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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Survival period after tube feeding in bedridden older patients

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Aim: We prospectively studied survival periods after tube feeding.

Methods: Participants were 163 bedridden older patients suffering from dysphagia.

Results: A wide range of survival periods after tube feeding were observed within half a year without tube feeding after being bedridden. After this initial period, survival periods after tube feeding were limited to approximately half a year. Survival periods after tube feeding were positively proportional to the length of time patients were free from pneumonia after tube feeding. After tube feeding, patients died from pneumonia within half a year, and the frequency of pneumonia was 3.1 ± 2.7 times (mean ± SD) before death.

Conclusion: Survival periods after tube feeding for less than 1 year were primarily determined by being bedridden for more than half a year without tube feeding and once pneumonia occurred; patients who were tube fed did not survive for more than half a year. **Geriatr Gerontol Int 2012; 12: 317–321.**

Keywords: bedridden, dysphagia, frail older patients, terminal medicine, tube feeding.

Introduction

A rapid increase in the number of frail older patients in Japan forces us to confront the serious decision of whether or not to treat frail older patients with feeding tubes in the terminal stage.[1] In Japan, as a result of a combination of strong family emotions, religion, social traditions and public opinion, it is very common to place feeding tubes when patients are suffering from serious dysphagia. Kosaka *et al.* surveyed families who cared for bedridden older patients in the terminal stage as to whether the families would choose a feeding tube or not to treat patients with dysphagia.[2] As a result, approximately 90% of families caring for such patients refused the option of feeding tubes if the patients suffered from dysphagia. After receiving informed consent by explaining that approximately 90% of families had denied feeding tubes, the proportion of feeding tubes for bedridden older patients in the terminal stage decreased by half.[3]

In either case of refusing or accepting the option of feeding tubes, families wanted to know the prognosis after tube feeding. There have been conflicting reports on the clinical benefit of tube feeding for patients with dementia.[4,5] However, the situation of terminal care in Japan is quite different from Western countries. So far, there have been no studies on the survival period and factors that determine survival periods after tube feeding in Japan. Families might make a reasonable decision on the option of feeding tubes if the prognosis after tube feeding was explained. In the present study, survival periods after tube feeding and factors that determine survival periods in 163 bedridden older patients suffering from dysphagia were prospectively analyzed for as long as 7 years.

Methods

Eligible bedridden older patients were aged >65 years and were terminal patients who required tube feeding, because they had developed difficulty maintaining

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Table 1 Primary diagnosis for patients who underwent feeding tubes

Cerebrovascular disease	No. patients
Acute stroke	46
CVD without acute stroke	52
Degenerative disorder	
Alzheimer's disease	29
Parkinsonism	8
Others	1
Traumatic brain damage	4
Infections diseases	2
Hypoxic brain damage	3
Others	
Congestive heart failure	6
Postoperation	6
Bone fracture	3
Debility	1
Epilepsy	1
Ileus	1
Total	163

CVD: cerebrovascular disease.

Table 2 Direct cause of death

Diagnosis	No. patients (%)
Pneumonia	111
Other infections	17
Decrepitude	16
Heart disease	8
Renal disease	3
Malignant tumor	3
Bleeding of digestive organ	1
Cerebrovascular disease	1
Others	3
Total	163

adequate nutrition orally, and their cognitive function was extremely poor and not improving. Bedridden older patients were patients who suffered three to six limitations of the activities of daily living (ADL), including eating, getting in and out of a bed or chair, getting around inside the home, dressing, bathing, and using the toilet.[6] Patients stayed in a long-term care facility for several reasons, including physical and mental disabilities as a result of cerebral strokes and/or neurodegenerative diseases, and at the request of the patients' families. Primary diagnosis for patients who underwent feeding tubes is shown in Table 1. The clinical conditions of these patients continued to deteriorate to the point where they did not have any conscious awareness, although they occasionally opened their eyes and expressed voices. However, the eye movements and voices they expressed were not discernible. With the consent of team staff, including nurses and caregivers, we took informed consent from patients' families to accept the option of feeding tubes. For the purpose of the present study, we excluded patients who had metastatic cancer who were or were not receiving cancer therapy ($n = 7$), because cancer itself limits survival period. Patients with brain stem infarcts were also excluded from the present study ($n = 1$), because brain stem lesions usually lead to difficulties in swallowing and are therefore known to be a potential risk for pneumonia. All other patients with well-documented cerebral hemisphere stroke were included.

We prospectively followed up 163 patients in the terminal stage with dysphagia (80.9 ± 7.9 years, mean ± SD): 77 women (83.0 ± 7.5 years, mean ± SD) and 86 men (79.0 ± 7.5 years, mean ± SD) who were bedridden at Hikarigaoka Sperman Hospital, a geriatric long-term care facility in Sendai City, Japan. Eligible patients were followed up from 1999 to 2007, and examined for frequency of tube feeding and incidence of pneumonia or other infections, such as urinary infection, decubitus and other episodes. Criteria for diagnosis of pneumonia were: (i) a new pulmonary infiltrate seen on a chest radiograph; and (ii) one of the following features: cough, and temperature greater than 37.8°C or subjective dyspnea.[7] Antibiotics and hydrations were medicated for treating pneumonia following the clinical standard. The protocol adhered to the recommendation of the declaration of Helsinki for Human Experimentation (World Medical Association, 2000). Informed consent was taken in every patient at the entrance of the study.

Tube feeding was placed through percutaneous endoscopic gastric tube (PEG). After consensus with families, nasogastric tubes were initially placed in 23 patients, but nasogastric tubes were substituted with PEG when tube feeding was prolonged by more than 2 weeks. We included both patients with PEG and nasogastric tubes for 2 weeks, followed by PEG together in the following analysis. Survival periods after tube feeding correlated with the duration without tube feeding after being bedridden and the duration free from pneumonia after tube feeding. Data are expressed as mean ± SD. An analysis of variance (ANOVA) was carried out to correlate survival periods and was followed by the least significant deference test for multiple comparisons. A P-value less than 0.05 was considered statistically significant.

Results

Direct causes of death are shown in Table 2. Pneumonia was the most frequent cause of death. The average

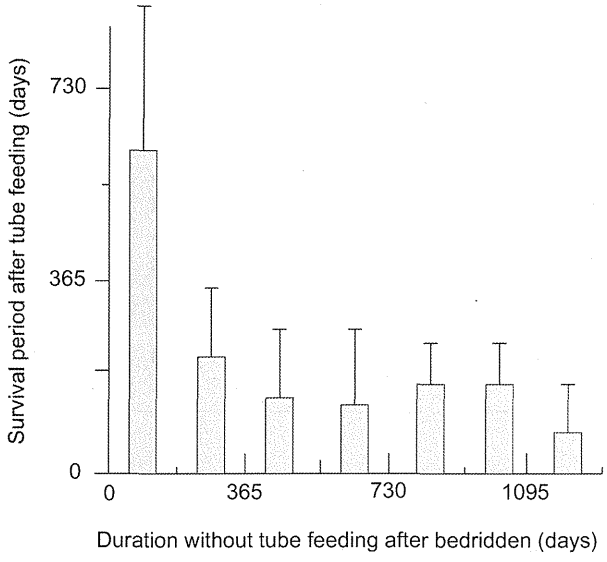

Figure 1 Average survival periods after tube feeding after half a year without tube feeding after being bedridden were significantly shorter than that before half a year ($P < 0.01$). Survival periods after tube feeding more than 3 years without tube feeding after being bedridden are summarized.

