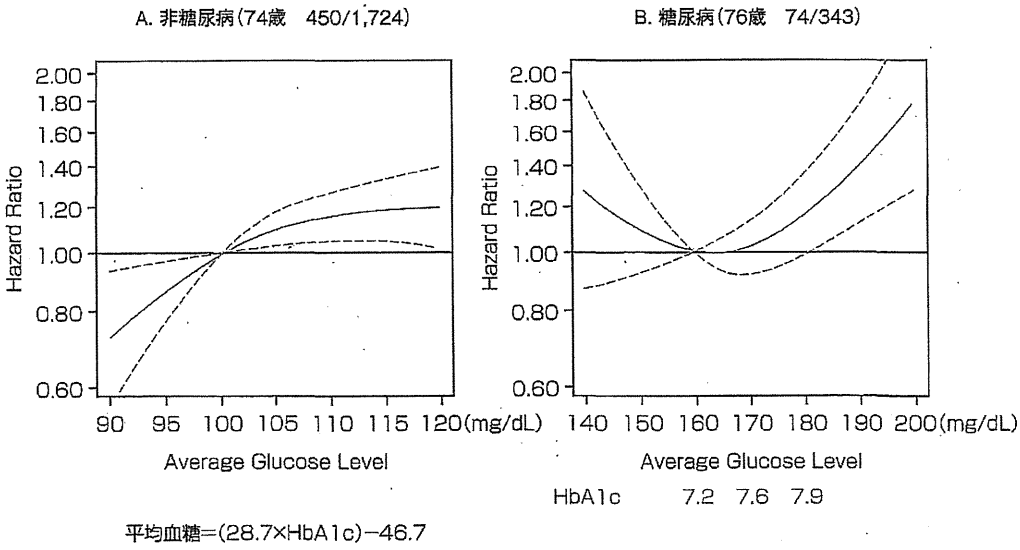

図5　血糖管理と認知症の発症予防
(文献8)より)

値を考えるのが基本的な考え方である．健常な高齢者糖尿病ではHbA1cを7.0±0.5%を目標とするが，5年以上の生命予後が期待できない例，あるいは虚弱な高齢者では，おおむね8.0±0.5%とすることが共通している[9]．

認知症を合併した高齢者糖尿病が，健常〜虚弱のどこに位置するかには議論が残る．しかし少なくともある程度進行した認知症では，身体虚弱が合併しており，HbA1cの目標値を8.0±0.5%とすることは合理的であろう．軽症の認知症の血糖管理目標値についてはエビデンスがない．血糖自己測定を行い，夜間低血糖が生じていないか注意すべきである．

糖尿病の薬剤選択（図6）[10]

インスリン分泌促進薬であるスルホニル尿素（SU）薬は，血糖降下作用は強力であるが，高齢者では遷延性低血糖に注意する．速効性インスリン分泌薬やα-グルコシダーゼ阻害薬は毎食直前に内服が必要で，高齢者ではコンプライアンスに問題がある．インスリン抵抗性改善薬であるチアゾリジン薬はADの認知障害を改善させるとの報告があり期待される．しかし認知機能の長期改善効果については，一定の結論に至っていない．ビグアナイド薬については，脳に対する効果はいまだ明確でない．インクレチン関連薬であるDPP-4阻害薬，およびGLP-1受容体作動薬は，単独では低血糖のリスクが低いこと，血糖の変動を改善する作用があり，認知症高齢者では理論上は第一選択薬となりえる．しかし現在のところ，DPP-4阻害薬が認知機能を改善したとする報告はない．最近，GLP-1受容体作動薬がParkinson病の運動障害と認知機能を抑制したと報告された[11]．インスリン療法では，低血糖のリスクが最も重要な問題となり，経口薬で血糖管理が困難な例では，GLP-1受容体作動薬の適応も積極的に考えたい．

おわりに

糖尿病における認知症の治療は，糖尿病の管理と認知症の治療を同時に行う．認知症を合併した高齢者糖尿病では，高血糖による代謝性脳症がオーバーラップしており，糖尿病を適正に管理することで，認知障害の少なくとも一部は改善しうる．認知症の予防では運

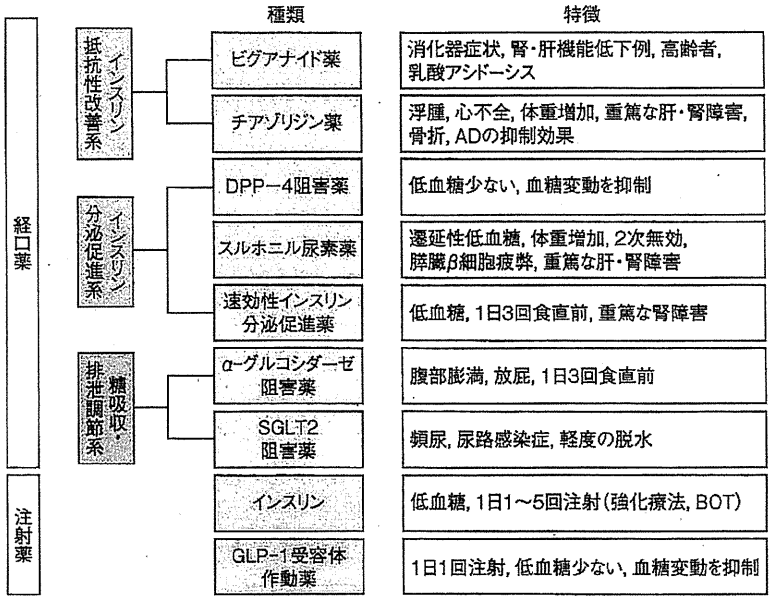

図6　糖尿病治療薬のまとめ
（文献10）より改変）

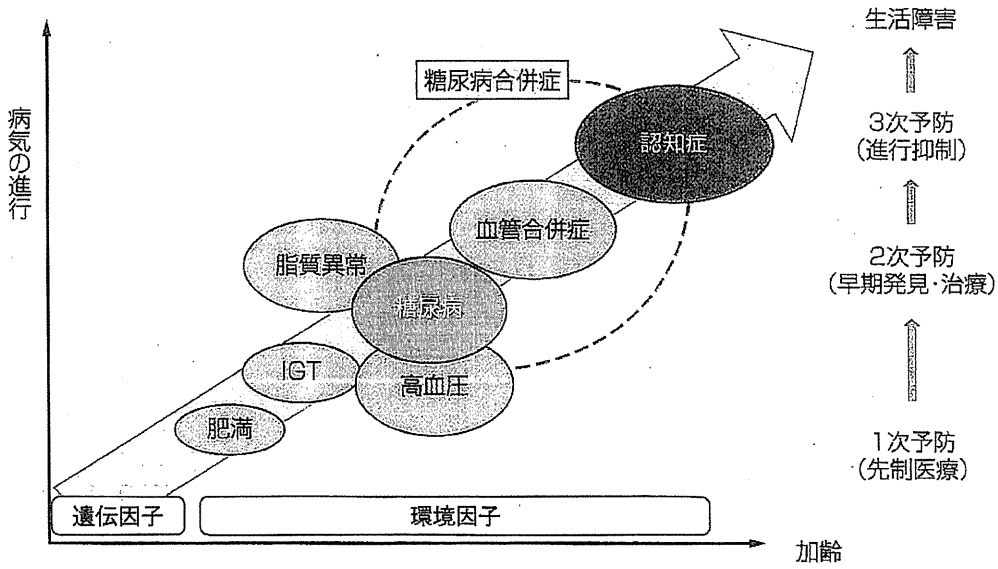

図7　認知症発症を見据えた糖尿病治療

動も有効で，糖尿病の治療との共通点も多い．

糖尿病の人生最後の合併症である認知症を，高齢者の病気としてとらえるのではなく，成年期からの糖尿病治療の延長上に考えることが重要である（図7）．認知症のリスク因子である糖尿病の管理により，将来のわが国では認知症が減少することを期待したい．

文献　1）Cukierman T, et al.:Cognitive decline and dementia in diabetes–systematic overview of prospective observational studies. Diabetologia 48:2460-2469, 2005
2）櫻井　孝：糖尿病治療薬による認知症治療への期待．月刊糖尿病4:88-97，2012
3）Matsuzaki T, et al.:Insulin resistance is associated with the pathology of Alzheimer disease:the Hisayama study. Neurology. 75:764-770, 2010

4) Sakurai T, et al.:Age-associated increase in abdominal obesity and insulin resistance, and usefulness of AHA/NHLBI definition of metabolic syndrome for predicting cardiovascular disease in Japanese elderly with type 2 diabetes mellitus. Gerontology 56:141-149, 2010
5) Luchsinger J, et al.:Improved diabetes control in the elderly delays global cognitive decline. J Nutr Health Aging 15:445-449, 2011
6) Umegaki H, et al.:Risk factors associated with cognitive decline in the elderly with type 2 diabetes:pooled logistic analysis of a 6-year observation in the Japanese elderly diabetes intervention trial (J-EDIT). Geriatr Gerontol Int 12 (Suppl 1):110-116, 2012
7) Ohara T, et al.:Glucose tolerance status and risk of dementia in the community:the Hisayama study. Neurology. 77:1126-1134, 2011
8) Crane PK, et al.:Glucose levels and risk of dementia. N Engl J Med 369:540-548, 2013
9) 井藤英喜：高齢者における肥満と糖尿病（2）糖尿病．長寿科学振興財団：高齢者における生活習慣病，101-111，2012
10) 日本糖尿病学会（編）：科学的根拠に基づく糖尿病診療ガイドライン2013．南江堂，2013
11) Aviles-Olmos I, et al.:Exenatide and the treatment of patients with Parkinson's disease. J Clin Invest 123:2730-2736, 2013

著者連絡先 （〒474-8511）愛知県大府市森岡町源吾35
国立長寿医療研究センター もの忘れセンター 櫻井 孝

高齢者の糖尿病
7. 高齢者糖尿病の管理（血糖管理を中心に）

櫻井　孝

Key words：elderly, diabetes, glycemic control, frail, cognitive decline
〔糖尿病 57(9)：696～698, 2014〕

はじめに

高齢者糖尿病は多様である．日常生活動作(ADL)の自立した元気な高齢者から，寝たきり，余命いくばくもない高齢者まで幅が広い．発症時期が重要で，若・壮年期に発症した糖尿病が高齢となった患者と，高齢期に初めて発症した糖尿病が混在する．高齢期に発症した糖尿病は，一般に軽症糖尿病が多い．一方，長期の糖尿病歴を有する患者が高齢化した場合は，高血糖の程度はより高度で，糖尿病性細小血管症を合併していることが多い．いずれのタイプの糖尿病であっても，動脈硬化性血管障害の合併率が高く，血管合併症が多いことが高齢者糖尿病の特徴である．

高齢者では高血糖・低血糖などの急性代謝失調に加え，糖尿病の慢性合併症や併発疾患のため，生命予後のみならず生活機能も低下する．このため血糖管理目標値の考え方にも様々な合併症を抑制する視点が含まれるべきである．

血糖コントロールが余命延長に及ぼす影響

糖尿病患者の死因は日本人一般と比較して，血管障害とくに虚血性心疾患と腎障害が多く，男性・女性とも約10年短命である．高齢者における血糖コントロールを考える上で重要な要因は平均余命である．Huangらは，通常コントロール群（HbA1c<7.9％）と厳格治療群（HbA1c<7.0％）で予想される平均余命の差を，UKPDSの結果に基づき数学的に計算した．平均余命に影響を与える因子からmortality indexを算出したところ，後期高齢者では，厳格な血糖管理による余命延長効果が短縮していた．併発疾患や生活機能障害が高度であると，HbA1cの改善による余命延長効果はさらに短縮する．つまり血糖コントロールの利益が少なくなる．年齢，合併疾患，生活障害から余命を考えた糖尿病管理を計画すべきである．

