1. 中核症状の薬物療法

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Key Point

- アルツハイマー型認知症では，昨年3種類の薬剤が新たに登場し，患者の病期や症状にあわせて薬剤を選択することができるようになった。
- ガランタミンでは，長期投与時の効果と早期投与の有用性が報告されており，介護時間が短縮したとの報告もあることから，臨床での有用性が高い薬剤といえる。
- リバスチグミンは，手段的ADL（IADL）の改善効果が認められており，認知症の早期または軽症に使用するとよい可能性がある。
- メマンチンには神経細胞保護作用があることから，認知機能の進行遅延が期待され，海馬の萎縮の抑制も報告されている。

はじめに

アルツハイマー型認知症（Alzheimer's disease：AD）治療薬は，これまでにさまざまな効果が示されている。ドネペジル塩酸塩やガランタミン臭化水素酸塩，リバスチグミンなどのアセチルコリンエステラーゼ（AchE）阻害薬は，認知機能の進行遅延のほか，日常生活動作（ADL）に関わる介護時間の短縮，介護の見守り時間の短縮，入所時期の遅延などの効果が報告されており，同様の効果はN-メチル-D-アスパラギン酸（NMDA）受容体拮抗薬のメマンチン塩酸塩においても認められている。AD患者の介護時間に対する効果や，その結果としての認知症の人や家族のQOL向上には重要な意義があるといえる。現在の治療薬では病気の完治はしないが，病状を修飾することができ，病気の進行を遅延させることができる。現在では，これらの薬剤を病期，症状にあわせて選択することができるようになった。すなわち，薬の差別化と選択が重要な課題となっている。

本稿では，昨年上市されたガランタミン，リバスチグミン，メマンチンを中心に薬物療法を解説する。

アルツハイマー型認知症（AD）の新薬

ADでは4種類の薬が使用可能となったことで，診断の重要性とともにステージ診断が重要となっており，そのうえで薬剤を適切に選択する必要がある。また，長期効果の視点やbehavioral and psychological symptoms of dementia（BPSD）の状態に応じて使用を検討することも重要であり，そこでは医師としての知識と経験が求められている。

表1に，4種類の薬剤の特徴を示した。AchE阻害薬が3種類とNMDA受容体拮抗薬が1種類である。わが国においてドネペジルは，軽度，中等度，高度のADで投与することが承認されている。これをフルステージ診療とよぶが，実際は予防から終末期医療を含めた形でフルステージ診療とよぶほうが適切であろう。これは，かかり

表1 アルツハイマー型認知症治療薬一覧

	リバスチグミン	ドネペジル	ガランタミン	メマンチン
作用機序	AChE阻害＋BuChE阻害	AChE阻害	AChE阻害＋nAChRへのAPL作用	NMDA受容体拮抗
用量（回/日）	4.5～18mg	3～10mg	8～24mg	5～20mg
用法	1日1回	1日1回	1日2回	1日1回
剤形	パッチ剤	錠剤 OD錠 細粒 内服ゼリー	錠剤 OD錠 内用液	錠剤

〔各薬剤の添付文書情報をもとに作成〕

つけ医が一人の患者を長く，終末期まで連続してフォローするという意味で，シームレスケアともよばれている。

AchE阻害薬がADにおいて有効であることはいうまでもない（認知症疾患治療ガイドライン2010ではグレードA）。薬剤投与は認知症になってから始めればいいのか，認知症の早期に治療を開始すべきなのか，それとも軽度認知障害（MCI）のレベルから開始すべきなのかは意見の分かれるところであるが，早期に治療を開始することが望ましい。

認知症の治療法は，日々研究が進められている。認知症を完全に治療できる薬剤はまだ開発されていないが，薬物療法と非薬物療法，介護という3つの方法で認知症の進行を遅らせ，症状を抑えることがある程度できるようになってきた。早期発見，早期治療はより有用性が高いことが知られている。

認知機能障害の進行抑制

認知症に対する薬物療法では，認知機能障害の進行抑制と，攻撃性や行動障害などのBPSDの進行抑制という2つの治療戦略が考えられる。ADにおける認知症症状の進行抑制を効能とする標準治療薬は，AchE阻害薬とNMDA受容体拮抗薬である。ADになると，脳内の神経伝達物質のアセチルコリン（Ach）が減少し，記憶障害などの認知機能障害が現れるが，AchE阻害薬は，脳内のAchを分解するAchEを選択的に阻害することで脳内のAchを一定量に保つ作用がある。一方でNMDA受容体拮抗薬は，AchE阻害薬とはまったく違った作用機序で認知機能障害の進行を抑制することが確かめられている。ADにはグルタミン酸神経系の機能異常が関与しており，グルタミン酸受容体のサブタイプであるNMDA受容体チャネルの過剰な活性化がその原因の一つと考えられている。ADの病態では，シナプス間隙のグルタミン酸濃度の持続的な上昇によってNMDA受容体が活性化され，細胞内へのカルシウム（Ca）イオンの流入，シナプティックノイズの発生などを通じて認知機能障害が引き起こされていると考えられている。メマンチンはNMDA受容体拮抗作用により，神経細胞内への過剰なCaイオンの流入抑制による神経細胞保護効果と，シナプティックノイズの抑制による記憶・学習機能障害抑制作用を有するとされている。認知症疾患治療ガイドラインの薬物選択のアルゴリズムを図1に示した。原則に則り，ステージや症状にあわせて薬剤を選択することが必要である。

BPSDの薬物療法

BPSDに対しては薬剤の適応がない薬剤が多い。以前は定型抗精神病薬が用いられてきたが，最近ではリスペリドンやクエチアピンなどの非定型抗精神病薬が用いられるようになってきた。しかし米国では，この種の薬剤は脳卒中の発生率が高いとして，ADに対しては禁忌となっている。日本では有用性があるため使用されているが，これらの薬剤では副作用の頻度が比較的高いため，副作用を軽減するためにも少量から投与することがポイントである。また，認知症のBPSDには抑肝散がよく用いられている。副作用として低カリウム血症に注意する必要があるが，特にレビー小体病のBPSDには有効性が高いとされている。

ガランタミン臭化水素酸塩

1．長期投与時の効果と早期投与の有用性

ガランタミンは，軽度および中等度のADにおける認

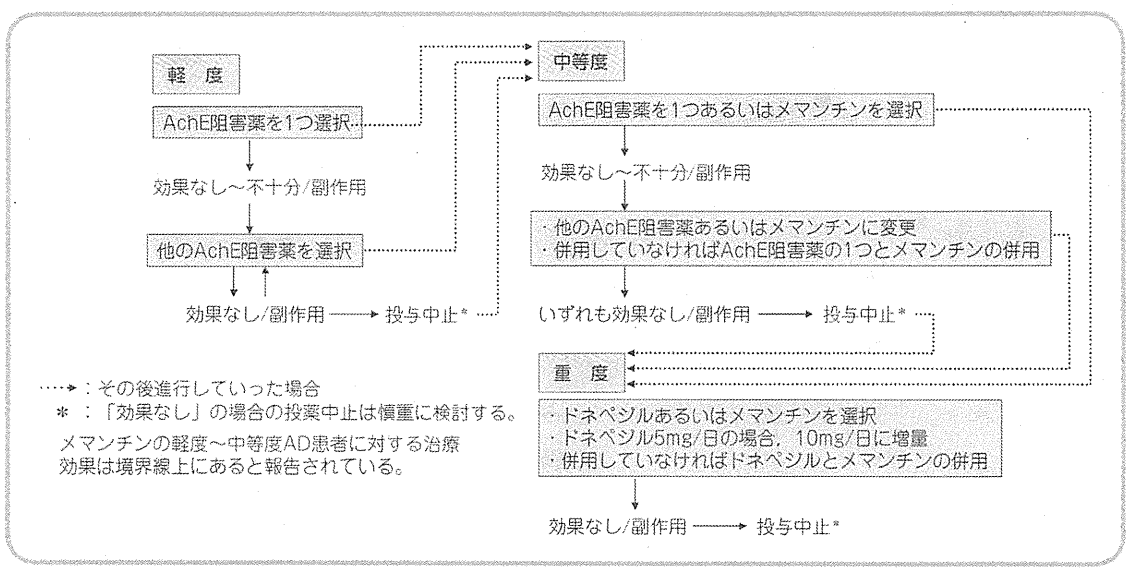


図1　病期別の治療薬剤の選択アルゴリズム

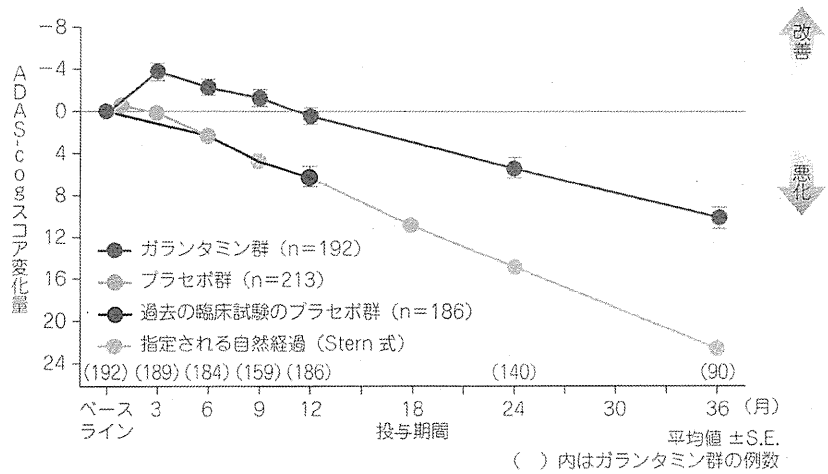
〔日本神経学会・監：認知症疾患治療ガイドライン2010 コンパクト版2012，医学書院，2012より〕