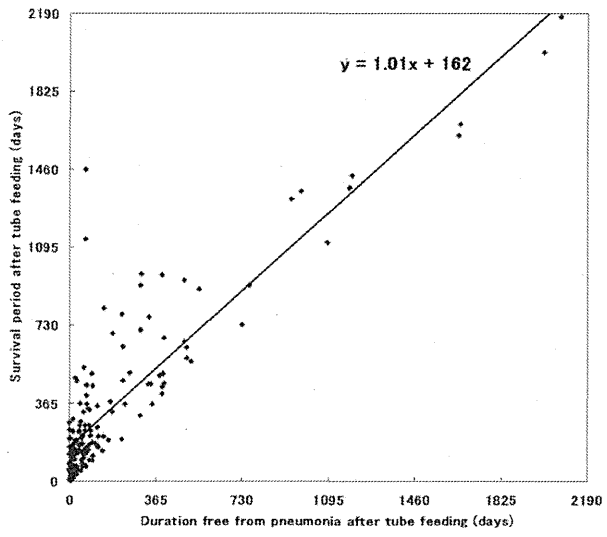

Figure 2 Survival period after tube feeding (y) was proportional to duration free from pneumonia after tube feeding (x), as $y = 1.01x + 162$ ($P < 0.001$).

survival period after tube feeding was 377 ± 35 days. The average survival period after tube feeding was more than one and half a years within half a year without tube feeding after being bedridden (Fig. 1). Average survival periods after tube feeding were approximately half a year or less after half a year without tube feeding after being bedridden. Survival periods after tube feeding (y) were positively proportional to length of time free from pneumonia after tube feeding (x) as $y = 1.01x + 162$ ($P < 0.001$; Fig. 2). Average survival periods after pneumonia were 156 ± 16 days. A total of 104 patients suffered from pneumonia before tube feeding, whereas 59 patients did not suffer from pneumonia before tube feeding. A previous history of pneumonia before tube feeding significantly shortened survival periods after tube feeding (279 ± 34 days) compared with patients without a previous history of pneumonia (554 ± 70 days; $P < 0.001$). After tube feeding, there were no significant differences in survival period after pneumonia between patients with and without a previous history of pneumonia before tube feeding, and both patients with and without a previous history of pneumonia are included in Figure 2. Frequencies of pneumonia after tube feeding averaged 3.1 ± 2.7 (mean ± SD) times and were independent of period after tube feeding. As the average survival period after tube feeding was approximately 1 year, the relative impact for a survival period less than 1 year (where less than 1 year and more than 1 year corresponded to 0 and 1, respectively) versus sex, age, primary diagnosis for patients, previous history of pneumonia before tube feeding, urinary infection, decubitus and duration of being bedridden of more than half a year without tube feeding were assessed using multiple logistic regression (where sexes of male and female corresponded to 0 and 1, ages more than 80 years and less than 80 years corresponded to 0 and 1, primary diagnosis of patients of cerebrovascular diseases and the others corresponded to 0 and 1, positive and negative previous history of pneumonia before tube feeding corresponded to 0 and 1, positive and negative urinary infection corresponded to 0 and 1, positive and negative decubitus corresponded to 0 and 1, and duration of being bedridden of more than half a year without tube feeding and less than half a year corresponded to 0 and 1, respectively). Multiple logistic regression of the relationship between survival period after tube feeding less than one year and duration of being bedridden of more than half a year without tube feeding was significant (odds ratio = 8.4; 95% CI 2.3–30.5, $P < 0.001$), and was not significant for other factors.

Discussion

In the present study, it was suggested that after being bedridden for more than a half year, feeding tubes could prolong the survival period by only half a year. For patients suffering from pneumonia after tube feeding, the average survival period was shorter than half a year, during which the patients suffered from frequent pneumonia and died. There have been contradictory reports

on the effect of tube feeding on the prevention of pneumonia. Survival after tube feeding was variable and survival was over a year in many of the patients.[8] In contrast, Murphy and Lipman suggested no survival benefit in patients with dementia who received artificial feeding by percutaneous endoscopic gastrostomy.[9] Tokunaga *et al.* suggested that a feeding tube neither reduces aspiration pneumonia nor improves survival in patients with a history of pneumonia.[10] Finucane *et al.*[4] reviewed whether tube feeding in patients with advanced dementia can prevent aspiration pneumonia, prolong survival, reduce the risk of pressure sores or infections, improve function, or provide palliation. They found no evidence to suggest that tube feeding improves any of these clinically important outcomes. Furthermore, the risk was substantial. They suggested that the widespread practice of tube feeding should be carefully reconsidered, and for severely demented patients the practice should be discouraged on clinical grounds. In patients aged more than 80 years, the ratio of aspiration pneumonia was approximately 90% in hospitalized pneumonia.[11] Nakajoh *et al.* found that tube feeding might be beneficial in patients with dysphagia, but when protective reflexes of aspiration, such as swallowing and cough reflexes, were degraded beyond certain thresholds, tube feeding could not prevent pneumonia anymore.[12] In the present study, we observed that pneumonia determined the survival period after tube feeding. It is likely that once pneumonia had developed under tube feeding, as a result of severely impaired protective reflexes of aspiration beyond certain thresholds, tube feeding was no longer effective to prevent pneumonia[13,14,15].

The prevalence of tube feeding has not been consistently reported.[16] According to the Ministry of Health and Welfare statistics in Japan in 2008, approximately 70 000 patients were tube fed per year. Of the 70 000 patients, more than 60 000 frail older patients were tube fed. The difference in the acceptance of tube feeding between the reality of being tube fed and the thought of rejecting tube feeding might be a result of Japanese morals. Japanese families find it hard to accept death, even in patients who have severely impaired cognition, no will and who are bed bound.[17] Rejecting tube feeding in approximately 90% of the families caring for these terminal patients might decrease tube feeding by half.[3] Onishi *et al.*[18] reported that approximately half of families were satisfied with gastrostomy tube feeding. The quality of informed consent for placement of the gastrostomy tube was inadequate in a large community-teaching hospital.[19] The present prognostic date might support the options to be decided by families as to whether or not to allow tube feeding. The present study might be important in constructing a medical consensus of life-extending care in terminally ill older patients.[20]

Acknowledgments

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Disclosure statement

The authors declare no conflict of interest.

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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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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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A big unmet need : Are we able to make a dementia-free society?

