flexor, knee extensor in non-fallers, which may imply that the hip strategy is used to restore equilibrium in response or perturbations when the support surface is smaller than the feet, making their muscles of hip and knee joints adjustable to sudden change of postures.

On the other hand, significant correlations were found between muscle strength of ankle dorsiflexor and plantar flexor and cognitive FIM in fallers.

This difference suggests that falls may tend to occur in those who are not capable of using the hip strategy for the initial perception of postural change.

As Daubney *et al.* tested, the ankle dorsiflexors were found to be the best predictor of falling.[39] During gait, the ankle dorsiflexors are involved, together with the hip and knee flexors, in lifting the lower limb during the swing phase to make sufficient clearance of the toes over the ground to prevent tripping. Taken together, lower extremity muscle strength may be an important predisposing factor in the pathogenesis of falls.

Going up and down the staircase is considered to depend mainly on functioning of the lower limbs, hence, the result that lower extremity muscle strength was not selected as significant variables in the logistic regression univariate analysis in the current study may be considered rather contradictory. A possible explanation as to why muscle strength in the lower extremities was not as predictive as handgrip strength might be found in the reliability of strength measures, which tend to be higher for handgrip strength than for leg strength when measured with a hand-held dynamometer, limiting somewhat the predictive value of leg muscle strength towards falling. Handgrip strength is correlated with muscle strength in the lower extremity,[40] and can therefore be a reliable measure of general muscle strength, as confirmed in a recent meta-analysis of prospective cohort studies.[41]

The relationship between reduction of muscle strength and difficulties in ADL may reflect an association with frailty and appears to be important in older women. When people withdraw from outdoor social contact, they become more susceptible to the negative effects of social isolation and physical inactivity.[17,42] The more activities that the older people avoid, the more difficulties they experience in doing these activities. Therefore, it is highly likely that avoidance of activities dramatically speeds up the process of physical frailty because of the devastating consequences of physical inactivity.[43] Avoidance of activities was not only related to the general status of physical frailty, but also to some specific components of physical function, including less muscle strength in the hip and knee, and less handgrip strength. Because the older people who avoid activities have decreased muscle strength, it is likely that they will experience limitations during activities such as shopping, going for a walk, walking around indoors and bending down to pick something up. This may further increase their feelings of insecurity and apprehension.

Maintenance of muscle strength throughout life reduces the prevalence of functional limitations that might closely relate to older persons.[44–47] It may also be expected to increase self-esteem and confidence in one's own abilities to perform physical activities, thereby avoiding social withdrawal. Increasing activity appears to be a simple and effective means of countering fall risk factors such as muscle weakness or functional limitations.

Limitations of the current study are as follows. First, there may be some uncertainties about the validity and reliability of self-reported falls even with a falls diary provided with sufficient instruction for use. The reliability of a fall questionnaire has been discussed by others,[48] and the discrepancy in this study confirms that there may be a recall bias. Therefore the variances in assessments may have affected the results. Second, the sample size was relatively small and the results shown in this study were obtained from a cross-sectional survey. The scale might perform differently in other populations. Longitudinal data are required to address this issue more carefully. Also, a longer period of intervention involving more participants would be warranted. Third, in the current study, subjects with significant depressive symptoms and those scoring lower than 15 on MMSE were excluded in order to endorse the reliability of a series of assessments and falls reports if they ever occurred. Although the physical performance in these subjects remains unknown, it is likely to substantially affect the outcomes if included. Lastly, lower extremity muscle strength was measured by a hand-held dynamometer, which may have resulted in inaccurate assessment of the muscle strength of the lower limbs in the current study. We assumed that the conflicting result we obtained in the present study might be due to a limitation other than small sample size and diverse background of the participants in that we used a hand-held dynamometer for measurements whose accuracy/test-retest reliability can possibly be questioned. The previous studies have reported some limitations of measuring muscle strength using a hand-held dynamometer as follows: consistency of the testing procedure,[49–51] patient effort,[50,52,53] degree of verbal inducements[51] and incentives.[49,53]

In conclusion, despite the limitations raised above, our findings indicate that a standard assessment of ADL may be a useful component in the risk assessment of falls in older women. The results confirmed that the sub-item in MFS has a possibility of being a significant predictor of falls in older women, therefore might prove useful in screening this population at risk of falls.

The results also permit further work investigating the individual effect of specific rehabilitation program on falls prevention in the older population.

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特集：高齢者のフットケア

各論

1．フットケアの理解に必要な高齢者の身体機能
―転倒など含む―

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各論

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KEY WORD
- 歩行機能
- 転倒
- 転倒リスク評価

SUMMARY

■フットケアは通常，糖尿病合併症や閉塞性動脈硬化症などによる下腿潰瘍のケアが主な目的とされるが，不適切なフットケアが高齢者の機能予後に最も重大な影響を及ぼす転倒の危険性を高めていることは，まだ十分認知されていない．高齢糖尿病患者の転倒リスクが高いのは足底の知覚，触覚の障害による歩行機能，バランスの障害が原因として推察されている．また，足背筋膜炎，外反母趾，胼胝，中足骨痛や不適切な靴の使用など，足の痛みの原因となる症候と転倒の関連性が近年の研究により明らかにされるようになった．今後，転倒リスク評価および予防において足病変に対するフットケア，靴や足関節機能への介入も含めた転倒予防効果に関する論拠の構築が期待される．

高齢者におけるフットケアの意義

日本においてフットケアが一般的な用語として普及してからまだ日が浅いが，他稿でも紹介されると思われるが，日本フットケア学会も設立され(http://footcare.main.jp/)，医療者のみでなく様々な職種の方々のフットケアに関する関心は，近年とみに高まっているといえる．海外においては，既に医療においてpodiatryとして専門性をもった臨床領域として認識されており，podiatryの専門医のための教育プログラムおよび専門資格も存在する．一部の英語圏ではchiropodistという旧来の呼称を用いられる国もあるが，近年はpodiatryという用語が一般的になっている．Podiatryは足，踵，下腿に関する障害の研究，診断，治療に関する学問と定義できる．その目的や意義は国によって異なる．全くの余談ではあるが，podiatryの専門家としてのpodiatristは，かつて雑誌『Forbes』において世界で14番目に所得の高い専門職にランクされたこともあるらしい．かように海外において“足の臨床”の専門性が高く認識され，先行して発達したのは，何も医学の先進性にその要因を求める類いのものではなく，下肢の主に血管疾患の有病率の高さと，その医療経済学的な意義によるものではないかと考える．したがって近年，日本においてフットケアが重要視されるようになったのも，生活習慣の欧米化に伴う疾病分布の変化と無関係ではないと考えられる．少し前になるが，米国における高齢者用の医療保険(Medicare)の対象者の糖尿病性下腿潰瘍の医療費負担およびフットケアによる費用

