ACE inhibitors have a beneficial role in reducing the risk of pneumonia as compared to other classes of antihypertensive drugs in elderly patients with stroke. Thus, we investigated whether ACE inhibitors can reduce the risk of pneumonia as compared to other antihypertensive drugs.

Methods. We recruited patients with stroke who were followed up for more than 6 months after their ictus from eight outpatient clinics. We enrolled 1,190 patients in April 1999, and prospectively followed them for 35 months. The criteria for diagnosis of pneumonia and the patients' inclusion and exclusion criteria were described previously.[5] Eligible patients were those who received antihypertensive therapy, had a history of stroke, but were not bedridden.

We analyzed the incidence of pneumonia in three groups of hypertensive patients with stroke who were classified on the basis of treatment with antihypertensive drugs as follows: patients who received ACE inhibitors, calcium-channel blockers, and diuretics. Our hypertensive patients received only the same class of antihypertensive drugs. The control group consisted of non-hypertensive patients with stroke who did not receive any antihypertensive drugs. Follow-up data were available for all participants.

For the main analyses, we used the log-rank procedure and Cox's proportional hazards model to calculate the CI. Cumulative incidence curves were generated by the Kaplan-Meier method for endpoints in the ACE inhibitors, calcium-channel blockers, diuretics, and control groups. Significance was set at $p < 0.05$.

Results. There were no significant differences in age, sex, stroke severity as assessed by NIH Stroke Scale,[6] and poststroke duration among the four groups (table). During the follow-up, new pneumonia was diagnosed in 12 (2.8%) of the 430 patients in the ACE inhibitors group, 36 (8.8%) of the 409 patients in the calcium-channel blockers group, 29 (8.3%) of the 351 patients in the diuretics group, and 14 (8.8%) of the 160 patients in the control group. The patients in the ACE inhibitors group had a lower risk of pneumonia than those in the control group; the hazard ratio was 0.30 (95% CI 0.14 to 0.66, $p = 0.0013$). However, the risk in the calcium-channel blockers group (1.01, 95% CI 0.53 to 1.92, $p > 0.40$) or the diuretics group (0.94, 95% CI 0.48 to 1.83, $p > 0.30$) did not differ from that in the control group.

Discussion. We found a significantly reduced risk of pneumonia in patients receiving ACE inhibitors vs control patients. No such decreased risk was noted in users of calcium-channel blockers or diuretics. Silent aspiration reportedly disappears by treatment with ACE inhibitors in association with an increase in the serum substance P levels in hypertensive patients with stroke.[3] ACE inhibitors may increase the serum substance P levels, thereby reducing aspiration pneumonia in elderly patients with stroke.

A recent large-scale randomized trial has demonstrated that treatment with ACE inhibitors significantly reduced the risk of pneumonia among the participants of Asian ethnicity, although the protective effects of ACE inhibitors against pneumonia were not observed in the non-Asian participants.[7] However, this trial[7] included patients with a history of transient ischemic attacks and the mean Barthel index score of the patients was quite high. Since the incidence of pneumonia increased in association with a decrease in the Barthel index score,[5] the effects of ACE inhibitors against pneumonia might be underestimated by a population of patients with a high activity of daily life. Our present study only included patients with well-documented cerebral hemispheric strokes.

The present study supports the hypothesis that treatment with ACE inhibitors may be beneficial in reducing the risk of pneumonia in elderly patients with stroke.

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***Table** Characteristics and clinical features of the four groups*

	ACE inhibitors	Calcium-channel blockers	Diuretics	Control
No.	430	409	351	160
Female/male	224/206	213/196	183/168	78/82
Mean age, y	75 (1)	75 (1)	75 (1)	76 (1)
Stroke severity	6 (1)	6 (1)	6 (1)	6 (2)
Poststroke duration, y	3.1 (1.1)	3.3 (0.9)	3.4 (1.1)	3.3 (1.2)

Values in parentheses are SD.

ACE = angiotensin-converting enzyme.

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Hypernatremia from a hunger strike as a cause of osmotic myelinolysis

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Too rapid correction of hyponatremia often causes osmotic myelinolysis. A rapid shift from normal to hypernatremia may also be dangerous. We report a hunger striker that developed an extreme serum sodium concentration followed by coma and radiologic abnormalities characteristic of osmotic myelinolysis.