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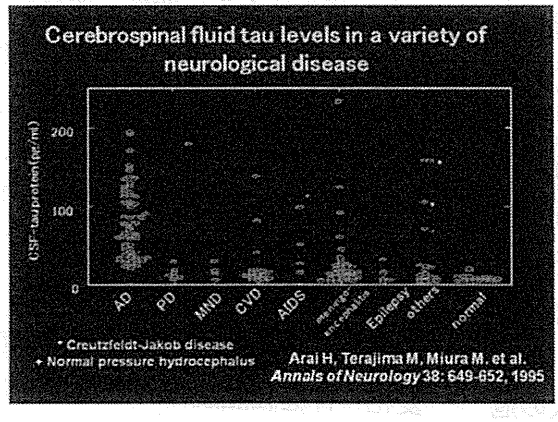
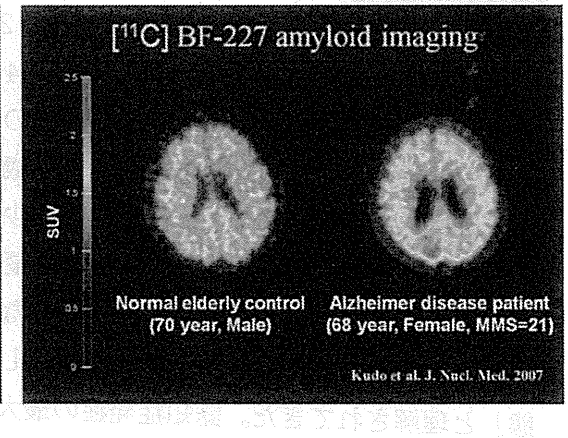
At present time, Alzheimer's disease (AD) drug development is costly and requires a considerable length of time. Trials of disease modifying drugs designed to slow the rate of decline necessary to demonstrate disease modification require at least one year of treatment or longer to see adequate clinical endpoints. The clinical diagnosis of AD is occasionally imprecise using consensus criteria for probable AD, and definite AD requires autopsy confirmation. Diagnostic accuracy is far lower at early and pre-symptomatic stages of AD when confusion with other dementias is common. Since therapy is likely to be most effective at symptom onset, early diagnosis of AD is highly desirable before a massive neurodegeneration becomes obvious. Thus, there is a great need for simple biomarkers that substantially aid early diagnosis and track disease progression of AD and mild cognitive impairment. Of currently available biomarkers for AD, imaging and cerebrospinal fluid biomarkers are of great importance. In particular, in Vivo detection of brain amyloid burden using positron emission tomography either by PIB or BF-227 would be attractive. The use of such ideal biomarkers could markedly speed up drug development by providing an earlier signal of drug efficacy.





Dementia , Alzheimer's disease , Biomarker development , Amyloid imaging , Cerebrospinal fluid , Traditional Medicine , Disease modifying therapy

Collaborative Researchers >> YANAI, Kazuhiko Professor (Department of Pharmacology, Graduate School of Medicine)
KUDO, Yukitsuka Professor (Innovation of New Biomedical Engineering Center)

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東北大学加齢医学研究所脳科学研究部門老年医学分野
教授　荒井　啓行

高齢化率すなわちある国の65歳以上の高齢者が全人口に占める比率が７％～14％の社会を高齢化社会、14％～21％を高齢社会、21％を超える場合を超高齢社会と呼ぶ。平成24年版高齢社会白書によれば、2011年のわが国の高齢化率は23.3％で、平均寿命は、男性79.6歳、女性86.4歳となった[1]。日本は世界で最も少子高齢化が進んだ超高齢社会である。一方、認知症とは「一度獲得された知的機能の後天的な障害によって、自立した日常生活機能を喪失した状態」と理解されてきた。認知症発症の最大の危険因子は加齢であり、認知症の中で60％以上を占め最も多い原因疾患とされるアルツハイマー病（Alzheimer' s disease, AD）が激増している背景はこの高齢化にある。日本は2007年以来人口減少社会に入っているが、75歳以上の後期高齢者層だけは増え続けている。2050年には高齢化率は40％に達すると予想される。ADとはどのような病態なのか。増え続けるADにどのように向き合い対応策を考えるべきであろうか。世界各国の多くの研究者の努力によってADの生化学的・分子遺伝学的理解はこの20年で飛躍的に進んだ[2]。AD脳では顕微鏡下に老人斑と神経原繊維変化が観察される。1984年、米国のGlennerらはAD脳髄膜血管から分子量約４kDaの蛋白をHPLC精製し、そのN末側24アミノ酸配列を決定した。翌年1985年、オーストラリアのMastersらによって同じペプチドがAD脳老人斑コアからも単離精製された。今日のアミロイドβ（Aβ）蛋白である。一方、神経原繊維変化の構成要素の同定はその著しい不溶性から困難を極めた。神経原繊維変化はそれまで免疫学的に神経特異的中間径線維であるニューロフィラメントによって構成されていると考えられてきたが、1980年代後半からは、日本のIhara、米国のLeeなどの研究者によって微小管関連蛋白であるタウ蛋白が高度にリン酸化されたため微小管結合能を失い脱落し神経細胞内の至る所で凝集・不溶化したものと理解されるに至った。老人斑と神経原繊維変化に加えて広範で高度な神経細胞脱落も認められる。これらの神経病理所見を一元的に説明するものとして、2002年HardyとSelkoeによってアミロイド仮説が提唱された[3]。アミロイド仮説とは、Aβ蛋白を起点として神経毒性→シナプス障害・神経原線維変化・神経細胞脱落→認知症としてAβ蛋白を根本的発症原因に最も近いものととらえ、カスケードの最上流に置き整然と理論化する考え方である。アミロイド仮説が生まれた背景にはAβ蓄積のADにおける高い疾患特異性がまず挙げられる。神経原繊維変化はAD以外にも、進行性核上性麻痺や皮質基底核変性症などの神経変性疾患やNiemann-Pick病などの先天性代謝異常

症など多彩な病気において出現する。これに対して老人斑アミロイドや脳血管アミロイドのようなAβ蓄積は、正常者、ADとダウン症に限って出現する。さらには、非認知症老人の剖検大脳皮質の連続切片をタウ免疫染色とAβ免疫染色で比較すると、不溶化し始めたAβ蛋白は多数のび慢性老人斑として沈着を始めているが、この段階ではタウ蛋白は全く沈着していない、つまり神経原繊維変化は形成されていないことが示された。しかもこの逆、つまりタウが陽性でAβが陰性というAD症例はいくら探しても見つからなかった。つまりAβ蛋白とタウ蛋白の変化には時間差があり前者が先行していることが示された。同様のことはアルツハイマー病のヒトモデルとされているダウン症脳においても観察される。また、Aβ蛋白前駆体をコードするアミロイド前駆体蛋白遺伝子は1988年にクローニングされ、第21番染色体上に存在することがわかっていたが、常染色体性優性遺伝形式を示すいくつかの家族性アルツハイマー病家系において、アミロイド前駆体蛋白遺伝子上にアミノ酸置換を伴う点突然変異が発見され、この変異によりAβ蛋白の産生過剰や産生異常がもたらされ家族性アルツハイマー病を発症することが明らかにされた。同じく常染色体性優性遺伝形式を示す家族性アルツハイマー病家系の原因遺伝子として同定されたプレセニリン-1遺伝子産物は、AβのC末端側の多様性を生む酵素であるγセクレターゼの構成成分となっていることが明らかにされたことである。家族性アルツハイマー病家系を対象にしたDIAN研究では、Aβ蓄積を反映して臨床症状出現の25年前から脳脊髄液Aβ42は低下し始め、アミロイドPET陽性となることが示された[4]。