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軽減効果に関する報告があった[1]．それによると，下腿潰瘍を有するMedicare利用者の医療費は有しない利用者の約3倍（$15,309 vs $5,226）であり，下腿潰瘍を有する高齢者の医療費の約1/4が下腿潰瘍のケアに費やされ，その大部分（73.7%）は入院治療に伴うコストであることがわかっている．また，20週間の治療により治癒率を約10%改善すると，患者1人当たり$189の費用削減効果に相当することもわかった．実際の臨床の枠組みにおいて，podiatryの関与する領域は老年医学に限らず，血管外科，スポーツ医学からプライマリーケアまで多岐にわたるが，本稿においては主に老年医学領域におけるフットケアが関与する病態を転倒という視点から論ずることとする．

高齢者の足の問題と歩行機能の関連

60～80歳までの健常高齢者213名の調査によると，全体の14%に何らかの足の痛みの訴えがみられ（男女比：1対4），その原因は足背筋膜炎，外反母趾，胼胝，中足骨痛，不適切な靴の使用など多岐にわたっていた．また当然のことではあるが，足の痛みの訴えは高齢者の歩行速度に影響することも確認されている．転倒歴との関連に関する足の問題については多変量解析の結果，足の痛み，特に足背の筋膜炎によるものと転倒に有意な関連が観察された．また男性においては，足の触覚の障害にも転倒との関連が指摘された[2]．これらは，従来より指摘されていた転倒のリスクとしての変形性関節症など下肢の問題に加えて，立位における唯一の接地面である足の問題が転倒のリスクを高めている可能性を示唆するものである．前述のごとく，足に関する訴えは通常女性に多くみられるが，長年の靴の使用状況と無関係ではない[3]．

高齢者の足の病態と転倒，骨折の関連

不適切なフットケアが転倒のリスクを高めていることと逆に，転倒が足の問題の要因となる可能性も考えられる．糖尿病性の神経障害により足底の痛覚，触覚が鈍麻することはよく知られている事実である．また，下腿，足の潰瘍形成が歩行機能に与える影響は看過できない問題である．55歳以上の糖尿病患者60名を対象にした調査によると，過去1年間に転倒した群と非転倒群を比較した場合，転倒群と非転倒群の末梢神経障害の有病率はそれぞれ86% vs 56%であった．ロジスティック回帰分析では，歩行速度，足関節の背屈力，末梢神経障害スコアが転倒の75%を予測するという結果を得ている[4]．さらに小規模ではあるが，2型糖尿病患者14名と同数の年齢，性別，BMIを調整した対照群との歩行パターンを比較したところ，糖尿病群においては末梢神経障害がないにもかかわらず踵の上がりが低く，つまづきやすい歩行パターンを示すことが報告されている[5]．健常高齢者を対象にした研究では，つま先の屈伸力が弱いこと，足の変形（外反母趾なし）が歩行不安定性，転倒のリスクを有意に高めていることが示されている[6,7]．足の病変を客観的に評価し，その程度と可動性障害，転倒の関連を検討した報告がある．それによると，Foot problem score（足の痛み，外反母趾の程度，そのほか足の変形，骨の突出，胼胝などの過角化）とバランス機能，転倒の有無を検討したところ，多変量解析によりFoot problem scoreとバランス，階段昇降などの歩行機能に有意な関連性があり，過去の複数回の転倒を有意に予測することがわかった[8]．176名の高齢者（平均年齢80.1歳）を対象にした足の機能と歩行バランスとの関連性を検討した報告によると，足関節の柔軟性，足底の痛覚，足底の屈曲筋力が，歩行バランス機能の独立した予測因子であるという結果を得ている[9]．また，同じ対象群を1年間追跡したところ，転倒群においては有意に上記の歩行バランス機能の規定要因以外に，外反母趾による足の変形と足痛が有意に関連していることが確認された．さらに判別分析により，ほかの転倒に関連する生理的な機能や年齢を除外した後でも，足底の屈曲力と足痛は独立した転倒の予測因子であった[10]．同様の研究デザインで312名の高齢者を1年間追跡したところ，転倒群においては有意

表1　転倒ハイリスク者の発見のための問診票

1）過去1年間転んだことがありますか(はい，いいえ)
　はいの場合転倒の回数(　　回/年)
2）つまづくことがありますか(はい，いいえ)*
3）手摺につかまらず，階段の昇り降りをできますか(はい，いいえ)
4）歩く速度が遅くなってきましたか(はい，いいえ)
5）横断歩道を青のうちに渡りきれますか(はい，いいえ)*
6）1kmくらい続けて歩けますか(はい，いいえ)
7）片足で5秒くらい立っていられますか(はい，いいえ)
8）杖を使っていますか(はい，いいえ)*
9）タオルを固くしぼれますか(はい，いいえ)*
10）めまい，ふらつきがありますか(はい，いいえ)*
11）背中が丸くなってきましたか(はい，いいえ)
12）膝が痛みますか(はい，いいえ)*
13）目が見にくいですか(はい，いいえ)
14）耳が聞こえにくいですか(はい，いいえ)
15）物忘れが気になりますか(はい，いいえ)
16）転ばないかと不安になりますか(はい，いいえ)
17）毎日薬を5種類以上飲んでいますか(はい，いいえ)
18）家の中で歩くとき暗く感じますか(はい，いいえ)
19）廊下，居間，玄関によけて通る物が置いてありますか(はい，いいえ)*
20）家の中に段差がありますか(はい，いいえ)
21）階段を使わなくてはなりませんか(はい，いいえ)
22）生活上家の近くの急な坂道を歩きますか(はい，いいえ)

文献18より一部改変引用　　*：独立した転倒の危険因子として抽出された項目

に足痛の訴えがあり，足底にかかる最大圧および圧時間積分値が有意に高いことが報告されている[11]．因果関係に関する考察には慎重を要するが，足底への過度な圧が足痛を引き起こし，結果として歩行の不安定性につながっている可能性が示唆される．ちなみに足の痛みを客観的に評価する指標としては，歩行や生活動作における痛みを考慮したManchester Foot Pain and Disability Indexがある[12]．

靴と足の病変，転倒の関連

足の病変(変形，潰瘍形成)などは，糖尿病などの身体疾患によってのみ引き起こされるものではなく，不適切な靴の選択も原因となることが過去の報告により確認されている．不適切な長さの靴を履いている高齢者においては足痛，足の潰瘍の発生が有意に高いことが観察されている[13]．サイズ以外にも，靴の形状が高齢者のバランス機能に与える影響に関する報告もある．それによれば，靴底が柔らかい材質の靴や踵の底面が高い靴は高齢者には推奨されない[14]．また，高齢者の歩行特性として急に立ち止まるのに時間がかかる傾向にあり，靴底が柔らかいものは不適切だが，踵周りの高い靴は止まる動作には適しているとの報告がある[15]．不適切な靴の着用の危険性は在宅高齢者のみに限ったものではなく，亜急性期病棟における転倒の危険性を高めることも指摘されている[16]．

