を対象に，病状申告書と同様の文面を用いたアンケート調査を行った[10]．対象は2002年6月～2004年12月の期間に高知大学神経科精神科を受診した認知症患者で，調査時において運転免許を保有している20名を対象とした．その結果，認知症患者20名中15名(75%)が医師からの中止勧告はないと回答していた．わずかに2名(10%)が中止勧告を受けていると回答していたが，いずれも脳血管性認知症(vascular dementia；以下VaD)の患者であった．運転免許更新にあたりなんらかの問題があるかどうかでは，実際は運転に問題があるにもかかわらず12名(60%)が問題ないと回答し，記入なしが7名(35%)であった．すなわち，免許更新時に病気に罹患しているため運転能力の評価を必要とする人を本申告書で選択し，その後公安委員会の規定する臨時適性検査につなげるという申告書本来の目的は，認知症患者では有効でないことが明らかとなった．そのため，認知症患者で，運転継続に危険のある者をスクリーニングできる，もしくは臨時適性検査につなげることが可能な，新たな評価方法を考案する必要があると思われた．

また，2002年改正道交法施行により，70歳以上に課される高齢者特定講習の際のドライビングシミュレーター(以下DS)を用いて研究班の一員である松本らは[11]，アルツハイマー病(Alzheimer's disease；以下AD)患者19名と健常高齢者20名の運転能力評価を試みた．健常群に比べ，総じてAD群では成績が悪い傾向であったが，健常群，AD群の重複が大きく，いずれにも有意差は認められなかった．また，各群内でも成績にバラつきが大きく，同プログラムの検査項目だけでは2群を明確に区別することができなかった．すなわち，DSの結果から認知症に起因する特異的な運転能力の低下を判断することは困難であることが明らかであり，今後認知症特有の神経心理学的特徴を踏まえた新たな検査プログラム開発の必要性を指摘している．

4．認知症の背景疾患の違いによる運転行動，交通事故リスクの差異の検討

認知症患者が健常高齢者と比較し交通事故を起こしやすいことはこれまでのデータから指摘されているが，さらに背景疾患の違いによっても運転行動や交通事故の危険性に差異があることが明らかにするため，上村らは運転免許を保持する認知症患者83人(男性63人，女性20人)を対象に実態調査を行った[12]．対象者の平均年齢は70.7±9.7歳で，臨床診断別ではAD 41人，VaD 20人，前頭側頭葉変性症(frontotemporal lobar degeneration；以下FTLD)22人であった．その結果，83人中34人(40.9%)が交通事故を起こしていた．認知症の原因別では，AD患者は41人中16人(39%)が事故を起こし，行き先を忘れてしまう，迷子運転や駐車場で車庫入れを行う際の枠入れがうまくできず接触事故を起こすことが運転行動/事故特徴として認められた．VaD患者では20人中4人(20%)が事故を起こし，ハンドル操作やギアチェンジミス，速度維持困難が要因と考えられた．FTLD患者では22人中14人(63.6%)と最も高い比率で事故を起こしており，その特徴として信号無視や注意維持困難やわき見運転による追突事故が多くみられた(表1)．また，それらの交通事故の内容分析では，AD患者では41人中13人が自損事故，7人が物損事故，4人が人身事故を起こし，VaD患者では20人中2人が自損事故，1人が物損事故，1人が人身事故，FTLD患者では22人中11人が自損事故，10人が物損事故，9人が人身事故を起こしていた．また谷勝らは，認知機能よりも精神症状や行動障害が病初期に目立つFTLDの自動車運転についてADと比較検討を行った[13]．対象はFTLD群8名(平均年齢65.8歳，男/女：5/3，平均MMSE 19.8)で，比較対象はAD群23名(平均年齢68.5歳，男/女：13/12，平均MMSE 17.0)である．評価として，運転行動/問題点(運転行為/違反・事故)を家族に聴

表1　認知症の背景疾患別の運転行動，危険性

	交通事故率(名)	事故危険運転特徴
・AD(n=41)	39.0%(16)	迷子運転 枠入れで接触事故
・VaD(n=20)	20%(4)	操作ミス 速度維持困難
・FTLD(n=22)	63.6%(14)	信号無視，追突事故 わき見運転
・全体(n=83)	40.9%(34)	認知症の原因で差異を認める

AD：Alzheimer's disease, VaD：vascular dementia, FTLD：frontotemporal lobar degeneration

(文献[12]より)