Case report. A 19-year-old Algerian asylum seeker started a hunger strike after his residence permit had been rejected. His medical history was unremarkable. He used no medications, including lithium. One month before fasting, he was placed in isolation because of behavioral disturbances. At this time, the weather was hot, and the patient refused sufficient intake of water and food. One day after he stopped eating and drinking, he became confused; after another 5 days, he became somnolent. He was transferred to a penitentiary hospital. On admission, his serum sodium level was 187 mmol/L, creatinine 213 μmol/L, and glucose 6.8 mmol/L. Urine osmolality was not measured. A feeding tube rehydration regimen was started with 2 L/day of water. His sodium level was 172 mmol/L the next day. After 2 days, he became comatose and was referred to our intensive care unit. On admission, his blood pressure was 105/55 mm Hg, temperature was 38.5°C, Glascow Coma Scale score was 6 (E1M4V1), the pupillary light reflex was delayed, and the Achilles tendon reflexes were absent. Sodium level was 152 mmol/L, potassium 2.5 mmol/L, creatinine 91 μmol/L, urea 7.3 mmol/L, phosphate 0.41 mmol/L, magnesium 0.96 mmol/L, and albumin 26 g/L. CT of the brain and CSF analysis were normal. EEG showed diffuse slowing. A chest radiograph showed bilateral infiltrates. The patient was intubated and treated for aspiration pneumonia. Potassium and phosphate were replaced.

Because of the extreme hypernatremia, osmotic myelinolysis was considered. Brain MRI 5 days after admission was consistent with pontine and extrapontine myelinolysis (figure, A and B). MRI also revealed acute hydrocephalus (see the figure, B) and posterior fossa edema (see the figure, C). An external ventricular drain was inserted. The intracranial pressure proved normal. As the patient did not respond to 6 days of drainage, the drain was removed. Over the next days, the pupillary light reflex normalized and the patient regained consciousness. When asked, he was able to open, close, and move his eyes and slightly move his fingers. No other voluntary movements were possible. After 1 month, his neurologic condition gradually improved. After 4 months, he was able to speak and walk short distances. After 7 months, he was fully recovered but needed a cane while walking.

Discussion. We present a hunger striker that developed osmotic myelinolysis due to extreme hypernatremia from dehydration. The clinical presentation with confusion and coma several days after onset of the severe electrolyte disturbance followed by spontaneous recovery in the course of months is consistent with osmotic myelinolysis.[1]

Central pontine myelinolysis was first described in 1959, associated with alcoholism and malnutrition.[2] In 1976, it was first linked to hyponatremia.[3] In hypotonic hyponatremia, water initially enters brain cells, resulting in cerebral edema. The brain cells adapt by losing electrolytes and organic osmolytes, thus arresting a further influx of water. If chronic hyponatremia is cor-