フットケアを考慮した転倒リスク評価，転倒予防について

高齢者の機能予後における転倒の重要性は疑いの余地のないところであり，転倒リスク評価および介入に関する指針も多く存在する[17]．高齢者の転倒の要因は内因，外因ともに複合的なものであることから，必然的に予防においても複合的なアプローチが必要であることはいうまでもない．予防に有効とされる介入方法に関しては，これまでに様々な試みがなされ，その有

効性が報告されてきた．予防的介入の効果を高めるという視点から，転倒リスクの適切な評価は最も重要なプロセスであるといえる．日本においても，転倒リスクの評価を目的とした過去の転倒歴と21の下位項目からなる転倒問診票（**表1**）が考案され，地域在住高齢者において転倒予測における有用性が確認されている[18]．海外においても，多因子的なアプローチで転倒予測因子を同定する試みがなされてはいるが，高齢者の個々の転倒要因を評価する上でフットケアによる介入を意識した転倒予防プログラムは，いまだ一般的であるとはいえないのが現状である[19,20]．今後，転倒リスク評価および予防において足病変に対するフットケア，靴や足関節機能への介入も含めた転倒予防効果に関する論拠[21]の蓄積に期待したい．

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Responses of hypothalamo–pituitary–adrenal axis to a cholinesterase inhibitor

Hiroyuki Umegaki, Aki Yamamoto, Yusuke Suzuki and Akihisa Iguchi

Acute gastrointestinal events (mostly manifested by nausea, vomiting, or loss of appetite) are class effects of all cholinesterase inhibitors, which are prescribed for the treatment of Alzheimer's disease. The underlying mechanism, however, has been unclear. Because corticotropin-releasing hormone is related to appetite control, we focused on the activation of the hypothalamo–pituitary–adrenal system and food intake following the administration of the cholinesterase inhibitor, donepezil, in rats. We monitored the plasma concentrations of adrenocorticotropic hormone, c-Fos, in the paraventricular nucleus, and intakes of rat chow for 3 h after the first administration of donepezil, and 2 weeks later, after daily administration of donepezil. The intragastric administration of 3 mg/kg of donepezil significantly increased the plasma adrenocorticotropic hormone levels and c-Fos expression in the paraventricular nucleus, and decreased the food intake on the first day. The increase in adrenocorticotropic hormone and loss of appetite after oral administration of the drug were attenuated after daily administration for 2 weeks. *NeuroReport* 20:1366–1370 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: adrenocorticotropic hormone, appetite, corticotropin-releasing hormone, glucocorticoid, hypothalamo–pituitary–adrenal axis

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Introduction

The administration of cholinesterase inhibitors increases acetylcholine concentrations in the synaptic cleft of the central nervous system [1]. The intravenous injection of the short-acting cholinesterase inhibitor, physostigmine, reportedly activates the hypothalamo–pituitary–adrenal system through central cholinergic neurons in young humans [2,3]; similar phenomena were observed in patients with Alzheimer's disease [4,5]. Our previous animal studies suggested that hippocampal cholinergic neuronal systems play an important role in these reactions [6,7].

Alzheimer's disease is a major neurodegenerative disease inducing dementia in humans. Long-acting oral cholinesterase inhibitors like donepezil are prescribed to treat this condition because memory dysfunction in Alzheimer's disease is closely related to the decrease in cholinergic neurons in the brain [1,8]. The effects of long-acting oral cholinesterase inhibitors on the hypothalamo–pituitary–adrenal axis, however, have not yet been investigated. These effects may have clinical relevance in two regards. First, activation of the hypothalamo–pituitary–adrenal axis would cause the corticotropin-releasing hormone to be released from the paraventricular hypothalamic nucleus in the hypothalamus. The corticotropin-releasing hormone has several physiological functions other than the ability to activate the hypothalamo–pituitary–adrenal axis [9]. In one of these functions, corticotropin-releasing hormone has anxiogenic-like effects [10]. Central injection of corticotropin-releasing hormone produces anorexia in rats [11–13]. Acute gastrointestinal events (mostly manifested by nausea, vomiting, or loss of appetites) are major side effects of all cholinesterase inhibitors [8]. Therefore, the release of corticotropin-releasing hormone may be involved in the mechanisms of cholinesterase inhibitor-induced gastrointestinal side effects. Second, the activation of the hypothalamo–pituitary–adrenal axis induces the release of glucocorticoids in the plasma from the adrenal gland cortex, and glucocorticoids are closely associated with memory functions [14]. Cholinesterase inhibitors are clinically prescribed to patients with Alzheimer's disease, in whom memory impairment is a key issue.

In this study, we assessed the profiles of hypothalamo–pituitary–adrenal axis activation and food intake after intragastric administration of the long-acting cholinesterase inhibitor, donepezil, in rats. As for the assessment of the hypothalamo–pituitary–adrenal axis activation, plasma levels of adrenocorticotropic hormone and corticosterone were measured and activation of corticotropin-releasing hormone-releasing neurons in the paraventricular nucleus were assessed by c-Fos expression.

Materials and methods

Animals

All experiments were conducted on adult male Wistar rats (250–300 g). Animals were housed individually under standard laboratory conditions in temperature-controlled

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rooms (25°C). The animals were maintained on a 12-h light/dark cycle (light on at 06:00 h) with food pellets and water available *ad libitum*. The rats were treated with 5 min of handling each day for 7 days before the experiments for habituation. This study was approved by the Animal Care and Use Committee of Nagoya University.

Procedure

The cholinesterase inhibitor, donepezil, (0, 1, 3 mg/kg) (Eisai Co., Ltd., Ibaraki, Japan) was diluted with saline and administered daily for 2 weeks through a cannula inserted into the stomach. The dose of donepezil was chosen according to the studies performed by Geerts *et al.* [15]. The plasma levels of adrenocorticotropic hormone and glucose were monitored for 3 h after the administration of donepezil on the first day and on days 7 and 14. To determine plasma adrenocorticotropic hormone levels, blood was sampled (0.8 ml) intermittently through a catheter inserted and implanted into the jugular vein, starting at time 0 min, before the administration of donepezil, and at 10, 30, 60, 120 and 180 min after donepezil administration. To minimize the effects of volume loss, an equal volume of heparinized saline was returned to the general circulation at each sampling. Sampled blood was kept on ice and then centrifuged. Plasma was taken and stored at −20°C in aliquots of approximately 400 µl for subsequent determination of adrenocorticotropic hormone and corticosterone levels by radioimmunoassay [16,17]. All experiments were completed between 10:00 h and 13:00 h to minimize variability resulting from circadian rhythms.