知症症状の進行抑制に適応が認められた新しい薬剤である。少量である1日8mgから開始し，4週間経過観察後に順次16mg，24mgへと増量する。本剤にはAchE阻害作用だけでなく，allosteric potentiating ligand（APL）作用や神経細胞保護など他の薬剤にはない神経代謝改善作用がある。これはdual actionとよばれ，中長期使用時の有用性の高さの根拠となる仮説である。実際，ADに対する長期投与時の効果を評価した試験では，Alzheimer's Disease Assessment Scale-Cognitive（ADAS cog）において投与後1週間以内の改善を認めたほか，半年後にはプラセボ群に比して，早期投与群でADAS cog，Clinician's Interview-Based Impression of Change plus（CIBIC-plus）ともに認知機能の改善をみた。最終的には，1年後においても早期投与群が有意に認知機能が高かったことが示されている（図2）[1]。他のAchE阻害薬の治験では半年で評価が行われることもあり，半年後の評価でプラセボ群に比して認知機能の維持効果があるという報告が多い。ガランタミンは他のAchE阻害薬に比べ長期に効果を発揮することが示されており，海外のデータをみても，半年後，1年後において他の薬剤に比べてレスポンダー率が有意に高かったという報告がなされている。実際の効果については今後，臨床現場で評価されるであろうが，これは興味深い事実であり，薬剤の特徴を踏まえて薬を選択することができる時代になったといえる。

また，ガランタミンを早期に投与することで認知機能と日常機能が維持されたとの報告がなされている。この試験では，試験開始時からの実薬群と，プラセボ投与から半年後に実薬に切り替えた群の間で認知機能が評価されており，6カ月後において当初からの実薬群はプラセボ群よりレスポンダー率が有意に高かった（図3）[2]。このことは，本剤を使用する場合には早期発見，早期治療が重要であり，早めの薬剤投与が重要であることを意味している。なお，ガランタミンの投与にあたっては，低用量から導入し患者の状態を観察しながら増量することが肝要である。

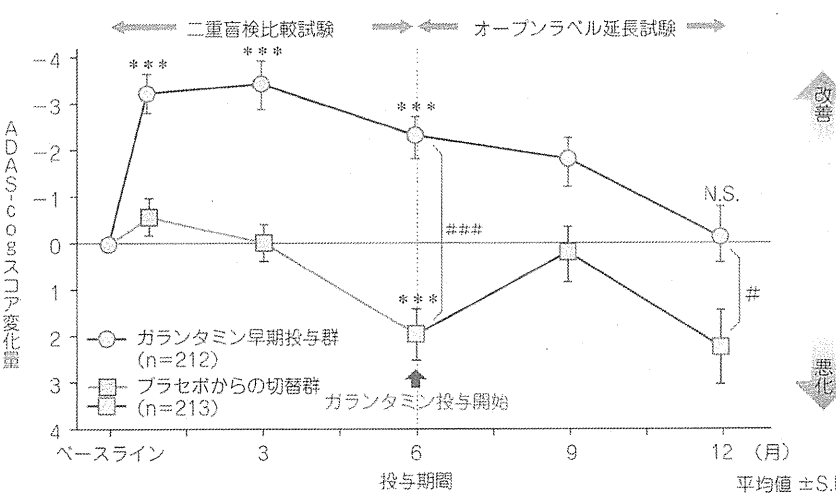
2. 介護時間の短縮

本剤では介護時間の短縮作用も報告されている。すなわち，本剤を投与された患者について長年縦断的に経過をみた海外の試験では，患者がナーシングホームに入所する時間を有意に延長したことが示されている（図4）[3]。認知機能への効果を通じて介護時間を短縮化でき，その結果，介護負担を軽減させることができるという事実は



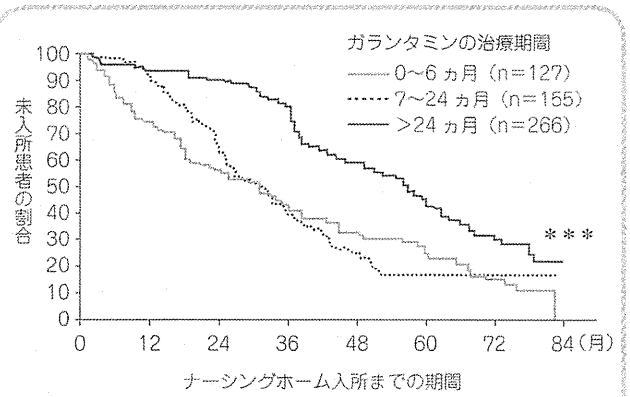
対象：軽度～中等度のAD患者194例
方法：プラセボ対照無作為化二重盲検比較試験においてガランタミン24mg/日または32mg/日の投与を受け，続くオープンラベル延長試験（それぞれ6カ月間，9カ月間）を完了した患者に，ガランタミン24mg/日を1日2回24カ月間継続投与し，認知機能に及ぼす影響をADAS-cogで評価した。なお，12カ月以降のプラセボ群のADAS-cogの推移は，過去の臨床試験のプラセボ群（Torfsら）から背景が近似した患者のデータを用い，Sternらの方法により数学的に推定した。

図2　長期投与時のアルツハイマー型認知症（AD）患者の認知機能に対する効果
〔Raskind MA, et al : Arch Neurol, 61 : 252-256, 2004より〕



＊＊＊：p<0.001（vs. ベースライン）pairwise Dunnett's test
N.S.：有意差なし（vs. ベースライン）ANOVA with pairwise Fisher's LSD test
＃：p<0.05，＃＃＃：p<0.001（vs. プラセボからの切り替え群）ANOVA
対象：軽度～中等度のAD患者425例
方法：ガランタミン24mg/日群またはプラセボ群に無作為に割り付け，1日2回6カ月間経口投与（二重盲検比較試験），オープンラベル延長試験では両群ともにガランタミン24mg/日を1日2回6カ月間経口投与し，認知機能に及ぼす影響をADAS-cogで評価した。なお，二重盲検比較試験とオープンラベル延長試験のいずれにおいてもガランタミンは8mg/日で投与を開始し，1週間後に16mg/日に増量，その1週間後に24mg/日に増量した。

図3　アルツハイマー型認知症（AD）患者の認知機能に対する効果
〔Raskind MA, et al : Neurology, 54 : 2261-2268, 2000より〕



＊＊＊：p＜0.0001（各群間比較）Kaplan-Meier log-rank test
対象：AD患者548例
方法：過去にガランタミンの海外臨床試験に参加し，ガランタミン 24mg/日を1日2回服用していた患者に追跡調査を行い，ナーシングホーム入所までの時間をガランタミン治療期間（短期：6カ月以下，中期：7～24カ月，長期：＞24カ月）により比較した。

図4　ナーシングホーム入所遅延に及ぼす影響
〔Feldman HH, et al : Int J Geriatr Psychiatry, 24 : 479-488, 2009より〕

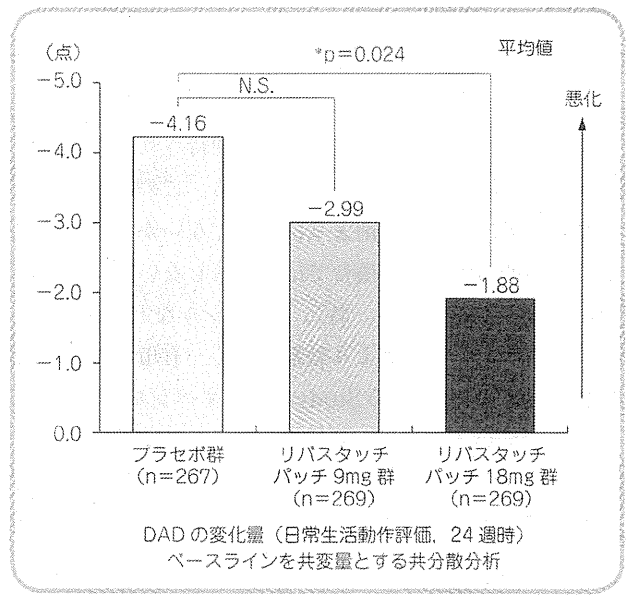


図5　手段的ADLの改善

非常に興味深い。最終的には医療経済的な観点からも，優れた結果が示されている。これも本剤が長期の効果を示すことのエビデンスの一つといえる。

リバスチグミン（図5，6）

リバスチグミンは，長期に投与した場合の有効性の報告もあり，また図5に示すように手段的ADL（IADL）（DAD尺度による）の改善効果もみられるため，認知症の早期または軽症に使用するとよい可能性がある。またパッチ剤の有用性として，1日1回貼付の簡便な投与方法で効果を示す。食事の有無および食事時間に配慮する必要がなく，他の併用薬剤の服薬時間によって本剤の投与タイミングが制約されることもない。介護者などが視覚的に容易に貼付状況（貼付の有無，投与量など）を確認できるため，コンプライアンスの向上が期待できる。患者が誤って過量投与した場合も，介護者などが貼付状況を確認することで早期発見できる。本剤投与により重大な副作用が認められた場合は，貼付した製剤を除去することで容易に投与を中止でき，副作用のさらなる重症化または重篤化を回避することができる。嚥下困難を有する場合など，経口剤で治療が困難な患者に対しても治療を容易にする。

