総　論

高齢者の排便障害とその対処法

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Headline

1. 排便には便意を感じてから適切な量と硬さの便を適切な場所で排泄し，保清・更衣が終了するまでの，一連の知覚・判断力・運動能力が要求される．このいずれかがうまくいかないことが排便障害である．
2. 高齢者では併存する疾患も多く，その治療薬により慢性便秘をきたしていることも多い．
3. 慢性便秘の治療はまず生活および食事の指導であり，次に薬物療法がくる．病態に即した生活食事指導および薬剤療法が大切である．漫然とした緩下剤の投与は難治性の便秘を招く．

はじめに

排便障害は加齢とともに増加する．2010年度の国民生活基礎調査では65歳以上の高齢者の約30%が排便に関する訴えを有している．排便は，正常な直腸・肛門機能だけでなく，便意を感じてから適切な場所で排泄し，保清，更衣ができるという一連の知覚・判断力・運動能力が要求される行為である．これら排便にかかわるメカニズムのいずれかが障害されても排便障害が生じる．排便障害は本人の生活の質（quality of life;QOL）を低下させるばかりでなく，精神的なダメージをも与える．また介護する家族にも大きな影響を及ぼす問題であるが，命にかかわる病気ではないため軽んじられ，医療機関受診をためらうケースも多い．一般内科医には受診患者の排便障害を拾い上げ，的確に診断して初期治療を行い，かつ適切なタイミングで専門医に紹介する役割があると考える．

排便障害とは

正常の排便とは適切な「量」の便（日本人では平均200 g/day程度）を，適切な「硬さ」（Bristol Stool Form Scaleの3～5）で，適切な回数（3回/day～3回/week），適切な「場所」で，適切な「時間」に，「快適」に排泄できることをさす[1]．

このいずれかが障害されたものが排便障害（便秘・下痢・便失禁）である．ここではおもに慢性便秘と便失禁について述べる．

排便障害の分類と原因

便秘は原発性と続発性に大きく分けられる．原発性便秘には機能性便秘（いわゆる慢性便秘）が，続発性便秘には器質性便秘，症候性便秘，薬剤性便秘が含まれる．便秘の診断ではまず大腸がんや腸閉塞などの器質性疾患による便秘かどうかを見極め，器質性疾患による便秘であれば，タイミングを逃さずその治療を行うことが最優先となる．症候性便秘は糖尿病や甲状腺機能低下症，Parkinson病，脳血管障害など疾患に伴って生じる便秘であり，薬剤性便秘は抗コリン薬や抗うつ薬など薬剤の使用によって起こる便秘である．機能性便秘はさらに弛緩性便秘・けいれん性

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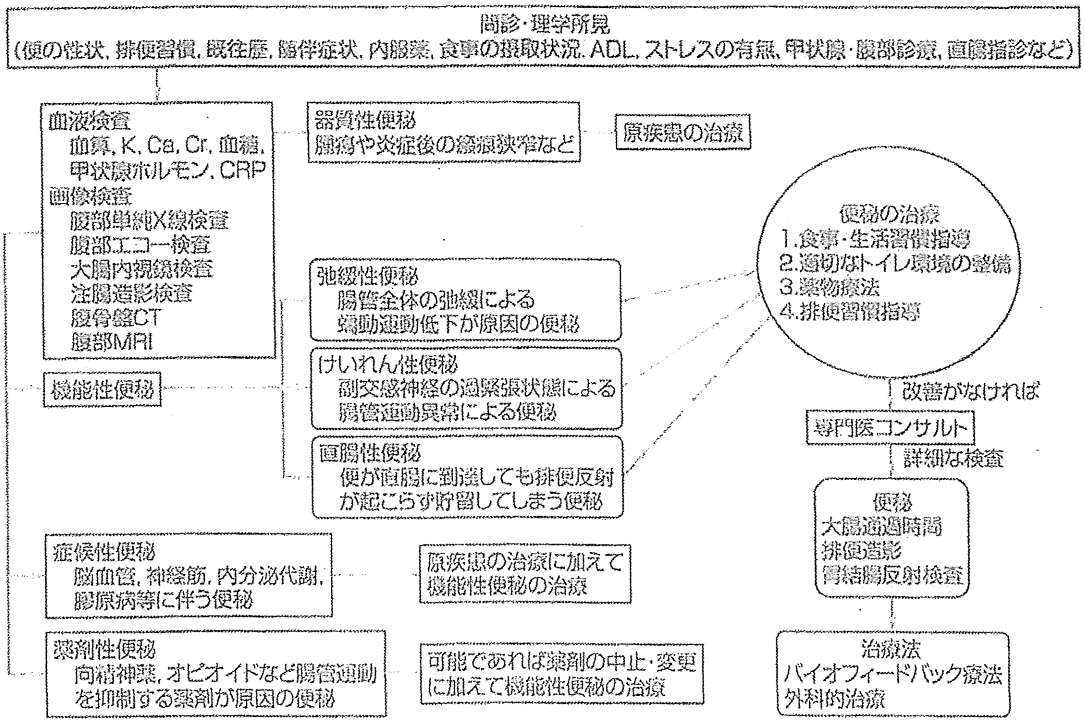

図1 便秘の分類・診断・治療
(文献2)より引用)

表1 高齢者に生じる便秘の病態とそのメカニズム

1. 身体活動や摂食量の低下→腸内容の減少→腸管壁への物理的拡張・刺激の低下, 局所血流の低下
2. 腸管筋層の萎縮, 結合織の増生→大腸の支持組織の緊張や運動の低下
3. 大腸憩室の増加→腸管壁緊張低下を助長
4. Auerbach神経叢の変化
5. 腸管の分泌低下→便硬度の増大
6. ガス吸収機能の低下→腸管の内腔拡張→左右結腸曲部の異常屈曲
7. 直腸壁感受性の低下→排便反射の低下～消失
8. 排便に関する筋力(腹筋・横紋筋・骨盤底筋群)の低下→腹圧の低下, 直腸肛門角開大力の低下
9. 高齢者に多い疾患との関連→脳血管障害, 肺気腫, 心不全
10. 高齢者のライフサイクルと心理的要因→少ない食事量, 繊維分の少ない食事内容, 水分摂取量の低下, 便意の抑制
11. 習慣的な浣腸や下剤の使用

