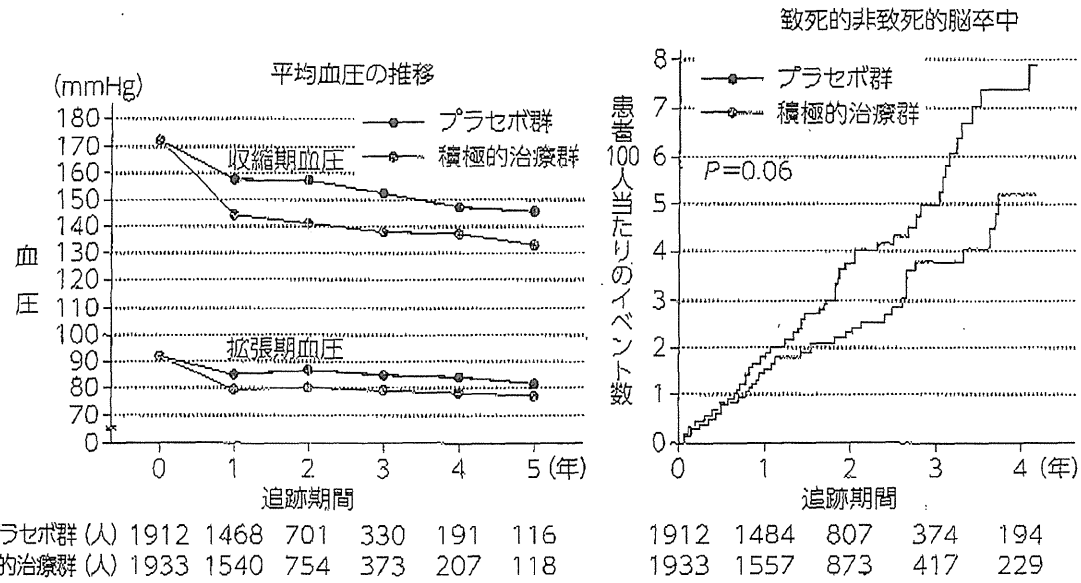

図2　HYVET試験

対象は80歳以上の高齢高血圧患者3845例.
薬物治療群は150/80mmHgを目標. 追跡期間中央値は1.8年.

(文献[5]より改変)

例(中国人1526例を含む)の80歳以上の高血圧患者(降圧薬を服用しない状態で収縮期血圧値が160～199mmHg)を, 降圧薬による治療(ファーストラインとして降圧利尿薬indapamide, セカンドラインとしてACE阻害薬perindopril)群とプラセボ群にランダムに割り付け, 脳卒中の発症を一次エンドポイントとして比較・検討したものである. 二次エンドポイントとして総死亡, 脳卒中による死亡, 心血管死, 心不全などを検討している. 降圧薬は150/80mmHgを目標に増量を図るプロトコールとなっていた.

対象の平均年齢は83.5歳, 女性が60%を占めていた. 脳卒中の既往が6.8%, 心筋梗塞の既往が3.1%, 糖尿病が6.8%に認められていた. 中等度以上の腎障害, 認知症患者, 要介護者は除外されていたことから, 心血管疾患発症リスクの比較的低い"元気"な超高齢高血圧患者が対象であったと考えられる.

試験開始2年の時点での血圧値は, 収縮期血圧値でプラセボ群が173mmHgから158.5mmHgに下がったのに対し, 降圧薬治療群は173mmHgから143.5mmHgまで低下し, 両群間で有意な血圧値の差(15mmHg)が認められた. 降圧薬治療群のうちindapamideとperindoprilの併用例が約75%, indapamide単独が約25%であった.

中間値で1.8年の追跡期間中に, 一次エンドポイントである脳卒中の発症に関しては, 降圧薬治療群において30%の相対的リスク減少率を示したが統計学的に有意には至らなかった($P=0.06$)(図2). しかしながら, 総死亡(相対的リスク減少率21%), 脳卒中による死亡(相対的リスク減少率39%), 心不全の発症(相対的リスク減少率64%), 心血管イベント(相対的リスク減少率34%)に関して有意な減少を認めた.

この結果から, ある程度"元気"な超高齢者の高血圧では, 少量の降圧利尿薬をベースにACE阻害薬を併用することで140mmHg

程度まで降圧することの有効性が実証されたと考えられる.

高血圧治療ガイドライン2009における推奨

高血圧治療ガイドライン2009においては,高齢者においても最終目標140/90mmHg未満達成のために積極的な降圧治療を行うことが推奨された.

降圧目標値としては,いずれの年齢層でも140/90mmHg未満を目指すべきであるが,高齢者の場合,降圧スピードに関しては副作用の発現に留意し,常用量の1/2から開始するなど緩徐な降圧を心がけるべきであるとされている.特に75歳以上で収縮期血圧160mmHg以上の場合は,150/90mmHg未満を中間目標として,慎重に降圧すべきであると記載されている.

治療の実際

(1) 生活習慣の改善

高齢者は食塩感受性が高いため,減塩は有効な治療となりうる.一般的には食塩6g/日を目指すが,特に後期高齢者では,かえって食欲が低下し低栄養を引き起こすこともある.