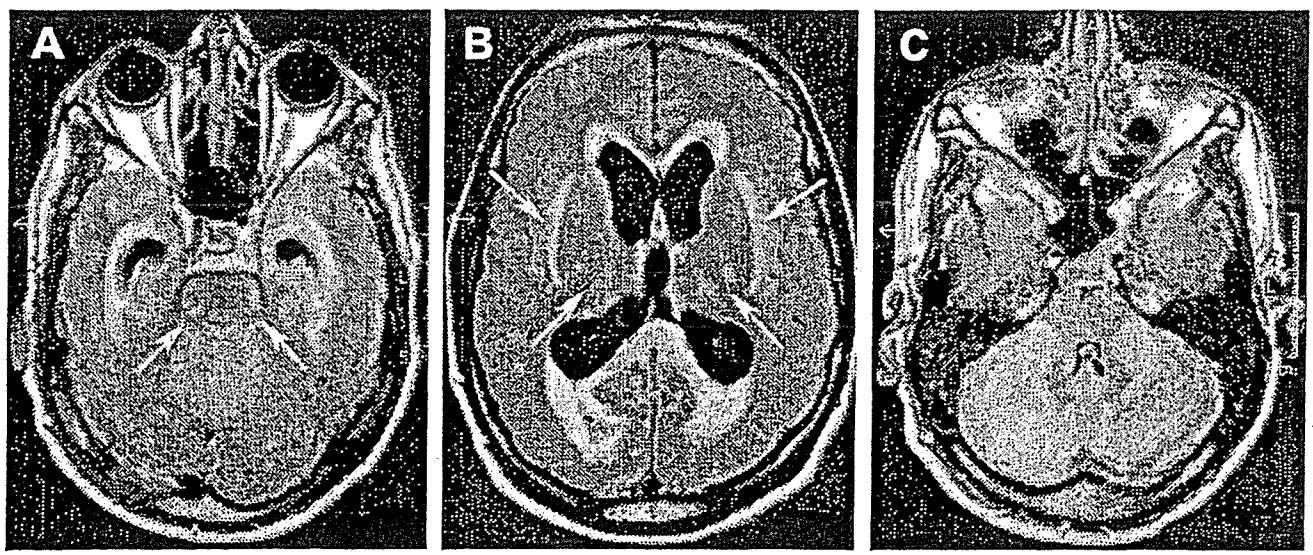

Figure. Axial fluid-attenuated inversion recovery MRI of the brain showing hyperintensities in the dorsolateral regions of the pons (A) and bilaterally in the thalamus, globus pallidus, and capsula extrema (B), consistent with osmotic myelinolysis. Also note the enlargement of the lateral and third ventricles with periventricular hyperintensities (B). This acute triventricular hydrocephalus was presumably caused by posterior fossa edema, yielding impaired CSF circulation (C).

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メタボリックシンドローム

—病因解明と予防・治療の最新戦略—

VII. 特　　論

Werner症候群とメタボリックシンドローム

横手幸太郎

VII. 特　論

Werner症候群とメタボリックシンドローム

Werner syndrome and metabolic syndrome

横手幸太郎

Key words：Werner症候群，早老症，ヘリカーゼ，lamin A，老化

1. Werner症候群とは

Werner症候群は，1904年ドイツの眼科医Otto Wernerにより‘強皮症を伴う白内障の一例’として初めて報告された代表的な遺伝的早老症である．臨床症状として，①低身長，②皮膚の萎縮・角化・潰瘍，③四肢の筋・脂肪組織の萎縮，④毛髪の変化(白髪・禿頭)，⑤音声の変化(高調性嗄声)，⑥白内障，⑦高インスリン血症を伴う耐糖能異常，⑧性腺機能低下，⑨軟部組織石灰化，⑩悪性腫瘍合併，⑪骨粗鬆症，などが知られ[1]，毛髪変化をはじめとする早老様徴候が20歳頃からみられるようになる．本症候群は常染色体劣性の遺伝形式をとり，第8染色体短腕に位置するRecQ型DNAヘリカーゼ(WRNヘリカーゼ)のホモ接合型遺伝子変異が原因である[2]．DNAヘリカーゼの異常に起因する疾患としては，ほかにBloom症候群，Cockayne症候群，Rothmund-Thomson症候群，色素性乾皮症などがある．

我が国におけるWerner症候群の頻度は100万人に1-3人といわれ，これまでは主に近親婚の多い地域で報告されてきた．しかし，神奈川県内で行われた研究によると，対象となった一般住民1,000人のうち少なくとも6人がWRN遺伝子の変異をヘテロ接合体として保有しており，単純に計算すれば，毎年少なくとも23人のホモ接合体(すなわちWerner症候群患者)が我が国で出生することが予測される[3]．

2. Werner症候群と早発性粥状動脈硬化

Werner症候群患者の平均寿命は47歳といわれている．その二大死因は間葉系細胞に由来する悪性腫瘍と心筋梗塞であり[1]，本症候群では同年代の健常者に比べて粥状動脈硬化が進みやすいと考えられている[4]．その機序についてはこれまでに様々な報告がある．例えば，本症候群の患者では低比重リポ蛋白(LDL)受容体の活性低下により動脈硬化の主要危険因子である高LDL血症を伴いやすく[5]，血栓形成を促進するPAI-I(plasminogen activator inhibitor-I)や白血球接着分子ICAM-1(intercellular adhesion molecule-1)の可溶型[6]，細胞の遊走や増殖に関与するフィブロネクチンなどがいずれも血中で高値を示す[7]．

また，Werner症候群はインスリン抵抗性を伴いやすいことから，代償性の高インスリン血症やそれに引き続いて生じる糖尿病[8]もまた動脈硬化の進展に寄与すると考えられる．一方，Werner症候群ではない心筋梗塞患者を対象とした検討から，ある種のWRN遺伝子多型が，糖尿病の合併とは無関係に心筋梗塞のリスク増加と関連することも示されており[9]，未知の機序を示唆する成績として興味がもたれる．