(文献3)より引用)

便秘・直腸性便秘に分類される(図1)[2]. 高齢者に最も多いのはこの機能性便秘, とりわけ弛緩性便秘である. 加齢に伴う食事量や飲水量, 運動量の低下, ライフサイクルや環境の変化, 腸管の生理機能の変化など様々な要因が, 単独あるいは相互に影響しあい高齢者の慢性便秘の原因となる(表1)[3]. 便秘は原因により上記四つの種類に分類されるが, 症候性便秘や薬剤性便秘は病態的には機能性便秘と重なる部分も多い.

一方, 便失禁も失禁の状態により漏出性, 切迫性, 溢流性, 医原性の4種類に分類される(図2)[2]. 肛門括約筋やこの周囲の神経組織の損傷(手術や放射線治療など), 直腸癌, 慢性の便秘や下痢, 糖尿病など全身疾患, 認知症, 下剤などの薬剤, 表1に示した生理的加齢変化, 出産なども便失禁の原因となる.

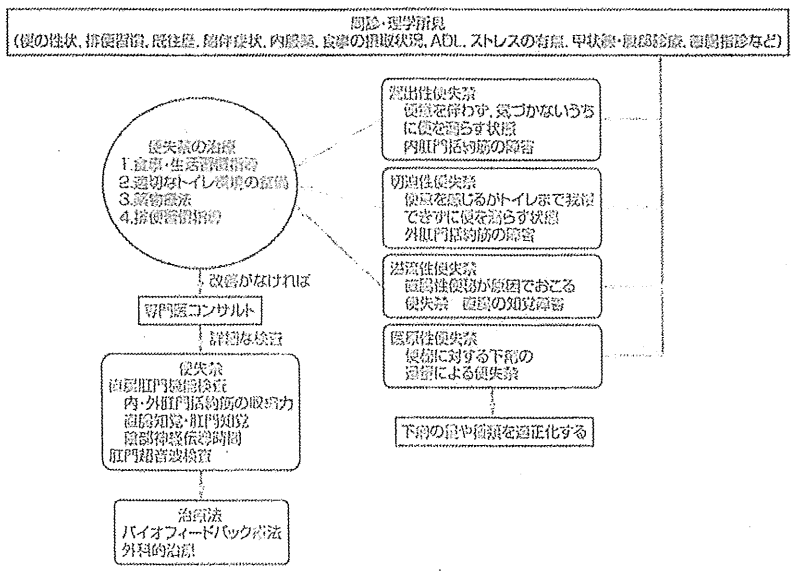

図2　排便障害の分類・検査・治療
(文献2)より引用)

便秘を引き起こす薬剤

高齢者は併存する疾患に対して複数の薬剤を処方されている場合が多い．これらの薬剤の副作用として便秘が誘発されることがある．便秘の原因となるおもな薬剤とそのメカニズムを表2にまとめた．

1．抗コリン薬

Parkinson病治療薬や抗うつ薬，抗てんかん薬などの神経・精神疾患領域で使われる薬剤の多くや頻尿・過活動膀胱治療薬，ジソピラミドなどの抗不整脈薬，抗ヒスタミン薬などはその抗コリン作用により腸管運動を抑制し，便秘を誘発する．Parkinson病などでは疾患そのものによる自律神経障害も加わり，便塊が長期間腸管内に停留する．腸管壁の伸展が続くと，腸管壁筋層の菲薄化や神経叢の変性が生じてさらに腸管運動が低下し便の貯留を招くという悪循環に陥ってしまう．

2．麻薬薬

モルヒネなどの麻薬系鎮痛薬は，腸管神経叢でのアセチルコリンの分泌を抑制し，かつ腸管壁からセロトニンを遊離することで蠕動運動を低下させ便秘をきたす．

高齢者では腰痛や膝関節痛，リウマチといった整形外科的疾患に対して非ステロイド性抗炎症薬（non-steroidal anti-inflammatory drugs;NSAIDs）を投与されている人も多い．NSAIDsの副作用としては消化性潰瘍や腎機能障害が有名であるが，NSAIDsによるプロスタグランジンの合成抑制は腸管運動を低下させ，便秘を引き起こす[1]ことも忘れてはならない．

3．緩下剤，制酸薬

センナなどの緩下剤は本来便秘の治療薬であるが，長期連用により腸平滑筋を萎縮させ，大腸や回腸末端の形態的変化を伴う大腸機能不全を引き起こすことにより難治性便秘を誘発する．一方，緩下剤の過剰投与は便失禁も引き起こす．

制酸薬もその収斂作用により便秘を引き起こす．

表2　便秘を生じる薬剤の種類とそのメカニズム

薬剤名	便秘のメカニズム
・抗コリン薬（Parkinson病治療薬など） ・ドパミン作動薬 ・三環系抗うつ薬 ・抗てんかん薬 ・抗ヒスタミン薬 ・抗不整脈薬（ジソピラミドなど） ・頻尿・過活動膀胱治療薬	抗コリン作用による消化管の緊張や運動の減少
・フェノチアジン系抗精神病薬	腸管の筋層間神経叢障害
・麻薬系鎮痛薬	腸管神経叢でのアセチルコリンの分泌抑制・腸管壁からのセロトニン遊離による腸平滑筋の静止緊張の上昇
・非ステロイド抗炎症薬（NSAIDs）	プロスタグランジンの合成を抑制し，腸管運動を低下させる
・緩下剤（センナなど）	腸平滑筋の緊張と収縮性消失による腸管の蠕動抑制
・制酸薬（水酸化アルミニウムなど）	収斂作用
・陰イオン交換樹脂の脂質異常症治療薬（コレスチミドなど） ・カルシウム製剤	腸管内での膨潤した本剤から大腸で水分が吸収されるため，本剤を含んだ内容物が硬くなる．
・鉄剤（硫酸鉄）	腸管の粘膜を刺激し副交感神経を抑制するため，腸管運動が低下する
・利尿薬	脱水による硬い便塊の形成
・カルシウム拮抗薬	直腸S状結腸の運動不全