そのほか,カリウムの積極的摂取,肥満者では減量,アルコール多飲者では節酒,さらには定期的な運動なども降圧には有効である.しかし,極端な生活習慣の変化は高齢者においてはかえってQOLの低下を引き起こすことがあるので,無理をしない.

(2) 薬物療法

生活習慣の改善により十分な降圧が認められなかった場合,薬物療法を考慮することになる.降圧薬の選択に関しては,ガイドラインにおいてはCa拮抗薬,ARB/ACE阻害薬,少量の利尿薬を第一選択とし,降圧効果不十分な場合は,これらの併用を行うことが推奨されている.

降圧利尿薬は多くの介入試験でその有用性が証明されているが,糖代謝,脂質代謝への悪影響や脱水などの懸念があり,使用する際には少量にとどめることが重要である.

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Geriatrics Gerontology 1st Impact Factor in June 2010 Medline Indexed

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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.

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.

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

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

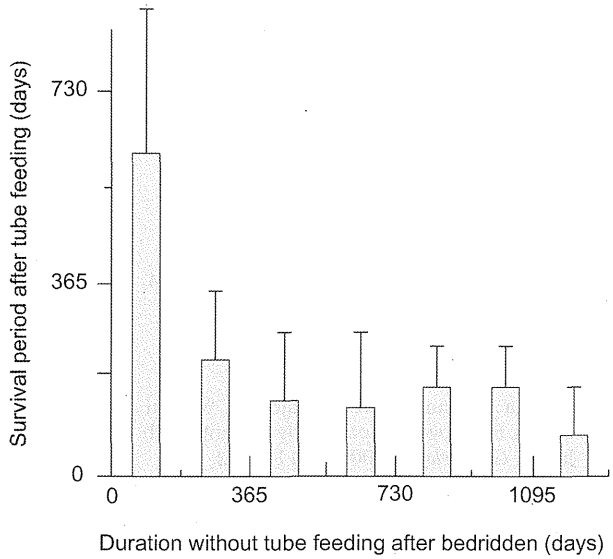

Figure 1 Average survival periods after tube feeding after half a year without tube feeding after being bedridden were significantly shorter than that before half a year ($P < 0.01$). Survival periods after tube feeding more than 3 years without tube feeding after being bedridden are summarized.

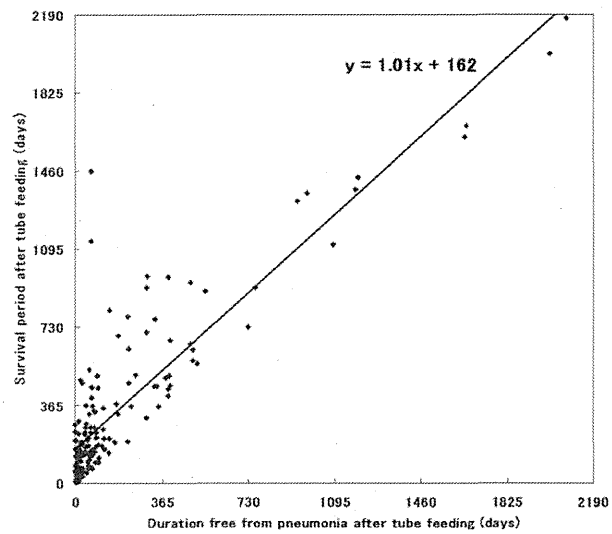

Figure 2 Survival period after tube feeding (y) was proportional to duration free from pneumonia after tube feeding (x), as $y = 1.01x + 162$ ($P < 0.001$).

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?

Department of Geriatrics and Gerontology, Institute of Development, Aging and Cancer

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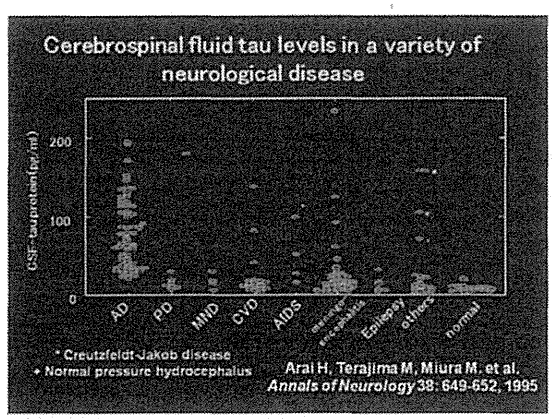
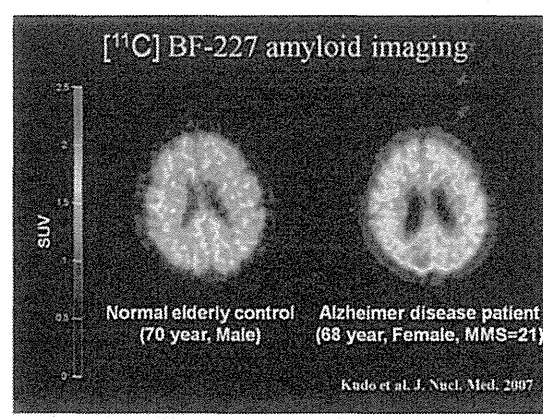
http://www.idac.tohoku.ac.jp/index.en.php