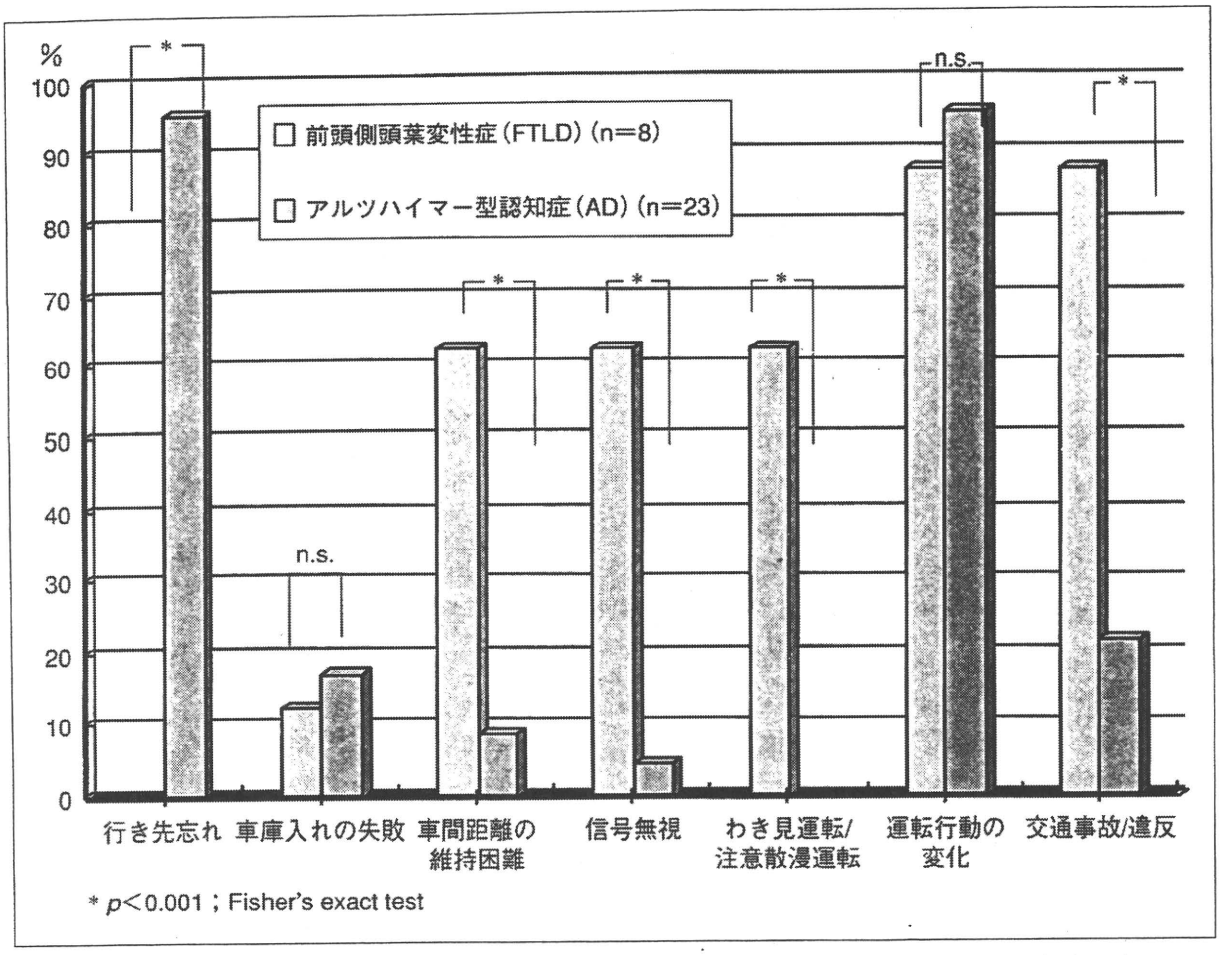

図2　認知症の原因別による運転行動・交通事故の危険性の相違（FTLD vs. DAT）（文献[13]より）

取した．その結果，FTLDでは車間距離の調整困難，接触事故，信号無視，注意散漫などが多く，ADでは行き先忘れ，車庫入れの失敗などが多かった．また，FTLDの交通事故や交通違反の危険性はADよりも高かった（図2）．

これまでの認知症と運転行動に関するRegerら[14]のメタアナリシスでは，視空間性能力が運転能力と関連している神経心理学的所見であったと報告している．今回のわれわれの検討でも，車庫入れの失敗がADに多くみられたことに関連していると思われる．しかしながら，FTLD群では視空間性の障害はほとんどないか稀である．FTLDでみられる運転行動の問題は，衝動性や脱抑制などの行動障害がより関連していると思われる．これらの検討から，認知症の背景疾患により運転行動には大きな差異があり，特にFTLD患者では運転行動や交通事故の危険性が異なることが示唆されるため，認知症という状態像だけではなく，背景疾患の違いによっても運転行動や危険運転，事故発生リスクは異なることを臨床医は知っておくべきであろう．

5．認知症ドライバーの運転中止に関するスクリーニング検査開発の試み

池田はなるべく簡便で，かかりつけ医などでも施行できるスクリーニング基準の検討を行った[15]．対象は愛媛大学と高知大学の専門外来を受診し，違反や運転で問題のあるAD患者27名（男：女＝21：5，年齢＝73.4±9.1，MMSE＝20.7±5.4，CDR 3＝1名，CDR 2＝6名，CDR 1＝10名，CDR 0.5＝8名）と，違反歴，運転上の問題のないAD患者23名（男：女＝15：8，年齢＝70.0±7.8，MMSE＝22.5±3.2，CDR 2＝0名，CDR 1＝10名，CDR 0.5＝14名）を比較検討した．その結果，CDR≧2の例は必ず運転に問題があり，CDR 1群では，MMSEの下位項目である「場所の見当識」，「Serial-7」ともに失点がある事例もすべて運転に問題があった．運転上の問題があるが前述の2項目の失点のないCDR 1の例は1名のみであった．CDR 0.5群

表２　基準別運転問題の有無

	問題あり	問題なし	計
・基準に合致する	19	8	27
・基準に合致しない	8	15	23
	27	23	50

スクリーニング基準としてMMSEの下位項目である「場所の見当識」と「Serial-7」の失点があるものを基準合致とした．基準による運転行動の問題の有無の判定では感度70.4％，特異度65.2％，陽性尤度比1.99，陰性尤度比0.47，陽性的中率70.4％，陰性的中率65.2％となる．

では，「場所の見当識」，「Serial-7」ともに失点があっても運転上の問題がない例が８名いた．また，問題「なし」群でありながら「場所の見当識」，「Serial-7」ともに失点があり，かつCDRが１以上という事例は存在しなかった(表２～4)．これらの検討から，AD患者の運転中止基準として，CDR≧2 または「場所の見当識」，「Serial-7」ともに失点がありかつCDRが１であれば即時中止を勧める，それ以外のADであれば運転シミュレーターをはじめとした実際の運転行動の詳細な評価を受けることを勧め，運転継続の許可，制限つき許可，中止などその後の対応を決定できるであろう．多くの海外の研究も認知症という診断や重症度だけで運転能力を判断するには限界があるため，このような指標は今後有用な指標となりうると考えられる．