2012年3月31日を以ってJapanese Alzheimer's Disease Neuroimaging Initiative（J-ADNI）の被験者の登録を終了した。腰椎穿刺同意率38%、FDG-PET同意率66%、アミロイドPET同意率41%と高い検査実施率を達成した。これら一連のJ-ADNI研究の成果として、正常として登録された高齢被験者の中から高率に脳脊髄液Aβ42濃度が低下し、かつアミロイドPETが陽性（さらには脳脊髄液総タウやりん酸化タウ濃度が上昇）であるものが見いだされている。バイオマーカー陽性者がすべて生前ADを発症するとは限らないが、バイオマーカーを追跡することにより正常を逸脱しADへと向かう初期段階を確実に捕捉することができるようになった。ADNIのバイオマーカー研究成果を基盤に今後の治験は国際共同治験の形をとって、初期ADから軽度認知障害、さらには軽度認知障害から発症前のADへとより軽症段階をターゲットとするものと思われ、将来は家族性アルツハイマー病家系で遺伝子変異キャリアーやApoE４遺伝子保有者などリスクの高い予備軍への先制医療や予防介入研究も視野に入れることが可能と思われる、米国ではAlzheimer Prevention Initiativeなど大きなプロジェクトが動き始めた。2010年からアルツハイマー病協会とNIA（米国国立老化研究所）は共同してアルツハイマー病の概念をリニューアルする試みを進めている[5、6]。つまり、アルツハイマー病は認知症としての症状がなくてもそのプロセスが始まったことの証拠（アミロイドイメージング陽性所見や脳脊髄液バイオマーカーの異常所見など）が認められれば、臨床症状がない段階であってもADと見なすという大胆な提案である。

大規模疫学調査からもいくつかの重要な示唆が得られている。中年期（40～65歳）の高血圧は高齢期（65歳以降）の認知症あるいはアルツハイマー病発症の危険因子であるため、積極的に治療すべきとされるようになった[7]。しかし、高齢期になってからの降圧治療が認知症予防に有効であることは明確にできなかった。久山町研究では、高血圧はアルツハイマー病の危険因子ではなかったが、糖尿病はアルツハイマー病

や血管性認知症の強い危険因子であった。スタチンを用いたコレステロール低下療法がアルツハイマー病予防となる明瞭なエビデンスは示されていない。一方、習慣的運動に関しては、認知症のない33,816名を対象に行われた15の試験をメタ解析し、ハザード比0.62で運動の予防的効果が示された[8]。日本神経学会監修の「認知症治療ガイドライン」でも運動は「認知症予防に科学的根拠があり行うよう積極的に勧める」とされている[9]。最近、運動がアミロイド蓄積を抑制する効果を持つことを示唆するいくつかの研究も報告されている[10、11]。

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prescribed an additional treatment of 5 mg of imidapril daily. Her swallowing reflex latency time normalized after ACE inhibitor treatment. She had been hospitalized three times because of COPD exacerbations in the previous year and experienced two exacerbations during the 6.1 years of follow-up.

In addition to the regular treatment of COPD, ACE inhibitor treatment improved the swallowing reflexes of these individuals and reduced the frequency of COPD exacerbations (from 3 to 0.46 per year in case 1, and from 3 to 0.33 per year in case 2). The patients had not recognized their impaired swallowing reflexes, because they were on entirely oral diets without complaints of dysphagia and had no prior history of symptomatic stroke or oropharyngeal or esophageal abnormalities.

Aspiration is associated with impairment of swallowing and cough reflex, which is mediated through substance P.[2] ACE inhibitors decrease the catabolism of substance P, resulting in prevention of aspiration[5,6] and protection against pneumonia in older adults.[6–8] The findings of the current study suggest that ACE inhibitors protect against aspiration tracheobronchitis and exacerbations of COPD.

ACE inhibitors have also been demonstrated to have beneficial effects on the heart,[9] although the follow-up examination of these individuals, including electrocardiogram and echocardiogram, did not indicate a significant change. The blood pressure of these individual did not decrease significantly during the follow-up period. Although symptomatic hypotension has been reported to be rare,[10] one should be careful about adverse effects of ACE inhibitor treatment in older adults.

ACE inhibitor therapy is a potential option for preventing COPD exacerbations in selected individuals with impaired swallowing reflexes. Large randomized controlled clinical trials will be useful.

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RESEARCH STUDIES

SHELTER-ACQUIRED PNEUMONIA AFTER A CATASTROPHIC EARTHQUAKE IN JAPAN

To the Editor: At 2:46 p.m. on March 11, 2011, a magnitude 9.0 earthquake hit the northeast part of Japan followed by enormous tsunamis, which destroyed many of the coastal cities. The tsunamis, which reached as high as 10 to 38 meters, completely destroyed more than 90% of dwellings. A large number of hospitals and nursing homes were also destroyed. Although more than 1 month had passed after the worst disaster in Japan's history, uncountable aftershocks continued as of April 18.

According to a report from the National Police Agency, more than 13,000 deaths were confirmed, and more than 14,000 people were still missing. Furthermore, 150,000 people were still forced to live in 2,400 shelters, such as gymnasiums and school halls, 40% of whom were aged 65 and older. These refugees were exposed to cold, unhygienic conditions and malnutrition because of power failures, insufficient food supply, and lack of running water. Under unfavorable circumstances, the refugees faced the threat of disease. As time went by, the number of individuals with respiratory diseases increased. Many older people were transferred to backup hospitals because of pneumonia from shelters located in severely damaged areas. Tohoku University Hospital was one of the backup hospitals.

To clarify clinical features of the new-onset pneumonia in refugees, called shelter-acquired pneumonia (SAP), the medical records of 17 individuals transferred to Tohoku University Hospital were examined. The mean duration of time living at a shelter until the onset of pneumonia was 15.2 ± 5.1 days. The mean age of the individuals was 81.6 ± 4.2 (male:female ratio 14:3). All of the individuals had a history of cerebrovascular accident or