高血糖と糖尿病血管症

高齢者においても高血糖は網膜症，腎症および大血管症の危険因子である．しかし高齢者で良好な血糖管理が血管合併症を抑制することを示したランダム化比較試験はない．長寿科学総合研究班によれば，HbA1c 7.4％以上，空腹時血糖140 mg/dl以上，75 g糖負荷試験の2時間血糖値が250 mg/dl以上では，網膜症あるいは糖尿病性腎症の発症が増加していた．糖尿病に特異的な細小血管症を予防する立場から，上記の基準を満たす患者では厳格な血糖管理が必要である[1]．

わが国で行われたJapanese Elderly Diabetes Intervention Trial（J-EDIT）研究では，HbA1c高値（≧8.8％）群では，脳卒中および糖尿病関連全イベント（冠動脈疾患＋脳卒中＋突然死＋腎不全死＋高・低血糖死＋糖尿病足病変＋心不全）のリスクが高いことが示された[2]．さらにHbA1c低値（≦7.2％）群では，脳卒中の頻度がHbA1c 7.3-7.8群，7.9-8.7群より高頻度であり，J-カーブ現象を認めた．高齢者糖尿病で薬物療法を行っている例では，HbA1cを7％未満に低下させることには慎重であるべきと思われる．

高齢者糖尿病に特有な視点

高齢者糖尿病では複数の血管合併症に加え，併存疾

国立長寿医療研究センターもの忘れセンター（〒474-8511　大府市森岡町源吾35番地）
連絡先：櫻井　孝（〒474-8511　大府市森岡町源吾35番地　国立長寿医療研究センターもの忘れセンター）

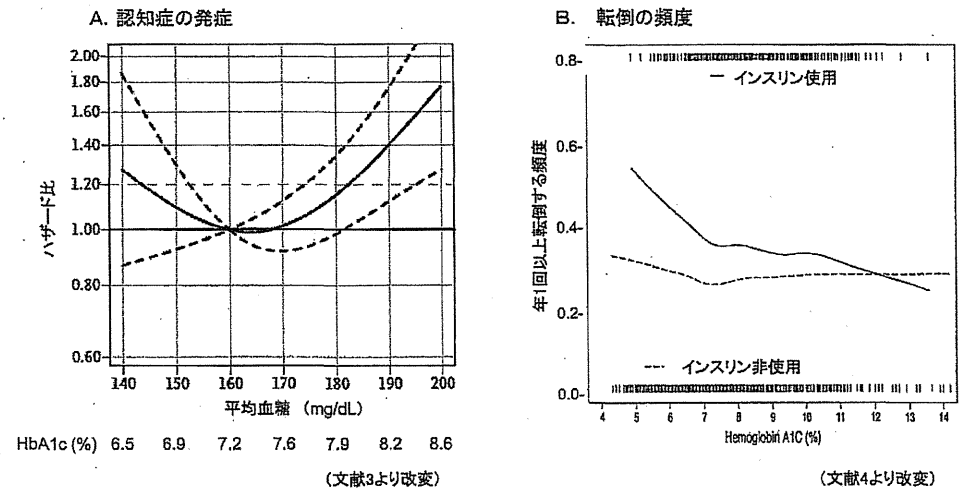

Fig. 高齢者糖尿病の血糖管理と転倒・認知症との関係

Table 高齢者糖尿病の治療ガイドライン（海外）

	健常高齢者	虚弱な高齢者	
		軽症～中等度	重度
EDEPOP（2011）[5]	HbA1c 7.0-7.5 %	HbA1c 7.6-8.5 %	
米国糖尿病学会（2012）[6]	HbA1c ＜7.5 % 空腹時または食前血糖 90-130 mg/dl 眠前血糖 90-150 mg/dl	HbA1c ＜8.0 % 空腹時または食前血糖 90-150 mg/dl 眠前血糖 100-180 mg/dl	HbA1c ＜8.5 % 空腹時または食前血糖 100-180 mg/dl 眠前血糖 110-200 mg/dl
IDF（2013）[7]	7.0-7.5 %	7.0-8.0 % フレイル ＜8.5 % 認知症 ＜8.5 %	終末期 高血糖症状を避ける

EDWPOP：European Diabetes Working Party for Older People
IDF：International Diabetes Federation

患，ADL低下や認知障害等のため，自立した糖尿病管理が困難となる例が多い．今日，糖尿病が認知症の危険因子であることはコンセンサスを得ている．また糖尿病では，身体機能や運動機能が低下し，転倒リスクが高まる．つまり高齢者糖尿病では，脳から，足から加齢による衰弱が忍び寄る．

脳を守る視点からの血糖管理目標

糖尿病に認知症が合併する機序として，遺伝的素因に加え，脳血管障害，高血糖に伴う代謝異常，低血糖，高インスリン血症，高血圧等の動脈硬化の危険因子が促進的に働き，認知症の病理を加速すると考えられる．高インスリン血症はアルツハイマー病の発症の根幹にかかわるという．高血糖も重要で，HbA1cが1％増加するごとに，軽度認知障害と認知症のリスクが約1.5倍高まる．一方，重症低血糖は認知症のリスクとなる．さらに血糖変動も認知能を低下させる．つまり糖尿病で認知症を抑制するためには，低血糖を避けること，高血糖の抑制が重要であろう．

高齢者糖尿病で血糖と認知症発症リスクの関連を調べた研究では，HbA1c 7.2-7.6 %でリスクが最も低く，≥7.9 %では有意に増加していた（Fig. A）[3]．認知症を予防する視点からは，HbA1c 7 %前半が目標値と考えられる．

一方，認知症を合併した糖尿病の管理目標値についてのエビデンスは乏しい．認知症がある程度進行すると，ADLや身体機能も低下する（虚弱）．少なくとも中等度以上の認知症では穏やかな血糖管理が望まれる（Table）．糖尿病と認知症合併例では，認知症による脳機能低下と高血糖による代謝性脳症が重複している．代謝性脳症を解除する目的から，随時血糖300 mg/dl以下は達成すべき目標値と思われる．

糖尿病管理と転倒との関連

高齢医学の領域ではフレイル(虚弱)，サルコペニアやロコモという概念は広く理解されつつある．いずれも骨・軟骨・筋肉の加齢性変化にもとづく運動器機能不全が主因となる高齢者に多い病態である．その代表的な症候として転倒・骨折がある．糖尿病では，糖尿病性末梢神経症，視力障害，自律神経障害，心不全や関節症，足病変，低血糖などの転倒の危険因子が多い．

インスリン治療によりHbA1cが6％以下にコントロールされた高齢者糖尿病では，転倒リスクが高いことが示されている（Fig. B）[4]．また地域在住の75歳以上の糖尿病を対象とした研究でも，HbA1c≦7％では，転倒リスクが高かったという．高齢者の低血糖は非典型的な症状(ふらつき，目が見えにくい，疲労感など)を呈することが多く，転倒の原因となる可能性が指摘されている．転倒予防の視点からも，低血糖を回避することが重要である．

高齢者糖尿病の治療ガイドライン

高齢者糖尿病でも血糖や血圧管理を適正に行うことで，生命予後や合併症を予防できる可能性が指摘されている．一方で高齢者に厳格な血糖管理を行うことの危険性も呈されている[1]．

近年，海外から提唱された高齢者糖尿病治療ガイドラインをTableにまとめた[5~7]．共通する考え方は，①個別に血糖管理目標値を設定すること，②機能障害がない健常な高齢者糖尿病と，虚弱な患者を分けて血糖管理目標値を設定することである．

米国糖尿病学会(2012年)は，併存疾患，ADL障害，認知障害の程度，施設入所の有無から，高齢者糖尿病を3群に分類し，各群で治療目標値を提言している．European Diabetes Working Party for Older People (EDWPOP) のガイドライン（2011年）では，単一システム障害で他の大きな併存疾患がない群と，虚弱な患者（要介護，多系統の疾患，認知症で施設入所）で低血糖リスクが高く，高血糖症状や糖代謝不全を避けるべき2群に分類している．2013年にはIDFからも指針が提唱されている．これらの血糖管理ガイドラインを統合すると，①健常高齢者ではHbA1c 7.0-7.5％，②虚弱な高齢者では7.5-8.5％（身体機能の低下した高齢者ほど血糖管理目標値は高め）ということが共通点として挙げられる．

わが国でも2013年に熊本宣言が提唱された．上記の考え方を当てはめると，高齢者糖尿病でも低血糖リスクの高い患者，その他の理由で治療の強化が難しい場合(認知症合併，併存疾患やADL低下が強い患者，社会的サポートの乏しい患者等)では，HbA1c 8.0％未満が目標値となる．一方，認知機能や身体機能が保たれた健常な高齢者糖尿病では7.0％未満となる．後期高齢者では認知症や転倒・骨折の臨床的意義は大きい．夜間低血糖，糖尿病治療薬を考慮した血糖管理目標値について，さらなるエビデンスが待たれる．

著者のCOI (conflicts of interest) 開示：櫻井孝：講演料(小野薬品工業)，奨学(奨励)寄付などの総額(小野薬品工業)

文　献

1) 日本糖尿病学会編 (2013) 高齢者の糖尿病 (骨代謝を含む) 科学的根拠に基づく糖尿病診療ガイドライン 2013，南江堂，p 245-261
2) Araki A, Iimuro S, Sakurai T, Umegaki H, Iijima K, Nakano H, Oba K, Yokono K, Sone H, Yamada N, Ako J, Kozaki K, Miura H, Kashiwagi A, Kikkawa R, Yoshimura Y, Nakano T, Ohashi Y, Ito H; Japanese Elderly Intervention Trial Research Group (2012) Non-high-density lipoprotein cholesterol: an important predictor of stroke and diabetes-related mortality in Japanese elderly diabetic patients. Geriatr Gerontol Int 12 (Suppl 1): 18-28
3) Crane PK, Walker R, Larson EB (2013) Glucose levels and risk of dementia. N Engl J Med 369: 1863-1864
4) Nelson JM, Dufraux K, Cook PF (2007) The relationship between glycemic control and falls in older adults. J Am Geriatr Soc 55: 2041-2044
5) Sinclair AJ, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez Mañas L; European Diabetes Working Party for Older People (2011) European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. Diabetes Metab 37 (Suppl 3): S27-38
6) Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, Huang ES, Korytkowski MT, Munshi MN, Odegard PS, Pratley RE, Swift CS (2012) Diabetes in older adults. Diabetes Care 35: 2650-2664
7) IDF global guideline for managing older people with type 2 diabetes. http://www.idf.org/sites/default/files/IDF-Guideline-for-older-people-T2D.pdf (2014.6.30)

doi:10.1111/psyg.12019 PSYCHOGERIATRICS 2013; 13: 157–163

ORIGINAL ARTICLE

Neuropsychological differentiation between Alzheimer's disease and dementia with Lewy bodies in a memory clinic

Yoshinari KAWAI,[1] Rina MIURA,[2] Masashi TSUJIMOTO,[1] Takashi SAKURAI,[2] Akiko YAMAOKA,[1] Akinori TAKEDA,[1] Yutaka ARAHATA,[1] Yukihiko WASHIMI,[1] Teruhiko KACHI[1] and Kenji TOBA[2]

[1]Department for Cognitive Disorders, and [2]Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics and Gerontology, Obu City, Japan

Correspondence: Dr Yukihiko Washimi MD, Department for Cognitive Disorders, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-cho, Obu City, Aichi 474-8511, Japan. Email: washimi@ncgg.go.jp

Received 31 October 2012; revision received 14 March 2013; accepted 10 April 2013.