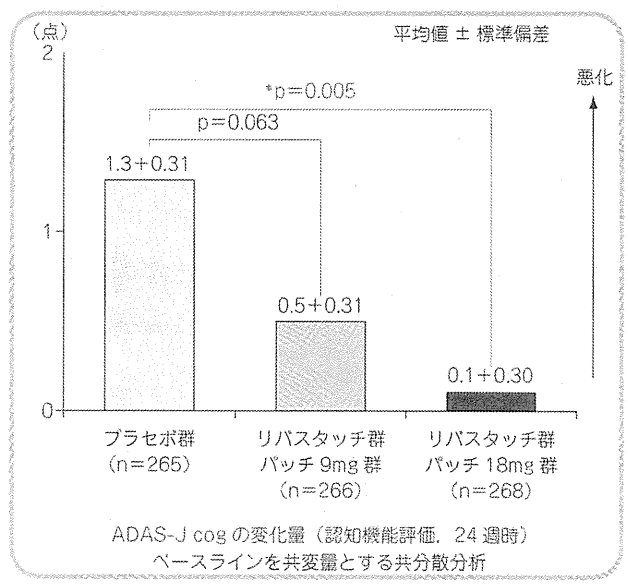


図6　認知機能の評価（ADAS-J cog）

メマンチン塩酸塩

メマンチンは，臨床的にはまず神経細胞保護作用があることから，認知機能の進行遅延が期待され，本剤による海馬の萎縮の抑制も報告されている。この認知機能に対する効果は，他の薬剤よりは大きくないかもしれないが，長期的に服用した場合では，服薬しない場合と比較して効果が認められる。特にドネペジルなどのAchE阻害薬と併用した場合はより効果が高く，有用である。最近発表されたDOMINO Studyは，ドネペジルを3カ月以上使用している中等度～重度のAD患者を対象に，ドネペジル継続，メマンチンへの変更，さらに両剤の併用による効果を比較した試験だが，メマンチンを1年ではなく2年以上投与した場合には有意差を認めたことが報告されている[4]。また，本剤には攻撃，興奮などのBPSDにも効果がある。長期処方が可能となり，その効果は広く示されはじめている。その一方で，めまい，便秘といった副作用のほか，傾眠がみられることもあるため，その場合は服用を夕方にしたり，服用量を10mg/日に抑えたりするなどの方法がある。

おわりに

ADに対して新たな薬剤を選べるようになった現在，ADを早期に発見し，早期から薬物療法を開始する有用性が期待されている。薬剤によっては長期使用時の効果についても一定のエビデンスが存在しており，その有用性は確かであろう。しかし，わが国での効果の検証は，今後一定の時間を経て判断される必要がある。新薬に対する認知症の人や家族の期待は大きいが，効果に対する過剰な期待は問題である。

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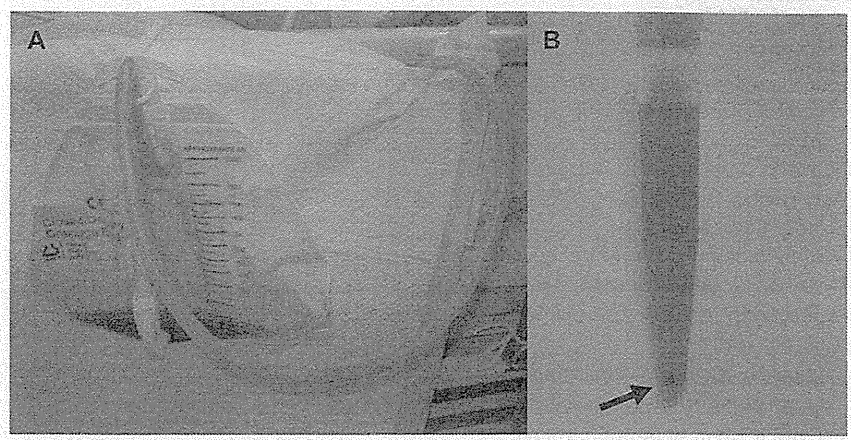

Figure 1 (a) Pink urine was noted staining the draining tube and collecting bag. (b) Pink sediment following centrifugation.

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Dysphagia in older adults at high risk of requiring care

Dear Editor,

The risk for disordered oropharyngeal swallowing (dysphagia) increases with age. Loss of swallowing function not only deprives older adults of the joy of eating, but it can have devastating health implications, including pneumonia by aspiration, which can reduce quality of life. Age-related changes, including sensory changes, new medications and sarcopenia, increase risk for dysphagia.[1]

A repetitive saliva swallowing test (RSST) was developed as a safe evaluation method for swallowing function, within an established normal range.[2,3]

In Japan, the public long-term care insurance system provides services to older adults who have been certified as requiring support (levels 1–2) or care (levels 1–5). Uncertified but not quite healthy older adults who are considered at high risk for needing support/care (termed as "specified elderly") are provided with preventive care services by the municipalities in which they reside. The specified elderly is community-dwelling and has neither basic activities of daily living impairments nor dementia.[4] Local governments provide an annual health check for the uncertified elderly in which all examined subjects complete a basic yes-no questionnaire consisting of simple assessments of instrumental activities of daily living (seven items), memory problems (three items), walking status (five items), dysphagia (three items), nutritional status (two items) and depressive mood (five items). In the current report, we compared the questionnaire answers of the group with normal swallowing function and the one with declined swallowing function, as defined by RSST, in order to characterize dysphagia among the specified elderly for a possible interventional approach to the symptom. Data for 1163 men and 2651 women considered specified elderly were obtained from municipality-sponsored annual health checks in central Japan during October and November 2009. Subjects with complete data, including RSST results, were included in the analysis. Continuous variables were compared using Student's *t*-test and others by χ^2 analysis.

As shown in Table 1, declined swallowing function by RSST was observed in 10.9% of the subjects. These subjects were older, less active, cognitively more impaired and more depressed. A multiple logistic analysis using statistically significant factors from the univariate analysis was performed (Table 2). Because of strong co-linearities with depressive mood, three items were thrown into the statistical model separately, only to find no difference in results regardless of the model.

Itoh *et al.* reported that 22% of dependent elderly already receiving care at nursing homes had dysphagia assessed by RSST.[5] The subjects in the current survey were those at risk of requiring care but not yet receiving it, which may explain the prevalence rate from the previous report. The causal relationship between dysphagia and depressive mood can be bidirectional. Declined swallowing function can spoil quality of life.[6] However, emotional factors are believed to cause disturbances in eating behavior.[7] Also cerebrovascular lesions may underlie

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Table 1 Subjects with normal swallowing function and declined function

	Normal swallowing function	Declined swallowing function	*P*-value
Number	3436	378	
Age, (years)	74.9 ± 6.1	77.1 ± 6.4	<0.01
Gender (men/women)	1053/2383	110/268	0.56
Systolic blood pressure (mmHg)	134.0 ± 17.8	134.7 ± 18.2	0.45
Dyastolic blood pressure (mmHg)	74.4 ± 10.9	73.7 ± 11.1	0.22
Hemoglobin (g/dL)	12.8 ± 1.4	12.7 ± 13.8	0.06
Albumin (g/dL)	4.3 ± 2.9	4.2 ± 2.5	0.28
Do you go out alone using transportation? (% yes)	85.4	82.0	<0.08
Do you shop for daily necessities by yourself? (% yes)	89.6	84.7	<0.01
Do you manage your bank account on your own? (% yes)	84.9	83.5	0.12
Do you visit your friends alone? (% yes)	84.7	81.5	0.12
Are you consulted by your family or friends? (% yes)	81.4	78.5	0.02
Do you climb the stairs without holding on to handrails or walls? (% yes)	39.0	35.7	0.22
Do you stand up without assistance? (% yes)	62.0	52.9	0.01
Can you walk for more than 15 minutes without rest? (% yes)	79.0	74.6	0.06
Have you fallen within the past year?	38.4	38.1	0.96
Are you anxious about falls? (% yes)	67.0	68.3	0.65
Have you lost more than 2–3 kg in weight in the past 6 months? (% yes)	28.2	25.9	0.37
BMI <18.5 kg/m^2 (% yes)	15.2	15.9	0.76
Do you have difficulty in eating hard food? (% yes)	54.3	56.1	0.51
Do you choke when you swallow liquid? (% yes)	43.7	49.7	0.03
Do you have problems with dry mouth? (% yes)	59.0	63.2	0.12
Do you go out more than once a week? (% yes)	89.3	88.4	0.60
Do you go out less frequently than last year? (% yes)	40.7	50.8	<0.01
Are you told that you repeatedly ask the same questions? (% yes)	30.0	34.1	0.10
Do you look up telephone numbers, dial and make phone calls without help? (% yes)	87.7	89.2	0.46
Do you sometimes forget the date? (% yes)	32.6	37.8	0.04
Have you felt unfulfilled with daily life (in the last two weeks)? (% yes)	21.5	27.0	0.02
I have not enjoyed my life as much as I used to (in the last 2 weeks). (% yes)	42.1	49.2	<0.01
I feel more bothered doing everyday things than I did before (in the last 2 weeks). (% yes)	38.8	49.1	<0.01
I have not felt that I am useful (in the last 2 weeks). (% yes)	27.3	28.3	0.72
I have felt tired for no reason (in the last 2 weeks). (recent 2 weeks) (% yes)	56.1	51.6	0.10