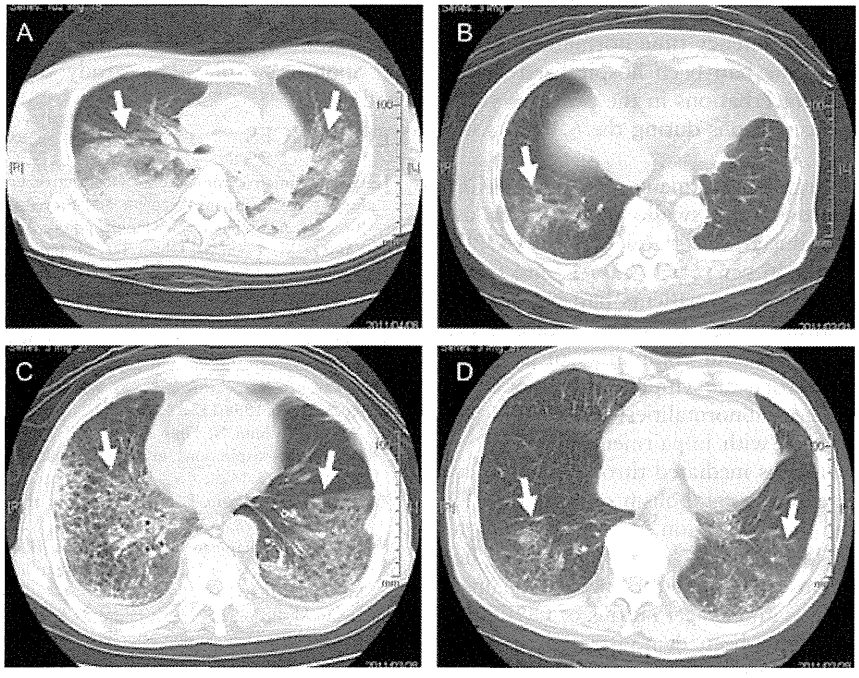

Figure 1. Chest computed tomography scans of four randomly selected individuals showed that the consolidation was distributed prominently in the lower part or back of both lungs (A, C, D) or in one lung (B).

neurodegenerative disorder with frailty. Laboratory examination on admission revealed low serum albumin (2.6 ± 0.8 g/dL) and cholesterol (110 ± 24 mg/dL) levels, low peripheral blood lymphocyte count (1,032 ± 527/μL), and high serum C-reactive protein levels (21.1 ± 14.6 mg/dL). Urine pneumococcal antigen was positive in three of these individuals. The individuals had prolonged swallowing reflexes (4.1 ± 0.6 seconds (normal < 2.0 seconds)) and low sensitivities of cough reflex (2.1 ± 0.5 log mg/mL (normal < 0.5 log mg/mL)), indicating higher risk for silent aspiration.[1] The chest computed tomography scans of the individuals showed that the consolidation was distributed prominently in the lower part or the back of the lung (Figure 1). These results suggest that silent aspiration might have triggered the pneumonia. The shelters were so crowded that people were forced to sleep on the narrow floor in a supine position and could not turn over during sleep. Furthermore, they hesitated to cough to avoid making noise in the shelter. Most of the individuals did not pay attention to oral care such as tooth brushing or cleaning false teeth. Oropharyngeal secretions containing bacteria might easily have gone down along the bronchial trees by gravity to the back and augmented pneumonia during sleep.

A previous survey reported that the major illnesses leading to hospital admission after the devastating earthquake were pneumonia, dehydration, heart failure, asthma attacks, peptic ulcer, cerebrovascular diseases, and ischemic heart disease.[2,3] This report focused on the cause of pneumonia and found that pneumonia in older refugees might have occurred because of impaired oral hygiene, frequent aspiration, undernutrition, and cold temperatures under unfavorable circumstances. It has previously been shown that oral care can decrease the prevalence of pneumonia in older institutionalized individuals.[4] Oral care might be important for preventing pneumonia in refugees living in shelters.

The final incidence of pneumonia in older refugees living in shelters remains unknown because the number of individuals is still increasing, but a previous report described that the hospital admission rate due to pneumonia was significantly correlated with destruction ratios of dwellings, suggesting that pneumonia occurred frequently in refugees living in shelters.[2] Furthermore, morbidity in those living in shelters was five times as high as in persons who remained in their own dwellings.[2] This current observation might provide additional insight into how life in a shelter affects the onset of pneumonia.

Insufficient support for many dependent older people and those with dementia who live in shelters will be a major concern in the near future. Investigation of a continuous care delivery system for these people will be a new challenge. We sincerely need your suggestions and ideas to allow us to facilitate long-term medical support to elderly refugees living in shelters.

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POPULATION-BASED SMOKING TRENDS IN OLDER ADULTS: THE MINNESOTA HEART SURVEY

To the Editor: As the population ages, there is a need to reevaluate current cardiovascular disease (CVD) prevention practices in older adults. Although the benefits of smoking cessation and of smoking abstinence in older adults are well established,[1–3] physicians are less likely to assess smoking status in older adults,[4] advise older adults to quit,[5] or introduce lifestyle modification for CVD prevention in older adults.[2] The study of smoking practices and their trends in older adults may help illustrate the importance of addressing smoking in this population. The present study examined cigarette smoking trends in a population-based sample of Minnesotans aged 75 to 84.

The Minnesota Heart Survey (MHS) has been described previously.[6] Briefly, it is a population-based surveillance study of CVD risk factors in residents of Minneapolis and Saint Paul (2000 census: 2.6 million). MHS has completed six surveys (1980–1982, 1985–1987, 1990–1992, 1995–1997, 2000–2002, and 2007–2009); the last four surveys included participants aged 75 to 84. The institutional review board of the University of Minnesota provided ethical approval, and participants provided informed consent.

Population-based sampling involved a two-stage strategy. The metropolitan area was divided into census-defined clusters, and households were then randomly selected within included clusters. Participants completed a home interview and a clinic visit. A total of 268, 318, 142, and 145 adults aged 75 to 84 participated in both components of each of the four most recent surveys, respectively.

Smoking status was assessed according to self-report. In earlier surveys, smoking status was validated using serum thiocyanate level. Validation was not performed in the 2007–2009 survey because of high concordance with self-report in previous surveys.[6] Sex-specific trends were examined using generalized linear mixed models that contained a random effect to account for the clustered sampling. Age-adjusted prevalence was estimated for an age of 80.

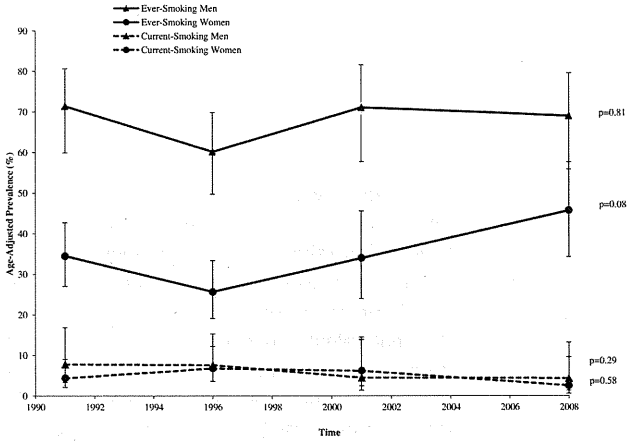

Figure 1. Population-based trends in age-adjusted prevalence of current and ever smoking in men and women aged 75 to 84 participating in the Minnesota Heart Survey. Data were plotted at the midpoint of each survey, and models were age-adjusted using generalized linear mixed models and setting the age term to 80. *P*-values are for linear trends.

Participants were predominantly Caucasian (range: 98.5–100%), and the majority were women (53.8–67.9%). The median age varied from 77.4 to 78.9.

The overall prevalence of current cigarette smoking was less than 8% in all surveys and did not change substantially over time ($P = .36$). In the 1990–1992 survey, the prevalence of current smoking was 7.8% in men and 4.4% in women (Figure 1). By the 2007–2009 survey, it was 4.3% ($P = .29$) and 2.5% ($P = .58$), respectively. Combining the four surveys, 20 of 23 currently smoking men and 27 of 28 currently smoking women smoked 20 cigarettes or fewer per day.