NSAIDs:non-steroidal anti-inflammatory drug

4．陰イオン交換樹脂，カルシウム製剤，鉄剤

脂質代謝異常症の治療薬である陰イオン交換樹脂やカルシウム製剤は，腸管内で膨潤したこれらの製剤から大腸で水分が吸収され，一方，これらの薬剤の成分を含んだ内容物（便）が硬くなるため便秘を起こす．ひどい場合は腸閉塞症状や腸管穿孔も起こすため注意が必要である．

貧血の治療薬である鉄剤は，それ自体の腸管粘膜への刺激作用により副交感神経が抑制され便秘を誘発する．

5．利尿薬，カルシウム拮抗薬

高血圧や心不全，腎不全などでは利尿薬やカルシウム拮抗薬がよく使われるが，利尿薬は血管内が脱水になることにより腸管からの水分吸収が増えるため，硬い便を形成することとなり便秘を引き起こす．またカルシウム拮抗薬はS状結腸から直腸にかけての腸管運動不全を引き起こすことにより便秘を誘発すると考えられている．

いずれの薬剤も高齢者で頻用されるものであるが，便秘のために服薬コンプライアンスそのものが低下することもまれではない．

診断

排便障害は詳細な問診によりほぼ診断できる．問診では，排便の状態（排便回数，排便困難感，残便感，排便に要する時間，排便補助の有無など）や排便に関して困っていること，手術歴を含む既往歴，併存疾患，薬の服薬状況などについて詳細に問診する．高齢者では食事や水分などの摂取状況，日常生活動作（activities of daily living;ADL）のレベル，心理的・社会的要素についての問診も重要である．次に腹部の理学所見や直腸指診，血液検査や便検査を行い，必要な画像検査（腹部

単純X線検査やCT，腹部エコー，大腸内視鏡検査など）を加え，アルゴリズム（図1，図2）に従い診断をすすめる．高齢者では担がん患者も多く，がんなど器質的疾患を見逃してはならない．器質性便秘，続発性便秘を除外したら，さらに機能性（慢性）便秘がどのタイプの便秘なのかを見極める．

治療

便秘の原因となる器質的疾患や基礎疾患がある場合は，まずその疾患の治療を行う．薬剤性便秘では，中止可能な薬であれば中止あるいは代替薬への変更を検討する．機能性便秘に対してはまず生活指導と食事療法を行い，改善がなければ必要に応じ適切な下剤を投与する．便失禁については食事・生活習慣の指導やバイオフィードバック療法が主となる．高齢者では，排便習慣の指導に介入する前に，生活指導を行う上でその患者さんにとって障害となっていること（例えば難聴，視力・歩行能力・認知機能の低下など）についてきちんと把握しておく．排便の頻度や形状（Bristol Stool Scale等を用いて），排便時に必要な動作（いきみや用手圧迫）などを記した排便日誌をつけてもらい，それをもとに個別化した排便訓練を行うことも有用である．

1．生活習慣・食事の指導

a）食事

日常的に食物繊維を多く含む食事や水分をきちんととるよう指導する．特に起床1時間以内に軽い運動と飲み物，シリアルなど食物繊維を含むものをとることにより，胃-結腸反射が起こって排便が誘発される．このような習慣をつけることが大切である．

小麦ふすまや果物，野菜，サッツといった食物繊維の多い食事は結腸通過時間を短縮させ，かつ便塊の量を増やすことで便秘の症状を改善する．プルーンジュースやプルーンも便秘を改善する食物である．結腸通過時間遅延型の便秘にはこのような高繊維食が有効であるが，高繊維食が有効でないタイプの便秘（腸管の緊張が強くて生じるような便秘）や骨盤底筋協調運動障害による便秘などにはむしろ低残渣食が有効となる[1]．

腸内常在菌のビフィズス菌の割合が低下すると，腸内の異常発酵に伴う便秘を誘発する．乳酸発酵食品を摂取し，ビフィズス菌を直接増やすか，ビフィズス菌増殖を助けるもの（オリゴ糖，ビタミンB_1・B_2，パントテン酸，ビオチンなどの水溶性ビタミン類）を摂取することで排便回数や便の硬さが改善される．

b）運動

骨盤底筋協調運動障害（排便強調障害）や便排出力低下がある場合は，腹圧を高めるための腹筋運動や腹式呼吸，ウォシュレットでの肛門マッサージ，排便時の姿勢（直腸肛門角を鈍角化させる和式トイレにしゃがむような姿勢）の指導も効果的である．排便協調障害や直腸知覚障害[4]などについてはこのような日常生活でできる指導のほか，専門施設でバイオフィードバック療法を行ってもらうと便秘や失禁などの排便障害の改善が望める．

ストレスは自律神経の緊張により交感神経の興奮状態を優位にさせるため，蠕動運動を低下させ便秘を誘発する．ストレスを取り除き，リラックスすることで副交感神経が優位の状態を作ると便秘は改善する．

また高齢者や長期臥床者では，腹圧がかからず直腸まで便が来ていても排便できないことも多々ある．このような場合は，摘便することで直腸肛門反射が誘発され排便が促されることも多い．

2．薬物療法と注意すべきこと[5]

便秘に対する薬物療法は食事・生活指導を行っても改善が難しいときに行う第二選択の治療である．緩下剤には，便量を増すもの，便の水分量を増し柔らかくするもの，腸運動

を亢進させるものなどがあり，便通や便の性状に合わせて下剤を選択し使用する．

a）機械的下剤

1）塩類下剤（酸化マグネシウム：マグラックス®など）

腸管内に水分を移行させて腸内容を軟化増大させることで腸管の運動を亢進させる．習慣性が少なく長期投与が可能であるため，慢性便秘の治療に向いている．腎疾患や心疾患のある症例では，高マグネシウム血症などを起こすことがあるため，定期的に血清マグネシウム値をモニターし，投与量を調整する．