Immunohistochemistry

The activation of neurons in the paraventricular nucleus assessed by c-Fos expression was examined at three time points (day 1, days 7 and 14). One hour after the administration of donepezil, the rats were deeply anesthetized with a lethal dose of sodium pentobarbital and perfused transcardially with saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). They were postfixed overnight and cryoprotected in phosphate-buffered saline containing 30% sucrose. Brains were immediately frozen with powdered dry ice. Serial coronal sections were cut throughout the regions of the paraventricular nucleus using a cryostat. The antibody for c-Fos was purchased from Santa Cruz Biotechnology (California, USA). For c-Fos immunostaining, every third paraventricular nucleus section (40-µm thick) was collected as a free-floating section and then subjected to the preformed avidin–biotin complex avidin–biotin peroxidase complex–diaminobenzidine tetrahydrochloride method, as described previously [6,7].

Measurement of food intake

Animals were housed individually in separate cages. The day before the experiment was performed, the food was removed at 17:00 h. On the experimental day at 9:00 h the rats were given a carefully measured amount of food pellets in spill-proof food containers. The leftover food in the container was weighed at 3, 6, and 24 h after the administration of saline with or without donepezil. Food intake was measured on day 1 and day 14 after daily administration of donepezil.

Data analysis and statistics

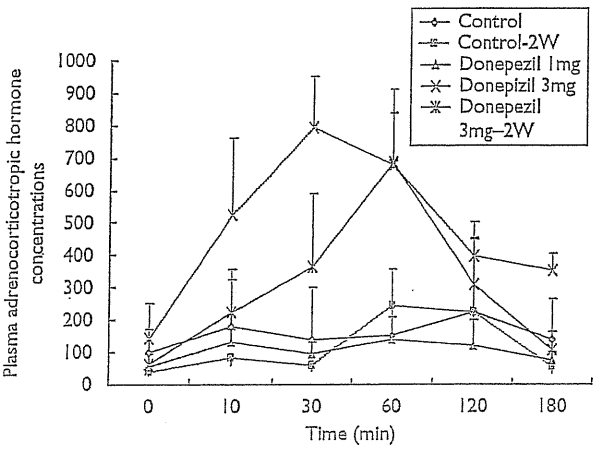
The plasma concentrations of glucose, adrenocorticotropic hormone, and corticosterone were expressed as means ± SD. Differences were assessed using repeated-measure one-factor analysis of variance (ANOVA) with Scheffe's post-hoc analysis. Food intake was analyzed with one-factor ANOVA. A level of P value less than 0.05 was accepted as statistically significant.

Results

Adrenocorticotropic hormone profiles

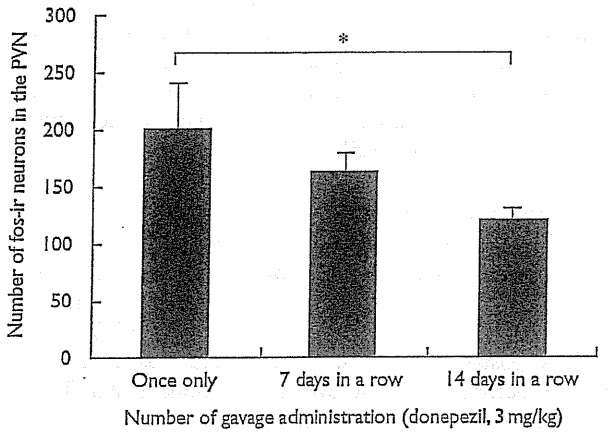
The cholinesterase inhibitor, donepezil (0, 1, 3 mg/kg) (Eisai Co., Ltd) was diluted with saline and administered daily for 2 weeks to experimental rats through a cannula inserted into the stomach. The profiles of adrenocorticotropic hormone response were shown in Fig. 1. Intragastric administration of donepezil (3 mg/kg) elevated plasma adrenocorticotropic hormone levels, whereas daily administration for 2 weeks attenuated the adrenocorticotropic hormone elevation; repeated ANOVA with Scheffe's post-hoc analysis showed the elevation was significantly less

Fig. 1



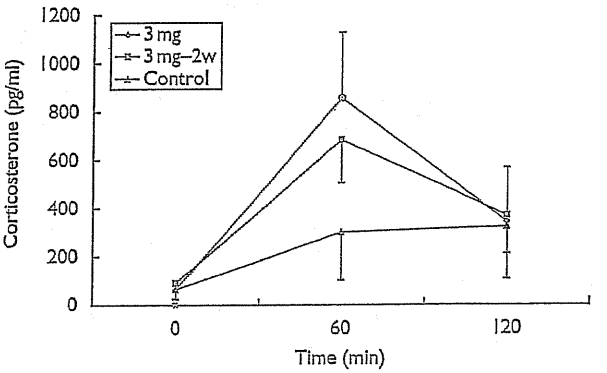
Changes in plasma adrenocorticotropic hormone concentrations. Adrenocorticotropic hormone responses by single administration of donepezil (3 mg/kg) and daily administration of high-dose (3 mg/kg) donepezil for 2 weeks were significantly higher than those of control and low-dose (1 mg/kg) donepezil ($P<0.01$). Control, 1 mg, 3 mg stand for the data at day 1 of rats administered saline, 1 mg/kg of donepezil, and 3 mg/kg of donepezil, respectively; 3 mg–2 W stands for the data after the daily administration of 3 mg/kg of donepezil for 14 days.

Fig. 2



Number of Fos-ir neurons (mean ± SD) in the paraventricular nucleus of rats in each experimental group. (Numbers of neurons were counted in four to five sections from five animals in each group.) There were statistically significant differences between day 1 and day 14. *($P<0.05$).

Fig. 3



Changes in plasma corticosterone concentrations. Corticosterone responses by single-dose donepezil (3 mg/kg) and donepezil (3 mg/kg) for 2 weeks were significantly higher than those of the control by repeated analysis of variance with Scheffe's post-hoc analysis ($P=0.097$ for donepezil and $P=0.046$ for donepezil for 2 weeks). Control and 3 mg stand for the data on day 1 of rats administered saline and 3 mg/kg of donepezil, respectively; 3 mg–2 W stands for the data of rats after daily administration of 3 mg/kg of donepezil for 14 days.

($P < 0.01$) on day 14 than on day 1. Significant elevation was not observed when the donepezil was administered at a lower dose (1 mg/kg) on day 1.

Fos-ir in paraventricular nucleus

A large number of Fos-ir neurons were observed in the paraventricular nucleus at 1 h after the administration of donepezil. The number of Fos-ir neurons was significantly reduced after 1 and 2 weeks of daily administration of donepezil (Fig. 2).

Corticosterone profiles

Intragastric administration of donepezil (3 mg/kg) significantly elevated the plasma corticosterone levels. The increase of plasma corticosterone levels was slightly lower after daily administration of donepezil for 2 weeks but this difference did not reach the level of statistical significance (Fig. 3).