Per RSST, subjects who can swallow saliva more than three times within 30 seconds were considered to have normal swallowing function.

Table 2 Results of multiple logistic analysis

	B	*P*-value	Odds ratio	95%CI
Sex	0.051	0.680	1.052	0.827–1.339
Age**	0.047	0.000	1.048	1.029–1.066
Shop for daily necessities	0.181	0.279	1.198	0.864–1.663
Consulted by your family or friends	−0.034	0.810	0.967	0.734–1.273
Climb the stairs without holding*	0.236	0.042	1.266	1.008–1.590
Choke on liquid*	0.294	0.009	1.342	1.078–1.672
Go out less frequently*	0.245	0.037	1.278	1.014–1.611
Forget the date	0.080	0.500	1.084	0.858–1.368
Unfulfilled with daily life	−0.109	0.404	0.897	0.694–1.158

**$P < 0.01$; *$P < 0.05$

the observed association between depressive mood and dyspagia,[8] although past histories, including ischemic stroke, were not taken, which limits the interpretation of the findings.

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Disclosure statement

We have no conflicts of interest to declare.

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Toe clearance rehabilitative slipper for fall risk in institutionalized older people

Dear Editor,

Prevention of falls is one of the important targets for care of self-care dependent older people. The UK government is facing up to the challenge through increased investment in research into factors associated with maintaining muscle mass and strength, the two main modulators of physical independence in healthy older age. Ribeiro *et al.*[1] proposed that low-cost strength training of dorsi- and plantar flexors improved strength, balance and functional mobility in institutionalized older people. Chiba *et al.*[2] suggested that among gait patterns, abnormally low toe clearance is one of the factors that contributes to tripping on small obstacles or surface roughness of the floor or ground. Mechanically, a shorter toe clearance can result from functional disturbance of the anterior tibial muscle during dorsiflexion.

Sato *et al.*[3] developed a new rehabilitative training slipper, which has a space on the top of the slipper to insert a weight made of lead beads (400 g). The slipper has a back strap to prevent it coming off during walking. The mechanism by which the slipper is simulative of the anterior tibials muscle is simple; adding a weight on the top of the foot induces a torque secondary to gravity and the distance of the weight's center of mass to the ankle joint. Proprioceptive control of the foot dorsiflexion during the swing phase of normal gait thus required increased anterior tibial tone, being an isotonic exercise load on the muscle during that phase. Sato *et al.*[3] observed an improved Timed Up & Go test after 3 months of exercise in the intervention group using the rehabilitation slipper. They suggested that the rehabilitation slipper might be a useful tool for older patients with gait disorders. In the present study using the rehabilitation slipper, risk of fall was studied during a 1-year prospective intervention.

Subjects were 61 self-care dependent in patients (54 women and 17 men, aged 80.4 ± 9 years) selected randomly from the patient pool at eight nursing homes. The ethics committee of Akita University of Nursing and Welfare approved this trial, and all subjects participated after written informed consent. Participants were randomly assigned into two groups. The intervention group comprised 28 patients. The other 33 patients were assigned to the control group and received usual care. Among the 28 patients in the intervention group, four patients refused to participate or stopped soon after intervention, three patients were discharged from the nursing home, and one patient suffered arthritis and stopped intervention. Finally, 20 patients participated in the full intervention study. Among the 33 control patients, seven patients refused to participate in the control group, one patient suffered lung cancer, one patient suffered pneumonia and three patients suffered hip fractures after falls. Finally, 21 patients completed a 1-year observation examination. Physical characteristics of both groups are shown in Table 1. Care level is followed by Care Insurance established by the Japanese Ministry of Health and Welfare (from 1 to 5 grade, the higher points show severer care level). The exercise protocol was as follows. Two to four days each week for 1 year, subjects walked wearing the slippers for 10 min at a self-chosen comfortable walking speed. This was followed by 10 min of

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ORIGINAL ARTICLE

Global brain atrophy is associated with physical performance and the risk of falls in older adults with cognitive impairment

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Aim: Falls are common in patients with cognitive disorder. The purpose of this study was to determine whether global brain atrophy is associated with cognitive function, physical performance and fall incidents in older adults with mild cognitive disorder.

Methods: A total of 31 older adults with mild cognitive disorders (mean age 78.9 ± 7.3 years) were studied, and 10 of them had experienced falls and the others had not in the past 1 year. Cognitive function and physical performance were measured in these patients. Global brain atrophy was determined by the Voxel-Based Specific Regional Analysis System for Alzheimer's Disease software.

Results: Fallers showed significantly worse scores than the non-fallers in the Global Brain Atrophy Index, Clock Drawing Test (CDT), Verbal Fluency Test (animal), maximum walking time and Timed Up & Go (TUG) Test. The Global Brain Atrophy Index was correlated with the Verbal Fluency Test (animal; $r = -0.522$), the Verbal Fluency Test with letter (ka; $r = -0.337$), CDT ($r = -0.547$), TUG ($r = 0.276$) and Five Chair Stands Test ($r = 0.303$) by age-adjusted correlation analyses. Stepwise regression analysis showed that the Global Brain Atrophy Index ($\beta = 1.265$, 95% CI 1.022–1.567) was a significant and independent determinant of falls ($R^2 = 0.356$, $P = 0.003$).

Conclusion: Global brain atrophy might be indicated as one of the risk factors for falls in older adults with mild cognitive disorders. **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: falls, global brain atrophy, mild cognitive disorder.

Introduction

Falls are a significant cause of injuries, loss of confidence, increased morbidity and mortality in older adults.[1,2] One-third of community-dwelling older adults aged 65 years and older, and up to 50% of those aged 80 years and older experience falls each year.[3,4] It has been noted that older adults with cognitive impairment are more likely to suffer falls.[5] In fact, the fall rate in patients with Alzheimer's disease (AD) was reported to be nearly twofold higher than age-matched controls.[6] Furthermore, older adults with cognitive disorders have impaired balance and gait,[7] as well as impaired executive functions.[8]

Although patients with cognitive disorders have a higher risk of falls, few studies have been reported on the relationship between morphological changes of the brain and fall incidents. White matter lesions, frequently found in magnetic resonance imaging (MRI) of the aging brain,[9] are attributed to cerebral microangiopathic changes.[10] White matter lesions in older adults are also associated with gait and balance impairment,[11,12] cognitive impairment[13] and frequent falling.[14] A previous study suggested that periventricular white matter lesions might be related to falls in patients with a mild to moderate cognitive disorder.[15] Furthermore, white matter lesions can predict the incident of hip fracture in persons younger than 80 years-of-age.[16]

Previous reports showed that measures of cognitive performance in old age, such as scores on tests of intelligence, information processing speed and memory, are predicted by global and local brain atrophy.[17] However, there have been no studies to address the relationship between global brain atrophy and fall incidents. Therefore, the purpose of the present study was to determine whether global brain atrophy is associated with cognitive function, physical performance and fall incidents in older adults with mild cognitive disorders.

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Methods

Participants

Patients with a cognitive disorder who were referred to the memory clinic of the Department of Geriatric Medicine in Kyoto University Hospital, Kyoto, Japan, were enrolled in the present study. All patients underwent brain MRI, as well as a battery of laboratory tests. The diagnosis of AD and mild cognitive impairment (MCI) was made according to the following criteria: AD, Diagnostic and Statistical Manual of Mental Disorders, 4th edition and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association;[18,19] and MCI, Petersen's criteria.[20] In the present study, we did not set the upper limit of the Mini-Mental State Examination (MMSE) for the diagnosis of MCI. Of the 31 patients with a cognitive disorder, 20 were classified as mild AD and 11 were classified as MCI by the criteria. Those with MMSE scores below 19 were excluded from the present study.[21] Other exclusion criteria used in the present study were vascular dementia, dementia with Lewy bodies, lacunar infarcts, Fazekas grade 3 periventricular hyperintensity (PVH)/deep white-matter hyperintensity (DWMH),[22] severe cardiac, pulmonary or musculoskeletal disorders, and the presence of comorbidities associated with greater risk of falls, such as Parkinson's disease and stroke.