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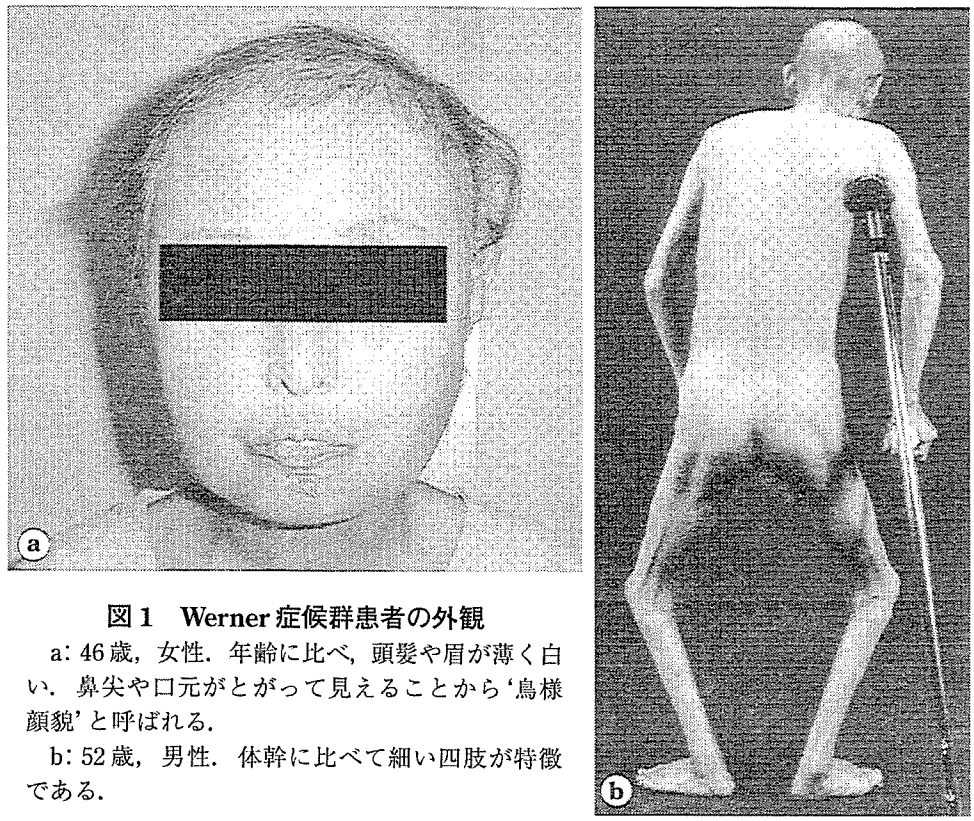

図1 Werner症候群患者の外観

a: 46歳，女性．年齢に比べ，頭髪や眉が薄く白い．鼻尖や口元がとがって見えることから'鳥様顔貌'と呼ばれる．

b: 52歳，男性．体幹に比べて細い四肢が特徴である．

3. Werner症候群にみられるメタボリックシンドローム様の病態

a. 腹部に限局した脂肪の蓄積

内臓型肥満とインスリン抵抗性を基盤に耐糖能障害，血圧高値，脂質代謝異常など複数の代謝性危険因子を合併し，粥状動脈硬化や糖尿病の発症リスクが高い病態としてメタボリックシンドロームが注目されている．一般にWerner症候群患者は枝のように細い上下肢を呈し(**図1-b**)，体格的には'肥満(body mass index: BMI ≧25)'に該当しないことが多い．しかし，体幹部の脂肪組織は通常保たれているため，著者らは，代謝性危険因子の重積と内臓脂肪蓄積の観点からWerner症候群患者を改めて評価することにした．

遺伝子検索により確定診断を得た当院外来通院中のWerner症候群患者5人を対象に検討したところ[10](**表1**)，全例に高トリグリセリド血症，高インスリン血症とヘモグロビンA_{1c}の高値を認め，うち2例は高血圧を合併していた．BMIは5例中3例が正常範囲，2例が18.5以下の低値(すなわち'やせ')を示し，肥満はみられなかった．ところが，臍高部のX線CT撮影による腹部脂肪の評価では，5例中3例が内臓脂肪面積100 cm^2以上と内臓型肥満に相当し，残る2例も内臓脂肪/皮下脂肪面積比(V/S比)が0.4を大きく上回った．したがって，これらの患者は絶対的もしくは相対的な内臓脂肪蓄積状態にあると推察された．

b. 血中アディポサイトカイン異常とチアゾリジン誘導体の効果

Werner症候群における代謝性危険因子の重積に，腹部内臓脂肪蓄積との関連が示唆されたため，病態を理解する目的で，Werner症候群患者の血中アディポサイトカイン濃度を検討した．すると，本症候群患者では年齢をマッチさせた健常対照者に比べてTNF-α値が有意に高いこと(**図2-a**)，糖尿病を発症した本症候群の患者ではアディポネクチン値が著しい低値を示すことがわかった[11]．すなわちWerner症候群は，インスリン抵抗性と内臓脂肪の蓄積，耐糖