Abstract

Objective: The aim of this study was to identify a useful neuropsychological instrument for making a differential clinical diagnosis between Alzheimer's disease (AD) and dementia with Lewy bodies (DLB).

Methods: We examined 402 AD and 38 DLB patients with neuropsychological tests that covered general cognition, frontal lobe cognitive function, non-verbal abstract reasoning, working memory and attention, and verbal memory. Discriminant analysis using a stepwise method was performed to identify the measures best able to discriminate between AD and DLB.

Results: The AD patients performed significantly worse than the DLB patients on orientation to time, delayed recall subtests on the Mini-Mental State Examination, and logical memory subtests 1 and 2 of the Revised Wechsler Memory Scale. The DLB patients performed significantly worse than the AD patients on the attention, repetition, and pentagon copying subtests of the Mini-Mental State Examination, the constructional praxis subtests of the Alzheimer's Disease Assessment Scale-cognitive component-Japanese version, the Frontal Assessment Battery total score, Raven's Coloured Progressive Matrices (RCPM) sets A, AB, and B, and backward digit span. Discriminant analyses between AD and DLB established the key variables as Logical Memory 1, Logical Memory 2, backward digit span, RCPM, and delayed recall on the Mini-Mental State Examination. We inferred the AD–DLB discriminant index from the following discriminant analyses: AD–DLB discriminant index = (Backward digit span score + RCPM set B score) − (Logical Memory 1 score + Logical Memory 2 score), which offered a highly favourable value for diagnostic utility.

Conclusions: The AD–DLB discriminant index, consisting of backward digit span, RCPM set B, and logical memory 1 and 2, is useful to differentiate between AD and DLB.

Key words: Alzheimer's disease, Lewy body disease, neuropsychological tests.

INTRODUCTION

A neuropsychological test is a tool for measuring the cognitive function of patients and examining various cognitive functions, such as memory, attention, visuospatial function, and executive function. For the diagnosis of dementia, a neuropsychological test is critical for understanding whether the cognitive function of a patient is impaired, which cognitive function is impaired, and how seriously the cognitive function has been impaired. It is an indispensable tool for objectively assessing cognitive dysfunction in two or more cognitive domains. As reported previously, neurodegenerative diseases responsible for dementia have impairments in distinct cognitive domains.[1] Thus, by clarifying which cognitive domains are impaired, a neuropsychological test can contribute to a confirmed diagnosis. Corey-Bloom *et al.* devised an algorithm for the diagnosis of dementia

© 2013 The Authors
Psychogeriatrics © 2013 Japanese Psychogeriatric Society

and its work-up, including a neuropsychological test.[1]

A comparison of Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), which are the most common neurodegenerative diseases causing dementia, reported that memory and orientation are more remarkably impaired in AD than DLB; attention, executive function, and visuospatial function are more remarkably impaired in DLB than AD.[2] However, the revised criteria for the clinical diagnosis of DLB refer to, but do not specify, the results of neuropsychological tests.[3]

Several studies have attempted to validate the utility of a neuropsychological test for differentiating between DLB and AD, but they have produced varying results.[4–12] In the current study, we aimed to differentiate DLB from AD on the basis of results from the neuropsychological test used in our memory clinic (Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics and Gerontology, Obu City, Japan).

METHODS

Subjects (Table 1)

We included 402 AD patients (110 men, 292 women; age, 77.9 ± 7.0 years; education, 10.0 ± 2.6 years; Mini-Mental State Examination (MMSE) = 19.1 ± 4.5) and 38 DLB patients (17 men, 21 women; age, 79.7 ± 5.6 years; education, 10.0 ± 2.5 years; MMSE = 18.7 ± 5.2) in this study. The AD and DLB patients were recruited through the Center for Comprehensive Care and Research on Memory Disorders between October 2010 and November 2011. The diagnosis of AD and DLB was made by neurologists, psychiatrists, geriatricians or a neurosurgeon, all specialists in dementia who are familiar with its diagnostic criteria.[3,13] In cases with an uncertain diagnosis, the diagnosis was determined at a case conference attended by neurologists, psychiatrists, geriatricians, a neurosurgeon, neuropsychologists, and neuroradiologists. Cases with an uncertain diagnosis after the case conference were excluded from this study. All patients underwent laboratory testing and brain magnetic resonance imaging or computed tomography, and cases with medical conditions or central nervous system diseases sufficient to disturb cognition, such as vitamin B12 deficiency, hypothyroidism, or cerebrovascular diseases, were excluded. Informed consent was obtained in advance from all AD and DLB patients and/or their families. This study was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology (approval number: 475-2).

Table 1 Clinical characteristics of the AD and DLB patients

	AD (n = 402)	DLB (n = 38)
Age (years)	77.9 ± 7.0	79.7 ± 5.6
Sex (men/women)	*110/292	*17/21
Education (years)	10.0 ± 2.6	10.0 ± 2.5
Mini-Mental State Examination	19.1 ± 4.5	18.7 ± 5.2

*P < 0.05. AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

Neuropsychological tests

A variety of neuropsychological tests are routinely performed in our memory clinic and were employed in this study. The MMSE and Alzheimer's Disease Assessment Scale-cognitive component-Japanese version (ADAS-Jcog) were used for the overall assessment of cognition.[14,15] Frontal lobe cognitive function was examined with the Frontal Assessment Battery (FAB).[16] Raven's Coloured Progressive Matrices (RCPM) test was used as a measure of non-verbal abstract reasoning.[17] To evaluate working memory and attention, the subjects underwent the digit span subtest of the Wechsler Adult Intelligence Scale-Revised,[18] the raw scores of which were used for statistical analysis. Verbal memory was examined using Logical Memory subtests 1 and 2 of the Wechsler Memory Scale-Revised (WMS-R).[19] All of the neuropsychological tests were completed within 3 months. The neuropsychological tests were not used to diagnose AD or DLB, and the total scores from the MMSE, ADAS-Jcog, and Logical Memory subtests 1 and 2 of the WMS-R were only used to determine the presence or absence of dementia.

Statistical analysis

All statistical calculations in this study were performed using PASW Statistics version 18.0 for Windows (IBM, Tokyo, Japan). Group comparisons between AD and DLB patients were performed by MANCOVA. Age, sex, and overall cognitive impairment, as measured by the MMSE, were entered as covariates in MANCOVA to account for any possible effects of these variables on group differences in neuropsychological performance. Sex was used as a covariate because AD is more prevalent than DLB in women. Even though the groups were matched in terms of their MMSE total

© 2013 The Authors
Psychogeriatrics © 2013 Japanese Psychogeriatric Society

scores and age, these variables were treated as covariates because their large variability within the groups could obscure the relationship between the diagnosis and the dependent variable of interest. Controlling for these variables provided a more powerful means for detecting the actual variance in the neuropsychological test scores than is accounted for by diagnosis. Differences were considered significant at $P < 0.05$, and the P-values were subsequently adjusted for multiple comparisons using the Holm-Sidak method in each test. Discriminant analysis using a stepwise method was then performed to identify the measures best able to discriminate between AD and DLB. In the first discriminant analysis, the total scores of the MMSE, ADAS-Jcog, FAB, and RCPM were entered in a stepwise manner, and in the second discriminant analysis, their subscores were used. By means of the same analysis, we also checked the number of correctly classified patients. From these discriminant analyses, we devised a simple mathematic formula, the AD–DLB discriminant index, which was then used in receiver-operator characteristic (ROC) curve analyses. An identical ROC analysis was then undertaken on an independent sample of new AD and DLB patients for validation purposes.

RESULTS

Comparison of the neuropsychological tests between AD and DLB patients

The mean scores obtained from the neuropsychological tests are reported in Table 2. The AD patients performed significantly worse on the MMSE than the DLB patients with regard to orientation to time and delayed recall subtests, while the DLB patients performed significantly worse than the AD patients on attention, repetition, and pentagon copying subtests. On the ADAS-Jcog, the DLB patients performed significantly worse than the AD patients only on the constructional praxis subtests. On the FAB total score, the DLB patients performed significantly worse than the AD patients. The phonemic fluency item in the FAB was more impaired in the DLB patients, but the corrected P-values did not reach significance. The DLB patients performed significantly worse than the AD patients on sets A, AB, and B of RCPM. Backward digit span was significantly impaired in the DLB patients compared to the AD patients, but there was no significant difference between the AD and DLB patients on forward digit span. The AD patients showed significant impairment on Logical Memory subtests 1 and 2 of the WMS-R compared to the DLB patients.

Discriminant analysis

The first discriminant analysis between AD and DLB established the key variables as Logical Memory 1, Logical Memory 2, backward digit span, and RCPM. The final equation using these four variables accurately assigned 86.7% of the AD patients and 68.2% of the DLB patients to the correct diagnostic group (85.5% of the patients were correctly classified): 0.472 × Backward digit span + 0.083 × RCPM – 0.212 × Logical Memory 1 – 0.338 × Logical Memory 2 (Table 3, Fig. 1).

The second discriminant analysis between AD and DLB established the key variables as delayed recall of the MMSE, Logical Memory 1, backward digit span, and RCPM set B. The final equation using these four variables accurately assigned 84.5% of the AD patients and 81.8% of the DLB patients to the correct diagnostic group (84.3% of the patients were correctly classified): 0.435 × Backward digit span + 0.221 × RCPM set B – 0.804 × Delayed recall of the MMSE – 0.186 × Logical Memory 1 (Table 3, Fig. 2).

These formulae are too difficult to use in clinical practice. Therefore, we devised a simpler formula by adding or subtracting the scores that were used in the first and second discriminant analyses and by avoiding the unnecessary duplication of scores of similar tests: AD–DLB discriminant index = (Backward digit span score + RCPM set B score) – (Logical Memory 1 score + Logical Memory 2 score). For the AD group, the mean ± SD of the AD–DLB discriminant index was 5.8 ± 3.8, and for the DLB group, it was –0.5 ± 5.8 ($P < 0.001$). ROC analysis gave a highly favourable value to the diagnostic utility of the AD–DLB discriminant index, with an area under the curve of 0.822 (0.725–0.919) (Fig. 3). When 4 or 5 on the AD–DLB discriminant index is used as the cut-off, 77.4% or 70.4% of the patients were correctly classified, respectively (Table 4).