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)

学術部

学術部勉強会

●とき：平成24年９月19日㈬　午後７時30分
●ところ：仙台市急患センター・
仙台市医師会館５階研修室

超高齢社会と認知症医療
―中高年からの健康管理と認知症予防―

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あげられる。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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Geriatr Gerontol Int 2012; **12:** *563–572*

LETTERS TO THE EDITOR

New dorsiflexion measure device: A simple method to assess fall risks in the elderly

Dear Editor,

Hip fracture is the third leading cause yielding bedridden status in Japan, and more than 80% of hip fractures are reported to be caused by falling. There are a variety of causes for falls in the elderly, and one of the significant causes is the inability to lift their toes when they walk. Here, we show a new device to measure dorsiflexion angle, an instrument that we developed to assess fall risks in the elderly.

Participants were requested to stand up straight and step back until the hip leaned on the wall (Fig. 1a). The fulcrum of the instrument was adjusted to the center of the external malleolus (Fig. 1b). The arm of the instrument was set to stay level, adjusting the branching thin arm placed on the ridge of the dorsum of the foot. Then, participants were asked to dorsiflex as much as possible. The mean time to measure bilateral dorsiflexion angles was within 5 min.

We measured dorsiflexion and Fall Risk Index (FRI),[1,2] including the history of falls within the past year, in 131 women (46–89 years, mean age 78.0 ± 7.1 years) and 88 men (46–93 years, mean age 76.2 ± 8.6 years) who visited the fall prevention clinic in Kyorin University Hospital. The occurrence of falls within the past year was 35.6%. Falls occurred 2.0 ± 0.1 times in fallers within 1 year, and women fell more frequently than men (42.7% *vs* 25.0%, $\chi^2 = 7.2$, $P \leq 0.01$). The average FRI score was 6.7 ± 3.4 in non-fallers and 10.6 ± 3.0 in fallers ($P < 0.0001$). Women showed a higher FRI score than men (8.8 ± 3.6 *vs* 7.0 ± 3.8, $P = 0.003$).

This new device appears promising in detecting the high-risk group of fallers, because the dorsiflexion angle was significantly smaller in fallers than non-fallers (right 9.6 ± 8.4 *vs* 13.7 ± 9.6 degrees, $P = 0.012$; left 10.0 ± 8.5 *vs* 14.2 ± 9.8 degrees, $P = 0.014$). Furthermore, the occurrence of falls was more frequent as the dorsiflexion angle decreased in women ($\chi^2 = 6.4$, $P = 0.042$; Fig. 1c), and half of the subjects, whose dorsiflexion angle was less than 10 degrees, experienced falls within a year.

Previously, it was reported that hip fractures occur more frequently in women than men, even though the incidence rate of falls was comparable until the age of 90 years. This is considered to be a result of the higher prevalence of osteoporosis in women.[3] In contrast, the present study found that women less than 90 years-of-age fell more frequently than men in the Japanese population of this age group. We also found that the FRI score was higher in women than men, as has been shown previously.[4] In addition, dorsiflexion angle was

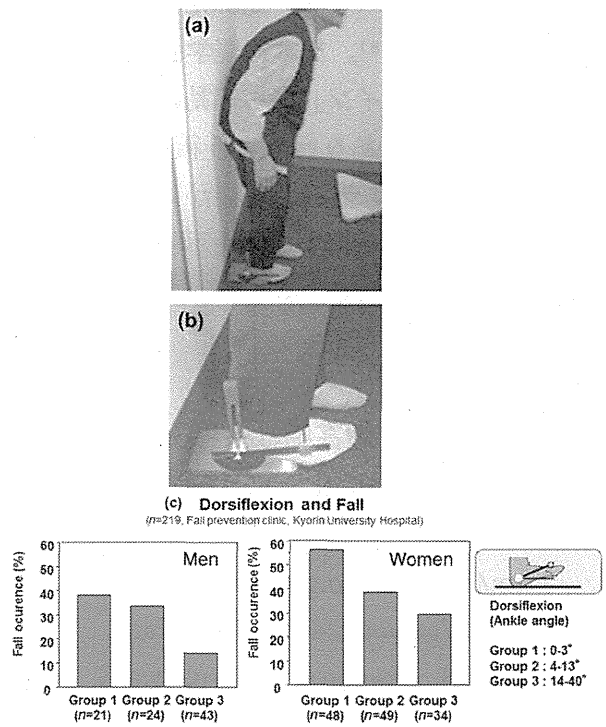

Figure 1 (a,b) How to measure dorsiflexion angle using a dorsiflexion measure device. (c) The relationship between dorsiflexion angle and the occurrence of falls within the past year. In men and women respectively, participants were grouped by tertile according to the dorsiflexion angle.

smaller in women than men (right 10.3 ± 8.4 *vs* 15.2 ± 10.1 degrees, $P = 0.0001$; left 11.0 ± 8.5 *vs* 15.2 ± 10.4 degrees, $P = 0.0013$), and a stepwise increase in the fall occurrence rate according to the level of dorsiflexion angle was evident in women (not significant in men). These results show that less ability to dorsiflex would partly explain the sex difference in the occurrence of falls and ensuing hip fracture.