The prevalence of ever smoking increased in women across surveys ($P = .08$) (Figure 1). This increase was due to a greater prevalence of past smoking ($P = .04$). In contrast, the prevalence of ever ($P = .81$) and past ($P = .44$) smoking was consistent across surveys in men.

Past smokers reported quitting at increasingly younger ages. In men, the reported quitting age decreased from 50.7 in the 1990–1992 survey to 44.6 in the 2007–2009 survey ($P < .001$). In women, it decreased from 56.0 to 45.7 ($P < .001$). The prevalence of quitting for health reasons was 25.0% in the 1995–1997 survey and 38.2% in the 2007–2009 survey in men ($P = .38$) and 45.5% and 40.7% in women, respectively ($P = .86$).

The benefits of smoking cessation and abstinence in older adults include lower morbidity and mortality due to CVD and smoking-related cancers, better physical function, and higher quality of life.[1–3] Many of these benefits occur within 1 to 2 years of quitting.[1,3] Although the prevalence of smoking has remained consistent over the last 20 years, the absolute number of elderly smokers is increasing as the population ages. Given the high underlying CVD risk in older adults, the absolute number of

We agree with L H Opie that, in individuals without previous vascular events, both the relative and absolute reductions in risk of death due to cancer on aspirin versus control are larger than the equivalent reductions in risk of fatal vascular events, and that effects on cancer outcomes will dominate the overall risk/benefit equation, particularly when the delayed effects on cancer death beyond the end of the trials is also factored in.

I have received honoraria for talks, advisory boards, and clinical trial committees from several pharmaceutical companies with an interest in antiplatelet agents, including AstraZeneca, Bayer, Boehringer Ingelheim, Sanofi-Aventis/Bristol-Myers Squibb, and Servier.

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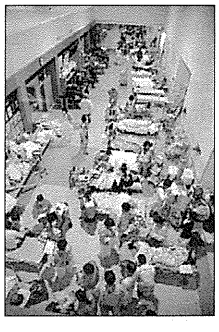

Reuters

Earthquake in Japan

At 1446 h on Friday, March 11, a magnitude 9·0 earthquake hit the northeastern part of Japan, followed by enormous tsunamis, which destroyed many of the coastal cities. Uncountable aftershocks continued even as late as April 27, and more than 10 000 people are still missing.

Japan experienced another strong earthquake in 1995, which caused serious damage in the Kobe area; however, the recent one is distinct from that. The area around Kobe is more clustered and has a denser population than the northeast coastal area, but the number of casualties this time is reported to be much larger than that of Kobe. This discrepancy is because Kobe's earthquake happened directly above its epicenter, but the recent one's epicenter was located beneath the sea and caused huge tsunamis. Most of the casualties were killed by the tsunamis this time, but the victims of Kobe's quake were due to collapses and fires.

Of course emergency medicine for the victims took first priority; the management of chronic illness and mental problems, however, is also a big issue now. Many, even those who did not have a major acute injury or illness, could not source enough medicine for their chronic illnesses such as hypertension, diabetes, thrombosis, Parkinson's disease, etc. In addition to physical problems, the number of people who need psychological support is not small. We saw a woman who was afraid emergency helicopters would fall on her, a teenage girl with hyperventilation syndrome and terrible anxiety and shivering, and a Parkinson's disease patient who could not move at all because he ran out of medicine.

The initial chaos has now abated somewhat, but medical needs are still high in Japan. Your support and help is welcome.

We declare that we have no conflicts of interest.

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Since the massive earthquake and consequent tsunami in eastern Japan on March 11, 2011, the resulting catastrophic damage has been apparent to the world. The secondary disaster is just in its infancy—that is, how to supply and manage stable medical resources for patients with chronic diseases.

Our patients on continuous-infusion prostacyclin for pulmonary hypertension were a particular concern. Forming a supply chain for such drugs in the earliest stages of the disaster was difficult; however, we found that social networking services could have a useful role. In the aftermath of the earthquake, telephone networks were unreliable even in the metropolitan areas. However, the internet was comparatively stable and thus enabled communication by email, Skype, and Twitter.

Twitter has an excellent system for disseminating information to other participants via the "re-tweet" facility. This system facilitates rapid sharing of other participants' messages with all of one's followers, resulting in an exponential proliferation of information dispersal. We were able to notify displaced patients via Twitter on where to acquire medications. These "tweets" immediately spread through patients' networks, and consequently most could attend to their essential treatments.

Obviously, direct human assistance available in parallel with the social media was also important for patients' care. Health-care providers and medical service staff went the extra mile to collaborate and deliver oxygen and drugs. We delivered prostacyclin to one patient by helicopter. Together, these efforts ensured that all patients on prostacyclin treatment received their required medication.

Our experience has shown that social networking services, run concurrently with physical support, were significant in triumphing over many difficulties in the recent catastrophe.

We declare that we have no conflicts of interest.

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A magnitude 9·0 earthquake struck the northeast mainland of Japan on March 11. In the affected areas, essential services such as water and electricity supplies were largely destroyed.

In such circumstances, haemodialysis therapy is extremely difficult. However, dialysis patients cannot survive without receiving regular dialysis. Thus, about 600 dialysis patients left Iwaki, a city located only 40 km south

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EDITORIAL

A comprehensive strategy for dementia from primary prevention to end-stage management

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On the afternoon of 11 March 2011, as I was writing this editorial comment, the 9.0-magnitude earthquake hit the north-east part of Japan.[1] Coastal cities and towns in Miyagi Prefecture and neighbouring Iwate and Fukushima prefectures were unimaginably damaged by tsunamis. It has been estimated that over 25 000 people lost their lives or are missing. Most of the victims are reported to have drowned.[2] I was deeply heartbroken that many precious lives were cut short; I pray for them in this time of immeasurable loss. I was worried about my son because I could not reach him by phone for 5 days, but fortunately he was safe. The temperature inside our institute dropped to below freezing in the mornings and evenings because the heating system broke. During this time, I uneasily continued writing at the institute while eating supplied rice balls and being frightened by frequent aftershocks.

CURRENT PRACTICAL APPROACH TOWARD ALZHEIMER'S DISEASE

Over the past 20 years, our understanding of the molecular pathology of dementia disorders has deepened, and new diagnostic techniques and therapeutic strategies have been developed.[3] However, the number of patients with dementia has been rapidly increasing, reflecting the advent of the super-aged society, which has a strong effect on the health-care system and medical economy. Currently, 27 million people in Japan, more than 23% of the population, are 65 years or older. To cope with these demographic shifts, Tohoku University Hospital's outpatient Department of Geriatrics & Gerontology opened a memory clinic in 1991 for patients with memory loss. Many other memory clinics have subsequently opened throughout Japan. In addition, both the Japanese Psychogeriatric Society and the Japanese Society of Dementia Research have established educational programs to ensure that physicians have the expertise necessary to treat dementia patients.