Written informed consent was obtained from each participant or his/her family members for the trial in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975.

MRI

MRI scans were carried out with a 1.5-T superconductive MRI unit (Magnetom Symphony; Siemens Medical, Erlanger, Germany). Whole-brain volumetric imaging with 3-D gradient refocused echo sequence (magnetization prepared rapid gradient echo, or MPRAGE) was carried out for voxel-based morphometry analysis using the following parameters: field of view (FOV) 22 × 22 cm, matrix 256 × 256, 120 contiguous 1.25-mm thick sagittal slices, TR/TE/TI 1700/3.93/800 ms and FA 15°.

Voxel-based morphometry

The voxel-based analysis system in the present study has been validated.[23] Currently, their software is distributed in Japan under the name, Voxel-Based Specific Regional Analysis System for Alzheimer's Disease (VSRAD). VSRAD automatically calculated the following analysis results, which reflect the severity of gray matter loss in the global brain by comparing the original normal database template. The severity of global brain gray matter loss was estimated with the Global Brain Atrophy Index, which was calculated as a percentage rate of voxels with a Z-score >2 compared with the whole brain.

Fall experience

Fall events in the past 1 year were recorded based on an interview with the family members. A fall was defined as "an event that results in a person coming to rest inadvertently on the ground or other lower level regardless of whether an injury was sustained, and not as a result of a major intrinsic event or overwhelming hazard".[5] The date, number, characteristics (e.g. while rising from a lying or sitting position, while turning in the opposite direction, while tripping over an obstacle) and consequences (e.g. bruise, fracture) of the falls were recorded using a standardized questionnaire.

Cognitive function measures

Cognitive functions were assessed by MMSE, Clock Drawing Test (CDT), Trail Making Test part A (TMT-A), Verbal Fluency Test (animal) and Verbal Fluency Test with letter (ka). MMSE is a short screening test to assess cognitive impairment, which consists of five areas: orientation, registration, attention and calculation, and recall language. The CDT is a sensitive test for executive function and early cognitive impairment. The participant was asked to draw a clock with all the numbers on it and to set the time to 10 min past 11. We used a 10-point scoring system by Rouleau *et al.*[24] The TMT-A assesses working memory capacity. Patients need to connect the numbers in order, beginning with 1 and ending with 25, as fast as possible. Word fluency is a sensitive test to detect early changes in cognitive function. In the Verbal Fluency Task (animal), patients were instructed to name as many animals as possible within 1 min. In the Verbal Fluency Task, the subject was asked to say as many words as possible beginning with the letters "ka" in 1 min.[25]

Physical performance measures

The participants were subjected to five physical function tests that are widely used to identify frail elderly. For each performance task, the participants performed two trials, and the better performance of two trials was used as scores in the analysis. The physical performance assessment, such as 10-m walking time,[26] Timed Up & Go (TUG) Test,[27] Functional Reach (FR),[28] One-Leg Stand (OLS) test[29] and Five Chair Stands (5CS) Test,[30] was carried out as previously described.

Physical activity measures

In physical activity, a valid, accurate and reliable pedometer, Yamax Power walker EX-510 (Yamasa, Tokyo, Japan) was used to measure free-living step counts.[31] Participants were instructed to wear the pedometer in their pocket on the side of the dominant leg for 14 consecutive days except when bathing, sleeping and carrying out water-based activities. This pedometer has a 30-day data storage capacity. We calculated the averages of their daily step counts for 2 weeks.

Statistical analysis

The *t*-test and χ^2-test were used to compare the results of measurements between faller and non-faller groups. The relationship between the global brain atrophy and the other measurements was investigated with the Spearman's correlation coefficient. The partial correlation coefficient between the global brain atrophy and the other measurements were adjusted for age. Multivariate logistic regression analysis using a stepwise method was carried out to investigate whether age, sex, body mass index (BMI), Global Brain Atrophy Index, word fluency animals, CDT, maximum walking time and TUG were independently associated with the fall incident. Data were analyzed using the Statistical Package for Social Science, Windows version 20.0 (SPSS, Chicago, IL, USA).

Results

There were no significant differences in age (fallers 78.2 ± 7.1 years, non-fallers 77.7 ± 5.4 years, $P = 0.53$), percentage of female (fallers 80.0%, non-fallers 71.4%, $P = 0.48$), height (fallers 150.7 ± 11.9 cm, non-fallers 153.2 ± 7.9 cm, $P = 0.37$), weight (fallers 52.9 ± 12.4 kg, non-fallers 50.5 ± 7.8 kg, $P = 0.74$) or BMI (fallers 23.2 ± 3.7, non-fallers 21.5 ± 2.8, $P = 0.39$) between the two groups (Table 1).

The fallers had significantly worse scores than the non-fallers in the Global Brain Atrophy Index (fallers 13.9 ± 8.3, non-fallers 6.8 ± 3.8, $P = 0.01$), CDT (fallers 8.2 ± 1.1, non-fallers 9.3 ± 0.8, $P = 0.01$), Verbal Fluency Test (animal; fallers 6.2 ± 2.7, non-fallers 9.5 ± 3.9, $P = 0.02$), maximum walking time (fallers 10.4 ± 4.4, non-fallers 7.5 ± 1.7, effect size 0.64, $P = 0.03$) and TUG (fallers 13.5 ± 7.0, non-fallers 8.9 ± 1.9, $P = 0.01$). However, the other measurements were not significantly different between the two groups ($P > 0.05$; Table 1, Fig. 1).

Table 1 Comparison of demographic characteristics and measurements between the groups

	Faller $n = 10$		Non-faller $n = 21$		E/S	*P*-value
	Mean	SD	Mean	SD		
Characteristics						
Age	78.2	7.1	77.7	5.4	0.08	0.53
BMI	23.2	3.7	21.5	2.8	0.45	0.39
Sex (female), n (%)	8 (80.0%)		15 (71.4%)			0.48
Disease (MCI), n (%)	5 (50.0%)		6 (28.5%)			0.32
Brain volume						
Global brain atrophy, %	13.9	8.3	6.8	3.8	0.86	0.01
Cognitive function						
Mini-Mental State Examination, points	24.7	3.8	23.7	2.5	0.27	0.59
Word Fluency Test (animals), number	6.2	2.7	9.5	3.9	0.84	0.02
Letter Fluency Test (ka), number	6.0	2.4	6.0	2.6	0.00	0.88
Clock Drawing Test, points	8.2	1.1	9.3	0.8	0.92	0.01
Trail Making Test Part-A, sec	78.7	43.2	72.3	16.1	0.15	0.53
Physical function						
Comfortable walking time, sec	12.1	4.0	10.1	2.5	0.53	0.07
Maximum walking time, sec	10.4	4.4	7.5	1.7	0.64	0.03
Timed Up & Go Test, sec	13.5	7.0	8.9	1.9	0.65	0.01
Functional Reach, cm	18.8	8.5	22.2	6.4	0.41	0.36
One-Leg Standing time, sec	6.5	11.3	16.7	18.8	0.91	0.06
Five Chair Stands, sec	11.9	2.8	10.5	3.2	0.48	0.18
Activity						
Physical activity, steps	3167.9	2213.1	4499.8	2934.4	0.45	0.21

MCI, mild cognitive impairment.

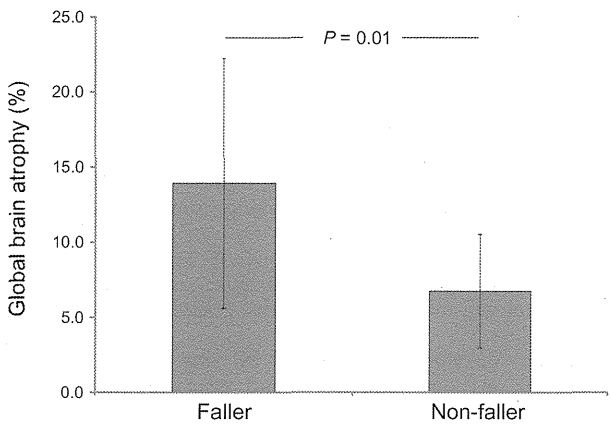

Figure 1 Comparison of Global Brain Atrophy Index (%) between the groups. The fallers ($n = 10$) had significantly worse scores than the non-fallers ($n = 21$) in the Global Brain Atrophy Index.