The new dorsiflexion measure device we report here is easy and less time-consuming to use, and will be sure to help identify a high-risk group of fallers in the elderly.

Disclosure statement

This study was approved by the Ethics Committee of Kyorin University School of Medicine. Accordingly, written informed consent was obtained from all patients. All authors contributed significantly to this work and are

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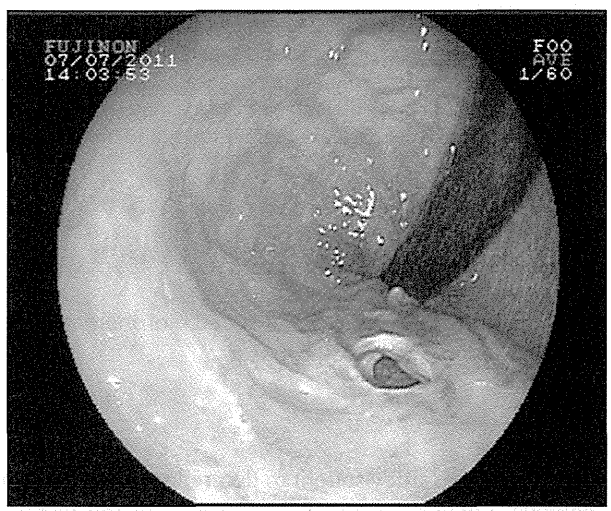
Rectal perforation as a result of self-administration of retrograde enema in an elderly dementia patient

Retrograde cleansing enemas are commonly used in the treatment of chronic constipation, especially in the elderly.[1] We report a case of colorectal perforation as a result of self-administered retrograde water enema in an elderly dementia patient.

A 76-year-old chronically constipated man was admitted to Turkiye Yuksek Ihtisas Hospital Gastroenterology Department in Ankara, Turkey, with a 1-week history of rectal pain. His medical history showed he had the diagnosis of dementia. Clinical examination at that time showed normal vital signs, on examination of the abdomen there was no defense or rebound, digital examination was normal, and respiratory and circulatory system examinations were normal. All laboratory investigations including full blood count, serum amylase, liver function tests, urea and electrolytes were within normal limits. There was no abnormality in abdominal X-ray and abdominal ultrasonography. He was started on a retrograde enema by his family practitioner 7 days earlier for constipation. He described that the pain was precipitated by the first self-administration of the retrograde irrigation enema and the patient denied subsequent use. A preplanned colonoscopy was carried out, and on retroflexion a rectal perforation was detected (Fig. 1). An abdominal computed tomography scan showed perirectal air. Conservative management with intestinal rest and intravenous antibiotics was carried out. The clinical course of the patient was favorable without sepsis or generalized peritonitis. He was discharged home after a 7-day inpatient stay.

Perforation of the rectum and sigmoid colon caused by cleansing enemas, used by chronically constipated patients, has rarely been reported. In the largest series, Paran *et al.* reported that three of 13 patients with rectal perforation as a result of retrograde enema died because of late diagnosis.[2] Gayer *et al.* reported 14 elderly patients (average age 80 years) with rectal perforation as



a result of cleansing enema. Surgery was carried out in 10 of 14 patients, and nine of the 14 patients died. Interestingly, in all of these cases the enema was given by paramedic personnel.[3] It is perhaps not so well known that the rectal wall, even in the absence of disease, can be perforated by the tip of a rubber catheter introduced for the purpose of administering a simple cleansing enema.[4] Because of the possible risk of morbidity and mortality, especially in elderly patients in whom the process can be more catastrophic, rectal perforation risk should be kept in mind and administration of rectal cleansing enemas should be carried out gently and carefully by paramedic personnel. Also, the position of the body when inserting the enema tip is important. An enema should be carried out, in principle, with the patient in the left lateral decubitus position.[5]

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Relationship between Atrophy of the Medial Temporal Areas and Cognitive Functions in Elderly Adults with Mild Cognitive Impairment

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Key Words
Entorhinal cortex · VSRAD · Voxel-based morphometry · Wechsler Memory Scale · Stroop test