Validation

We applied the AD–DLB discriminant index to an independent sample of 90 newly diagnosed AD (22 men, 68 women; age, 77.5 ± 7.2 years; education, 10.4 ± 2.6 years; MMSE = 18.8 ± 4.4) and 11 DLB patients (six men, five women; age, 74.6 ± 4.5 years; education, 11.6 ± 3.0 years; MMSE = 16.2 ± 5.1). ROC analysis of

© 2013 The Authors
Psychogeriatrics © 2013 Japanese Psychogeriatric Society

Table 2 Results of neuropsychological tests in the AD and DLB patients

Test	Subtest	AD (n = 402)	DLB (n = 38)	P-value
MMSE	Orientation to time	2.74 ± 0.56	3.18 ± 1.69	0.002
	Orientation to place	2.79 ± 1.30	2.55 ± 1.48	
	Registration	2.93 ± 0.37	2.84 ± 0.44	
	Serial sevens	2.16 ± 1.57	1.42 ± 1.45	0.000
	Delayed recall	0.54 ± 0.86	1.53 ± 0.95	0.000
	Naming	1.97 ± 0.23	1.95 ± 0.23	
	Repeat	0.75 ± 0.44	0.53 ± 0.51	0.006
	Three-step command	2.52 ± 0.68	2.34 ± 0.78	
	Read and follow instruction	0.96 ± 0.21	0.87 ± 0.34	*0.030*
	Write a complete sentence	0.85 ± 0.36	0.79 ± 0.41	
	Overlapping pentagon	0.84 ± 0.36	0.66 ± 0.48	0.006
	MMSE total	19.02 ± 4.53	18.66 ± 5.17	
ADAS-Jcog	Word recall	6.55 ± 1.39	6.62 ± 1.62	
	Expressive language	0.52 ± 0.99	0.97 ± 1.24	*0.011*
	Comprehension	0.24 ± 0.74	0.29 ± 0.80	
	Word finding difficulty	0.19 ± 0.61	0.08 ± 0.36	
	Follow oral commands	0.55 ± 0.87	0.83 ± 1.16	
	Naming (fingers and objects)	0.10 ± 0.41	0.18 ± 0.51	
	Constructional praxis	0.63 ± 0.87	1.05 ± 0.93	0.004
	Ideational praxis	2.87 ± 1.74	2.82 ± 1.72	
	Orientation	3.41 ± 2.19	2.82 ± 2.07	*0.030*
	Word recognition	3.69 ± 2.93	3.92 ± 2.93	
	Remembering instructions	0.14 ± 0.63	0.05 ± 0.23	
	ADAS-Jcog total	18.52 ± 7.30	19.20 ± 7.23	
FAB	Similarities (0–3)	1.07 ± 0.94	0.94 ± 0.85	
	Phonemic fluency (0–3)	1.62 ± 0.88	1.15 ± 0.96	*0.023*
	Motor series (0–3)	0.57 ± 0.74	0.47 ± 0.83	
	Conflicting instructions (0–3)	1.93 ± 1.25	1.50 ± 1.26	
	'Go-no go' (0–3)	1.23 ± 0.85	1.03 ± 0.67	
	Prehension behaviour (0–3)	2.95 ± 0.34	2.94 ± 0.34	
	FAB total (0–18)	9.36 ± 2.85	8.03 ± 2.79	0.026
RCPM	RCPM set A	8.42 ± 2.32	6.96 ± 3.10	0.001
	RCPM set AB	7.82 ± 2.82	6.44 ± 2.50	0.002
	RCPM set B	6.02 ± 2.05	4.92 ± 2.22	0.002
	RCPM total	22.46 ± 5.97	18.64 ± 6.89	0.000
Digit span	Forward digit span	5.01 ± 0.95	4.76 ± 0.98	
	Backward digit span	3.23 ± 0.83	2.84 ± 0.69	0.006
Logical Memory	Logical Memory 1	2.97 ± 2.92	4.63 ± 4.95	0.000
	Logical Memory 2	0.35 ± 1.14	1.06 ± 2.18	0.000

Statistical significance was set at $P < 0.05$, adjusted for multiple comparisons using the Holm-Sidak method in each test. P-values that were not significant after correction are indicated in italics. AD, Alzheimer's disease; ADAS-Jcog, Alzheimer's disease assessment scale-cognitive component-Japanese version; DLB, dementia with Lewy bodies; FAB, Frontal Assessment Battery; MMSE, Mini-Mental State Examination; RCPM, Raven's Coloured Progressive Matrices.

Table 3 Distribution of patients according to their original and predicted group membership on the basis of the discriminant analyses

	AD	DLB	Correct diagnosis
First discriminant analysis			
AD (n = 309)	268	41	86.7%
DLB (n = 22)	7	15	68.2%
Total	275	56	85.5%
Second discriminant analysis			
AD (n = 309)	261	48	84.5%
DLB (n = 22)	4	18	81.8%
Total	265	66	84.3%

AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

the AD–DLB discriminant index provided striking confirmation of its diagnostic value with an area under the ROC curve of 0.899 (0.793–1.00) (Fig. 4).

DISCUSSION

In the present study, we compared the results of neuropsychological tests between AD and DLB patients. As previously reported, we found that AD patients had significant memory impairment, such as delayed recall on the MMSE and Logical Memory 1 and 2 of the WMS-R, and disorientation, such as orientation to time on the MMSE. DLB patients had significant impairment to the following: visuospatial

© 2013 The Authors
Psychogeriatrics © 2013 Japanese Psychogeriatric Society

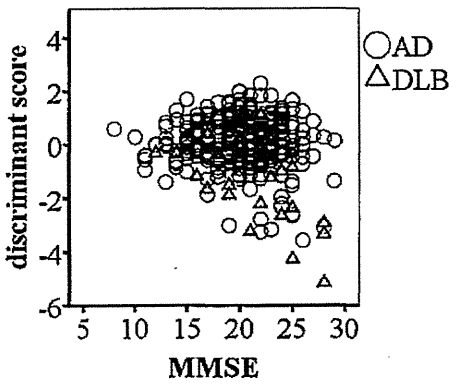

Figure 1 Scattergrams of the final equation using Logical Memory 1, Logical Memory 2, backward digit span, and Raven's Coloured Progressive Matrices from the first discriminant analysis in patients with Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). MMSE, Mini-Mental State Examination.

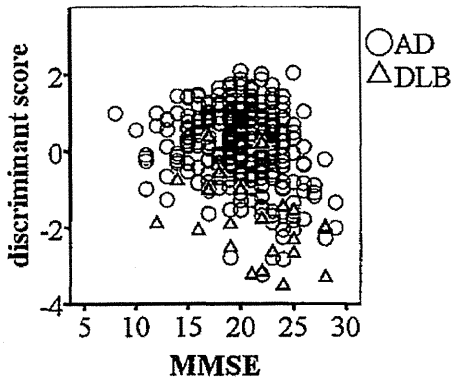

Figure 2 Scattergrams of the final equation using delayed recall of the Mini-Mental State Examination (MMSE), Logical Memory 1, backward digit span, and Raven's Coloured Progressive Matrices set B from the second discriminant analysis in patients with Alzheimer's disease (AD) and dementia with Lewy bodies (DLB).

function or visual information processing, as indicated by the RCPM, pentagon copying on the MMSE, constructional praxis per the ADAS-Jcog results; attention and working memory according to the MMSE and backward digit span; and executive function per the FAB. Aarsland *et al.* found that DLB patients had higher memory subscores on the Dementia Rating Scale than AD patients but lower initiation and perseveration, construction, and conceptualization subscores.[20] Calderon *et al.* showed that AD patients performed worse on tests of immediate and delayed story recall, while DLB patients had substantial impairments on several subtests involving visual object and space perception, selective attention,

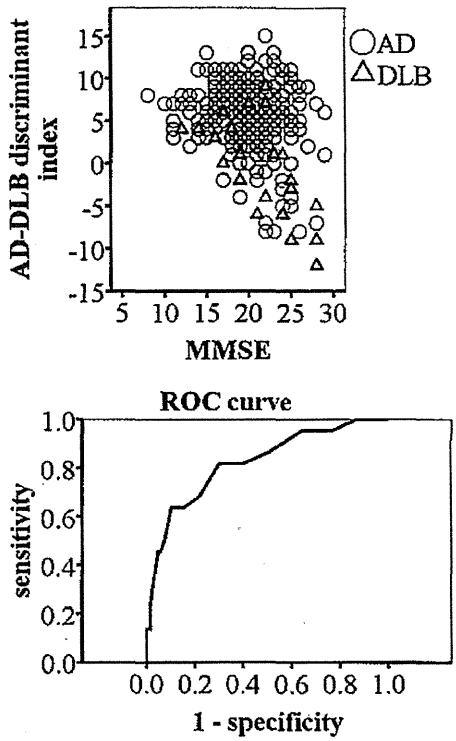

Figure 3 (top) Scattergrams of the AD–DLB discriminant index in patients with Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). (bottom) Receiver-operator characteristic (ROC) curve for the AD–DLB discriminant index.

Table 4 Distribution of patients according to the AD–DLB discriminant index

	AD	DLB	Correct diagnosis
≥5: AD, ≤4: DLB			
AD (n = 310)	216	94	69.7%
DLB (n = 22)	4	18	81.8%
Total	220	112	70.4%
≥4: AD, ≤3: DLB			
AD (n = 310)	242	68	78.1%
DLB (n = 22)	7	15	68.2%
Total	249	83	77.4%

AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

and set shifting.[21] In most studies that have investigated cognitive impairments in AD and DLB, the overall pattern that has emerged indicates that DLB patients tend to develop earlier and more severe visuoperceptual, attentional, and frontal-executive impairments than AD patients, whereas AD patients tend to show earlier and stronger impairments in memory tasks.[2] Our findings are consistent with the results of previous studies, which likely reflects brain involvement in AD and DLB.[22,23]

© 2013 The Authors
Psychogeriatrics © 2013 Japanese Psychogeriatric Society

We then attempted to differentiate between AD and DLB using the results from the neuropsychological tests. We found that discriminant analyses using either Logical Memory 1, Logical Memory 2, backward digit span, and RCPM, or delayed recall on the MMSE, Logical Memory 1, backward digit span, and RCPM set B are useful in discriminating between AD and DLB. These discriminant analyses had highly favourable values for diagnostic utility. When we differentiate between AD and DLB with the results from the neuropsychological tests, we assume that using as many cognitive domains as possible enhances and stabilizes their discriminatory ability. However, it is difficult to add more detailed neuropsychological tests, such as the Wechsler Adult Intelligence Scale-Revised, to routine medical care, as they are time-consuming and increase the burden on patients.

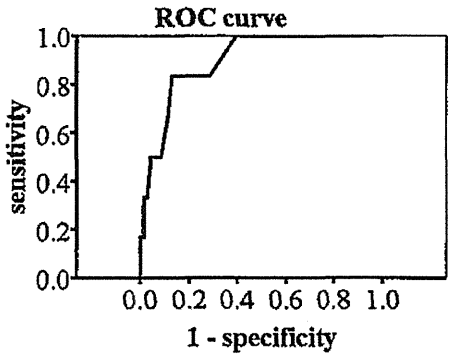

Figure 4 Receiver-operator characteristic (ROC) curve for the AD–DLB discriminant index in an independent sample of newly diagnosed patients with Alzheimer's disease (AD) and dementia with Lewy bodies (DLB).