Food intake

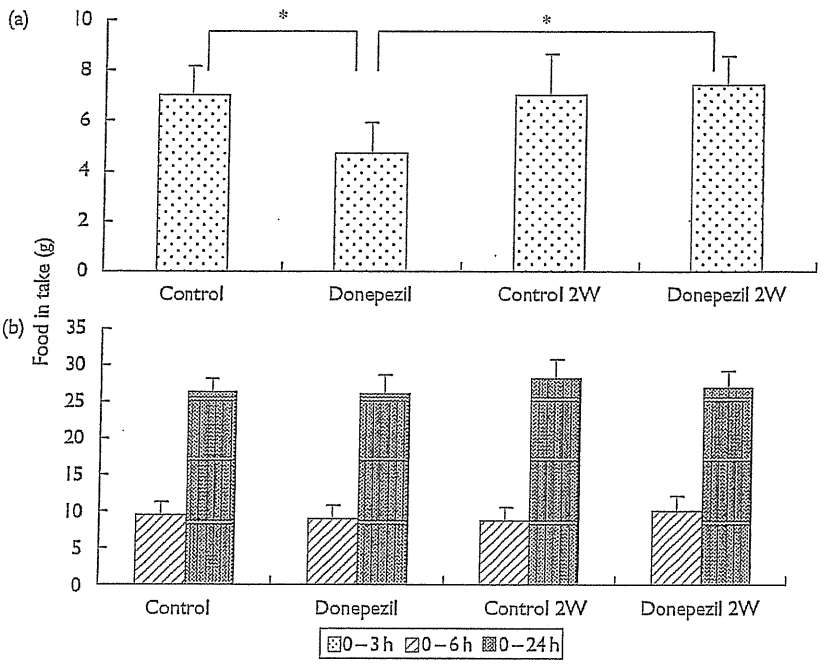
On day 1 the food intake during the initial 3 h after the administration of donepezil was significantly lower in the donepezil-treated group than in the control group (Fig. 4a). The food intakes for 6 and 24 h were not significantly different (Fig. 4b). The immediate reduction of food intake in the donepezil-treated group was not observed on day 14 after daily donepezil administration (Fig. 4a).

Discussion

In this study, we have demonstrated that the oral intake of a cholinesterase inhibitor, donepezil, significantly increases plasma levels of adrenocorticotropic hormone and corticosterone along with the expression of c-Fos in the paraventricular nucleus. During the initial 3 h when the adrenocorticotropic hormone is thus elevated, the food intake of the animals decreased. The increase in adrenocorticotropic hormone after the oral administration of the drug was attenuated after daily administration for 2 weeks, concomitant with the disappearance of appetite loss after 2-week administration of donepezil.

Chronically stressful stimuli may induce the desensitization of the responsiveness of the hypothalamo–pituitary–adrenal axis [18]. In this study, we have observed the desensitization of the hypothalamo–pituitary–adrenal axis activation by the daily administration of long-acting cholinesterase inhibitors for 2 weeks. Acute gastrointestinal events (mostly manifested by nausea, vomiting or loss of appetites) are class effects of all cholinesterase inhibitors, and reportedly occur most frequently during the dose-escalation phase of pharmacotherapy, and usually not in the maintenance phase [8]. These events can be minimized using slow escalation of the dose [19,20]. In Japan, an initial lower dose is administered for 1 to 2 weeks before the treatment dose is prescribed for Alzheimer's patients. The current results correspond well with these clinical findings. The release of adrenocorticotropic hormone, possibly corticotropin-releasing hormone as suggested by the c-Fos expression in the paraventricular nucleus, was stimulated by the administration of cholinesterase inhibitor, but the effect was attenuated over time. Given the anorexic effects of corticotropin-releasing hormone, the current results may explain the mechanisms of cholinesterase inhibitor-induced gastrointestinal side effects in the acute phase, but not in the maintenance phase. Further investigation of the involvement of appetite-controlling hormones

Fig. 4



(a) Food intake during initial 3 h after the administration of donepezil (3 mg/kg) or saline on day 1 and after daily administration for 2 weeks. The donepezil group had significantly less food intake on day 1 ($P=0.005$) than the control group and the donepezil group on day 14 ($P=0.003$). *$P<0.01$. (b) Food intake during initial 6 and 24 h after the administration of donepezil (3 mg/kg) or saline on day 1 and after daily administration for 2 weeks. There were no statistically significant differences among the groups.

including corticotropin-releasing hormone and others should lead to the discovery of therapeutic measures to prevent gastrointestinal side effects with cholinesterase inhibitors.

The activation of the hypothalamo–pituitary–adrenal axis by donepezil led to elevation of plasma corticosterone levels in this study, and these effects did not decrease significantly after 2 weeks of daily administration although the response of adrenocorticotropic hormone was attenuated. The control group also had a slight elevation of corticosterone in the later period of observation in this study. This may be as a result of repeated collections of blood samples although the effects seemed minimal. The effects of glucocorticoids on brain function are still controversial [21]. Some studies have shown that glucocorticoids have negative effects on memory performance [9,22], whereas others have indicated positive effects [23,24]. Despite these conflicting results, it may be possible that elevated glucocorticoid levels induced by cholinesterase inhibitors interact with the effects on memory of cholinergic stimulation in Alzheimer's disease patients. Further investigations examining associations between the increase in glucocorticoids induced by cholinesterase inhibitor administration and the effects on memory of treatment by cholinesterase inhibitors will be necessary to clarify this point.

As a potential limitation of this study, we used young rats with intact cholinergic systems for our experiments. It should be investigated whether the hypothalamo–pituitary–adrenal axis is activated by long-acting oral cholinesterase inhibitors in Alzheimer's disease patients with decreased cholinergic activities [1,8]. In patients with Alzheimer's disease, the activities of the hypothalamo–pituitary–adrenal axis is also altered [25]. Investigations of the effects of cholinesterase inhibitors in Alzheimer's disease patients may be warranted.

Conclusion

The oral administration of the cholinesterase inhibitor, donepezil, induced plasma adrenocorticotropic hormone and corticosterone elevation along with activation of paraventricular nucleus neurons; these effects were attenuated after daily administration for 2 weeks. The initial increase of adrenocorticotropic hormone with possibly corticotropin-releasing hormone and the subsequent attenuation of those responses observed in this study may explain the patterns of cholinesterase inhibitor-induced gastrointestinal side effects in Alzheimer's disease patients.

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LETTERS

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Changes in the perception of dementia in Japan

In parallel with the aging of Japanese society, the number of older Japanese with dementia has been steadily increasing. In response to this trend, the Japanese government has established long-term care insurance and an adult guardianship system. At the same time, national and local governments, medical associations, the Alzheimer's Association and pharmaceutical companies have tried to promulgate knowledge regarding dementia. It is therefore important to assess whether these social movements are having an impact on the perception of dementia among the general population in Japan.

In 2004 we surveyed both younger and older citizens in some urban areas of Japan to determine their perceptions regarding dementia (Umegaki *et al.*, 2007). The survey revealed that the perception of dementia was very similar between older and younger individuals, although the perceptions of the older individuals tended to be slightly more "inaccurate" and "negative." This result was in agreement with the report by Tanaka *et al.* (2004), which showed that age is a significant factor for stigma against mental disorders in Japan. In the current study, we resurveyed the same urban area after an interval of four years to determine the changes in the perception of dementia.