Abstract
Aim: The current study sought to determine which types of cognitive function are related to atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) in elderly adults. ***Methods:*** The subjects were 96 elderly adults (mean age 75.3 years) with mild cognitive impairment. Subjects underwent Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II), Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backword (DSB), digit symbol-coding (DSC), Stroop Color and Word Test-Interference List (SCWT-IL) as well as magnetic resonance imaging (MRI) and were divided into elderly adults without or with mild to moderate MTA-ERC atrophy, and those with severe atrophy. ***Results:*** In all subjects, MTA-ERC atrophy showed significant relationships with age (r = 0.43), education (r = −0.25), WMS-R, LM I (r = −0.21), DSC (r = −0.32), and SCWT-IL (r = 0.32). The mild to moderate atrophy group showed significant relationships between MTA-ERC atrophy and age (r = 0.34), DSC (r = −0.28), and SCWT-IL (r = 0.25). In contrast, in the severe atrophy group, MTA-ERC atrophy was correlated significantly with RCF-3 min (r = −0.70) and RCF-30 min (r = −0.74). The linear regression model included demographic variables and cognitive tests; two variables to survive the step-wise analysis were age (β = 0.374) and SCWT-IL (β = 0.247) in all subjects. Age (β = 0.301), and RCF-30 min (β = −0.521) and age (β = 0.460) remained as a significant variable in the mild to moderate atrophy and severe atrophy groups, respectively. ***Conclusion:*** Executive function tests such as SCWT-IL may be useful as a screening tool to identify mild to moderate MTA-ERC atrophy and a decline in the RCF test may suggest severe MTA-ERC atrophy in elderly adults with MCI.

Introduction

There is increasing evidence for baseline structural magnetic resonance imaging (MRI) correlates of cognitive impairment in elderly adults exhibiting mild cognitive impairment (MCI) and Alzheimer's disease (AD) [1–4]. To date, the most reliable and well-documented finding is an association between impaired memory ability

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and medial temporal lobe atrophy, which is particularly robust in the hippocampus and entorhinal cortex (ERC) [5]. Several studies have reported that hippocampal and ERC atrophy can predict conversion to AD [6–9], as well as memory decline in MCI and AD [10, 11]. Although memory deficits constitute the hallmark feature of MCI, many patients exhibit deficits in other cognitive domains, such as mild anomia [12, 13], reductions in semantic fluency [14] and executive dysfunction, characterized by impaired working memory, inhibition, set-shifting, and phonemic fluency [15, 16]. The pathological hallmarks of AD (e.g. neurofibrillary tangles and senile plaques) have been found in the ERC in the earliest phase of disease, leading to an overall neuronal loss of 32% compared with control subjects [17]. An MRI investigation of the ERC reported a 37% decrease in patients who went on to develop AD, in comparison with control subjects [18]. These findings indicate that a strong relationship exists between in vivo measures of ERC atrophy in the early stages of AD.

The region of interest (ROI) method and more automated methods such as voxel-based morphometry (VBM) are the most common MR analysis techniques used for examining brain atrophy. Automated analytical methods such as VBM enable objective examination of anatomical group differences in controls, MCI patients, and AD patients across the whole brain. With this statistical parametric mapping technique, researchers are able to evaluate group differences in gray matter, white matter, and cerebrospinal fluid (CSF) volume with high spatial resolution. Whole-brain VBM has the important advantage of not requiring a priori assumptions about the size, location, or shape of the brain ROI(s). Furthermore, VBM allows the quantification of brain changes that are not easily revealed by visual inspection, such as atrophy that is not fully encompassed by sulcal boundaries between structures.

Recent research has led to the development of a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which enables the examination of atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) using VBM [19–21]. The VSRAD has been shown to achieve high accuracy (87.8%) in discriminating patients in the very early stages of AD with MCI from normal control subjects using Z-scores [21]. Atrophy of the MTA-ERC was indicated by VSRAD to exhibit a clear functional relationship with blood flow changes in the hippocampus, thalamus and temporal lobe, which were suggested to be closely related to interregional anatomical and physiological connections [22]. In cognitive function, Nagata et al. [23] reported that Z-scores of the VSRAD was associated with executive function, although there was no relationship between Z-scores and memory function which was assessed by the Mini-Mental State Examination (MMSE) in the amnestic MCI and early AD patients. These authors suggested that detailed examination such as the Wechsler Memory Scale was required to reveal the relationship between MTA atrophy and memory function. Moreover, it is currently unclear which aspects of cognitive function including memory and executive function are related to the atrophy of the MTA-ERC identified by VSRAD in elderly adults with MCI.

In the current study, we measured volumetric MRI and performance in a range of cognitive domains, including logical memory, visual memory, working memory, processing speed, and executive function in elderly adults with MCI. Overall, we sought to determine which aspects of cognitive performance were associated with MTA-ERC atrophy in elderly adults with MCI.

Methods

Subjects

Subjects in this study were recruited from two volunteer databases (n = 1,543), which included elderly individuals (65 years and over) selected either by random sampling, or when they attended a medical check-up in Obu, Japan. 528 prospective subjects with a Clinical Dementia Rating (CDR) of 0.5, or who complained of memory impairment, were recruited in the first eligibility assessments. 165 subjects responded to the second eligibility assessments, and 125 out of 165 subjects completed the neuropsychological tests which included language and memory tests, attention and executive function tests, clinical diagnosis, activities of daily living (ADL), educational level, and MRI scanning. Out of 125 subjects, 25 were excluded and the remaining 100 subjects met definition of MCI using Petersen criteria [24]. All MCI subjects had objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. Final classification of subjects was based on the above factors and consensus of a team of neuroscientists. Exclusion criteria included CDR 0, or 1–3, a history of neurological, psychiatric, and cardiac disorders or other severe health issues, use of donepezil, impairments in basic ADL, and participation in other research projects. 96 elderly adults remained after these exclusions (mean age 75.3 ± 6.8 years, range 65–93, men n = 48, 50%), and were included in the final analysis. Table 1 shows the characteristics of the subjects.