In this study, we assumed that it was useful to integrate neuropsychological results from multiple cognitive domains. Cormack *et al.* attempted to differentiate between AD and DLB using the pentagon copying test of the MMSE,[6] and Hanyu *et al.* used the FAB.[8] Indeed, our results were superior to those of these studies.[6,8] Oda *et al.* administered the MMSE, ADAS-Jcog, WMS-R, and Wechsler Adult Intelligence Scale-Revised to AD and DLB patients, and utilized their results to differentiate AD and DLB.[11] In the current study, we attempted to differentiate between AD and DLB using neuropsychological tests that are routinely used in our memory clinic and that can be completed in approximately 1 hour. Therefore, we believe that our results are applicable to clinical practice. Table 5 summarizes the results of previous studies.[4–12]

Additionally, we applied a simple formula from the results of these discriminant analyses, which can be used in clinical practice: AD–DLB discriminant index = (Backward digit span score + RCPM score) (Logical Memory score 1 + Logical Memory 2 score). The rate of correctly classifying AD and DLB patients acquired

Table 5 Neuropsychological tests used to discriminate AD and DLB

Study	Neuropsychological tests	Sensitivity†	Specificity‡
Ala *et al.*[5]	Attention – 5/3 × Memory (delayed recall) + 5 × Construction (overlapping pentagon)	82	81
Hanyu *et al.*[9]	Attention – 5/3 × Memory (delayed recall) + 5 × Construction (overlapping pentagon)	72	75
Ferman *et al.*[7]	Trail Making Part A, Boston Naming Test, AVLT Percent Retention, Rey-Osterrieth Complex Figure-Copy	83.3	91.4
Tiraboschi *et al.*[12]	Visuospatial impairment on DRS-C	74	55
Hanyu *et al.*[8]	FAB item 2: cut-off 1.5	61	65
Oda *et al.*[11]	0.3452 × Scaled score of object assembly – 0.2719 × Percentile of Logical Memory 2, Cut-off = –1.23	80.8	75.6
Cormack *et al.*[6]	Pentagon drawing, cut-off = 2	60	66
Ala *et al.*[4]	Pentagon copying	88	59
Murayama *et al.*[10]	Bender Gestalt Test, cut-off = 98	94	Late-onset = 93, early-onset = 50
Present study: first discriminant analysis	0.472 × Backward digit span + 0.083 × RCPM – 0.212 × Logical Memory 1 – 0.338 × Logical Memory 2	68.2	78.1
Present study: second discriminant analysis	0.435 × Backward digit span + 0.221 × RCPM set B – 0.804 × Delayed recall of MMSE – 0.186 × Logical Memory 1	81.8	84.5

†Sensitivity is the proportion of clinically diagnosed DLB patients with neuropsychological tests indicating DLB.
‡Specificity is the proportion of not clinically diagnosed DLB with neuropsychological tests not indicating DLB.
AD, Alzheimer's disease; AVLT, Auditory Verbal Learning Test; DLB, dementia with Lewy bodies; DRS-C, Dementia Rating Scale, construction subscale; FAB, Frontal Assessment Battery; MMSE, Mini-Mental State Examination; RCPM, Raven's Coloured Progressive Matrices.

© 2013 The Authors
Psychogeriatrics © 2013 Japanese Psychogeriatric Society

from the AD–DLB discriminant index was comparable to those from more complicated formulae obtained from discriminant analysis that was considered to be sufficiently useful in clinical practice. The reliability of the AD–DLB discriminant index in correctly assigning AD and DLB patients was confirmed using new AD and DLB samples.

The present study had some limitations that merit discussion. First, the subjects were recruited from our memory clinic during the stated period, and we had a smaller sample of DLB cases than AD cases, which may have some impact on our findings. Second, the neuropsychological tests used in this study are used routinely in our memory clinic; therefore, these results are not directly applicable to other medical settings where these neuropsychological tests are not used. Previous studies have ascertained the cognitive domains in which AD and DLB patients are differentially impaired, and further studies are needed to clarify which is the most suitable to differentiate the neuropsychological tests for these cognitive domains.

ACKNOWLEDGMENTS

We are grateful to Drs H. Endo, M. Bundo, and H. Hattori for referring AD and DLB patients to our department and to Dr K. Ito for help with the magnetic resonance imaging and single-photon emission computed tomography scans. This work was supported by Research Funding for Longevity Sciences (23-14) from the National Center for Geriatrics and Gerontology (Obu City, Japan).

REFERENCES

1 Corey-Bloom J, Thal LJ, Galasko D *et al.* Diagnosis and evaluation of dementia. *Neurology* 1995; **45**: 211–218.
2 Metzler-Baddeley C. A review of cognitive impairments in dementia with Lewy bodies relative to Alzheimer's disease and Parkinson's disease with dementia. *Cortex* 2007; **43**: 583–600.
3 McKeith IG, Dickson DW, Lowe J *et al.* Diagnosis and management of dementia with Lewy bodies—Third report of the DLB consortium. *Neurology* 2005; **65**: 1863–1872.
4 Ala TA, Hughes LF, Kyrouac GA, Ghobrial MW, Elble RJ. Pentagon copying is more impaired in dementia with Lewy bodies than in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2001; **70**: 483–488.
5 Ala TA, Hughes LF, Kyrouac GA, Ghobrial MW, Elble RJ. The Mini-Mental State exam may help in the differentiation of dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry* 2002; **17**: 503–509.
6 Cormack F, Aarsland D, Ballard C, Tovee MJ. Pentagon drawing and neuropsychological performance in Dementia with Lewy Bodies, Alzheimer's disease, Parkinson's disease and Parkinson's disease with dementia. *Int J Geriatr Psychiatry* 2004; **19**: 371–377.
7 Ferman TJ, Smith GE, Boeve BF *et al.* Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. *Clin Neuropsychol* 2006; **20**: 623–636.
8 Hanyu H, Sato T, Kume K, Takada Y, Onuma T, Iwamoto T. Differentiation of dementia with Lewy bodies from Alzheimer disease using the Frontal Assessment Battery test. *Int J Geriatr Psychiatry* 2009; **24**: 1034–1035.
9 Hanyu H, Shimizu S, Hirao K *et al.* Differentiation of dementia with Lewy bodies from Alzheimer's disease using mini-mental state examination and brain perfusion SPECT. *J Neurol Sci* 2006; **250**: 97–102.
10 Murayama N, Iseki E, Yamamoto R, Kimura M, Eto K, Arai H. Utility of the Bender Gestalt Test for differentiation of dementia with Lewy bodies from Alzheimer's disease in patients showing mild to moderate dementia. *Dement Geriatr Cogn Disord* 2007; **23**: 258–263.
11 Oda H, Yamamoto Y, Maeda K. The neuropsychological profile in dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry* 2009; **24**: 125–131.
12 Tiraboschi P, Salmon DP, Hansen LA, Hofstetter RC, Thal LJ, Corey-Bloom J. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? *Brain* 2006; **129**: 729–735.
13 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; **34**: 939–944.
14 Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.
15 Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984; **141**: 1356–1364.
16 Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000; **55**: 1621–1626.
17 Raven J. *Guide to Using the Coloured Progressive Matrices*. London: H.K. Lewis, 1965.
18 Wechsler D. *Wechsler Adult Intelligence Scale-III*. New York: Psychological Corporation, 1997.
19 Wechsler D. *Wechsler Memory Scale-Revised*. San Antonio, TX: Psychological Corporation, 1981.
20 Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP. Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2003; **74**: 1215–1220.
21 Calderon J, Perry RJ, Erzinclioglu SW, Berrios GE, Dening TR, Hodges JR. Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2001; **70**: 157–164.
22 Lobotesis K, Fenwick JD, Phipps A *et al.* Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. *Neurology* 2001; **56**: 643–649.
23 Rodriguez MJ, Potter E, Shen Q *et al.* Cognitive and structural magnetic resonance imaging features of Lewy body dementia and Alzheimer's disease. *Alzheimers Dement* 2012; **8**: 211–218.

© 2013 The Authors
Psychogeriatrics © 2013 Japanese Psychogeriatric Society

JAMDA 15 (2014) 36–41

JAMDA

journal homepage: www.jamda.com

Original Study

Regional White Matter Lesions Predict Falls in Patients With Amnestic Mild Cognitive Impairment and Alzheimer's Disease

Noriko Ogama MA, Takashi Sakurai MD, PhD *, Atsuya Shimizu MD, PhD, Kenji Toba MD, PhD

Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics and Gerontology, Obu, Japan

Keywords:
White matter lesions
falls
amnestic mild cognitive impairment
Alzheimer's disease

A B S T R A C T

Objectives: Preventive strategy for falls in demented elderly is a clinical challenge. From early-stage of Alzheimer's disease (AD), patients show impaired balance and gait. The purpose of this study is to determine whether regional white matter lesions (WMLs) can predict balance/gait disturbance and falls in elderly with amnestic mild cognitive impairment (aMCI) or AD.
Design: Cross-sectional.
Settings: Hospital out-patient clinic.
Participants: One hundred sixty-three patients diagnosed with aMCI or AD were classified into groups having experienced falls (n = 63) or not (n = 100) in the previous year.
Measurements: Cognition, depression, behavior and psychological symptoms of dementia, medication, and balance/gait function were evaluated. Regional WMLs were visually analyzed as periventricular hyperintensity in frontal caps, bands, and occipital caps, and as deep white matter hyperintensity in frontal, parietal, temporal, and occipital lobes, basal ganglia, thalamus, and brain stem. Brain atrophy was linearly measured.
Results: The fallers had a greater volume of WMLs and their posture/gait performance tended to be worse than nonfallers. Several WMLs in particular brain regions were closely associated with balance and gait impairment. Besides polypharmacy, periventricular hyperintensity in frontal caps and occipital WMLs were strong predictors for falls, even after potential risk factors for falls were considered.
Conclusions: Regional white matter burden, independent of cognitive decline, correlates with balance/gait disturbance and predicts falls in elderly with aMCI and AD. Careful insight into regional WMLs on brain magnetic resonance may greatly help to diagnose demented elderly with a higher risk of falls.
Copyright © 2014 - American Medical Directors Association, Inc.

The incidence of falls increases with age. Falls often cause fractures, disability, and injury-related death. Even if falls are not accompanied by fractures, the elderly are reluctant to be active for fear of falls.[1] In Japan, a super-aged society, falls have become not only a medical problem, but also a social and medico-economic concern.

Falls are induced by the interaction of intrinsic, pharmacologic, and environmental factors in older persons. Intrinsic risks include balance impairments and muscle weakness, which are caused by a number of sensory, neurologic, depressive, or musculoskeletal diseases. Age-related physical changes, medications, and cognitive decline also affect gait function in the elderly.[2,3] Although gait impairment is not typically seen early in the course of Alzheimer's disease (AD), patients with AD show balance impairment and a slower walking pace, and the incidence of falls in this population is approximately 3-fold higher than that of age-matched controls.[2,4] Clinical features of AD might play a role in increasing falls in the early stages of the disease. The involvement of executive dysfunction, visuoconstructional deficits, and behavior and psychological symptoms of dementia (BPSD) has been suggested.[5,6] Another factor accounting for impaired balance and gait could be the underlying burden of white matter lesions (WMLs) in AD patients.

Previous studies of the aging brain have reported the correlation of WMLs with measurements of balance, gait, and falls in the elderly.[7–14] Frontotemporal cortex and periventricular white matter are particularly vulnerable to hypoperfusion, and WMLs in these

This work was supported by the research fund for Longevity Sciences (22-5, 25-5) from the National Center for Geriatrics and Gerontology, Japan and Health and Labor Sciences Research Grants (H21-choju-005, H25-Ninchisho-008).
The authors declare no conflicts of interest.
* Address correspondence to Takashi Sakurai, MD, PhD, Center for Comprehensive Care and Research on Memory Disorders, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-cho, Obu 474-8511, Japan.
E-mail address: tsakurai@ncgg.go.jp (T. Sakurai).

1525-8610/$ - see front matter Copyright © 2014 - American Medical Directors Association, Inc.
http://dx.doi.org/10.1016/j.jamda.2013.11.004

structures could have the consequence of impaired balance and gait in the elderly.[14] However, little is known about the interaction between WMLs and gait disturbance in dementia disorders.[7,8]

The purpose of the present study is to clarify the effects of WMLs on balance/gait function and falls in patients with amnestic mild cognitive impairment (aMCI) and AD. In the present study, we hypothesized that white matter burden (both its location and volume) is critical for manifesting clinical symptoms. We investigated the features of regional distribution of WMLs, which are responsible for deterioration of posture control and gait. Finally, we aimed to determine whether regional WMLs could be predictive to find high risk individuals for falls among elderly with aMCI and AD.