2009年開始の講習予備検査（認知機能検査）と課題

これまで研究班での成果を紹介してきたが，第１期の研究班の終了後，警察庁は認知症ドライバー対策として新たな制度の導入を決定した．その内容は免許更新時に75歳以上の高齢者に対して簡易認知機能検査を導入し，その結果で認知症の疑いがある者には臨時適性検査と専門医の診断を受けさせ，認知症である者には免許停止あるいは取り消しの行政処分を行うといった新たな改正案を提示し，2009年度から実施されることとなった[16]．図３にその流れを示すが具体的な検査内容は時間の見当識(年，月，日，曜日，時間)，手がかり再生(16カテゴリー線画の遅延再生：自由，手がかり)，時計描画(文字盤を描き，11：10の針を記入)からなっている．これらの成績の結果から，

表３　CDR１群の基準適合

	問題あり	問題なし	計
・基準に合致する	10	0	10
・基準に合致しない	1	9	10
	11	9	20

CDR１群20名での運転行動の問題有無の判定では，感度90.9％，特異度100.0％，陽性尤度比∞，陰性尤度比0.09，陽性的中率100.0％，陰性的中率90.0％となる．

表４　CDR 0.5群の基準適合

	問題あり	問題なし	計
・基準に合致する	2	8	10
・基準に合致しない	6	6	12
	8	14	22

CDR 0.5群22名での運転行動の問題の有無の判定では，感度25.0％，特異度42.9％，陽性尤度比0.43，陰性尤度比1.75，陽性的中率20.0％，陰性的中率50.0％となる．（文献[15]より）

第１分類から第３分類に区分することになる．第１分類とは「認知症のおそれがある者」，第２分類とは「認知機能が低下しているおそれがある者」，第3分類とは「こうしたおそれがない者」である．その後，検査結果に基づいた講習が実施され，いったん免許更新がされるが，第１分類に該当する者のうち，免許期間満了日１年前以後に以下で述べる基準行為をしていた場合や，更新後に基準行為をした場合は臨時適性検査が行われる．なお予備的調査結果では[17]，75歳以上の免許更新者の3.3％が第１分類(認知症のおそれがある者)に分類されると予測されている．臨時適性検査では公安委員会で認める専門医またはかかりつけの専門医による認知症の有無の判定が行われる．そして，認知症と判明すれば公安委員会の聴聞の結果，免許の取り消し・停止が行われる．ここでいう基準行為とは，信号無視や指定場所一時不停止，通行区分違反などであり，警察庁主導で行われた検査の結果，認知症のおそれがあるとされた者の運転行動の大きな特徴とされたものである．

本制度は開始されたばかりであり，認知症を伴う高齢者の運転規制がはじめて具体化されたことは高く評価すべきである．しかし，認知機能検査を受ける対象の年齢が75歳以上である点や，認知機能検査の内容が主としてADのスクリー

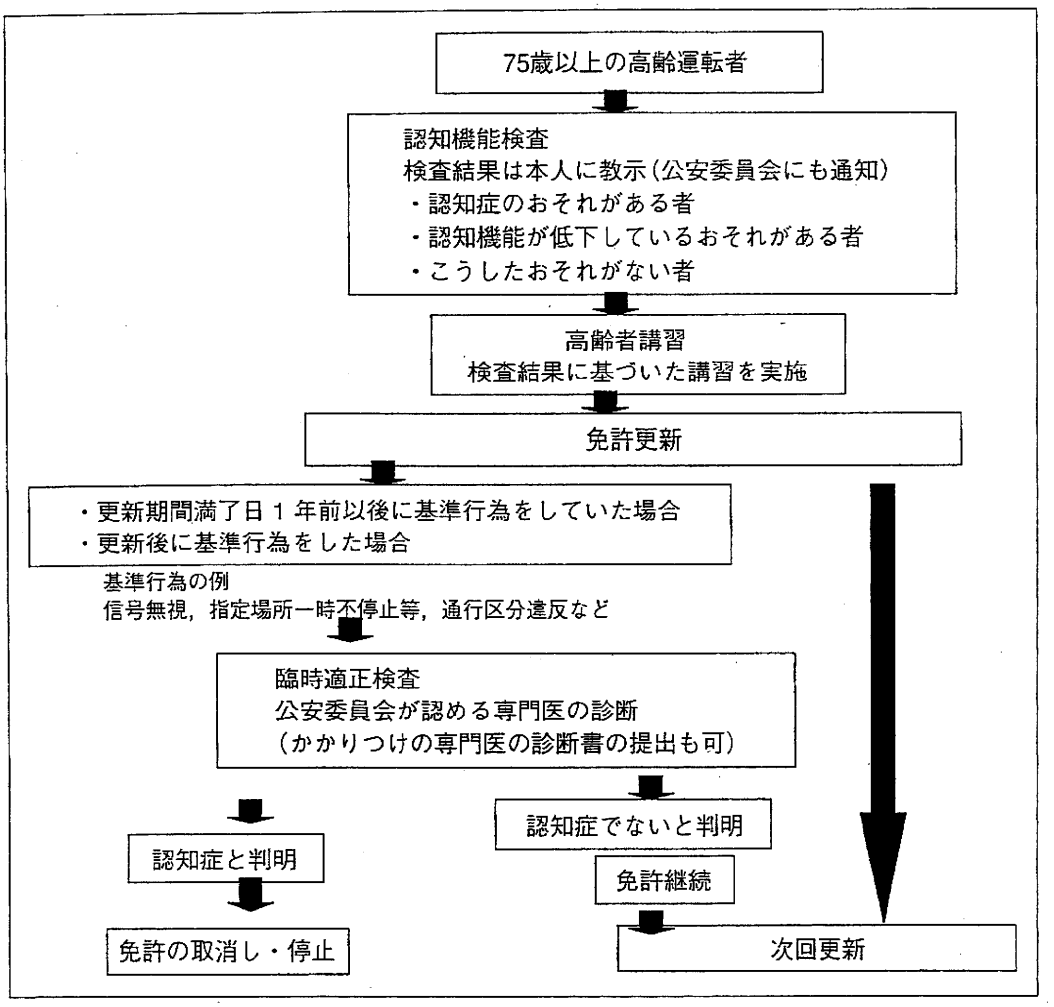

図3　新たな免許更新制度；75歳以上の運転者の免許更新(文献[16]より)