The purpose, nature, and potential risks of the experiments were fully explained to subjects. All subjects gave written, informed consent before participating in the study. The study protocol was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology.

Table 1. Characteristics of subjects (mean ± SD)

Age, years	75.3 ± 6.8
Male, %	50
Education, years	10.6 ± 2.5
Body mass index	23.0 ± 3.1
Cognitive functions	
MMSE, points	26.5 ± 2.5
WMS-R, LM I, points	14.4 ± 7.1
WMS-R, LM II, points	10.0 ± 7.4
RCF-3 min, points	15.5 ± 6.3
RCF-30 min, points	14.9 ± 6.7
DSB, points	5.2 ± 1.6
DSC, points	46.1 ± 15.9
SCWT-IL, s	21.1 ± 17.2
Medication, yes, %	
Hypertension	44.8
Heart disease	5.2
Diabetes mellitus or hyperlipidemia	20.9
Total number ± SD	2.3 ± 2.1

WMS-R, LM = Wechsler Memory Scale-Revised, Logical Memory; RCF = Rey complex figure retention test; DSB = digit span backward; DSC = digit symbol coding; SCWT-IL = Stroop Color and Word Test-Interference List.

MRI

MRI was performed with a 1.5-T system (Magnetom Avanto; Siemens, Germany). Three-dimensional volumetric acquisition with a T_1-weighted gradient echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time 1,700 ms, echo time 4.0 ms, flip angle 15°, acquisition matrix 256 × 256, 1.3 mm slice thickness).

The MRI images acquired from the subjects were formatted to gapless, transaxial images, followed by extraction of the gray matter images using SPM2. Anatomical standardization was used to fit each individual brain to the standard template MRIs in the common coordinate system of the MNI T_1 MRI template [25, 26]. The segmented gray matter images were then subjected to affine and non-linear standardization using a template of prior gray matter.

The anatomically standardized gray matter images were then smoothed again using an isotropic Gaussian kernel 12 mm in full width at half maximum, to determine the partial volume effect and create a spectrum of gray matter intensities. Gray matter intensities were equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensity was considered equivalent to gray matter concentration. We compared the gray matter image of each patient with the mean and standard deviation (SD) of gray matter images of healthy volunteers using voxel-by-voxel Z-score analysis. In the final step, the Z-score was calculated according to the following equation: (Z-score = ((control mean) – (individual value))/control SD). The Z-score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z-scores indicated clearer MTA-ERC atrophy.

Cognitive Tests

Speech therapists conducted all of the memory tests, and a speech therapist recalculated all of the results. The Wechsler Memory Scale-Revised, logical memory I and II (WMS-R, LM I and II) [27], Rey complex figure retention tests after 3 and 30 min (RCF-3 min and RCF-30 min), digit span backward (DSB) and digit symbol-coding (DSC) subset of the Wechsler Adult Intelligence Scale III [28], and Stroop Color and Word Test-Interference List (SCWT-IL) [29] were included as cognitive tests.

Modified versions of the logical memory subtest from the WMS-R and RCF were used to assess logical and visual memory ability, respectively. In the WMS-R, two short stories (story a and b) were read aloud to the subject, who was instructed to recall details of the stories immediately (LM I) and after 30 min (LM II) [27]. We calculated the total score, i.e. sum score of story a and b, of WMS-R in LM I and LM II. In the RCF, subjects were requested to copy the RCF figure (construction ability) and reproduce it after 3- and 30-min delays. One rater independently scored the RCF using the system described by Osterrieth and Rey [30] and translated by Corwin and Bylsma [31]. DSB and DSC were used to assess working memory and processing speed, respectively. DSB required subjects to repeat a series of verbally presented digits of increasing length in backward order. In the DSC, subjects copied symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant drew the symbol under the corresponding number. The score of DSC was the number of correct symbols drawn within 120 s. In the SCWT-IL as a test of executive function, subjects were presented with a series of color words. Our test version consisted of two subtasks. The first subtask showed color words in random order (red, blue, yellow, green) printed in black ink. The second subtask contains color words printed in an incongruous ink color, for example, the word *yellow* printed in red ink. The subjects were instructed to read the words and name the ink color of the printed words as quickly and as accurately as possible in the two subsequent subtasks. The score was measured as the total time taken to complete the task with 24 words [32]. The time limit to complete a subtask was set at 120 s. An interference measure was calculated by subtracting the average time needed to complete the first subtask from the time needed to complete the second subtask.