2）膨張性下剤（カルボキシメチルセルロース：バルコーゼ®，カンテン®）

高繊維食による自然な排便促進作用を薬理的に行う薬剤である．多量の水分で膨張し，軽症の弛緩性便秘に有効である．難治性便秘の患者の場合，過剰な食物繊維の摂取は便量を増大させすぎてかえって便秘が悪化してしまうため，摂取を控えるよう指導する．狭窄性腸疾患には禁忌である．

3）浸潤性下剤（ジオクチルソジウムスルホサクシネート：ビーマス®）

界面活性作用により，便の表面張力を低下させて軟化膨張させ排便を容易にする．重度の硬結便には禁忌である．

4）糖類下剤（ラクツロース：モニラック®）

浸透圧作用で腸管内に水と電解質が保持されるとともに，腸管内で菌により分解されて生じた有機酸（乳酸，酢酸など）により腸管蠕動運動を亢進させる．また有機酸により腸管内のpHを下げ，アンモニアの産生と吸収を抑制することで血中アンモニア濃度を下げる．長期的に高齢者に使用しても安全性が高いが，高アンモニア血症・産婦人科術後の排便障害・小児の便秘以外は保険適応がない．

b）大腸刺激性下剤

腸管内で分解され，その分解産物の腸粘膜直接刺激作用や腸管平滑筋の粘膜下神経叢を刺激して腸管蠕動運動を亢進させる．また大腸粘膜上皮細胞のNa^+-K^+ ATPaseを抑制し，水分，Na^+の吸収を阻害する．このため過剰投与で結腸における水や電解質の吸収が低下し，腸管のけいれんや電解質障害，脱水などが生じるほか，習慣性があり，かつ，粘膜の炎症を起こすなどの欠点があり，長期使用は避けたほうがよい．坐剤も大腸刺激性下剤に分類される．直腸粘膜を刺激して腸蠕動を促進し，排便を促す．坐剤は弛緩性便秘でも腸蠕動を促進し，排便のきっかけを作る．浣腸は大腸の拡張に反応した刺激や洗浄によって腸管運動を誘発するものであるが，頻回の使用は電解質異常や粘膜の機械的損傷を招くことがあり，注意が必要である．

・アントラキノン系誘導体（ダイオウ：セチロ®，センナ：プルゼニド®，アローゼン®，ヨーデルS®，アロエ）
・ジフェノール誘導体（ピコスルファートナトリウム水和物：ラキソベロン®）
・坐剤（炭酸水素ナトリウム配合坐剤：新レシカルボン®，ビサコジル：テレミンソフト®）
・浣腸（グリセリン）

c）クロライドチャネルアクチベーター（ルビプロストン：アミティーザ®）[6]

小腸粘膜上皮細胞内に取り込まれたクロルイオンが小腸粘膜内腔側にある選択的タイプ2クロライドチャネルを活性化することで，Na^+イオンも腸管内腔に移動させ，腸管内への水分分泌を促進し，便を柔らかくして腸管内の輸送を高め，排便を促進する．新しい機序の慢性便秘治療薬である．アメリカでは2006年より承認されているが，日本では最近使用可能となった．高齢者では比較的有害作用が少ないとされるが，今後のわが国での有用性，有害事象に関する報告を待ちたい．

このほか，緩下剤ではないが，セロトニン受容体作動薬のモサプリド（ガスモチン®）や

パントテン酸（パントール®，パントシン®），大建中湯[7]は腸管運動促進作用により便秘を改善させる．また腸管の収縮や緊張が強いため起こっている排便障害に対しては緊張をとる目的で小建中湯を投与すると便秘が改善することもある．

おわりに

便秘はそれ自体の不快感のみならず，悪心・嘔吐，糞便イレウスや宿便性潰瘍，腸穿孔の原因となったり，QOLの著しい低下につながる．高齢者の便秘では，まずがんなどの器質的疾患を除外したうえで，便秘のタイプを見極め，適切な食事や生活習慣の改善，運動療法，薬物療法を組み合わせて治療していく必要がある．そして下剤の乱用による難治性便秘を作らないよう細やかな対応を心がける．

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Original Study

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

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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.

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

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The authors declare no conflicts of interest.

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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	Nonfaller	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: $\text{Log } p/(1\text{-}p) = -0.0534x1 + 0.0282x2 + 0.0948x3 + 0.0140x4 + 0.0852x5 + 0.0069x6 + 0.0061x7 + 0.0004x8 + 0.0130x9 + 0.0041x10 +$