ニングを目的としたものである点，さらに，医師の責任範囲などの点が今後の検討事項として残っている．臨床医は医師会や所属学会などを通じて，その動向に積極的にかかわることが要求されると思われる．

本制度が開始され1年間が経過したが，認知症者の免許の停止が増加しているとは筆者らの実感としてまだないものの，患者やその家族に認知症者の運転の危険性について説明しやすくなったことや，中断を受容れる認知症患者や家族も増えつつあること，免許更新前に諦めるという家族が増加している印象もある．一方で，認知症の運転は家族の悩みとしてますます増加しており増大しており，今後の免許保有率と認知症患者の増大からさらに社会的な問題となりうると思われる．

おわりに

本稿では厚生労働科学研究費補助金長寿科学総合研究事業「痴呆性高齢者の自動車運転と権利擁護に関する研究」班(主任研究者：池田　学)と「認知症高齢者の自動車運転に対する社会支援のあり方に関する検討」班(主任研究者：荒井由美子)からの成果の一部を紹介した．この研究班の活動は認知症高齢者の自動車運転に関する本邦でははじめて包括的に取り組んだプロジェクトである．この問題は，特に日本では社会の高齢化とモタリゼーションの狭間で今後もますます深刻さが増していく社会問題ということができる．近年，社会的にもわれわれ精神科医の周辺でも認知症患者の自動車事故が頻繁に起こり始めていることを考えれば，近い将来日本政府の行政指針に資するなんらかのエビデンスが求められており，そのニーズ対して一定の成果を提供できたのではないかと思われる．しかしながら，スクリーニング方法の多数例による妥当性の検討や公安委員会における最終決定のための

運転シミュレーターのプログラムの開発など，結論の出ていない課題も残されており今後の研究成果を待つ必要があろう．

なお，さらに詳細な資料を希望される方は，厚生労働省総合報告書(H15-17；班長 池田　学「厚生労働科学省長寿科学研究 H15年度「痴呆性高齢者の自動車運転と権利擁護に関する研究」(課題番号H15－長寿－032)」，認知症対策総合研究事業総合研究報告書(H19-21：班長 荒井由美子「認知症高齢者の自動車運転に対する社会支援のあり方に関する検討」班(主任研究者：荒井由美子)」(課題番号H19－認知症－25)を，新制度については老年精神医学雑誌第20巻第 1 号2009, 谷勝良子ほか：最新精神医学Vol 13, NO 4 を参照されたい．また，最近研究班が作成した家族支援マニュアル(荒井由美子．認知症高齢者の自動車運転を考える―認知症高齢者の安全と安心のために．http://www.nils.go.jp/department/dgp/index-dgp-j.htm)も日常臨床の参考にしていただければ幸いである．

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11. 社会的・制度的支援と家族介護
3）認知症患者の運転免許*

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Key Words : dementia, driving, driving license, older people, traffic law

キーセンテンス
・高齢者の運転が社会問題となっている．
・免許更新に際して，医師は認知症の診断を求められることがある．

はじめに

わが国は高齢社会を迎え，65歳以上の高齢者の運転免許保有者数が1,000万人を超えた．一方で，近年交通事故における被害者・加害者として高齢者の割合が増加しており，認知症ドライバーの運転が社会問題となってきている．高齢化率の上昇と免許保有率の増加から，免許をもつ認知症患者は今後ますます増えていくと考えられる．

本稿では，認知症患者の自動車運転の問題点と，法的整備など医師が知っておくべき事項について述べる．

認知症患者の自動車運転の問題点

1．認知症患者の自動車運転の特徴

諸隈ら[1]は，運転免許を保持する認知症患者83人（男性63人，女性20人）を対象に，交通事故の有無や免許更新の有無などの中長期的予後の実態調査を行った．対象者の平均年齢は70.7±9.7歳で，臨床診断別ではAlzheimer病（AD）患者41人，脳血管性認知症（vascular dementia：VaD）患者20人，前頭側頭葉変性症（frontotemporal lobar degeneration：FTLD）患者22人であった．その結果，83人中34人（41.0%）が交通事故を起こしていた．認知症の原因別では，AD患者は41人中16人（39%）が事故を起こし，行き先を忘れてしまう，迷子運転や駐車場で車庫入れを行う際の枠入れがうまくできず接触事故を起こすことが運転行動/事故特徴として認められた．VaD患者では20人中4人（20%）が事故を起こし，ハンドル操作やギアチェンジミス，速度維持困難が要因と考えられた．FTLD患者では22人中14人（63.6%）ともっとも高い比率で事故を起こしており，その特徴として信号無視や注意維持困難やわき見運転による追突事故が多くみられた．また，それらの交通事故の内容分析では，AD患者では41人中13人が自損事故，7人が物損事故，4人が人身事故を起こし，以下，VaD患者では20人中2人が自損事故，1人が物損事故，1人が人身事故，FTLD患者では22人中11人が自損事故，10人が物損事故，9人が人身事故を起こしていた．医学的管理上の問題として，83人中42人50.6%（AD患者63.4%，VaD患者30%，FTLD患者45.4%）が免許更新を試み，認知症の原因に関係なく全員が更新に成功していた．そして，免許更新成功者42

* 11. Social support system and nursing care. 3) Driving license of patients with dementia.