Analysis

The relationships between atrophy of the MTA-ERC and cognitive measurements were examined with Pearson correlations. The independent associations between MTA-ERC atrophy and cognitive ability with each demographic (i.e. sex, age, and educational level) and diagnosis (aMCI and non-aMCI) variables were tested using a linear regression model with a step-wise analysis. To examine differences in MTA-ERC atrophy level, subjects were divided into the following two groups according to the Z-score: (1) mild to moderate atrophy group (Z-score: 0–1.99) and (2) severe atrophy group (Z-score: 2.00 and over) in the MTA-ERC, according to the results of the VSRAD [23]. Pearson correlations and the linear regression model with a step-wise analysis were used to examine the relationships between MTA-ERC atrophy and cognitive tests in each group. SPSS 18.0 software (SPSS Inc., Chicago, Ill., USA) was used for all data management and statistical analysis. The statistical threshold was set at a $p < 0.05$.

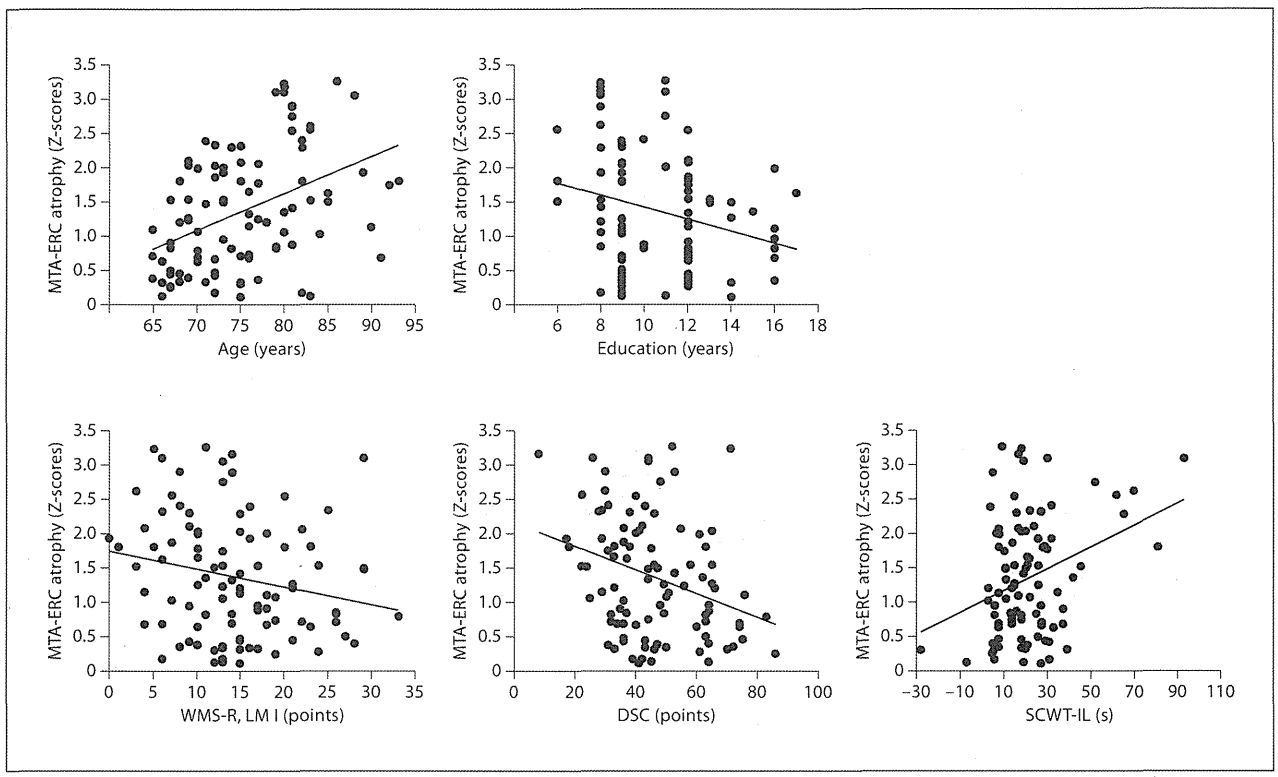

Fig. 1. Relationship between the Z-score of MTA-ERC and age, education, and cognitive test scores. MTA-ERC atrophy was correlated significantly with age ($r = 0.43$, $p < 0.001$), educational level ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$).

Table 2. Pearson correlation coefficients between MTA-ERC atrophy and age, educational level, and cognitive measurements

	All subjects (n = 96)		Mild to moderate atrophy group (n = 72)		Severe atrophy group (n = 24)	
	r	p value	r	p value	r	p value
Age	0.43	**<0.001**	0.34	**0.003**	0.71	**<0.001**
Education	−0.25	**0.012**	0.01	0.921	−0.26	0.224
WMS-R, LM I	−0.21	**0.040**	−0.17	0.155	−0.06	0.774
WMS-R, LM II	−0.09	0.370	0.03	0.812	−0.22	0.308
RCF-3 min	−0.16	0.119	−0.10	0.396	−0.70	**<0.001**
RCF-30 min	−0.13	0.201	−0.11	0.386	−0.74	**<0.001**
DSB	−0.15	0.134	−0.12	0.298	−0.14	0.511
DSC	−0.32	**0.002**	−0.28	**0.016**	−0.05	0.825
SCWT-IL	0.32	**0.002**	0.25	**0.031**	0.18	0.404

For abbreviations, see table 1.