To determine the association of global brain atrophy with their demography, cognitive function, physical performance and physical activity, we determined Pearson's correlation coefficients. Table 2 shows that the Global Grain Atrophy Index was correlated with age ($r = 0.435$, $P < 0.05$), Verbal Fluency Test (animal; $r = -0.641$, $P < 0.05$), Verbal Fluency Test with letter (ka; $r = -0.320$, $P < 0.05$), CDT ($r = -0.338$, $P < 0.05$), comfortable walking time ($r = 0.555$, $P < 0.05$), maximum walking time ($r = 0.543$, $P < 0.05$), TUG ($r = 0.630$, $P < 0.05$), OLS ($r = -0.581$, $P < 0.05$), 5CS ($r = 0.437$, $P < 0.05$) and physical activity ($r = -0.389$, $P < 0.05$; Table 2).

To age-adjust the association of Global Brain Atrophy Index with their demography, cognitive function, physical performance and physical activity, we analyzed partial correlation coefficients. Table 2 shows that global brain atrophy was correlated with BMI ($r = 0.308$), Verbal Fluency Test (animal; $r = -0.522$, $P < 0.05$), Verbal Fluency Test with letter (ka; $r = -0.337$, $P < 0.05$), CDT ($r = -0.547$, $P < 0.05$), TUG ($r = 0.276$, $P < 0.05$) and 5CS ($r = 0.303$, $P < 0.05$; Table 2).

Stepwise regression analysis showed that the Global Brain Atrophy Index ($\beta = 1.265$, 95% CI 1.022–1.567) was a significant and independent determinant of falls ($R^2 = 0.356$, $P = 0.003$; Table 3).

Discussions

The present study showed that the fall incident might relate to global brain atrophy in older adults with mild cognitive disorders. The fallers also showed a significantly higher Global Brain Atrophy Index, and lower physical and cognitive performance scores than the non-fallers. Age-adjusted correlation analyses showed that the Global Brain Atrophy Index was weakly correlated with several cognitive and motor performances. Furthermore, stepwise regression analysis showed that the Global Brain Atrophy Index was a significant

Table 2 Correlation coefficients for global brain atrophy and other measurements

	Global brain atrophy	Global brain atrophy (adjusted for age)
Characteristics		
Age	0.435	
Cognitive function		
Mini-Mental State Examination	0.019	−0.147
Word Fluency Test (animals)	−0.641	−0.522
Letter fluency Test (ka)	−0.320	−0.337
Clock Drawing Test	−0.338	−0.547
Trail Making Test Part-A	0.067	0.053
Geriatric Depression Scale	0.210	0.181
Physical function		
Comfortable walking time	0.555	0.205
Maximum walking time	0.543	0.221
Timed Up & Go Test	0.630	0.276
Functional reach	−0.121	−0.009
One-Leg Standing time	−0.581	−0.204
Five Chair Stands	0.473	0.303
Activity		
Physical activity	−0.389	−0.169

Table 3 Logistic regression analysis

Independent variables	Adjusted R^2 value = 0.356 Standard regression value	95% CI
Age	–	–
Sex	–	–
BMI	–	–
Brain atrophy index	1.265	1.022–1.567
Word Fluency (animals)	–	–
Clock Drawing Test	–	–
Maximum walking time	–	–
Timed Up & Go Test	–	–

BMI, body mass index.

and independent determinant of the fall incident. Taken together, these findings led us to conclude that measuring global brain atrophy is potentially important to predict falls in patients with mild cognitive disorders.

The mechanisms by which global brain atrophy associates with fall incident and poor physical performance are not well understood. It is possible that global brain atrophy is related to poor neural connectivity. However, we assume that global brain atrophy is mostly attributed to the volume loss in the frontal lobe, because Rosano *et al.* suggested that a smaller prefrontal region was associated with slower gait speed.[32] In contrast, it has been shown that atrophy of dorsolateral prefrontal regions is associated with poorer executive function.[33] Previous imaging research has also shown that brain atrophy is associated with impaired physical and executive functions.[17,34] As expected, physical and executive functions have been associated with an increased fall risk in older adults.[35,36] These reports and the present study suggested that the function of the frontal lobe is associated with the risk of falls, and brain atrophy index can be a biomarker to predict falls.

There are several limitations in the present study. First, the limited sample size might introduce some error of inference, reduce the power of the analysis and limit generalization. Second, global brain atrophy might not be able to predict falls in more robust older adults, as the present study was based on the participants having experienced falls in the previous year. Further study is required to confirm our finding in patients who do not have an experience of falls. Finally, detailed information on falls was lacking. Therefore, the relationship between the decline of frontal lobe function and fall incidents requires further investigation. Thus, the results of the present study should be interpreted with caution.

In conclusion, this is the first study to show that global brain atrophy is associated with fall incident, motor and cognitive performance in older adults with mild cognitive disorders. From the present results, global atrophy might be indicted as one of risk factors for falls in older adults with mild cognitive disorders. Further investigation, such as a prospective study, is required to confirm the present study.

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Original Study

Community-Based Exercise Program is Cost-Effective by Preventing Care and Disability in Japanese Frail Older Adults

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Keywords:
Care prevention program
long term care insurance
older adults
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A B S T R A C T

Background: In Japan, older adults are assessed by frailty checklist for care prevention. However, the effect of care prevention programs in community-dwelling frail older adults is still unclear.
Objectives: The purpose of this study was to investigate whether the care prevention program would reduce care and disability and to measure its cost-effectiveness in frail older adults.
Design: This is a prospective study using propensity score matching.
Setting and subjects: A total of 610 community-dwelling older adults were recruited in 2 cities of Japan.
Intervention: Subjects in the exercise group (n = 305) attended physical exercise sessions once a week for 16 consecutive weeks. The exercise sessions were in a standardized format consisting of moderate-intensity aerobic exercise, progressive strength training, flexibility and balance exercises, and cool-down activities. The control group (n = 305) received only screening evaluation.
Measurements: Primary outcome was long term care insurance requirement certification during the 1-year follow-up period. Secondary outcome measurements were changes of frailty checklist, and care and medical cost.
Results: Twenty-five subjects (8.1%) in the exercise group and 55 (18%) in the control group were newly certified for long-term care insurance service requirement in 1 year after the intervention (RR = 2.16, 95% CI = 1.46–3.20). Consequently, the health care cost for the subjects in the exercise group was significantly lower than in the control group ($P < .001$). Moreover, subjects in the exercise group had significant improvements in total scores of the frailty checklist compared with the control group that worsened after 1 year (exercise group: from 7.41 ± 3.98 to 7.11 ± 4.00, control group: from 7.34 ± 4.27 to 8.02 ± 4.81, F = 12.84, $P < .001$).
Conclusion: These results suggested that physical exercise is effective in preventing the progression of frailty and further disability in older adults living in the community. We could save heath care costs by our care prevention program.

The aged population in Japan is increasing faster than in any other country. Frailty in older adults is a serious problem in aged countries, such as in Japan. In general, frailty can be defined as a vulnerable state that places older adults at high risk for adverse health outcomes, such as falls, hospitalization, and mortality.[1] Therefore, to prevent the adverse outcomes of frailty, multicomponent exercise programs have been implemented and provided a beneficial effect on activities of daily living (ADLs) and instrumental ADL disability for community-dwelling moderately frail older adults.[2]

Japan implemented a long term care insurance (LTCI) system in April 2000 to deal with the extremely rapid aging process of our population. Before 2000, long term care services were provided under a tax-based social welfare system targeting seniors with limited economic resources and family support.[3] After LTCI implementation, however, LTCI services have been provided to the elderly who are certified, as a support requirement or care requirement according to their care needs and certification assessment.[4] The selection process for classifying dependent older adults is first based on a questionnaire that evaluates a person's current mental and physical condition (74 items), and then the first decision is reached by computerized algorithm. The second decision is made by a long term care approval board based on the first computer decision, doctor's recommendation, and the home-visit report. Finally, people who are certified as dependent older adults are subdivided into 7 levels (requiring support levels 1 and 2 and care levels 1 to 5) depending on their conditions. They are provided home- and community-based or institutional services according to the care needs. Individuals who are not eligible for long term care or support care may use preventive care services.

The authors declare no conflicts of interest.

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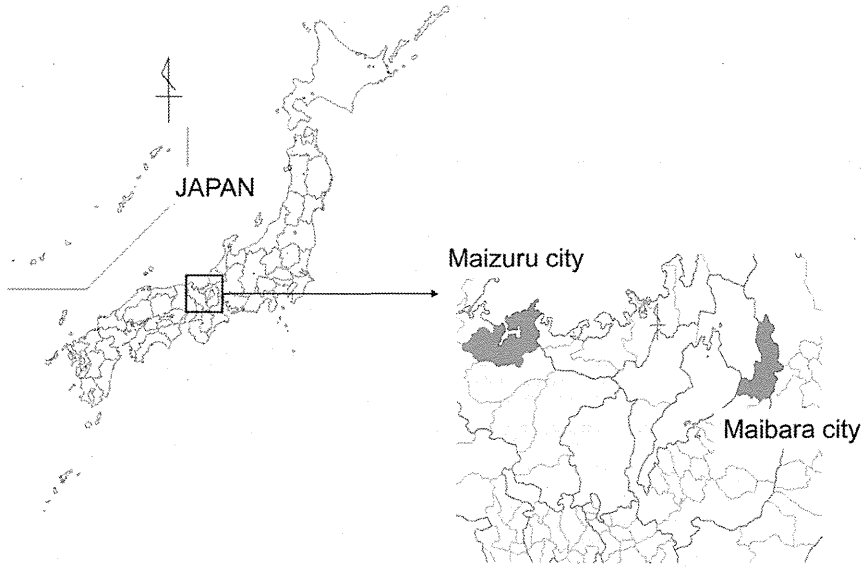

Fig. 1. Location of Maibara and Maizuru City in Japan.