表1 Werner症候群患者の糖・脂質プロファイルと内臓脂肪

症 例	1	2	3	4	5
年齢（歳）/性別	52/男性	57/女性	54/男性	39/女性	46/女性
BMI（kg/m²）	21	17 ↓	20	20	17 ↓
高血圧	あ り	な し	な し	あ り	な し
T-CHO（mg/dl）	353 ↑	297 ↑	163	210	270 ↑
TG（mg/dl）	530 ↑	340 ↑	180 ↑	410 ↑	300 ↑
FPG（mg/dl）	92	98	128 ↑	210 ↑	198 ↑
HbA_{1c}（%）	6.0 ↑	7.2 ↑	6.8 ↑	7.4 ↑	8.4 ↑
空腹時IRI（μU/ml）	20 ↑	28 ↑	70 ↑	14 ↑	28 ↑
内臓脂肪面積（cm²）	175 ↑	96	75	134 ↑	112 ↑
V/S比（基準値<0.4）	1.5 ↑	2.2 ↑	2.6 ↑	0.9 ↑	0.7 ↑

BMI: body mass index, V: 内臓脂肪面積, S: 皮下脂肪面積.
（文献[10]および未発表データより作成）

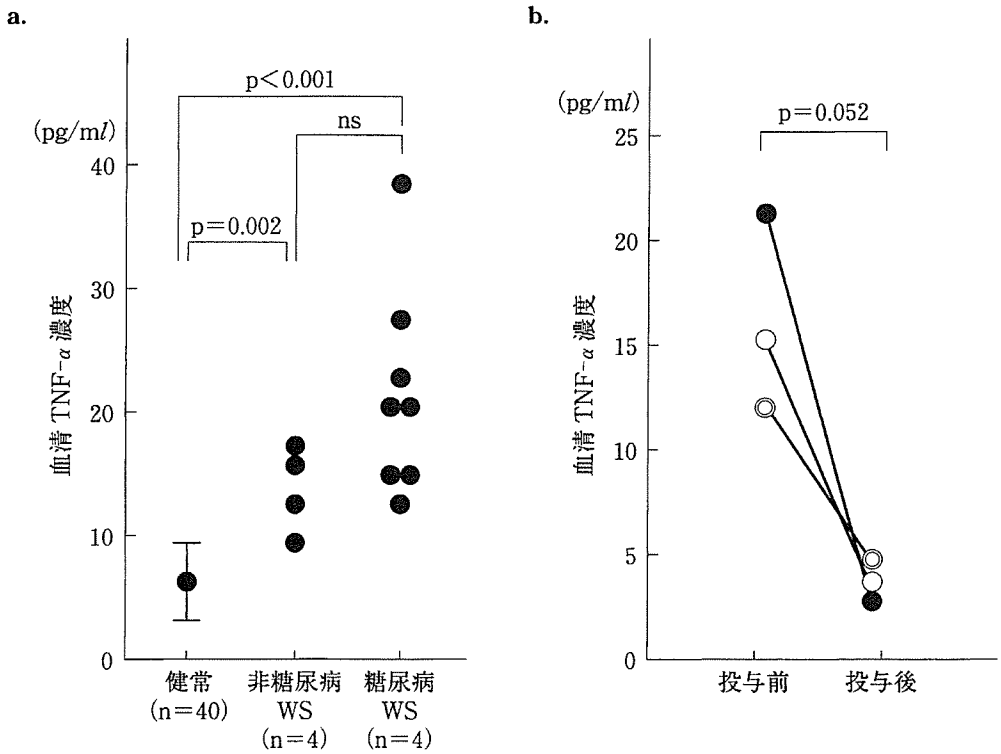

図2 Werner症候群患者の血中TNF-α濃度（文献[11]および未発表データより作成）
a: Werner症候群患者（WS）では，糖尿病の有無にかかわらず，健常コントロール（健常）に比べ血中のTNF-α濃度が有意に高値を示した．
b: 糖尿病を合併するWerner症候群患者3症例にピオグリタゾンを16週間投与したところ，血中TNF-α濃度の低下を認めた．

能障害，脂質代謝異常と高血圧を合併しやすく，メタボリックシンドロームに類する病態を呈することが明らかとなった．

脂肪細胞の分化を促し，インスリン感受性を改善させる薬剤としてPPARγ（peroxisome proliferator-activated receptor γ）のアゴニストであるチアゾリジン誘導体が用いられている．糖尿病を合併したWerner症候群患者にピオグリ