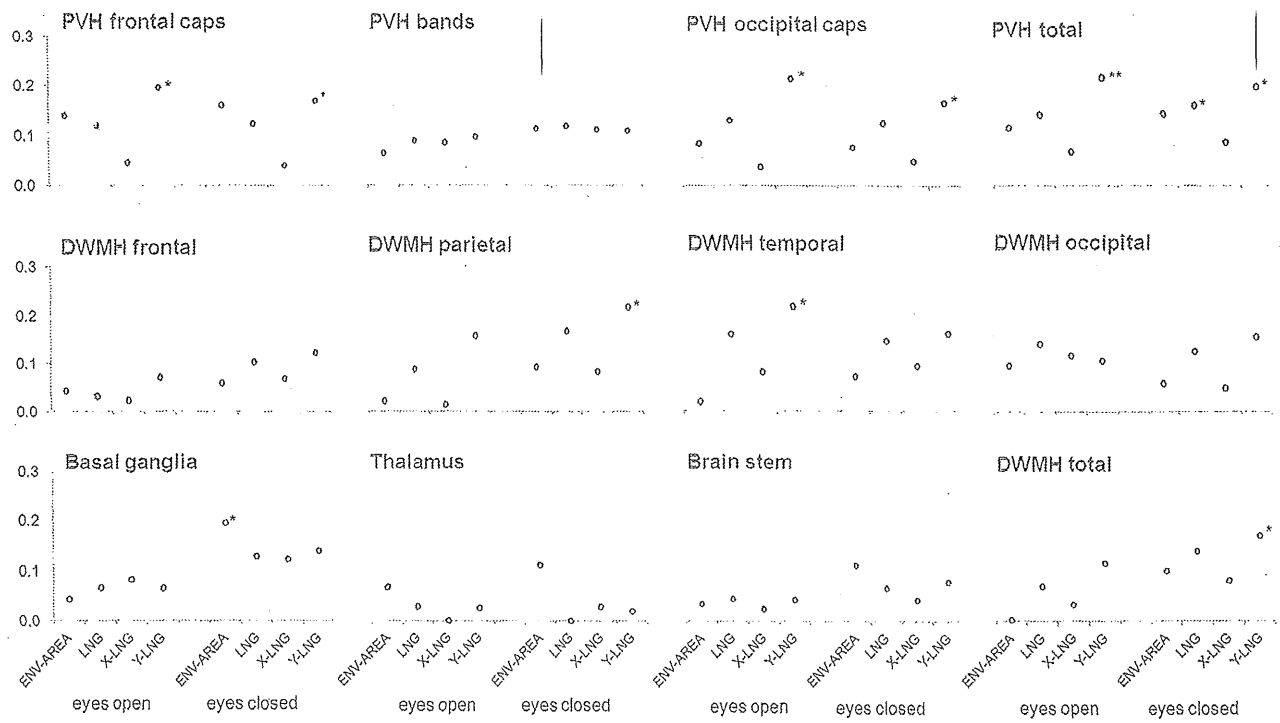

Fig. 1. Effects of regional white matter lesions (WMLs) on posture control. Effects of regional periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) on balance function are shown. The Y-axis denotes the absolute values of the partial Spearman rank order correlation after adjusting 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

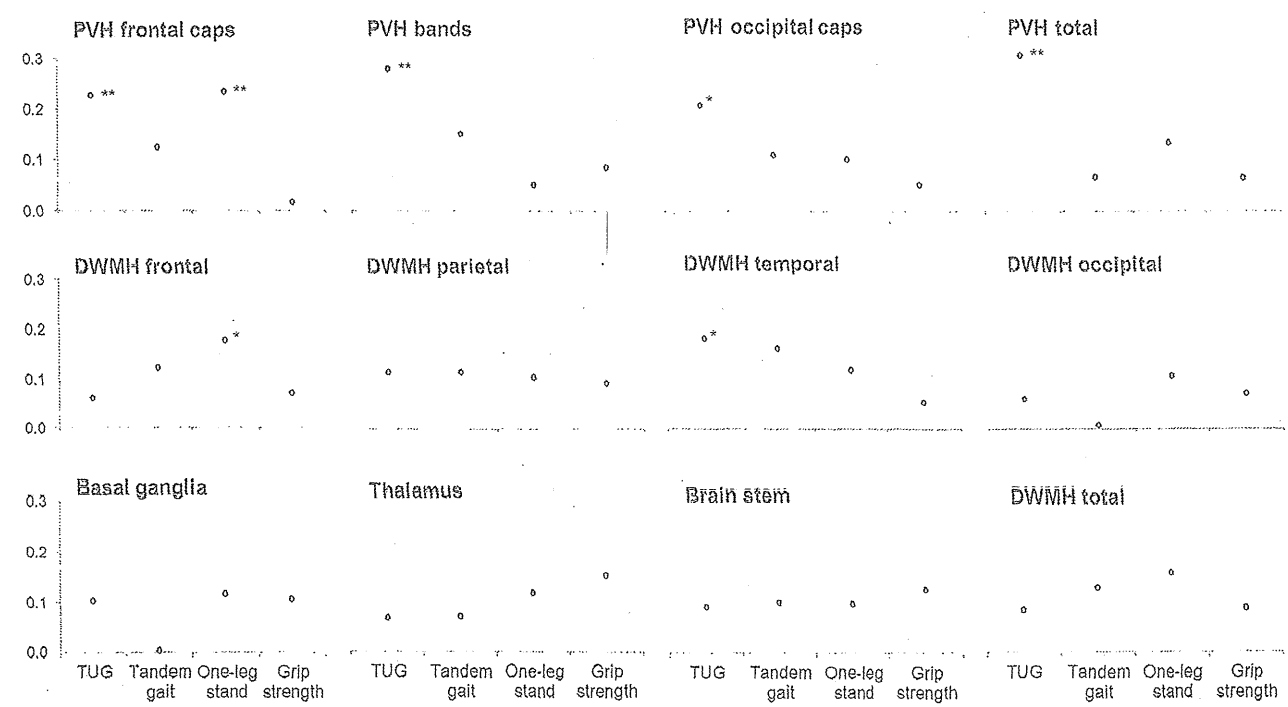

Fig. 2. Impacts o. regional white matter lesions (WMLs) on gait performance. Effects of regional periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) on motor performance are demonstrated. The Y-axis indicates absolute values of the partial Spearman rank order correlation 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.

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ORIGINAL ARTICLE

Intensive rehabilitation for dementia improved cognitive function and reduced behavioral disturbance in geriatric health service facilities in Japan

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Aim: To examine the efficacy of rehabilitation for elderly individuals with dementia at intermediate facilities between hospitals and home, based on the policies for elderly individuals to promote community-based care at home and dehospitalization.

Methods: Participants were older adults with dementia newly admitted to intermediate facilities. A total of 158 in the intervention group who claimed Long-Term Care Insurance for three consecutive months, and 54 in the control group were included in the analysis. The interventions were carried out in a tailor-made manner to meet individual needs. The personal sessions were carried out three times a week for 3 months after admission by physical, occupational or speech therapists. Outcome measures were cognitive tests (Hasegawa Dementia Scale revised [HDS-R] and Mini-Mental State Examination), and observational assessments of dementia severity, activities of daily living (ADL), social activities, behavioral and psychological symptoms of dementia (BPSD) using a short version of the Dementia Disturbance Scale (DBD13), depressive mood, and vitality.