Two thousand younger residents aged 40–64 years and 5,000 older residents aged 65 or older were randomly selected for receipt of a structured questionnaire by mail in December 2004, and an identically sized random selection and mailing were made in the same area in August 2008. People residing in long-term care facilities and those admitted to hospitals were excluded. The questionnaire included items about the backgrounds of participants and their perceptions regarding dementia. Both surveys were conducted in Nagoya City, which is located in the central part of Japan. In April 2004 the population of Nagoya City was 2,191,864, with 17.7% of residents being aged 65 years or older; in 2008, the population was 2,236,844, with 19.9% being 65 or older.

A total of 942 younger residents (47.1%) and 3273 (65.5%) older residents returned the questionnaire in 2004, and 950 younger (47.5%) and 3132 older (62.6%) residents answered the questionnaire in 2008 (Table 1). The backgrounds of the respondents were similar between the two surveys. Among the older residents who responded in 2004, 173 were excluded because they had been admitted to hospitals (n = 53), were residing in long-term care facilities (n = 85), had moved or had died (n = 5), or because the address of residence was unknown (n = 9). In the 2008 survey, 145 were excluded because they had been admitted to hospital (n = 39), were residing in long-term care facilities (n = 85), had moved or had died (n = 8).

The perceptions of dementia in 2004 and 2008 are shown in Table 2. The four possible responses (yes, tend to yes, tend to no, no) were grouped into two categories (yes or tend to yes; no or tend to no), and χ^2 analysis was performed. In younger respondents, the ratio between the two combined-response categories changed significantly for three of the nine items, whereas in older respondents, significant changes in the ratio between the two combined-response categories were found for seven of the nine items after four years. While the ratio of both older and younger respondents who answered that anyone may suffer from dementia (i.e. who answered yes or tend to yes on this item) increased, the ratio of those who answered that dementia is unrecognized by society and is untreatable significantly decreased. For three items (dementia is an unfamiliar and scary disease, dementia is a fatal disease, and dementia is a shameful disease), a significant decrease in answering yes or tend to yes was found only in the older responders.

The current survey revealed that the perception of dementia in an urban area in Japan has clearly changed over the past four years. The results may suggest that changes in the perception of dementia

Table 1. The gender and age characteristics of the two survey populations in 2004 and 2008 (values are n (%))

	YOUNGER		OLDER	
	2004	2008	2004	2008
Gender				
Male	395 (42.3)	388 (40.8)	1403 (45.6)	1260 (42.2)
Female	538 (57.7)	561 (59.2)	1673 (54.4)	1723 (57.8)
Age (years)				
40–49	306 (32.5)	339 (37.8)		
50–59	394 (41.9)	410 (43.2)		
60–64	241 (25.6)	181 (19.0)		
65–69			934 (30.3)	851 (28.5)
70–79			1548 (50.3)	1486 (49.8)
80–89			541 (17.6)	571 (19.1)
90+			57 (1.9)	79 (2.6)

Table 2. Changes in the perception of dementia

		YOUNGER		OLDER	
	YEAR	YES OR TEND TO YES (%)	P VALUE	YES OR TEND TO YES (%)	P VALUE
Morbid condition	2004	91.2	0.128	86.8	0.149
	2008	92.9		85.8	
Disease of rising frequency	2004	92.2	0.179	90.6	0.006**
	2008	93.5		88.3	
Anyone may suffer from dementia	2004	86	<0.001**	78.3	0.008**
	2008	93.1		81	
Unfamiliar and scary disease	2004	76.9	0.172	84	0.009**
	2008	74.9		81.4	
Familiar disease	2004	81.7	0.487	83.6	0.088
	2008	81.9		82.2	
Fatal disease	2004	69.8	0.353	85.1	<0.001**
	2008	68.9		65.2	
Disease unrecognized by society	2004	74.2	<0.001**	78.2	<0.001**
	2008	66.9		69.7	
Shameful disease	2004	42.4	0.179	57	0.004**
	2008	39.1		53.2	
Untreatable disease	2004	29.1	0.026*	39.2	<0.001**
	2008	24.9		31.9	

*$p < 0.05$.
**$P < 0.01$.

in the general population have been directed toward a more "accurate" or "positive" understanding of the disease. In particular, the reduction in the ratio of people who think that dementia is untreatable has some significance with regard to public health. As more people recognize that dementia is a treatable disease, patients with dementia will have a greater chance of receiving treatment. The changes in perception observed in the elderly participants appear to have been greater than those in the younger, with elderly participants showing three more items that changed significantly than the younger participants.

Why have perceptions changed over such a short period? During the interval between the two questionnaires, the aging of Japanese society accelerated, with the proportion of those aged 65 or older growing from 19.5% in 2004 to 22.0% in 2008, and 17.7% to 19.9% in Nagoya City, where the current surveys took place. The rapid increase in the number of individuals with dementia is synchronous with the above demographic changes, and the dissemination of the public long-term care system must surely have raised public awareness (Fukuda *et al.*, 2008). In addition, both national and local administrative efforts to spread knowledge regarding dementia may have contributed to the observed changes in perception (Schomerus *et al.*, 2006). Another possible explanation for the current results is that a substantial number of older individuals who held unfavorable attitudes regarding dementia died in the interval between surveys. However, because this interval was only four years, this explanation seems unlikely.

Despite the favorable changes, the current study also showed that approximately 40% of younger and 50% of older individuals still think that dementia is a shameful condition. Although the trend is changing, it is clear that some prejudice against individuals with dementia is still present in the Japanese population, and these trends are similar to the results of recent surveys in Australia regarding mental disorders (Jorm *et al.*, 2006).

The primary limitation of the current study was that it was carried out in only one urban area. Surveys in rural areas, where access to the media and community values are different, as well as surveys in other countries, where cultural and social backgrounds are different, would further illuminate the current results.

The current survey, which was carried out in an urban area of Japan, suggests that public perceptions of dementia may be changing rather more rapidly than expected, especially in the older population.

Conflict of interest

None.

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Is hypertension a predictor of hippocampal atrophy in Alzheimer's disease?

Hypertension affects millions of people worldwide and has been reported in patients with Alzheimer's disease (AD) some decades before the onset of the disease. High blood pressure has also been related to pathological manifestations of AD (Skoog and Gustafson, 2006). The hippocampus is a highly vulnerable and plastic structure that gets damaged by stimuli, e.g. hypoxia. In order to establish whether hypertension could damage the hippocampus and play a role in its atrophy we undertook a study to examine the relationship between hypertension and hippocampal atrophy in patients with AD.