Methods

Participants

The protocol of the study was approved by the Institutional Review Board of the National Center for Geriatrics and Gerontology (NCGG), Japan. Candidate patients and their caregivers submitted informed consent before participation in the study.

We enrolled 163 patients (111 females) consecutively. Patients were >65 years old, visited the NCGG hospital in 2010 and 2011, and were diagnosed with aMCI (n = 14) or AD (n = 149). Patients were classified into a group that had experienced falls (fallers group; 63 subjects) and a group that had not experienced falls (nonfallers group; 100 subjects) in the past year. Mild to moderate AD was diagnosed as possible or probable AD according to the criteria from the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association,[15] and their total Mini-Mental State Examination (MMSE) scores were 15 or over. Patients with aMCI were diagnosed based on the criteria defined by Petersen et al.[16] Patients with severe conditions of cardiac failure, renal disorder, liver dysfunction, musculoskeletal disease, optic or neurological disorders other than AD, and patients with a history of stroke or cortical lesions on brain magnetic resonance (MR) imaging were excluded.

Evaluation of Fall Risk Factors

Experience of falls was ascertained by interviews with patients and their caregivers. Risk of falls was evaluated by the Fall Risk Index, comprising 21 questionnaires for physical function, geriatric syndrome, and environmental hazards.[17] The presence or absence of knee joint pain was examined as a subitem of the FRI. Information about previous history and medication was obtained from the patients' clinical charts. Polypharmacy was defined as taking 5 or more types of oral medicine.[18] The patient's drinking habit was assessed by 1 of the questionnaires on a 4-point scale (0: daily drinking ≥56 g ethanol, 1: daily drinking <56 g ethanol, 2: occasional drinking, 3: none). Anemia was assumed to be present if the patient's hemoglobin was less than 11.0 g/dL.

Cognitive function was evaluated by MMSE, Alzheimer's Disease Assessment Scale (ADAS), and digit span.[19,20] Depression and BPSD were estimated by the Geriatric Depression Scale-15 and Dementia Behavior Disturbance Scale, respectively.[21,22]

Balance control was assessed from the center of gravity sway during 1 minute of standing on a stabilometer (Stabilometry analysis SYSTEM GP-5000; ANIMA Co., Tokyo, Japan) with eyes opened and closed. Parameters of the postural sway included enveloped area (ENV-AREA), which is an area inside of the envelope of the center of gravity sway, total trajectory length of traced sway (LNG), and trajectory length of X direction (X-LNG) and Y direction (Y-LNG), which measure the length from displacement of sway in mediolateral and anteroposterior directions, respectively.

Gait function was evaluated by the Timed Up and Go test (TUG), tandem gait steps, and time of standing on one leg. Muscle strength was measured by a hand grip test.

Brain MR Imaging

A standard series of axial T1-weighted (repetition time [TR], 485 ms; echo time [TE], 11 ms), T2-weighted (TR, 3800 ms; TE, 93 ms) and fluid-attenuated inversion recovery (TR, 8000 ms; TE 101 ms; inversion time, 2500 ms; a 256 × 256 matrix) MR sequences of the brain were performed using 1.5 T MR scanner (Siemens Avanto, Munich, Germany). Scans in parallel with the anterior commissure-posterior commissure line were performed from the vertex to the foramen magnum with 6-mm thick slices and an interslice gap of 1.2 mm.

Rating of WMLs and Brain Atrophy

WMLs appeared as hyperintense on T2-weighted images but did not leave a clear hypointense hole on T1-weighted images. WMLs were visually assessed as periventricular hyperintensity (PVH) or deep white matter hyperintensity (DWMH). WMLs were considered periventricular if the largest diameter was adjacent to the ventricular lining; they were otherwise considered subcortical.[23] PVH was classified by a 5-point scale measured at frontal caps, wall of the lateral ventricle (bands), and occipital caps (0: no, 1: pencil thin lining <3 mm, 2: smooth halo or thick lining 3–10 mm, 3: extending caps 10–25 mm, 4: large confluent white matter >25 mm). The overall degree of PVH was calculated by adding up the scores for the 3 separate compartments.[23] The number and size of DWMH were counted in the frontal, parietal, temporal, and occipital lobes, basal ganglia, thalamus, and brain stem. The size of DWMH was classified according to the largest diameter: small (1–3 mm), medium (3–10 mm), or large (>10 mm). To calculate the volume, DWMH was assumed to be spherical with a fixed diameter of 2, 6, and 12 mm for each of the 3 respective categories.[23]

For analysis of brain atrophy, Evans ratio (ER), inverse cella media index (iCMI), caudate head index (CHI), and basal cistern index (BCI) were calculated.[23] The following were measured with slide calipers: the maximum distance between the tips of the anterior horns (A); the width between the bilateral heads of the caudate nuclei (B); the maximum transverse inner diameter of the intracranial space (C); the maximum width of the cella media (D); the maximum transverse inner diameter (E); the internal width between the bilateral temporal lobe (F); and the maximum transverse inner diameter (G). The ER, iCMI, CHI, and BCI were calculated with the following respective formulae: ER = A/C; iCMI = D/E; CHI = B/C; and BCI = F/G, respectively.

WMLs in all participants were collectively evaluated by 2 trained raters, who had no knowledge of the clinical data. To test the inter-rater reliability, the results of the 2 raters were subjected to correlation analysis for comparison in a random sample of 10 subjects. The analysis showed a strong correlation ($r = 0.87–0.91$, $P < .0001$), which suggested that the method of measurement used for this study was reliable.

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 for Windows (SPSS Inc, Chicago, IL). Since WMLs did not show normal distribution, they were converted to rank variables and analyzed by nonparametric tests. Clinical information and results of neuropsychological tests, posture sway, and gait were compared between the fallers and the nonfallers by Mann–Whitney U-test. Association between WMLs and balance/gait functions was analyzed by partial Spearman rank order correlation analysis. Independent risk factors of falls were

Table 1
Clinical Characteristics

	Fallers (n = 63)	Nonfallers (n = 100)	*P* Value
Age, years	78.6 (4.9)	76.4 (5.9)	.020
Females, n (%)	45 (71.4)	68 (68.0)	.644
Education, years	10.4 (2.5)	10.5 (2.4)	.713
Polypharmacy, n (%)	27 (42.9)	21 (21.0)	.003
Dementia Behavior Disturbance Scale	18.9 (11.1)	15.1 (10.8)	.013
Geriatric Depression Scale	5.0 (2.4)	3.9 (2.9)	.008
Fall Risk Index	9.0 (2.3)	2.5 (2.1)	<.001
Mini-Mental State Examination	21.1 (3.9)	20.9 (3.6)	.709
Alzheimer's Disease Assessment Scale	16.7 (6.0)	16.2 (6.2)	.659

SD, standard deviation.
Data are presented as mean (SD) unless otherwise indicated.

analyzed by the multivariate logistic regression, and prediction of falls was tested by receiver operating characteristic analysis. Significance was considered at $P < .05$.

Results

Clinical Characteristics and Balance/Gait Performance

The subjects in the fallers group were older than the nonfallers (Table 1). The percentage of patients on polypharmacy was higher in the fallers group. The fallers group had higher total scores of BPSD and depression. Total score of FRI was elevated in the fallers, while environmental factors were not different (data not shown). The prevalence of hypertension, diabetes mellitus, heart disease, anemia, and knee joint pain as well as drinking habit and use of psychotropic medicine were not significantly different among the groups (data not shown). Concerning cognitive status, there was no difference between the groups in terms of performance of MMSE and ADAS, as well as performance of constructional praxis in a subscale of ADAS and digit span, an indicator of attention (data not shown).

Among measurements with the stabilometer, ENV-AREA was enlarged in the fallers compared with the nonfallers with eyes opened or closed (Table 2). In gait performance, the number of steps in tandem gait was significantly fewer in the fallers, whereas results of TUG tended to be worse in the fallers. There was no difference in the grip strength between the groups.

Regional WMLs and Brain Atrophy

The PVH total score and overall products of DWMH were significantly higher in the fallers (Table 3). This group showed higher PVH in frontal caps and occipital caps, and higher DWMH in all regions measured except the brain stem. Concerning progression of brain atrophy, inverse cella media index increased in the fallers, whereas the other indices were unchanged.

Table 2
Balance and Gait Performance

		Fallers	Nonfallers	*P* Value
Measurements of balance				
ENV-AREA, cm^2	Eyes open	6.0 (3.4)	4.7 (2.3)	.032
LNG, cm		121.6 (39.4)	113.5 (39.5)	.185
X-LNG, cm		77.4 (24.3)	70.3 (25.0)	.062
Y-LNG, cm		76.4 (29.0)	74.2 (29.3)	.540
ENV-AREA, cm^2	Eyes closed	8.9 (5.4)	7.1 (4.3)	.017
LNG, cm		172.8 (58.5)	163.0 (73.6)	.117
X-LNG, cm		107.1 (33.7)	99.5 (44.9)	.052
Y-LNG, cm		112.0 (44.8)	108.3 (53.9)	.303
Gait performance				
Timed Up and Go, s		11.4 (4.0)	10.6 (3.0)	.077
Tandem gait, steps		11.4 (7.1)	14.2 (6.9)	.021
One-leg stand, s		26.7 (28.7)	32.8 (33.5)	.177
Grip strength, kg		20.0 (7.5)	22.2 (8.5)	.151

ENV-AREA, enveloped area of the center of gravity sway; LNG, total trajectory length of traced sway; SD, standard deviation; X-LNG, trajectory length of X direction; Y-LNG, trajectory length of Y direction.
Data are presented as mean (SD).

Table 3
Regional WMLs and Brain Atrophy

	Fallers	Nonfallers	*P* Value
PVH			
Frontal caps	4.4 (1.0)	3.6 (1.0)	<.001
Bands	3.1 (1.0)	2.9 (0.9)	.302
Occipital caps	4.5 (1.4)	3.5 (1.4)	<.001
Total	12.0 (2.6)	10.0 (2.8)	<.001
DWMH, μL			
Frontal	2179.4 (1967.1)	1606.6 (1582.3)	.023
Parietal	878.2 (867.5)	700.7 (845.9)	.031
Temporal	273.4 (281.2)	160.8 (188.8)	.007
Occipital	193.7 (217.2)	93.1 (97.1)	<.001
Basal ganglia	354.7 (365.8)	252.8 (303.7)	.026
Thalamus	177.5 (202.2)	124.2 (157.3)	.011
Brain stem	220.0 (228.9)	170.2 (173.6)	.100
Total	4277.0 (3143.3)	3108.4 (2765.2)	.005
Atrophy			
Evans ratio	0.27 (0.04)	0.27 (0.03)	.813
Caudate head index	0.16 (0.03)	0.16 (0.02)	.567
Inverse cella media index	0.24 (0.04)	0.22 (0.03)	.018
Basal cistern index	0.20 (0.02)	0.20 (0.03)	.865

DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity; SD, standard deviation; WML, white matter lesion.
Data are presented as mean (SD).

Correlation of WMLs With Balance/Gait Function

Figure 1 summarizes the correlation between WMLs and posture control for the entire cohort. Absolute values of the partial Spearman rank order correlation after adjusting for age, sex, and MMSE are shown on the Y-axes. PVH total, as well as PVH frontal and occipital caps correlated with Y-LNG with eyes opened ($P = .008$, $P = .019$, and $P = .011$, respectively) and with eyes closed ($P = .015$, $P = .042$, and $P = .044$, respectively). Total PVH also correlated with LNG with eyes closed ($P = .049$). Total DWMH and parietal DWMH correlated with Y-LNG with eyes closed ($P = .032$ and $P = .013$, respectively). Temporal DWMH correlated with Y-LNG with eyes open ($P = .013$), and DWMH in basal ganglia correlated with eyes-closed ENV-AREA ($P = .019$).