Results: Significant improvement in the intervention group was shown in cognitive function measured by HDS-R (interaction $F[1, 196] = 5.190$, $P = 0.024$), observational evaluation of dementia severity ($F[1,198] = 9.550$, $P = 0.002$) and BPSD (DBD13; $F[1,197] = 4.506$, $P = 0.035$). Vitality, social activities, depressive mood and ADL were significantly improved only in the intervention group, although interaction was not significant.

Conclusions: Significant improvement by intervention was shown in multiple domains including cognitive function and BPSD. Cognitive decline and worsening of BPSD are predictors of care burden and hospitalization, thus intensive rehabilitation for dementia was beneficial for both individuals with dementia and their caregivers. **Geriatr Gerontol Int 2013; ○○: ○○–○○.**

Keywords: behavioral and psychological symptoms of dementia, clinical medicine, Dementia Disturbance Scale short version, dementia, geriatric medicine, rehabilitation, tailor-made.

Introduction

Promoting community-based care at home and dehospitalization is one of the main policies for elderly individuals. In order to reduce the length of hospital stay, it is recommended to establish a rehabilitation and care system for the elderly just after leaving hospital. Thus, the Japanese government established the "Geriatric Health Service Facility" in 1986 (Long-Term Care Health Facility after 2000; Roken), which is a transitional facility between hospital and home or nursing home to provide medical treatment, nursing care, and rehabilitation. Elderly individuals are admitted to Roken after their condition has become stable in hospital, and stay until they are ready to return home. After returning home, Roken offers community-based rehabilitation and various care services to support home-based care, and facilitates networks for intraregional exchanges among municipalities, local healthcare and social welfare services.

Since Roken was launched, the number of inpatients with dementia has markedly increased. Hospitalization

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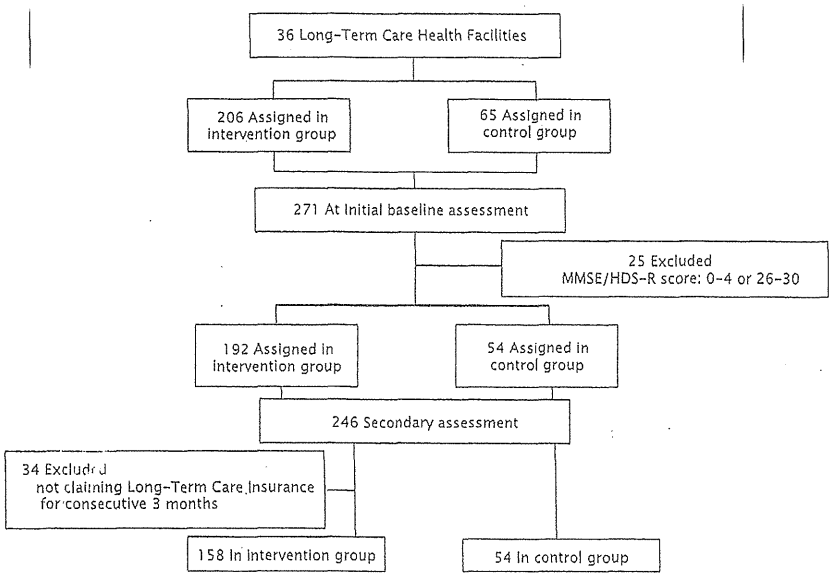

Figure 1 Flow of participants in the intervention and control groups. HDS-R, Hasegawa Dementia Scale revised. MMSE, Mini-Mental State Examination.

itself can cause cognitive deterioration, even during a hospital stay for diseases other than dementia, and patients are often not expected to recover to their pre-hospitalization level.[1] Other predictors of hospitalization are caregivers' burden and the interrelationship with caregivers.[2] Behavioral and psychological symptoms of dementia (BPSD) are a source of distress for caregivers and a major reason for hospitalization.[3,4] Additionally, disuse syndrome is triggered by psychological factors associated with dementia, such as a depressive and apathetic mood.[5–9] Disuse syndrome can lead to deterioration of cognitive and physical function, which can result in repeated hospitalization.

To break the vicious cycle of repeated hospitalization, effective rehabilitation just after discharge from hospital is required, and Roken was singled out as the appropriate facility for the rehabilitation. Thus, in 2006, the Japanese Long-term Care Insurance system introduced intensive rehabilitation for individuals with dementia who were newly admitted to Roken, consisting of personal rehabilitation three times a week for 3 months. This rehabilitation has become widely practiced since its introduction. However, the efficacy has not been examined, although the rehabilitation is payable under long-term insurance. Thus, a model project was organized to examine the efficacy of the rehabilitation for dementia in Roken throughout Japan.

Methods

Study members

Study committee members were researchers excluding stakeholders of any Roken, and committee observers were staff of the Health and Welfare Bureau for the Elderly, Ministry of Health, Labour and Welfare. The committee designed the research, selected 36 Rokens, and interpreted the data. Data were collected by rehabilitation staff in the 36 Rokens.

Participants

The study was carried out between July 2007 and February 2008. The flow of participants is shown in Figure 1. Survey slips were sent to the facilities in July 2007. The facilities were required to send them back after the pre-intervention and post-intervention assessment, respectively. Inclusion criteria of the intervention group were: (i) newly admitted patients with dementia diagnosed by *The Diagnostic and Statistical Manual of Mental Disorders IV*; (ii) with Mini-Mental State Examination (MMSE) or Hasegawa Dementia Scale revised (HDS-R) score between 5 and 25 at pre-intervention assessment; and (iii) who claimed Long-Term Care Insurance for three consecutive months. Inclusion criteria of the control group were: (i) and (ii), and (iii) who did not receive interventions. The participants were not randomized. We received 271 responses, and among them, 212 individuals met the inclusion criteria (158 in intervention group and 54 in control group; Table 1). Informed consent was given from all participants or their responsible care giver. The research plan was approved by the Ethics Board of the Japan Association of Geriatric Health Services Facilities.