A total of 32 patients fulfilling Neurological and Communicative Diseases and Stroke Alzheimer's Disease and Related Disorders (NINCDS-ARDA) Diagnostic Criteria for AD (M/F = 27/5, age range = 61–84 years, mean = 74.28 ± 5.8), with Mini-mental State Examination scores of 12.44 ± 6.6 (Stage I = 4, II = 22, III = 10) were included in the study. Mean duration of AD onset was 4.66 ± 2.6 years. Secondary causes of dementia were excluded by appropriate investigations. Delineation of entire hippocampal formation was done using the National Institutes of Health *Image* program (available at http://rsb.info.nih.gov/nih-image/).

Hypertension (defined as blood pressure equal or greater than 140/90) was present in 24 out of the 32 patients (75%) and atrophy of hippocampus was seen in 15 (46.8%) out of the 32 patients. In all except one, atrophy was associated with hypertension. Family history and history of head injury was present in two cases each (12.5%), and nine cases were diabetic (28.1%). Six patients (18.75%) had a history of coronary artery disease, and 15 (46.8%) had behavioral and psychological symptoms of dementia. Twenty patients were graduates, six (18.75%) illiterate and another six (18.75%) were postgraduates. There was no history of trauma or epileptic fits in any of them.

Hipppcampal atrophy is an important milestone in AD. Studies indicate that atrophy of this region correlates well with cognitive decline in AD patients (den Heijer *et al.*, 2005). We have previously reported hippocampal atrophy as a seizure predictor (Dhikav and Anand, 2007), and a large study of over 500 subjects with no dementia showed that blood pressure and indicators of small-vessel disease in the brain may be associated with the atrophy of structures affected by AD pathology (Yavuz *et al.*, 2006).

The study by Wiseman *et al.* (2004) involving 103 hypertensive patients showed an adverse influence of hypertension on brain structures. Although patients in the present study had more factors that could potentially contribute to hippocampal atrophy, hypertension is the main one. The mechanism by which hypertension could be contributing towards atrophy of hippocampus is unknown, but we assume that hypo-perfusion and hypoxia of the hippocampus may be involved. If

運転中止が認知機能低下を有する高齢者の日常交通利用に与える影響
—都市部大学病院もの忘れ外来における調査—

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〈原　著〉

運転中止が認知機能低下を有する高齢者の日常交通利用に与える影響
―都市部大学病院もの忘れ外来における調査―

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要　約　**目的**：自動車運転の中止が認知機能低下を有する高齢者の日常的な交通利用に与える影響について，実態を把握することを目的とした．**方法**：名古屋大学医学部附属病院老年科のもの忘れ外来を利用する101名の高齢者が，自動車運転の状況と交通利用の状況に関する調査に参加した．調査協力者のうち48名（47.5％）が免許保持者，16名（15.8％）が免許失効済者，37名（36.6％）が免許未取得者であった．**結果**：免許保持者の大多数（77.1％）が現役のドライバーであり，免許保持者は免許未取得者に比べて公共交通機関を利用する割合の低いことが確認された．また，免許失効済者においては，認知症の有無により利用する交通機関に違いが認められ，認知症を有する免許失効済者は認知症のない免許失効済者と比べて，公共交通機関の利用割合の低いことが確認された．**考察**：医療者が認知機能低下を有するドライバーに運転中止を求める場合には，公共交通機関を代替利用する難しさへの配慮が不可欠と考えられる．

Key words：認知症，自動車，運転中止，もの忘れ外来，交通利用

（日老医誌　2009；46：420-427）

緒　言

日本の自動車運転人口は，高齢化が著しい．2002年に65歳以上の運転免許証保有者数が24歳以下を追い越したことは，この事実を端的に示す[1)]．それに伴い，認知症臨床の現場で，自動車運転を巡る問題への対応を迫られる機会が，増大している．認知症臨床に従事する者は，どんな事柄に配慮してこの問題に対応すべきなのだろうか．

認知機能は自動車運転を支える重要因子のひとつであり[2)]，公共の安全に鑑みて，認知症者の「運転中止」を求める社会的要請は強い[3)]．日本では，2009年6月に75歳以上の高齢ドライバーに対して免許更新時の認知機能検査を義務付ける「道路交通法の一部を改正する法律（法律第九十号第百一条の四，2007）」が施行される．これを受けて社会的関心がさらに高まることは必至である．しかし，認知症臨床において個人の運転生活へ介入する上では，大きく「中断時期を判断することの困難」と「心理社会的問題への対処」の2課題が存在し，各々，研究途上にある[4)]．前者については，認知症者の運転能力の評価法が医学的に確立されておらず，個別の事例を対象とした中断時期の決定に試行錯誤が伴うことが議論されている[5)6)]．確かに，認知症のドライバーは健常高齢ドライバーに比べて，自動車事故の危険性が2.5～4.7倍とされ[6)7)]，中等度や高度の認知症者には運転中止を勧告すべきとする一致した見解が得られている[8)9)]．しかし，最軽度から軽度の認知症を有するドライバーを対象とした研究は，全員が危険なドライバーとはいえないことを示唆しており[10)～13)]，この時期の患者の中から運転中止の勧告が必要なドライバーを選定する方法が求められている．特に，高齢者の運転能力の低下には，認知機能だけでなく，視力，運動機能などの要因が影響する[2)14)]．これらの交絡要因を現場の評価にどう反映させるのか，認知症の原因疾患ごとに異なる運転上の課題をどのように加味して評価するのかといった課題が残されている[15)16)]．

他方，「心理社会的問題への対処」の視点からも，2種類の問題が指摘されている．第一は，「運転できること」が高齢者の自尊心や生活の自立を支える要因の一つであることに関する[4)]．運転中止というライフイベントが社会や介護者の安堵感とひきかえに，高齢者の心理社会的側面にマイナスの影響を及ぼす要因になること[17)]，医師

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が運転中止を勧告することで患者―医療者間の関係悪化を招くこと[5]，などが指摘されている．こうした心理社会的問題が存在し，さらに，最軽度～軽度の認知症に対する明確な指針も得られていないために，運転中止の勧告をためらう医師は多いという報告もある[18]．第二は，勧告をするだけの介入には実効力が伴わないことの指摘である．上村ら（2005）は，認知症臨床の場で運転中止を勧告する場合，患者本人のみならず介護家族の生活環境への配慮も無視できないことを指摘している[6]．これまで運転を生活の一部としてきた高齢者に，運転の中止を求めることは生活スタイルの大きな改変を強制することである．認知症者のその後の生活を意識した実現可能な介入を進めるためには，認知機能低下を有する高齢者が運転中止することの生活への影響の把握と，代替手段の導入方法について，検討する必要がある[4]．