Similarly, correlation of WMLs with gait performance was demonstrated (Figure 2). PVH scores at frontal caps, bands, occipital caps, as well as PVH total correlated with performance of TUG ($P = .005$, $P = .001$, $P = .013$, and $P < .001$, respectively). PVH in frontal caps also correlated with 1-leg standing time ($P = .007$). Frontal DWMH and temporal DWMH correlated with performance of 1-leg standing and TUG ($P = .040$ and $P = .030$, respectively). In contrast, muscle strength did not show any correlation with WMLs. Caudate head index was negatively correlated with 1-leg standing ($P = .008$), but no other correlation was found between brain atrophy and balance/gait function.

Association of WMLs With Previous History of Falls

The effect of regional WMLs on falls was tested by multivariate logistic regression (Table 4). Cofactors included age, sex, MMSE, polypharmacy, Dementia Behavior Disturbance Scale, Geriatric Depression Scale-15, and brain atrophy. The analysis indicated that polypharmacy, PVH frontal caps, and occipital DWMH were specific risk factors for falls. The predicted probabilities for fallers from the multivariate logistic regression analysis were as follows: $\text{Log } p/(1\text{-}p) = -0.0534x1 + 0.0282x2 + 0.0948x3 + 0.0140x4 + 0.0852x5 + 0.0069x6 + 0.0061x7 + 0.0004x8 + 0.0130x9 + 0.0041x10 +$

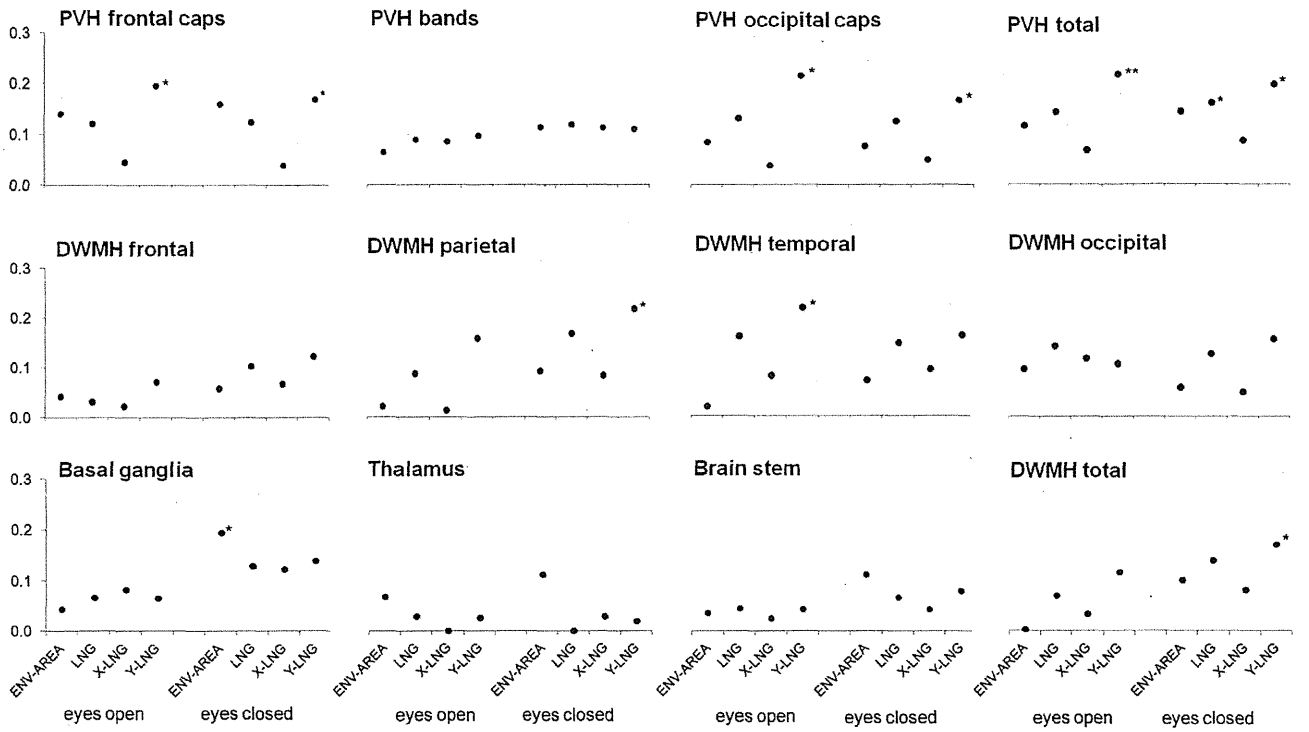

Fig. 1. Effects of regional white matter lesions (WMLs) on posture control. Effects of regional periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) on balance function are shown. The Y-axis denotes the absolute values of the partial Spearman rank order correlation after adjusting for age, sex, and Mini-Mental State Examination (MMSE). $^{*}P < .05$, $^{**}P < .01$. ENV-AREA, enveloped area of the center of gravity sway; LNG, total trajectory length of traced sway; X-LNG, trajectory length of X direction; Y-LNG, trajectory length of Y direction.

$0.0082x11 - 0.0027x12 - 0.0236x13 + 0.0525x14 + 0.239x15 + 0.0500x16 - 0.0797x17 + 0.9387x18 - 10.4655$; where $x1$ = Sex (Male:1, Female:0), $x2$ = Age (years), $x3$ = MMSE, $x4$ = Dementia Behavior Disturbance Scale, $x5$ = Geriatric Depression Scale, $x6$ = frontal DWMH (μL), $x7$ = parietal DWMH (μL), $x8$ = temporal DWMH (μL), $x9$ = occipital DWMH (μL), $x10$ = basal ganglia DWMH

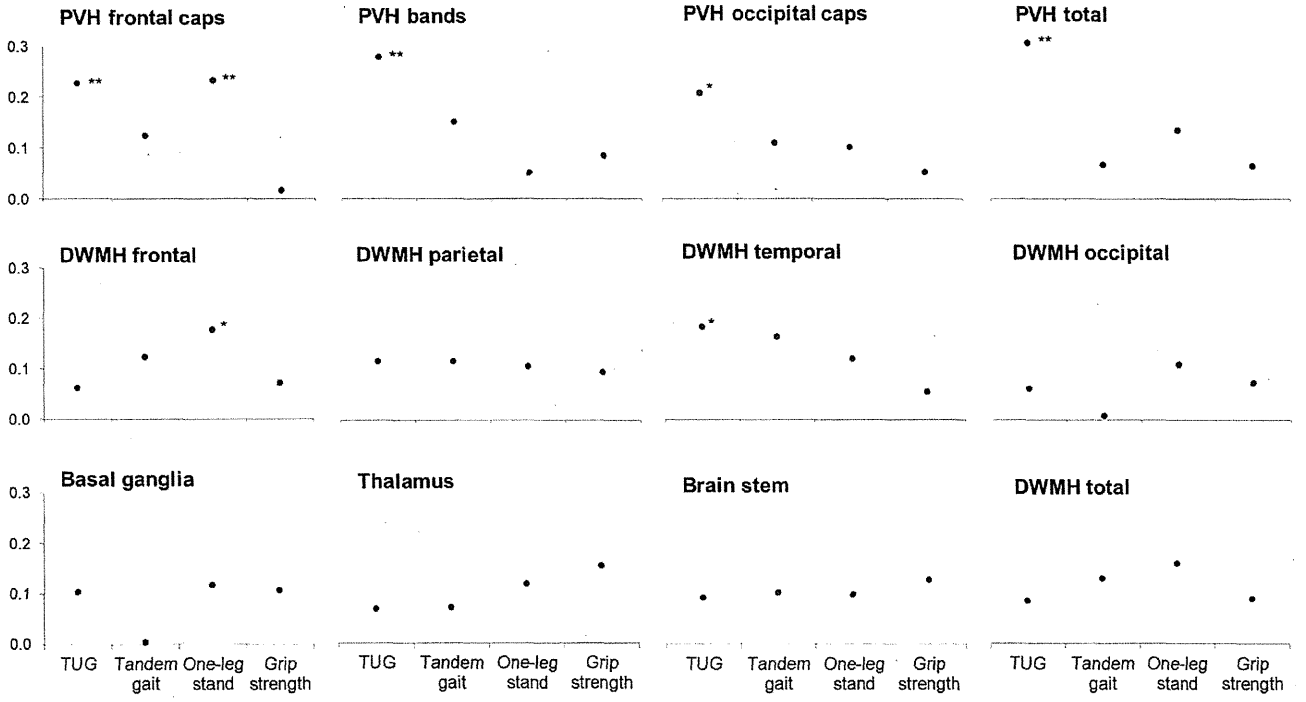

Fig. 2. Impacts of regional white matter lesions (WMLs) on gait performance. Effects of regional periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) on motor performance are demonstrated. The Y-axis indicates absolute values of the partial Spearman rank order correlation after adjusting for age, sex, and Mini-Mental State Examination (MMSE). $^{*}P < .05$, $^{**}P < .01$. TUG, Timed Up and Go.

Table 4
Association of WMLs With Previous History of Falls

	Odds Ratio	95% CI	*P* Value
Age	1.029	0.946–1.118	.508
Sex	0.948	0.393–2.285	.905
Mini-Mental State Examination	1.099	0.981–1.232	.103
Polypharmacy	2.557	1.078–6.062	.033
Dementia Behavior Disturbance Scale	1.014	0.977–1.053	.465
Geriatric Depression Scale	1.089	0.939–1.263	.259
PVH			
Frontal caps	1.054	1.011–1.098	.013
Bands	1.024	0.985–1.065	.234
Occipital caps	1.051	0.988–1.119	.116
Total	0.923	0.831–1.026	.138
DWMH			
Frontal	1.007	0.965–1.051	.749
Parietal	1.006	0.986–1.026	.553
Temporal	1.000	0.987–1.014	.956
Occipital	1.013	1.003–1.023	.012
Basal ganglia	1.004	0.992–1.016	.497
Thalamus	1.008	0.997–1.020	.164
Brain stem	0.997	0.986–1.008	.629
Total	0.977	0.916–1.041	.467
Brain atrophy			
Evans ratio	0.995	0.975–1.015	.608
Caudate head index	0.996	0.973–1.020	.750
Inverse cella media index	1.005	0.990–1.019	.543
Basal cistern index	0.996	0.984–1.008	.476

CI, confidence interval; DWMH, deep white matter hyperintensity; PVH, periventricular hyperintensity; SD, standard deviation; WML, white matter lesion.

(μL), $x11$ = thalamus DWMH (μL), $x12$ = brain stem DWMH (μL), $x13$ = total DWMH (μL), $x14$ = PVH frontal caps (1 grade), $x15$ = PVH bands (1 grade), $x16$ = PVH occipital caps (1 grade), $x17$ = PVH total (1 grade), and $x18$ = Polypharmacy (yes: 1, no: 0). The receiver operating characteristic analysis revealed satisfactory discrimination for predicting falls with a sensitivity value of 76.2% and a specificity value of 75.8% when the cutoff point of this model was set at 0.403. The AUC was 0.81 (95% confidence interval, 0.74–0.88). When we added only total PVH and DWMH values in the prediction model, the AUC was decreased to 0.73 (95% confidence interval, 0.65–0.81). When results of balance/gait performance were added as variables in a similar analysis, PVH frontal caps and occipital DWMH were again extracted as predictive factors for falls (data not shown).