Assessment

The assessment was minimized to reduce the burden of facilities staff. As the interventions were carried out by therapists during working time, it would have been

Table 1 Demographic data

		Intervention	Control	
n		158	54	
Male/female (%)		30.2/69.8	39.6/60.4	NS
Age		84.1 ± 7.1	87.3 ± 7.1	P = 0.005†
Dementia	AD	22	7	NS
	VD	52	15	NS
	DLB	3	0	NS
	FTD	2	0	NS
	Others/unknown	79	32	NS

†Significant difference by two-sample *t*-test. AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, front-temporal dementia; M/F, male/female; NS, no significant difference by χ^2-test; VD, vascular dementia.

difficult to collect many data if the assessment were complicated. The assessment scales were chosen based on preliminary studies, which were carried out in the last 2 years.

Cognitive tests

The MMSE and HDS-R were carried out. HDS-R is similar to MMSE, but lays more weight on memory than does MMSE.

Questionnaires

For the assessment of subjective mood, the participants were required to answer the interview of a short version of the Geriatric Depression Scale (GDS;[10] scores are between 0–5, high scores indicate more depressive mood). Facility care staff assessed activities of daily living (ADL), BPSD, N-Memory Scale (NM),[11] vitality index[12] and the Social Activity Scale. ADL was assessed using the Barthel Index (scoring was changed: total assistance of 0 to independence of 3 for each item, and full score of 15).[13] In addition to ADL, the capacity for social interaction was measured using the Social Activity Scale, whose sub-items were conversation with facility staff members, conversation with other residents, organizing own belongings, participation in recreational activities, and outings (total assistance of 0 to independence of 3 for each item, and full score of 15). BPSD was evaluated using a short version of the Dementia Behavior Disturbance Scale (DBD;[13] "never" of 0 to "usually" of 3 for each item and full score of 48).[14] The NM Scale is an observational scale, which evaluates the stages of dementia in five domains: housework, social interaction and interest, communication, memory, and orientation ("impossible" of 0 to "normal" of 10 and full score of 50). The Vitality Index evaluates motivation in daily living, with sub-items of waking up, greetings, having meals, elimination, and participation in rehabilitation and/or recreation ("indifferent" of 0 to "voluntarily" of 2 and full score of 10).

Intervention

Before commencement of the study, a training workshop was held to introduce the intervention methods, whose efficacy was suggested by previous studies: such as reminiscence, reality orientation, memory rehabilitation, music therapy, physical exercise, occupational therapy, speech communication therapy and learning sessions.

The intervention was carried out in an individualized tailor-made manner.[15] First, the individual functional profiles were assessed with regard to both abilities and disabilities to evaluate how to enhance the abilities and compensate for disabilities. Second, training activities were selected; the decision was shared between therapists and participants. Each personal session was took place three times a week for 3 months after admission by physical, occupational or speech therapists. Individuals in the control group took usual group therapies including exercise, singing songs and games.

Analysis of data

The data were analyzed using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, Armonk, NY, USA). For an initial baseline comparison between the intervention and control groups, two-sample *t*-tests were carried out; there was no significant difference between the two groups for any outcome measure. Participants who underwent the initial baseline and post-intervention assessments were included in the final analysis; dropout participants were excluded from the analysis. Repeated measures analysis of covariance (ANCOVA) with the covariate of age was used to analyze the completed cases. Age was used as a covariate, because the ages were significantly different between the two groups (Table 1). The interaction was examined to assess the differential effect between the intervention and control groups, and post-hoc "within subjects" analysis was carried out with Bonferroni correction. Regarding the measures where significant

interaction was shown, intention-to-treat analysis was also carried out; the participants who received the intervention but did not claim Long-Term Care Insurance for three consecutive months were included in the intention-to-treat analysis. A significant difference was set as $P < 0.05$.

Results

Demographic data of the participants are shown in Table 1. Analysis of 158 participants in the intervention group and 54 in the control group was carried out (Fig. 1). The number of participants who took donepezil during the intervention/observation period was two in both groups ($P = 0.269$, χ^2-test).

Cognitive tests

Participants in the intervention group showed significant improvement in HDS-R score compared with those in the control group (interaction F[1, 196] = 5.190, $P = 0.024$; post-hoc intra-subject analysis: intervention group, $P = 0.001$, control group $P = 0.480$). There were no significant differences observed in MMSE (Table 2).

Questionnaire

The intervention group showed significant improvement compared with the control group in DBD[13] (F[1,197] = 4.506, $P = 0.035$; post-hoc intra-subject analysis: intervention group, $P = 0.004$, control group $P = 0.413$) and NM Scale (F[1,198] = 9.550, $P = 0.002$; post-hoc intra-subject analysis: intervention group, $P < 0.001$, control group $P = 0.380$). Regarding the sub-items of the NM Scale, significant differences in interaction were observed for social interaction (F[1,198] = 15.736, $P < 0.001$), memory (F[1,198] = 7.635, $P = 0.006$) and orientation (F[1,198] = 4.220, $P = 0.041$).

Although the interaction was not significant, comparison between pre- and post-intervention showed significant improvement in ADL (Barthel Index), Social Activity Scale, motivation (Vitality Index) and mood (GDS) only in the intervention group after multiple correction (Table 2).