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人中，半数の21人が事故を起こしており，なかでもFTLD患者は10人中8人(80%)と高率に事故を起こしていた．これらの結果から認知症の原因によっても交通事故の発生率には大きな差があることが判明した．

2．認知症患者の運転中断について

上村ら[1]は，認知症患者の運転実態について医療機関レベルでの調査を行った．調査対象は，免許を保持する認知症患者30人(男性19人，女性11人)で，臨床診断はAD患者20人，VaD患者3人，混合型認知症患者2人，FTLD患者4人，その他の認知症患者1人であった．その結果，多くの認知症患者が発症後も運転を継続していることが明らかとなった(30人中22人73.3%)．中等度認知症患者ではほとんどが運転を中断していたが，軽度認知症患者では運転中断を拒否したり，助手席から方向を指示してもらうなどの対処で運転を継続していた．軽度認知症患者の場合，運転の危険性が高いにもかかわらず運転中断に至っている例は少なく，家族が対応に苦慮している実態が明らかとなった．

高齢者ドライバーへの法的整備

警察庁は，さまざまな高齢ドライバーへの施策を行ってきた[2]．平成9年には高齢ドライバー標識(通称もみじマーク)の試み，さらに平成10年からは運転免許の返上制度が実施された．平成10年秋からは，75歳以上の高齢ドライバーに対して更新時の講習が義務づけられ，平成13年6月からは，その講習が70歳以上にひき下げられた．

その後，平成14年には改正道路交通法が施行された．改正道路交通法において，「公安委員会は痴呆症患者の運転免許証を停止，あるいは取り消すことができる」とされ，認知症患者は行政から運転免許を停止または取り消されうる可能性があると定められた．

そして，平成21年6月1日から，75歳以上の高齢者の免許更新に際して認知機能検査(講習予備検査)が導入された(図1)[3]．認知機能検査により認知症が強く疑われる場合には，専門医の受診を義務づけることとなった．

認知機能検査の所要時間は30分程度であり，内容は時間の見当識(年，月，日，曜日，時間)，手がかり再生(16カテゴリー線画の遅延再生：自由，手がかり)，時計描画(文字盤を描き，11：10の針を記入)からなる．これにより，受検者を第1分類から第3分類に区分することになる．第1分類とは，「認知症のおそれがある者」，第2分類とは「認知機能が低下しているおそれがある者」，第3分類とは「こうしたおそれがない者」である．その後，検査結果に基づいた講習が実施され免許更新がされるが，第1分類に該当する者のうち，免許期間満了日1年前以後に以下で述べる基準行為をしていた場合や，更新後に基準行為をした場合は臨時適性検査が行われる．臨時適性検査により，公安委員会で認める専門医またはかかりつけの専門医による認知症の診断が行われる．そして，認知症と判明すれば，免許の取り消し・停止が行われる．ここでいう基準行為とは，信号無視や指定場所一時不停止，通行区分違反などであり，警察庁主導で行われた検査の結果，認知症のおそれがあるとされた者の運転行動の大きな特徴とされたものである．

また，上記以外にわれわれ医師が知っておくべきこととして，免許更新時に記入する病状申請書がある．これには健康上の問題に関するチェック項目があり，これにより交通安全上問題ありと予測される更新者には，各都道府県の免許センターが主治医診断書を提出させて，医学的見地からの意見を聴いた上で公安委員会が免許更新可否を判定する場合と，診断書の提出がない場合は公安委員会の権限で臨時適正検査を実施できることになっている．

認知症の疑いのあるドライバーの把握には，上記認知機能検査，病状申請書による自己申告のほかに家族などからの適正相談，あるいは交通法規違反や事故で露呈する場合があげられる．

認知症ドライバーに対する医師の役割

医師は認知症の診断は可能としても，患者の運転能力の評価に関しては非専門である．法令では医師が作成した診断書や臨時適性検査をもとに公安委員会が運転免許証を発行した場合，その最終的な責任の所在は公安委員会にあるとされている．