Discussion

Several cross-sectional and longitudinal studies have reported the correlation of global WMLs with measurements of balance, gait, and falls in the elderly;[7–14,24–29] however, the role of regional WMLs in relation to motor performance remains uncertain.[8,14,24–29] To date, only 2 studies have investigated the effects of WML burden in demented disorders.[7,8] The current study revealed the correlation of regional WMLs with posture control, gait, and falls in patients with aMCI and AD. The fallers group had a greater volume of WMLs than nonfallers, with several WMLs in particular brain regions closely associated with balance/gait function. Besides polypharmacy, PVH in frontal caps and DWMH in the occipital lobe were strong predictors for falls, independent of cognitive decline. Preventative strategies for falls in the demented elderly are a clinical challenge. Our observation indicates that careful insight into regional WMLs may greatly help to diagnose elderly patients with a higher risk of falls.

This study showed that the more severe the PVH, the more impaired balance and gait function was.[7,11,14,24–29] PVH at all sites, particularly PVH in frontal caps, was closely correlated with balance, gait, and falls, suggesting the role of frontal neural circuit in maintaining mobility function. Periventricular fibers are predominantly critical to posture control and motor function. Compared with more superficially located fibers, the deeper white matter tracts connect remote motor and sensory cortical and subcortical sites that are needed for posture control and gait. Benson et al[24] reported that frontal periventricular regions are sensitive and occipitoparietal PVH specific for lower mobility.[4] Anterior and posterior corona radiata lesions are involved in mobility decline.[28,29] Frontal and periventricular WMLs correlate with poor gait function, presumably because of disconnecting major anterior projection fibers and adjacent association fibers.[27]

Prior studies have reported that severe WMLs in the frontal lobe, basal ganglia and brain stem deteriorate walking speed and balance control.[8,14,25–29] This study revealed that DWMH in basal ganglia, parietal, and temporal lobes correlated with posture control, whereas DWMH in frontal and temporal lobes correlated with gait disturbance. DWMH in several brain regions could affect balance and mobility coordinately, contributing to a higher incidence of falls.

One of the most important findings of this study is that occipital DWMH is a strong predictor for falls. Despite this, DWMH in the occipital lobe did not show any obvious correlation with balance and gait parameters, which differed from the findings for PVH in frontal caps. We examined the possibility that occipital DWMH compromises the processing of visual information to keep body balance. This, however, seems unlikely because performance of several cognitive tests measuring visuospatial function was unchanged in the fallers. Relatedly, Van Impe et al[30] recently demonstrated that WMLs in the occipital lobe plays a significant role in balance function by using the diffusion tensor images. Static balance and movement rely on the integration of vestibular, visual, and tactile-proprioceptive information. When information from the vestibule is the only information available, WMLs in the occipital lobe account for 42% of balance disturbances.[30] The occipital subcortical region communicates not only between bilateral visual cortexes, but also between the dorsa prefrontal area, and posterior parietal and occipital areas, through the inferior front-occipital fasciculus.[30,31] This study exhibited PVH at occipital caps correlated with posture sway in the anteroposterior direction and occipital DWMH correlated with falls. It has been suggested that categorization of WMLs as periventricular or DWMH may be arbitrary and merely a reflection of total WML volume. Although these distinctions need further corroboration, occipital WMLs seem crucial for predicting falls in the demented elderly.

WMLs are composed of heterogeneous pathologic changes, including axonal and myelin loss and pallor, scattered microinfarcts, astrogliosis, dilatation of perivascular spaces, and cerebral amyloid angiopathy.[32] Although the etiology of WMLs is not fully understood, there is increasing evidence that chronic cerebral ischemia because of small-vessel disease plays a central role in the pathogenesis of WMLs.[32] Small-vessel disease is more common in subjects with AD than in nondemented elderly.[33,34] Previous studies have shown a differential distribution of WMLs between cognitively normal and AD patients.[34] In the ageing brain, WMLs are most prevalent in the frontal areas, whereas posterior regions are minimally affected. In contrast, WMLs in AD patients show more posterior involvement. Subjects with MCI had an intermediate periventricular WML burden in extent and location between cognitive normal and AD patients.[34] Although a few studies have found a role of WMLs in posterior brain for balance/gait impairment in nondemented elderly patients,[24,29,30] our study clearly demonstrated deleterious effects of posterior WMLs on gait performance in patients with aMCI and AD. Greater WMLs in posterior brain with AD pathology could account for an increased prevalence of falls.

This study has inherent limitations. First, this is a cross-sectional study and, therefore, no causality can be inferred between WMLs and falls. Prospective studies are needed to test a new hypothesis that

falls among the demented elderly are not accidental events, but rather are important clinical manifestations of cerebral WMLs. Second, we used a visual rating of WMLs, but not objective evaluation using automated MR imaging analysis. However, it has been suggested that visual rating on high-resolution MR images and automated volumetric measurements are equally sensitive in detecting larger lesions.[35] More importantly, visual rating of WMLs can be more commonly available in the clinical practice. Finally, detailed data on musculoskeletal disease including arthritis were not obtained. However, we evaluated a wide range of risk factors for falls in the elderly, including age, sex, cognition, medication, BPSD, depression, muscle strength, environmental factors, and brain atrophy, and we demonstrated the specific contribution of WMLs to mobility decline in patients with AD or aMCI.

Conclusions

This study provides the first evidence of interaction between regional WMLs and balance/gait impairment in patients with aMCI and AD (mild to moderate stage). Besides polypharmacy, PVH in frontal caps and occipital WMLs are strong risk factors for falls; independent of cognitive decline. Our observations imply WML burden, but not progression of dementia, is predictive for falls in patients with AD pathology. Brain MR imaging is a routine examination for diagnosis of demented disorders. Physicians should pay greater attention to WMLs to prevent falls in the demented elderly. Intensive studies to clarify the relevant risks, natural history, and efficient treatments for WMLs are needed.

Acknowledgments

The authors thank the BioBank, NCGG for the quality control of the clinical data.

References

1. Tinetti M, Williams C. The effect of falls and fall injuries on functioning in community-dwelling older persons. J Gerontol A Biol Sci Med Sci 1998;53: M112–M119.
2. Morris J, Rubin E, Morris E, et al. Senile dementia of the Alzheimer's type: An important risk factor for serious falls. J Gerontol 1987;42:412–417.
3. Tinetti M, Speechley M, Ginter S. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701–1707.
4. Goldman W, Baty J, Buckles V, et al. Motor dysfunction in mildly demented AD individuals without extrapyramidal signs. Neurology 1999;53:956–962.
5. Alexander N, Mollo J, Giordani B, et al. Maintenance of balance, gait patterns, and obstacle clearance in Alzheimer's disease. Neurology 1995;45:908–914.
6. Sheridan P, Solomont J, Kowall N, et al. Influence of executive function on locomotor function: Divided attention increases gait variability in Alzheimer's disease. J Am Geriatr Soc 2003;51:1633–1637.
7. Horikawa E, Matsui T, Arai H, et al. Risk of falls in Alzheimer's disease: A prospective study. Intern Med 2005;44:717–721.
8. Nadkarni N, McIlroy W, Mawji E, et al. Gait and subcortical hyperintensities in mild Alzheimer's disease and aging. Dement Geriatr Cogn Disord 2009;28: 295–301.
9. Baezner H, Blahak C, Poggesi A, et al. Association of gait and balance disorders with age-related white matter changes: The LADIS study. Neurology 2008;70: 935–942.
10. Sonohara K, Kozaki K, Akishita M, et al. White matter lesions as a feature of cognitive impairment, low vitality and other symptoms of geriatric syndrome in the elderly. Geriatr Gerontol Int 2008;8:93–100.
11. Soumare A, Elbaz A, Zhu Y, et al. White matter lesions volume and motor performances in the elderly. Ann Neurol 2009;65:706–715.
12. Silbert L, Nelson C, Howieson D, et al. Impact of white matter hyperintensity volume progression on rate of cognitive and motor decline. Neurology 2008; 71:108–113.
13. Srikanth V, Beare R, Blizzard L, et al. Cerebral white matter lesions, gait, and the risk of incident falls: A prospective population-based study. Stroke 2009;40: 175–180.
14. Novak V, Haertle M, Zhao P, et al. White matter hyperintensities and dynamics of postural control. Magn Reson Imaging 2009;27:752–759.
15. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
16. Petersen R, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–1992.
17. Okochi J, Toba K, Takahashi T, et al. Simple screening test for risk of falls in the elderly. Geriatr Gerontol Int 2006;6:223–227.
18. Kojima T, Akishita M, Nakamura T, et al. Polypharmacy as a risk for fall occurrence in geriatric outpatients. Geriatr Gerontol Int 2012;12:425–430.
19. Folstein M, Folstein S, McHugh P. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12: 189–198.
20. Mohs R, Rosen W, Davis K. The Alzheimer's disease assessment scale: An instrument for assessing treatment efficacy. Psychopharmacol Bull 1983;19: 448–450.
21. Yesavage J, Brink T, Rose T, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 1983;17: 37–49.
22. Baumgarten M, Becker R, Gauthier S. Validity and reliability of the dementia behavior disturbance scale. J Am Geriatr Soc 1990;38:221–226.
23. Akisaki T, Sakurai T, Takata T, et al. Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus. Japanese Elderly Diabetes Intervention Trial (J-EDIT). Diabetes Metab Res Rev 2006;22:376–384.
24. Benson R, Guttmann C, Wei X, et al. Older people with impaired mobility have specific loci of periventricular abnormality on MRI. Neurology 2002;58:48–55.
25. Starr J, Leaper S, Murray A, et al. Brain white matter lesions detected by magnetic resonance imaging are associated with balance and gait speed. J Neurol Neurosurg Psychiatry 2003;74:94–98.
26. Blahak C, Baezner H, Pantoni L, et al. Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: Cross-sectional results from the LADIS study. J Neurol Neurosurg Psychiatry 2009;80:608–613.
27. Srikanth V, Phan TG, Chen J, et al. The location of white matter lesions and gait—a voxel-based study. Ann Neurol 2010;67:265–269.
28. Wakefield D, Moscufo N, Guttmann C, et al. White matter hyperintensities predict functional decline in voiding, mobility, and cognition in older adults. J Am Geriatr Soc 2010;58:275–281.
29. Moscufo N, Guttmann C, Meier D, et al. Brain regional lesion burden and impaired mobility in the elderly. Neurobiol Aging 2011;32:646–654.
30. Van Impe A, Coxon J, Goble D, et al. White matter fractional anisotropy predicts balance performance in older adults. Neurobiol Aging 2012;33:1900–1912.
31. Martino J, Brogna C, Robles S, et al. Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. Cortex 2010;46:691–699.
32. Schmidt R, Schmidt H, Haybaeck J, et al. Heterogeneity in age-related white matter changes. Acta Neuropathol 2011;122:171–185.
33. Snowdon D, Greiner L, Mortimer J, et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997;277:813–817.
34. Yoshita M, Fletcher E, Harvey D, et al. Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. Neurology 2006;67: 2192–2198.
35. Zheng J, Delbaere K, Close J, et al. Impact of white matter lesions on physical functioning and fall risk in older people: A systematic review. Stroke 2011;42: 2086–2090.

日老医誌　第50巻　第1号　平成25年1月25日発行（奇数月25日発行）平成4年11月20日第3種郵便物認可　ISSN 0300-9173

日本老年医学会雑誌

Japanese Journal of Geriatrics

VOL.50
NO.1
2013
January

社団法人日本老年医学会

日　老　医　誌
Nippon Ronen Igakkai Zasshi