Intention-to-treat analysis

Significant differences remained in the intention-to-treat analysis in the HDS-R and NM Scale; HDS-R, interaction (F[1, 230] = 4.466, $P = 0.036$), post-hoc analysis within subjects: intervention group $P < 0.001$, control group $P = 0.585$; NM Scale, interaction (F[1, 236) = 8.113, $P = 0.005$), post-hoc analysis: intervention

Table 2 Outcome of intensive cognitive rehabilitation

	Intervention group			Control group			Interaction		Intra-subject†	
	Pre	Post	*n*	Pre	Post	*n*	F (DF)	*P*	Intervention	Control
	mean ± SD	mean ± SD		mean ± SD	mean ± SD					
Cognitive test										
MMSE	19.1 ± 4.5	19.4 ± 5.5	100	19.5 ± 4.9	18.2 ± 7.4	13	1.780 (1,110)	0.185	0.542	0.234
HDS-R	16.9 ± 5.7	17.9 ± 6.5	149	17.0 ± 5.9	16.7 ± 6.3	50	5.190 (1,196)	0.024*	0.001**	0.480
Questionnaire										
NM	30.4 ± 9.1	32.1 ± 9.5	149	31.4 ± 9.8	30.7 ± 10.9	52	9.550 (1,198)	0.002**	$P < 0.001$***	0.380
ADL	16.4 ± 7.1	17.3 ± 7.1	152	15.7 ± 7.0	15.9 ± 6.9	53	1.448 (1,202)	0.230	0.001**	0.621
Activity	8.6 ± 3.3	8.8 ± 3.4	150	8.5 ± 3.1	8.6 ± 3.2	53	1.169 (1,200)	0.281	0.038*	0.972
Vitality	8.0 ± 1.7	8.2 ± 1.6	149	8.1 ± 1.8	8.2 ± 1.8	53	1.792 (1,199)	0.182	0.004**	0.864
DBD	4.5 ± 5.1	4.0 ± 4.1	150	4.5 ± 4.2	4.8 ± 4.7	50	4.506 (1,197)	0.035*	0.004**	0.413
GDS	2.5 ± 1.8	2.4 ± 1.9	148	2.3 ± 1.5	2.4 ± 1.5	51	2.048 (1,196)	0.154	0.042*	0.634

†Intra-subject: post-hoc analysis of intra-subject (comparison between pre- and post-intervention analysis). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Activity, Original Activity Scale; ADL, Activities of daily living; DBD, Dementia Behavior Disturbance Scale; DF, degree of freedom; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale revised; MMSE, Mini-Mental State Examination; NM, N-Memory Scale; Post, post-intervention assessment; Pre, pre-intervention assessment; Vitality, Vitality Index.

group $P < 0.001$, control group $P = 0.410$. The interaction of DBD was marginal; interaction ($F[1, 232] = 3.717$, $P = 0.055$), post-hoc analysis: intervention group $P = 0.007$, control group $P = 0.439$.

Discussion

Significant improvement by the intervention was shown in multiple domains; therefore, the intensive rehabilitation for dementia was beneficial for the individuals with dementia and also their caregivers. Pharmacological effects were thought to be negligible, as just two participants in both groups took donepezil during the intervention/observation period.

Regarding cognitive function, the effects of intensive rehabilitation for dementia were shown in both a cognitive test and observational evaluation of memory and orientation measured by NM Scale. In the symptomatic treatment of dementia, amelioration in daily living rather than in neuropsychological factors should be the therapeutic objectives, and thus the emphasis would be laid on improving performance in everyday life rather than on scores of cognitive tests.[16] Besides, it is often pointed out that scores of cognitive tests cannot always be generalized to daily living, although cognitive tests are moderately predictive of functional status in everyday life.[17] Therefore, mere enhancement of cognitive test scores is not sufficient, and beneficial changes in daily living are required. In the present study, cognitive improvement was shown in observational evaluation, in addition to a cognitive test. Cognitive enhancement is also beneficial for caregivers, because the severity of cognitive impairment could be a predictor of burden, in addition to BPSD.[18,19] The effects of non-pharmacological approaches on cognitive function have not yet been established,[16,19] and the present study could provide additional evidence for their benefit.

Amelioration of BPSD was also attained in the present study. Care for demented individuals requires allocation of longer times than for care of the elderly suffering from physical diseases. In particular, the presence of BPSD might induce more stress than do medical problems,[4,20–23] and could result in depression or strain in caregivers.[24] Consequently, caregivers' burden is associated with an increased risk of institutionalization.[25] However, institutionalization could not solve caregivers' distress; a year after institutionalization, distress still persisted in caregivers.[26] In contrast, treatment of BPSD could help diminish caregiver burden.[27] Thus, it is beneficial both for individuals with dementia and their caregivers to reduce BPSD by rehabilitation in intermediate facilities between hospital and home.

In addition to enhancement of cognitive function and reduction of BPSD, improvement of social functioning and quality of life (QOL) should be the main outcomes of rehabilitation for dementia.[16]

Social isolation is associated with increased risk of mental decline,[28] whereas a rich social network and interaction might protect against mental decline.[29,30] In demented individuals, symptoms of depression were a consistent predictor of QOL.[31] In the present study, the intervention group showed improvement of social functioning measured by the Social Activity Scale, and amelioration of depressive mood measured by GDS.

Regarding the intervention, individualized tailor-made therapies were carried out, because the aim of the present study was to enhance each participant's ability to meet their individual needs, and not to show the efficacy of any specific method. Personally-relevant goals were identified, and the therapist worked with the individuals with dementia to devise strategies to cope with difficulties in their everyday lives by building on the person's strengths and developing ways of compensating for impairment.[15] Personal selection was considered an essential therapeutic element to enhance the motivation and optimize the emotional impact of the training. Changing and combining methods were allowed during the intervention period.

The present study showed that intensive rehabilitation should be beneficial for both individuals with dementia and caregivers. To promote community-based care and dehospitalization, continuity of rehabilitation is desirable to maintain function after returning home; another mission of Roken is to offer community-based rehabilitation and various care services to support home-based care.

As a limitation, the participants were not randomized. By data cleaning, data including missing values were excluded so that the numbers of valid data were different among assessments. Finally, for evaluation of the effects on dehospitalization, a longitudinal follow-up study is required.

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Disclosure statement

The authors declare no conflict of interest.

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手段的日常生活動作を用いた軽度認知症スクリーニング項目の検討

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