In 2006, the LTCI system was revised and new preventive benefits were introduced. The aim of this system was to allocate the limited resources to impaired elderly by providing services intended to improve physical strength, nutritional status, oral function, and mental health.[5] The LTCI system also increased emphasis on preventive care services for those with lower needs and those at risk for needing care in the future, in which pre-frail and frail older adults can be selected by a frailty checklist. The local governments provide a frailty checklist to uncertified older adults, and all older adults are required to fill out a basic yes or no questionnaire consisting of assessments of their lifestyle, motor abilities, nutrition, oral function, seclusion, forgetfulness, and emotions. According to the results of impairment on a specific domain, the government provides several intervention programs to prevent care and disability of older adults; however, the effect of the care prevention program on frail older adults is still unclear.

The aim of the current study, therefore, was to evaluate the effect of an exercise intervention on care and disability classified by LTCI service requirement certification and health care cost in community-dwelling older adults. We hypothesized that subjects who attend the care prevention program have a lower chance of being certified for the LTCI service requirement than nonparticipants, and as a result, the intervention can save health care costs.

Methods

Subjects

We analyzed the cohort data from a prospective study: the Japan Multi-center Aging Cohort for Care prevention. In this study, in 2009, we recruited community-dwelling older adults who were

Table 1
Frailty Checklist of Japan

Domain	Question	Items	Yes	No
Lifestyle	1	Do you ride the bus or train alone?	0	1
	2	Do you buy household goods for everyday use?	0	1
	3	Do you withdraw and deposit savings?	0	1
	4	Do you visit your friends' homes?	0	1
	5	Do you give advice to family and friends?	0	1
Motor abilities	6	Can you climb stairs without holding onto a handrail or the wall?	0	1
	7	Can you get up from a chair without grabbing something?	0	1
	8	Are you able to keep walking for about 15 minutes?	0	1
	9	Have you fallen in the past year?	1	0
	10	Are you very worried about falling?	1	0
Nutrition	11	Have you ever lost more than 2–3 kg of weight in a 6-month period?	1	0
	12	BMI is less than 18.5.	1	0
Oral function	13	I cannot eat hard foods as well as 6 months ago.	1	0
	14	Have you ever choked on tea or soups?	1	0
	15	Are you concerned with being thirsty?	1	0
Seclusion	16	Do you leave your home at least once a week?	0	1
	17	Compared to last year, has the number of times you go out decreased?	1	0
Forgetfulness	18	Are you told that you are forgetful or you always tell me the same thing?	1	0
	19	Do you look up phone numbers and make phone calls yourself?	0	1
	20	Do you sometimes forget the date and month?	1	0
Emotions	21	(In the past 2 weeks) I do not feel fulfillment in my daily life.	1	0
	22	(In the past 2 weeks) The activities I used to enjoy are no longer enjoyable.	1	0
	23	(In the past 2 weeks) The activities I used to carry out with ease have become troublesome.	1	0
	24	(In the past 2 weeks) I do not think I am a useful person.	1	0
	25	(In the past 2 weeks) I feel tired for no reason.	1	0

BMI, body mass index.

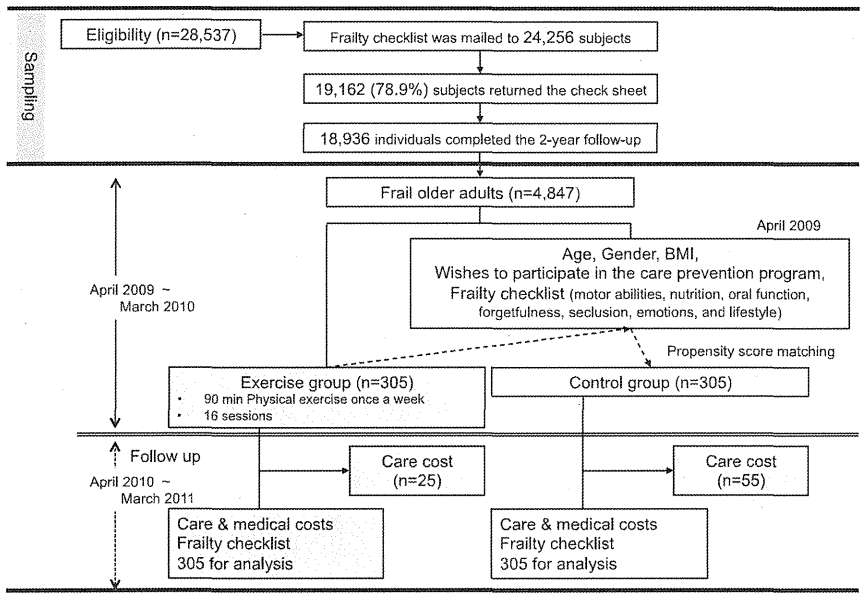

Fig. 2. A flow chart showing the distribution of subjects throughout the trial.

independent in ADLs in 2 cities (Maibara City in Shiga Prefecture and Maizuru City in Kyoto Prefecture) (Figure 1). The exclusion criteria were older adults who were already ADL-dependent and were eligible to receive benefits from LTCI services.

A total of 28,537 residents were eligible for this study in April 2009. The self-administered frailty checklist was mailed to 24,256 subjects, and the response rate was 78.9%. We further excluded individuals who died or moved from the cities in the 2-year follow-up, and analyzed 18,936 elderly. Subjects for the care prevention program were recruited using direct mail. We screened subjects in an initial interview and recruited frail older adults 65 years or older.

This study was conducted in accordance with the guidelines proposed by the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of Kyoto University Graduate School of Medicine.

Frailty Checklist

The frailty checklist includes simple yes/no questions concerning lifestyle (questions 1 to 5), motor abilities (questions 6 to 10), nutrition (questions 11 to 12), oral functions (questions 13 to 15), seclusion (questions 16 to 17), forgetfulness (questions 18 to 20), and emotions (questions 21 to 25) (Table 1). We calculated the scores in each of these 7 domains.

Table 2
Baseline Characteristics of the Study Subjects in Exercise and Control Groups

	Exercise Group (n = 305)		Control Group (n = 305)		*P* Value
	Mean	SD	Mean	SD	
Age, y	79.7	6.3	80.3	6.6	.275
Gender, female	231 (75.4%)		238 (78.0%)		.560*
Height	151.5	8.0	151.1	8.3	.509
Weight	53.1	10.0	51.8	10.2	.128
BMI, kg/m^2	23.0	3.4	22.6	3.5	.129
Falls in past year	107 (35.1%)		114 (37.4%)		.670*
Total scores of frailty checklist	7.41	3.98	7.34	4.27	.814

BMI, body mass index.
*Chi-square test.

Impaired physical condition was defined as having 3 points or more in motor ability items according to the Japanese Ministry of Health, Labor, and Welfare. Malnutrition was defined as having 2 points in nutrition items, poor oral health as having 1 point or more in oral function items, seclusion as having 1 point or more in seclusion items, cognitive decline as having 1 point or more in forgetfulness items, and depressive mood as having 2 points or more in emotion items. Frailty was defined by scores of 10 or more points on questions 1 to 20.

Definition of Frail Older Adults in this Study

In this study, we defined frail older adults as those who need to maintain or to improve daily functions. These individuals are not eligible for the LTCI service requirement as defined by the government, but have a high risk of becoming dependent based on the results of the frailty checklist.[5] Those older adults are defined as having impaired motor abilities, malnutrition, poor oral health, or impaired lifestyle as described in the previous paragraph.

Care Prevention Program

The subjects received 90 minutes of group training sessions once a week for 16 consecutive weeks. The exercise class was supervised by a physiotherapist. The exercise sessions were conducted according

Table 3
Comparison of New LTCI Service Requirement Certification Between the 2 Groups

	Exercise Group, n (%)	Control Group, n (%)	RR	95% CI
LTCI requirement	25 (8.1%)	55 (18.0%)	2.16	1.46–3.20
Support level				
1	11	15		
2	7	14		
Care level				
1	4	13		
2	3	7		
3	0	3		
4	0	3		
5	0	0		

CI, confidence interval; LTCI, long term care insurance; RR, relative risk.