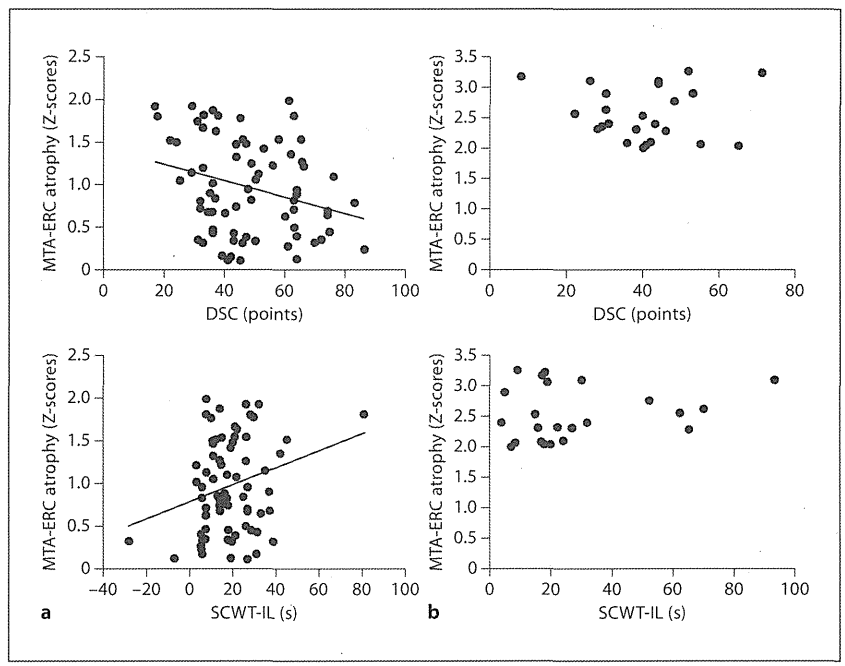

Fig. 2. Relationship between the Z-score of MTA-ERC and processing speed and executive function in the mild to moderate atrophy and severe atrophy groups. The upper panel shows scatter plots between MTA-ERC atrophy and DSC and the lower panel shows scatter plots between MTA-ERC atrophy and SCWT-IL. Correlations of the mild and moderate and severe atrophy groups are shown in panels **a** and **b**, respectively. MTA-ERC atrophy was correlated significantly with DSC ($r = -0.28$, $p = 0.016$) and SCWT-IL ($r = 0.25$, $p = 0.031$) in the mild and moderate atrophy group.

Table 3. Multivariate regression analysis between MTA-ERC atrophy and age, educational level, and cognitive measurements

	β	t value	p value	R^2
All subjects				
Age	0.374	4.0	<0.001	0.236
SCWT-IL	0.247	2.6	0.01	
Mild to moderate atrophy group				
Age	0.301	2.6	0.011	0.091
Severe atrophy group				
RCF-30 min	−0.521	−3.8	0.001	0.706
Age	0.460	3.4	0.003	

For abbreviations, see table 1.

Results

In all subjects, Z-score showed significant relationships with age ($r = 0.43$, $p < 0.001$), education ($r = -0.25$, $p = 0.012$), WMS-R, LM I ($r = -0.21$, $p = 0.040$), DSC ($r = -0.32$, $p = 0.002$), and SCWT-IL ($r = 0.32$, $p = 0.002$) (fig. 1; table 2). There were no significant relationships between Z-score and WMS-R, LM II, RCF-3 min, RCF-30 min, and DSB (table 2). In linear regression model, two variables to survive the step-wise analysis were age ($\beta = 0.374$, $p < 0.001$) and SCWT-IL ($\beta = 0.247$, $p < 0.010$) (table 3).

Of the 96 MCI elderly adults tested, the mild to moderate atrophy and severe atrophy groups included 72 (75%) and 24 (25%) subjects, respectively. In the Pearson correlation analysis, the mild to moderate atrophy group showed significant relationships between Z-score and age ($r = 0.34$, $p = 0.003$), DSC ($r = -0.28$, $p = 0.016$), and SCWT-IL ($r = 0.25$, $p = 0.031$) (fig. 2; table 2). In contrast, Z-scores were correlated significantly with RCF-3 min ($r = -0.70$, $p < 0.001$) and RCF-30 min ($r = -0.74$, $p < 0.001$) in the severe atrophy group (fig. 3; table 2).

A multivariate regression model indicated that age ($\beta = 0.301$, $p = 0.011$) remained as the only significant variable in the mild to moderate atrophy group (table 3). DSC and SCWT-IL did not reach significance in this group. In the severe atrophy group, two variables to survive the step-wise analysis were RCF-30 min ($\beta = -0.521$, $p = 0.001$) and age ($\beta = 0.460$, $p = 0.003$) (table 3).

Discussion

It is well established that structures in the medial temporal lobe, particularly the hippocampus and ERC, are essential for normal memory function [33]. There is evi-