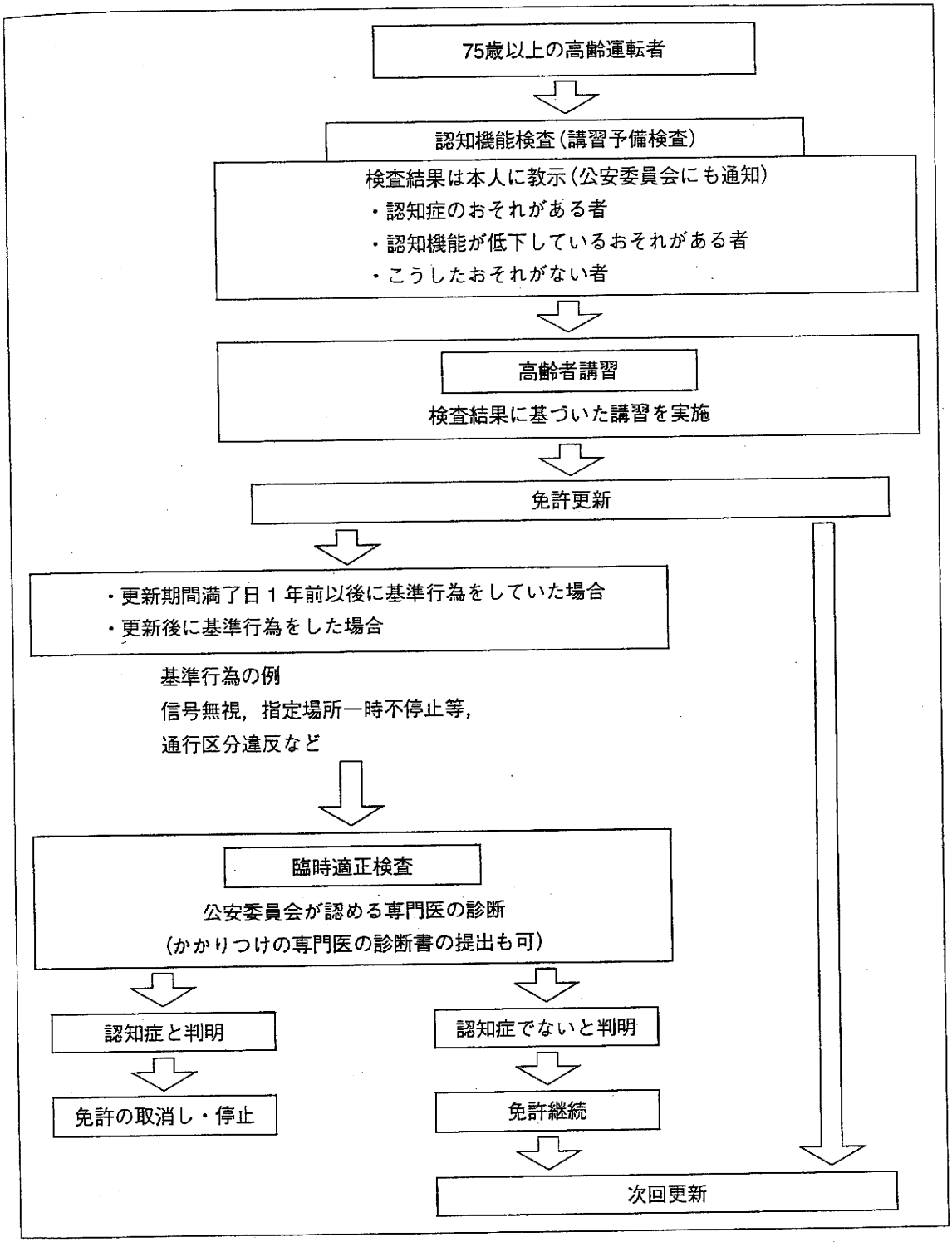

図１　75歳以上の運転者の免許証更新手続等の流れ（文献[3]より一部改変引用）

一方で，新井は司法の立場から，医師には善管注意義務と説明報告義務があると述べている[4]．すなわち，医師が認知症の診断をした後に患者が交通事故を起こした場合や，医師が認知症を見逃していた場合などでは，医師の法的責任を問われる可能性がある．

また，日本神経学会が作成した「痴呆患者の自動車運転に関する指針」では，軽度認知症患者は運転を中断すべきであるとされている[5]．米国精神医学会の治療ガイドラインによれば，「精神科医はすべての痴呆患者およびその家族と運転の危険性について話し合い，その話し合いの内容

を詳細に書きとどめておく必要がある」，「中等度から重度の障害をもつ患者には運転しないよう強く忠告すべきである．過失により交通事故を起こした経験があり，判断力，空間認知，もしくは実行力に重大な障害を有する軽度痴呆症患者についても同様の忠告を行うのが適当と思われる」，「障害がより軽度な患者に対しても，運転を諦めるよう説得すべきである」とある[6]．したがって医師は，目の前にいる患者に対して，認知症性疾患の存在を常に念頭において診療することが必要であるし，患者が認知症であるならば，自動車運転について患者本人や家族とよく話し合った上で，運転中断勧告をした場合は，その旨をカルテに記載しておくことが必要である．

おわりに

認知症患者の運転について，問題点や法的整備，医師の役割について概説した．免許更新に際して，われわれ医師は認知症の診断を求められる可能性があり，認知症患者と運転免許の問題について関心をもつ必要がある．

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Relationship of frontal lobe dysfunction and aberrant motor behaviors in patients with Alzheimer's disease

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ABSTRACT

Background: In order to address the neuropsychological pathogenesis of aberrant motor behaviors in Alzheimer's disease (AD), we used a cross-sectional study design to investigate the association between frontal lobe function, including executive function, and activity disturbances (wandering, purposeless activities and inappropriate activities).

Methods: Among 75 consecutive outpatients with AD, 50 subjects with a Clinical Dementia Rating (CDR) score of 1 or 2 were selected and divided into two groups based on data obtained from interviews with their caregivers: an aberrant motor behaviors (AMB) group (n = 22), and a non-aberrant motor behaviors (NAMB) group (n = 28). Aberrant motor behavior was defined according to whether the "activity disturbance" score (ranging from 0 to 9) of the Behavioral Pathology in Alzheimer Disease (Behave-AD) scale was 0 or ≥1. The total and subtest scores of the Frontal Assessment Battery (FAB) were then compared between the two groups.

Results: Significant differences were found between the FAB total ($P < 0.05$) and the subtest scores (lexical fluency, conflicting instructions; $P < 0.05$) in the two groups. The FAB score was significantly associated with the activity disturbance score ($r = -0.49$; $P<0.001$). A stepwise multiple regression analysis showed that only the FAB score significantly influenced the activity disturbance score ($P < 0.001$).

Conclusions: This finding suggested that in addition to episodic memory disturbance, frontal lobe dysfunctions might lead patients with AD to develop aberrant motor behavior.

Key words: Frontal Assessment Battery, dementia, activity disturbances, wandering, executive function

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is mainly characterized by episodic memory disorder, visuospatial impairment, attentional impairment, and executive dysfunction (Perry *et al.*, 2000; Baudic *et al.*, 2006). During the course of this disease, aberrant motor behaviors are reportedly observed as behavioral and psychological symptoms of dementia (BPSD) (Mega *et al.*, 1996; Devanand *et al.*, 1997).