Table 4
Frailty Checklist Scores in Each Group at Baseline and After Intervention

	Baseline		After Intervention		Group × Time Interaction	
	n (%)	*P* Value	n (%)	*P* Value	F Value	*P* Value
Motor ability domain score						
Exercise (n = 305)	181 (59.5)	.414	177 (58.0)	.087		
Control (n = 305)	185 (60.7)		158 (51.7)			
Nutrition domain score						
Exercise (n = 305)	10 (3.4)	.348	11 (3.5)	.364		
Control (n = 305)	13 (4.3)		8 (2.6)			
Oral function domain score						
Exercise (n = 305)	114 (37.5)	.210	113 (37.0)	.073		
Control (n = 305)	104 (34.0)		94 (30.7)			
Forgetfulness domain score						
Exercise (n = 305)	139 (45.6)	.430	120 (39.3)	.037		
Control (n = 305)	142 (46.7)		145 (47.6)			
Seclusion domain score						
Exercise (n = 305)	66 (21.6)	.349	19 (6.2)	<.001		
Control (n = 305)	61 (20.0)		50 (16.5)			
Emotions domain score						
Exercise (n = 305)	144 (47.3)	.407	133 (43.6)	.008		
Control (n = 305)	140 (46.0)		167 (54.7)			
Lifestyle domain score						
Exercise (n = 305)	47 (15.5)	.517	36 (11.7)	.003		
Control (n = 305)	46 (15.1)		64 (21.0)			
Total score						
Exercise (n = 305)	7.41 ± 3.98		7.11 ± 4.00		12.84	<.001*
Control (n = 305)	7.34 ± 4.27		8.02 ± 4.81			

*Two-way analysis of variance adjusted for age and gender.

to a standardized format consisting of 20 minutes of moderate-intensity aerobic exercise, 30 minutes of progressive strength training, 20 minutes of flexibility and balance exercises, and 20 minutes of cool-down activities. The aerobic exercise was composed of global movement of the legs, trunk, and arms involving all joints and major muscle groups in activities such as dance. Strength training consisted of progressive resistive exercises using an elastic band. A sequence of progressively difficult exercises was also performed to improve static and dynamic balance. The control group received screening evaluation only.

Propensity Score Matching

We used propensity score matching to assemble a cohort of the exercise group, then the 2 groups would be well matched on all measured baseline characteristics, such as age, gender, body mass index, wishes to participate in the care prevention program, motor abilities, nutrition, oral function, forgetfulness, seclusion, and emotions. We estimated the scores of the exercise group for each subject using a multivariable logistic regression model. We were able to match 305 pairs of exercise and control subjects who had similar propensity scores.

Outcome Measures

Primary outcome was the new LTCI service requirement certification at 1 year after the conclusion of the intervention. Secondary outcomes were changes of frailty checklist, LTCI cost, and medical cost. The LTCI cost indicates use of home care services, nursing care, or day care services and nursing home. The utilization records of LTCI benefit services during 1 year were collected from the local governmental office. The medical cost covers almost all medical treatment, including diagnostic tests, medications, surgery, supplies and materials, physicians, and other personal cost.

Statistical Analysis

Baseline characteristics of the intervention and control groups were examined for comparability of the 2 groups. Differences in the demographic variables between the 2 groups were analyzed using the Student *t* test or chi-square test. Relative risk was then calculated, and the chi-square test was used to evaluate the effect of the care prevention program on the new LTCI service requirement and the influence on each domain of frailty checklist. Analysis of covariance was used to determine the effect of the care prevention program on total points of frailty checklist, using age as covariates. Post hoc Tukey tests were used to assess whether group or time periods showed significant differences. Multiple logistic regressions using a stepwise method was performed to investigate which of age, gender, or the decline in frailty checklist for each category was independently associated with the change of frailty checklist (improvement, maintenance, or deterioration). Finally, differences in the care and medical cost between the 2 groups were analyzed using the Student *t* test. Data were entered and analyzed using the Predictive Analytics Software (Windows version 18.0, SPSS, Inc., Chicago, IL). A *P* value less than .05 was considered statistically significant for all analyses.

Table 5
Change of Each Domain in Frailty Checklist After Exercise Intervention

Dependent Variables	Adjusted Odds Ratio (95% Confidence Interval)						
	Motor Abilities	Nutrition	Oral Functions	Forgetfulness	Seclusion	Emotions	Lifestyle
Change in checklist	2.29 (1.58–3.31)	5.32 (1.52–18.62)	—	1.77 (1.22–2.57)	—	—	—

1 = improvement, 0 = maintenance or deterioration.

Table 6
Comparison of Long Term Care Insurance and Medical Costs Between the 2 Groups

	Exercise Group, n = 305	Control Group, n = 305	*P* Value
	Mean ± SD	Mean ± SD	
Care costs* dollars	1126.8 ± 1797.9	4430.7 ± 6324.7	<.001
Medical costs dollars	2458.7 ± 1968.7	3458.0 ± 5847.1	<.001

One dollar = 88 yen.
*Exercise group: n = 25, control group: n = 55.

Results

Of the 610 individuals, all subjects completed the 1-year follow-up: 305 in the exercise group, and the others in the control group (Figure 2). All 16 scheduled intervention sessions were completed. The median relative adherence was 100% (25th–75th percentile, 88%–100%) in the exercise group. No fall incidents or health problems, such as cardiovascular or musculoskeletal complications, occurred during training sessions or testing. Minor problems were muscle ache and fatigue. All problems were managed easily using adjustment of the intervention, and they improved during the intervention. Subjects in the exercise and control groups were comparable and well matched with regard to their baseline characteristics (Table 2).

During 1 year after the intervention, 25 subjects (8.1%) in the exercise group and 55 (18.0%) in the control group were newly certified for the LTCI service requirement. Therefore, the relative risk for new LTCI service requirement in the control group compared with the exercise group was 2.16 (95% confidence interval [CI] = 1.46–3.20) (Table 3).

At baseline, all domains of the frailty checklist were not significantly different between the 2 groups (Table 3). Subjects in the exercise group had significant improvements in total scores of the frailty checklist compared with the control group that worsened after 1 year (exercise group: from 7.41 ± 3.98 to 7.11 ± 4.00, control group: from 7.34 ± 4.27 to 8.02 ± 4.81, F = 12.84, $P < .001$) (Table 4) as well as in forgetfulness, seclusion, emotion, and daily life domains ($P < .05$); however, the other domains were not significantly different between them ($P > 0.05$).

Stepwise logistic regression analysis revealed that motor ability domain (OR = 2.29, 95% CI 1.58–3.31), nutrition domain (OR = 5.32, 95% CI 1.52–18.62), and forgetfulness domain (OR = 1.77, 95% CI 1.22–2.57) were significant and independent determinants of the change in frailty checklist ($P < .001$) (Table 5).

Finally, we calculated the cost-effectiveness of this intervention, and found that subjects in the exercise group spent significantly lower care cost than the control group (exercise group: $1126.8 ± 1797.9, control group: $4430.7 ± 6324.7, $P < .001$) (Table 5), whereas subjects in the exercise group spent significantly less on medical costs than the control group (exercise group: $2458.7 ± 1968.7, control group: $3458.0 ± 5847.1, $P < .001$) (Table 6).

Discussion

In this study, we addressed the role of the physical exercise program for frail older adults, and have shown that the subjects who received physical exercise sessions demonstrated a lower incidence of new LTCI service requirement, improved frailty checklist, and reduced care and medical costs.

The current results indicated that the care prevention program had a beneficial effect on frailty in older adults. Specifically, the physical exercise program showed more beneficial effects on older adults with impaired motor ability, malnutrition, and forgetfulness. Previous studies also confirmed the benefits of physical exercise training on frail older adults.[6,7] In addition, a systematic review by Daniels and colleagues[2] suggested that multicomponent exercise programs have a positive effect on ADL and instrumental ADL disability for community-living moderate physically frail older adults. These reports and our findings suggested that the physical exercise program is effective in preventing frailty.

Moreover, our results indicated that the care prevention program could reduce health care costs. Owing to the positive effect on cognition, seclusion, depression, and instrumental ADLs, the program might also be associated with fewer medical costs. In addition, intervention by the prevention program showed a lower incidence of new LTCI service requirement certification, resulting in lower care costs. On the other hand, Frick and colleagues[8] reported that the physical exercise program was not cost-effective by evaluating the cost-effectiveness of fall-prevention programs for fall-related hip fractures in older adults. These results suggest that all the physical exercise programs are not always cost-effective. Further study is required to determine how to perform cost-effective interventions in frail older adults.

There were several limitations of this study that warrant mention. First, we did not measure physical performance, and used only the frailty checklist to define frailty. There is a possibility that the frailty checklist may not be the best instrument to define frailty, such as the Short Physical Performance Battery that evaluates balance, gait, strength, and endurance by examining an individual's ability.[9] Second, our study design was not a randomized controlled trial. Therefore, these findings should be interpreted with caution.

This is the first study to demonstrate that the care prevention program is effective to improve the scores of the frailty checklist. In addition, subjects who received the care prevention program demonstrated a lower incidence of new certification of LTCI service requirement with a lower cost during the follow-up period. These results implicated the importance of care prevention programs to reduce care and disabilities in older adults. A larger study is needed to confirm the present results and to evaluate the most effective exercises for the prevention of disability in older adults.

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