From its earliest stages, dementia has a lifespan of approximately 30 years. Figure 1 outlines the life of the disease, spanning from an individual's cognitively healthy condition to the development of dementia and death, as well as important medical issues in each phase. The first two-thirds of the chart cover 20 years during which a healthy person gradually changes and develops a mild cognitive impairment and dementia. The latter third covers 10 years, over which dementia progressively worsens from mild stage to advanced stage and eventually leads to death. In patients with Alzheimer's disease, the first change in the brain is believed to be triggered by aggregation and accumulation of a small hydrophobic peptide called amyloid-β protein that is known to be toxic to neurons.[3] Toxicity may develop extremely slowly, inducing abnormal phosphorylation and polymerisation of tau protein, loss of microtubule function and eventually neuronal death. The clinical symptoms such as memory loss first become obvious when the residual ability of surviving neurons is outpaced by neuron death. For dementia

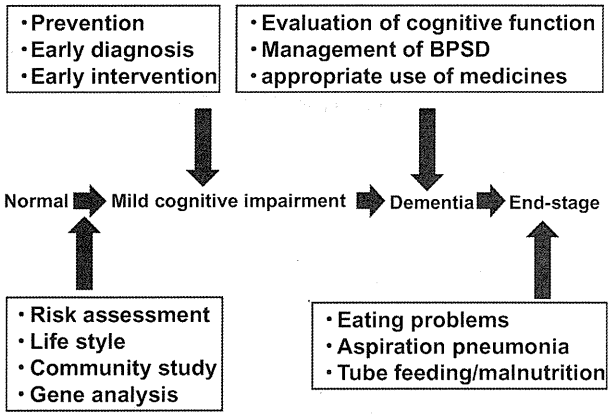

Figure 1. Several important issues at various stages of dementia are shown in a timeline beginning with the development of dementia in healthy persons and ending at the terminal stage and death. Medical assessment of dementia should be a persistent and comprehensive process involving prevention of dementia in the pre-symptomatic stage, pharmacological and non-pharmacological treatment, and treatment of eating problems, aspiration pneumonia and nutritional problem in the end-stage. In the future, the treatment framework for dementia will shift from treatment after cognitive decline begins to prevention with preemptive therapy for high-risk individuals.

in general, understanding of pathological conditions has increased along with our growing knowledge of molecular species that accumulate in the brain, such as α-synuclein in dementia with Lewy bodies and TDP-43 in frontotemporal lobar degeneration.

To fight dementia, it is essential that doctors approach treatment with a clear understanding of the entire process, from primary prevention and preemptive care to end-stage management. Since all people do not develop dementia, it is important to know the risk factors, including genetic predisposition and environmental factors, related to the development of dementia. For this purpose, a prospective cohort study with healthy community residents is valuable. The strongest genetic risk factor widely confirmed in a large-scale epidemiological study was the apolipoprotein (Apo)E4 gene. Along with biomarker development, including amyloid imaging techniques, the Alzheimer's Disease Neuroimaging Initiative has shown that amyloid-β protein may begin to accumulate in people with the apoE4 gene in their 50s, when their cognitive function is subjectively and objectively still considered to be normal.[4,5] Furthermore, several prospective cohort studies have clarified the close relationship between dementia development and mid-life lifestyle, specifically factors such as physical exercise and social engagement.[6,7] Amyloid imaging, fluorodeoxyglucose-PET, and cerebrospinal fluid biomarkers have contributed to early detection of dementia by acting as surrogate biomarkers that reflect the underlying pathological process.[8,9] In the future, standardisation and quality control of biomarkers in clinical trials of new drugs will be needed.

In 2011, new pharmacological treatments for dementia were released in Japan for the first time since 1999, when donepezil hydrochloride developed by Mr Hachiro Sugimoto of Eisai Co., Ltd. (Tokyo, Japan) was approved. Three new drugs, including two cholinesterase inhibitors and one *N*-methyl *D*-aspartate receptor antagonist, have become available for symptomatic treatment of Alzheimer's disease. Though they were released at least 10 years ago in the USA and Europe, the launch of these new drugs in Japan increased the options for the treatment of dementia. It is anticipated that general physicians will use anti-dementia drugs more frequently, but if they have little experience with diagnosing and treating dementia, doctors should introduce their patients to memory clinics to ensure that the treatment is appropriate for the diagnosis. In actual clinical practice, physicians require a large body of knowledge pertaining to management of lifestyle-related diseases,[6] diagnosis of rare dementia such as prion disease, differential diagnosis for depression and delirium, pharmacological and non-pharmacological approaches to behavioural and psychological symptoms of dementia,[10] and information on the safety/adverse effects of drug treatments, particularly with regard to older patients.[11]

DEVELOPMENT OF DISEASE-MODIFYING DRUGS AND PREEMPTIVE THERAPY

Many clinical trials of disease-modifying drugs have been suspended or unsuccessful.[12] Disease modification is a therapeutic method that aims to produce clinical benefits by stopping or delaying the process of nerve cell death and damage to nerve function. The clinical trial of active immunisation of amyloid (AN-1792) was suspended due to the serious adverse effect of autoimmune meningoencephalitis. Although a Phase II clinical trial of bapineuzumab, a passive immunisation of humanised monoclonal antibodies to amyloid, was performed in patients with mild to moderate Alzheimer's dementia for 18 months, no efficacy was observed on cognitive function or daily activities.

At present, a Phase III clinical trial comparing subject groups with apoE4 gene to those without the gene is being performed. The clinical trial of semagacestat, a γ-secretase inhibitor, was highly anticipated, but it has been discontinued because members of the active treatment group experienced a significant decrease in cognitive function and developed skin cancer; this did not occur in the placebo group. Phase III clinical trials were completed for tramiprosate, an amyloid aggregation inhibitor, and tarenflurbil, a γ-secretase modulator, but results were negative because no significant difference was found between the active treatment and placebo groups. Why did the clinical trials of these disease-modifying drugs not succeed? Many researchers think that these disease-modifying drugs might have been administered too late. Even in patients with mild Alzheimer's disease, a massive accumulation of amyloid and extensive nerve cell death may have already occurred. This raises the question of what benefits can be obtained by disease-modification – the elimination of amyloid – at this stage. To answer this question, the Alzheimer's Association and the National Institute on Aging in the USA plan to renew common conceptions of Alzheimer's disease.[13] This bold proposal involves diagnosing Alzheimer's disease when evidence shows the beginning of the disease process. For example, a positive finding of amyloid imaging or abnormal tau values in cerebrospinal fluid, even if no symptoms of Alzheimer's disease are observed, would be initial evidence of the disease process. This stage is referred to 'preclinical Alzheimer's disease'. Influenced by the Alzheimer's Prevention Initiative, led by Dr Reiman at the Banner Alzheimer's Institute (Phoenix, Arizona, USA), preemptive therapy with disease-modifying drugs in the preclinical Alzheimer's disease phase is rapidly gaining adherents.[14,15]

In Antioqiua in the northwest of Colombia, there is a significant occurrence of familial Alzheimer's disease related to the E280A presenilin (PS)–1 mutation. The E280A PS-1mutation results in the clinical presentation of Alzheimer's disease usually when the affected individual is 48 years old. Currently, 1235 persons have undergone genetic testing, and of the people carrying the mutation, 480 have not developed the disease yet. There are plans for 1000 persons with the mutation, including some as young as 18, to eventually participate in clinical trials. According to Dr Lopera of the University of Antioquia, the study will include functional MRI, fluorodeoxyglucose-PET, Pittsburgh compound B-PET, and will sample cerebrospinal fluids in as many as subjects during the 18-month clinical trial.