The prevalence of aberrant motor behaviors is estimated to be in the range of 14–60% among patients with AD (Mega *et al.*, 1996; Devanand *et al.*, 1997; Liu *et al.*, 2004; Chiu *et al.*, 2006). On the other hand, the prevalence of aberrant motor behaviors among patients with frontotemporal lobar degeneration (FTLD) has been reported to be about 60–92% (Mendez *et al.*, 1998; Liu *et al.*, 2004; Chiu *et al.*, 2006).

Murman *et al.* (2002) reported that BPSD in patients with AD significantly increases the direct costs of care. In particular, aberrant motor behaviors in patients with dementia can create a distressful burden and cause suffering among caregivers, triggering or predicting nursing home placement (Donaldson *et al.*, 1997; Shinoda-Tagawa *et al.*, 2004; Scarmeas *et al.*, 2007). Thus, research on the etiology and treatment of these disturbances in patients with AD is urgently needed.

From a neuroanatomical aspect, the manifestation of aberrant motor behaviors in patients with neurodegenerative disease is associated with the right dorsal anterior cingulate cortex (dACC) and

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left premotor cortex in voxel-based morphometry (VBM) studies using magnetic resonance imaging (MRI) (Rosen *et al.*, 2005). However, a single-photon emission computed tomography (SPECT) study indicated that AD patients with wandering had a more severe decline in regional cerebral blood flow (rCBF) in the left parietal-temporal lobe (Rolland *et al.*, 2005).

From the neuropsychological perspective, previous studies have reported that behavioral problems or aberrant behaviors, such as wandering, purposeless activity and inappropriate activities, in patients with AD were significantly correlated with a decline in the Mini-mental State Examination (MMSE) score, which reflects global cognitive function (Folstein *et al.*, 1975; Devanand *et al.*, 1997; Harwood *et al.*, 2000). Moreover, in those studies, a positive correlation between the level of activities of daily living (ADL) and the severity of the aberrant motor behaviors in patients with AD was reported (Devanand *et al.*, 1997; Harwood *et al.*, 2000). Chiu *et al.* (2004) stated that behaviors that led to AD patients getting lost and beginning to wander might be caused not only by visuospatial impairments (O'Brien *et al.*, 2001), but also by executive and attentional dysfunction when navigating in unfamiliar environments. In another study, the severity and frequency of aberrant motor behaviors in patients with AD were associated with a decline in the scores of the behavioral assessment scale reflecting frontal lobe features (Engelborghs *et al.*, 2006).

For these reasons, the association between aberrant motor behaviors and cognitive impairment remains unclear, and the relationship between frontal lobe dysfunction and aberrant motor behavior is controversial. The Frontal Assessment Battery (FAB) is an easily administered test that can be completed at bedside within 10 minutes (Dubois *et al.*, 2000; Nakaaki *et al.*, 2007). Moreover, the FAB total and subtest scores differ significantly between FTLD and AD, but the MMSE scores do not; the ability of FAB to reflect frontal lobe function was previously confirmed in two studies examining different types of degenerative diseases (Slachevsky *et al.*, 2004; Lipton *et al.*, 2005). We previously reported that the manifestation of delusional thoughts in patients with AD was associated with a reduction in the FAB scores (Nagata *et al.*, 2009), reflecting executive function. However, the manifestation of aberrant motor behaviors has not been discussed as a cognitive aspect in conjunction with frontal lobe function. In the present cross-sectional study, we investigated the relationship between frontal lobe function and aberrant motor behavior using the FAB.

Methods

Participants

Seventy-five consecutive AD patients who had been referred to the Jikei University Kashiwa Hospital outpatient clinic were enrolled in this study. All the patients were diagnosed as having probable AD based on the National Institute of Neurology and Communicative Disorder and Stroke/Alzheimer Disease and Related Disorder Association (NINCDS/ADRDA) criteria (McKhann *et al.*, 1984). All diagnoses were made after an examination of the patients' past medical history, an evaluation of physical or neurological examinations, routine blood tests, and magnetic resonance imaging (MRI) findings by a geriatric psychiatrist (one of the four authors). The exclusion criteria were a history of alcohol or other substance abuse, brain injury, major depressive or psychotic disorder, epilepsy, delirium, metabolic disorder, or treatment with acetylcholine esterase inhibitor. Neuropsychological tests (FAB and MMSE) were administrated by a clinical psychologist. To determine the severity of each patient's dementia, the geriatric psychiatrists used the Clinical Dementia Rating scale (global CDR scores ranging from 0 to 3, where 0 = normal; 0.5 = questionable; 1 = mild; 2 = moderate; 3 = severe) (Hughes *et al.*, 1982) while interviewing each patient's caregiver. To recruit patients with mild- or moderate-stage AD, we selected patients (N = 50) with a global CDR score of either 1 or 2. Patients with a global CDR score of either 0.5 or 3 were excluded from this study. The patients were divided into two groups: an aberrant motor behaviors (AMB) group, and a non-aberrant motor behaviors (NAMB) group. The manifestation of aberrant motor behavior was assessed based on information obtained from a structured interview with each patient's caregiver by the same geriatric psychiatrists, and the aberrant motor behaviors were rated using the "activity disturbance" score of the Behavioral Pathology in Alzheimer's Disease (Behave-AD) scale (Reisberg *et al.*, 1987). The four geriatric psychiatrists and clinical psychologist were experienced at performing neuropsychological and behavioral examinations, and the inter-rater validity of the scales was sustained by periodic discussions and exchanges of views. This study was approved by the Ethics Committee of the Jikei University School of Medicine.