即ち，どのように危険運転を評価するのかという基準の確立とともに，心理社会的問題への対処法の確立が，認知症者が自ら運転する生活から離脱することを可能とする．しかし，認知機能低下を有する高齢者が，運転中止を求められた際に対峙することになる心理・社会的な課題は，未だ十分に記述されていない．運転中止がその後の生活に与えるインパクトは不明である．そこで本研究では，運転中止によって直接的に影響を受けると考えられる日常の交通利用に着目し，運転中止が高齢者のその後の生活に与えるインパクトを確認する．具体的には，次の仮説を検証する．もし運転を生活の一部としていた高齢者が運転を中止することで（以下，免許失効済者と呼ぶ），その生活に影響が残り，元来運転を生活の一部にしていない高齢者（以下，免許未取得者と呼ぶ）の生活に比べて交通利用に困難が生じるならば，両者の日常の交通利用形態には差が生じているはずである．

本研究の目的は，認知機能低下を有する高齢者群の運転中止の実態を後向きに調査して，運転中止の有無と高齢者の交通利用の状況との関係を検討することである．具体的には，都市部大学病院もの忘れ外来を受診する高齢者が日常の移動と通院に利用する交通手段について調査し，免許保持者，免許失効済者，免許未取得者の3群間で，交通利用の状況を比較する．

方　法

1．期間

2007年12月から2008年7月末日までの8カ月間であった．

2．対象

期間中に名古屋大学医学部附属病院老年科外来「もの忘れ検査枠」[19]を利用した連続122名のうち，調査に協力が得られ，回答内容の研究利用に対する同意が紙面によって確認され，認知症か否かについて診断が確定した101名を分析対象とした．

主治医による診察内容および，頭部SPECT，MRIまたはCT検査，血液生化学検査，各種神経心理学的検査の施行結果に基づき，認知症専門医2名によって「認知症か否か」，および認知症の場合にはその原因疾患に関する鑑別が，非認知症の場合には軽度認知障害（MCI：mild cognitive impairment）の有無に関する鑑別が，すべての対象者についてなされた．認知症の診断はDiagnostic and Manual of Mental Disorders. 3rd Ed. Revised Ed.[20]に依拠した．また，アルツハイマー病についてはNational Institute of Neurological and Communicative Disorders and the Stroke and the Alzheimer's Disease and Related Disorders Associationの基準に[21]，脳血管性認知症についてはDiagnostic and Statistical Manual of Mental Disorders. 4th ed.の基準に[22]，前頭側頭型認知症についてはThe Lund and Manchester Groupsの基準に[23]，MCIについてはThe MCI Working Group the European Consortium on Alzheimer's Diseaseの基準に[24]，それぞれ依拠した．

3．地誌的背景

名古屋大学医学部附属病院は，29診療科，4医療部，1医療センターから成る国立大学法人附属の総合病院で，人口224万人の愛知県名古屋市の中心部（昭和区）に位置する．病院へは，市営バス，市営地下鉄，JR線，タクシー，自家用車を用いたアクセスが可能である．なお，2008年4月時点における，名古屋市の65歳以上人口比率は19.9%であり，全国平均20.7%（2006年8月時点）よりやや少ない．

4．利用交通調査

調査紙は原則自記式とした．ただし，自記での回答が困難な者に対しては半構造化面接を行い，同一内容を聞き取った．調査紙は，以下の内容から構成された．

(1) 説明と同意：紙面をもって研究の説明を行い，回答内容の研究利用に対する同意を確認した．通院に付添う家族があった場合には，家族に対しても紙面による研究の説明を行い，同意を確認した．

(2) 利用交通状況：近接1カ月間に3回以上利用した日常的に利用する交通機関と，生命維持に直結すると考えられる通院に用いる交通機関とを，「バス，地下鉄，地下鉄以外の電車，タクシー，自家用車（自分で運転），自家用車（家族が運転），自転車，徒歩のみ」の8種類の中から，全て回答させた．

表3　運転免許保有条件群ごとの各種交通機関の利用者数（群内の利用％）

	運転免許所有条件		
	保持 (n = 48)	失効済 (n = 16)	未取得 (n = 37)
日常交通			
バス	13 (27.1)	7 (43.8)	22 (59.5)
地下鉄	13 (27.1)	7 (43.8)	24 (64.9)
電車	9 (18.8)	2 (12.5)	11 (29.7)
タクシー	4 (8.3)	3 (18.8)	13 (35.1)
自家用車（自分で運転）	37 (77.1)	0 (0.0)	0 (0.0)
自家用車（家族が運転）	7 (14.6)	9 (56.3)	19 (51.4)
自転車	11 (22.9)	2 (12.5)	11 (29.7)
徒歩のみ	6 (12.5)	0 (0.0)	3 (8.1)
通院			
バス	14 (29.2)	5 (31.3)	16 (43.2)
地下鉄	13 (27.1)	5 (31.3)	11 (29.7)
電車	20 (41.7)	4 (25.0)	7 (18.9)
タクシー	1 (2.1)	2 (12.5)	8 (21.6)
自家用車（自分で運転）	11 (22.9)	0 (0.0)	0 (0.0)
自家用車（家族が運転）	7 (14.6)	8 (50.0)	12 (32.4)
自転車	5 (10.4)	2 (12.5)	1 (2.7)
徒歩のみ	1 (2.1)	0 (0.0)	4 (10.8)

表4　認知症群内における，運転免許の保有条件群ごとの各交通機関の利用者数（群内の利用％）

	運転免許所有条件		
	保持 (n = 25)	失効済 (n = 10)	未取得 (n = 28)
日常交通			
バス	5 (20.0)	1 (10.0)	18 (64.3)
地下鉄	5 (20.0)	2 (20.0)	17 (60.7)
電車	3 (12.0)	2 (20.0)	6 (21.4)
タクシー	1 (4.0)	1 (10.0)	10 (35.7)
自家用車（自分で運転）	21 (84.0)	0 (0.0)	0 (0.0)
自家用車（家族が運転）	2 (8.0)	6 (60.0)	14 (50.0)
自転車	5 (20.0)	1 (10.0)	8 (28.6)
徒歩のみ	4 (16.0)	0 (0.0)	2 (7.1)
通院			
バス	6 (24.0)	2 (33.3)	3 (30.0)
地下鉄	6 (24.0)	4 (66.7)	1 (10.0)
電車	8 (32.0)	1 (16.7)	3 (30.0)
タクシー	1 (4.0)	0 (0.0)	2 (20.0)
自家用車（自分で運転）	7 (28.0)	0 (0.0)	0 (0.0)
自家用車（家族が運転）	6 (24.0)	2 (33.3)	6 (60.0)
自転車	3 (12.0)	1 (16.7)	1 (10.0)
徒歩のみ	1 (4.0)	0 (0.0)	0 (0.0)

るか否かをχ^2検定によって検討した結果，日常的に利用する交通機関についてはバスと地下鉄において，通院についてはバスにおいて，免許失効済者の利用頻度に有意な偏りが認められた(χ^2=12.34；6.11；5.61，a<.05)．残差分析の結果，認知症の免許失効済者は，未だ認知症ではない免許失効済者に比べて有意にこれらの交通機関