The unsuccessful clinical trials of disease-modifying drugs suggest there are potentially other underlying causes of the failure such as insufficient understanding on Alzheimer's disease pathology, pitfalls in clinical diagnosis, inappropriate drug development based on the amyloid hypothesis and insufficient study design. It is intuitively understandable that developing disease-modifying drugs can no longer simply be expected to improve symptoms. Given these issues, it is important to consider how we should promote drug development for dementia. Dr Tariot of the Banner Institute has advocated that clinical trial should first be performed with healthy but high-risk subjects, such as carriers of the ApoE4 gene. If the safety of an anti-amyloid drug can be sufficiently ensured, then clinical benefits should be tested in patients who have developed Alzheimer's disease. We should redevelop research and drug development strategies for disease-modifying drugs by examining whether preemptive treatment will be the best defence. With the development of disease-modifying drugs, Alzheimer's Disease Neuroimaging Initiative will potentially take the lead in preventing Alzheimer's disease.[7]

MANAGEMENT OF DEMENTIA IN END-OF LIFE

At the 52nd annual meeting of the Japanese Geriatrics Society in Kobe City in 2010, a symposium was held that outlined the public's expectations of geriatricians. Geriatricians were expected to correctly diagnose dementia and to provide consultations concerning patients in the terminal stages. Similarly, over the next decade, the appropriate use of anti-dementia drugs, managing behavioural and psychological symptoms of dementia, and helping caregivers manage the stress resulting from their duties will be major issues relating to latter period of dementia treatment. The last phase of treatment will be care for patients in the terminal stage and deathwatch. Unlike cancer patients, dementia patients in Japan are not allowed to be treated in hospice. However, I believe that this should be changed and hospice should cover terminal stages. For this reason, there is a great need for continuous collaboration between medical service providers and caregivers. In 2009 in the *New England Journal of Medicine*, Mitchell *et al.* published the

results of their prospective study of patients with advanced dementia who were living at several nursing home facilities near Boston.[16] Most patients were at the FAST 7 stage, as they spent entire days in a wheelchair, spoke only several words and required support for eating and excretion. After a follow-up of approximately 600 days, the shocking results indicated that eating/deglutition disorder, pneumonia, and death during the observation period occurred in nearly 80%, 40%, and 50% of the patients, respectively. The Kaplan–Meier curve prepared based on development of eating/deglutition disorder clearly showed that most deaths were observed in the patients with an eating/deglutition disorder. Therefore, dementia should be appropriately managed within the scope of geriatric syndromes at the end-of-life stage. For example, repeated episodes of pneumonia will disturb nutrition and cause dehydration, which leads to sarcopenia and an increased risk of falls and fractures. A long-term bedridden state due to hip or vertebral fractures will result in the worsening of dementia, and such patients are also prone to develop oesophageal regurgitation and aspiration. The eating/deglutition function is actually controlled by the brain. Capsiate and other drugs that up-regulate brain dopaminergic function are occasionally beneficial to prevent aspiration pneumonia.[17,18] Oral care is another simple but most helpful method.[19,20] Even if a feeding tube such as a percutaneous endoscopic gastrostomy is inserted, it may not improve survival or reduce the risk of aspiration. Recently, a new order called 'comfort feeding only' has been proposed; it states what steps are to be taken to ensure the patient's goals of an individualized feeding care plan.[21]

In summary, medical assessment of dementia should be conducted as a persistent and comprehensive process involving primary prevention, pharmacological and non-pharmacological treatment, and treatment for eating problems, aspiration pneumonia and nutritional impairment in the end-stage.

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Invited Review for the 90th Anniversary

Geriatric Medicine, Japanese Alzheimer's Disease Neuroimaging Initiative and Biomarker Development

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Due to a change in disease spectrum in aged countries, the primary role of geriatricians should be directed to an appropriate management and prevention of 1) cognitive decline and dementia, 2) swallowing and aspiration pneumonia and 3) falls and fractures. Management of dementia constitutes a central part in the practice of geriatric medicine in order to support independence of life in elderly people. The current paradigm of cognitive function-based testing for the diagnosis and treatment of Alzheimer's disease (AD) is going to drastically shift to a biomarker-based test approach, a shift that will correspond to the emergence of disease-modifying drugs. In addition, a new molecular imaging technique that visualizes neuronal protein deposits or pathological features has been developed in Japan and the U.S.A. Based on these achievements, the Alzheimer's Disease Neuroimaging Initiative (ADNI) was proposed and initiated in 2005. The ADNI is a long-term observational study being conducted in the U.S.A., Europe, Australia, and Japan using identical protocols. The objectives of ADNI are: 1) to establish methodology which will allow standard values related to long-term changes in imaging data, such as MRI and PET, in patients with AD and mild cognitive impairment and normal elderly persons; 2) to obtain clinical indices, psychological test data, and blood/cerebrospinal fluid biomarkers to demonstrate the validity of image-based surrogate markers; and 3) to establish optimum methods to monitor the therapeutic effects of disease-modifying drugs for AD. Patient enrollment in the Japanese ADNI has begun in July 2008. Imaging of AD pathology not only acts as a reliable biomarker with which to assay curative drug development by novel pharmaceutical companies, but it also helps health promotion toward AD prevention.

Keywords: geriatric medicine; Alzheimer's disease; Amyloid β-peptide; Biomarker; Amyloid imaging; ADNI
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Geriatrician's role and proposal of "Geriatric Triangle"

Geriatric medicine is an independent internal medicine division that is specialized for management of medical problems of elderly people. Despite a fact that elderly people appear healthy, a variable latent organ dysfunction may be present due to a limited residual capacity. A condition referred to as geriatric syndrome is a complex and multi-organ disease especially suffered by elderly people. The geriatric syndrome consists of more than 50 medical conditions such as dementia, depression, delirium, pneumonia, urinary incontinence, osteoporosis and fractures as well as malnutrition, sarcopenia, skin ulceration and renal failure. Importantly, these clinical conditions often occur in combination rather than separately. As illustrated in Fig.1, most important functions which support independence of life in later years are: 1) Thinking and judgments; 2) Eating and swallowing; and 3) Standing and walking. Loss of these basic functions alone or in combination will directly lead to devastating health implications and reduced quality of life. Disturbance of cognitive ability manifests as dementia. Impairment of ordered oropharyngeal functions causes a disturbed swallowing or dysphasia followed by development of aspiration pneumonia. Failure of standing and walking results in repeated falls and fractures. — all being hardly present before the age of 65 but highly prevalent over the age of 75. Moreover, these problems not merely occur in separate occasions but they also are inter-related each other. For example, people with advanced dementia are likely to develop eating problems and aspiration (Nakagawa et al. 1997; Wada et al. 2001; Mitchell et al.

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