Definition of aberrant motor behaviors

To determine whether the patients had aberrant motor behaviors, we used the activity disturbance scale of the Behave-AD (total behavioral or

psychological problems scale). This scale was completed based on the results of an interview with each patient's caregiver, who was asked whether the patient had experienced any of the following aberrant motor behaviors in the previous four weeks: (1) "wandering away from home or caregivers", (2) "purposeless activity", and (3) "inappropriate activity" (Reisberg *et al.*, 1987). The severity range of each score was from 0 to 3, and the range of the total activity disturbance score was from 0 (not present) to 9 points. If the total score was $\geq$1 point, the patient was classified in the aberrant motor behaviors (AMB) group. If the total score was 0, the patient was classified in the non-aberrant motor behaviors (NAMB) group.

FAB assessment

The Japanese FAB version consists of six subtests: (1) similarities (conceptualization); (2) lexical fluency (mental flexibility); (3) motor series (programming); (4) conflicting instructions (sensitivity to interference); (5) go - no go (inhibition control); and (6) prehension behavior (environmental autonomy) (Takagi *et al.*, 2002). Each subtest was rated from 3 to 0, with the total score ranging from 18 to 0.

Statistical analysis

SPSS 16.0J for Windows (SPSS Japan Inc) was used for all statistical analyses. To compare differences between the two groups, we used a one-way ANOVA with post-hoc testing for age, education (years), duration of illness (months), the MMSE total score, the CDR Scale sum of boxes (CDR SB: ranging from 0 to 18), the FAB total score, and the FAB subtest scores. The sex ratio (female to male) was assessed using a χ^2 test. Other behavioral or psychological problems (delusion, hallucination, and anxiety score of the Behave-AD subscale) were compared between the two groups using a one-way ANOVA with Tukey post-hoc test. Pearson correlation coefficients were used to evaluate the associations between FAB or MMSE and the activity disturbance score (ranging from 0 to 9). Finally, a stepwise multiple regression analysis was performed to examine the contribution of age, sex, education, duration of illness, FAB total score, MMSE score and CDR SB score as independent variables of the activity disturbance score. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

Fifty AD patients (11 males and 39 females; average age, 78.2 ± 7.1 years; range, 59–91 years) were classified as belonging to either the AMB group (n = 22) or the NAMB group (n = 28). These two groups were not significantly different with regard to the sex ratio ($\chi^2 = 1.601$; $df = 1$; $P = 0.206$), age ($F = 1.483$; $df = 1$; $P = 0.229$), duration of illness (months) ($F = 0.421$; $df = 1$; $P = 0.405$), education (years) ($F = 0.704$; $df = 1$; $P = 0.519$), MMSE score ($F = 3.350$; $df = 1$; $P = 0.074$), or CDR SB score ($F = 3.271$; $df = 1$; $P = 0.077$). However, the FAB total scores ($F = 7.044$; $df = 1$; $P = 0.011$) were significantly different between the two groups (Table 1). The mean ± standard deviations (SDs) of the FAB scores were 12.3 ± 3.3 (NAMB) and 9.3 ± 4.5 (AMB). The two subscores of the FAB, lexical fluency ($F = 6.390$; $df = 1$; $P = 0.015$) and conflicting instructions ($F = 5.469$; $df = 1$; $P = 0.024$), were both significantly lower in the AMB group than in the NAMB group (Table 2). The mean ± SDs of the lexical fluency scores were 1.86 ± 1.01 (NAMB) and 1.10±1.09 (AMB), while those of the conflicting instrument scores were 2.71±0.53 (NAMB) and 2.10±1.26 (AMB).

Table 1. Subject characteristics (mean ± SD)

GROUP	AMB (n = 22) (MEAN ± SD)	NAMB (n = 28) (MEAN ± SD)	χ^2 OR F SCORE	P VALUE
Sex (male/female)	3/19	8/20	1.601	0.206
Age	79.5 ± 6.6	77.1 ± 7.3	1.483	0.229
Education (years)	10.8 ± 3.4	11.6 ± 2.5	0.421	0.519
Duration of illness (months)	28.7 ± 18.3	24.2 ± 19.3	0.704	0.405
MMSE score	18.2 ± 5.3	20.3 ± 2.8	3.35	0.074
FAB score	9.3 ± 4.5	12.3 ± 3.3	7.044	0.011*
CDR SB	8.18 ± 3.20	6.80 ± 2.17	3.271	0.077

AMB = aberrant motor behavior, NAMB = non-aberrant motor behavior; CDR SB = Clinical Dementia Rating Scale sum of boxes (ranging from 0 to 18).
*$P<0.05$ (ANOVA with post-hoc test).
The sex ratio was analyzed using the χ^2 test.

Table 2. FAB subtest scores (mean ± SD)

SUBTEST	AMB (n = 22) (MEAN ± SD)	NAMB (n = 28) (MEAN ± SD)	*F* SCORE	*P* VALUE
Similarities	1.00 ± 0.95	1.25 ± 1.17	0.638	0.428
Lexical fluency	1.10 ± 1.09	1.86 ± 1.01	6.39	0.015*
Motor series	1.57 ± 1.25	2.04 ± 1.17	1.785	0.188
Conflicting instructions	2.10 ± 1.26	2.71 ± 0.53	5.469	0.024*
Go-no go	1.14 ± 1.24	1.61 ± 1.10	1.922	0.172
Prehension behavior	2.38 ± 1.02	2.82 ± 0.48	4.044	0.05

AMB = aberrant motor behavior; NAMB = non-aberrant motor behavior.
*$P<0.05$ (ANOVA with post-hoc test).

Table 3. Stepwise multiple regression analysis for activity disturbance scores of Behave-AD

VARIABLE	B	SE	β	t value	P VALUE
Constant	2.856	0.512		5.577	P<0.001
FAB	−0.18	0.43	−0.522	−4.156	P<0.001

Stepwise multiple regression analysis of FAB score, age, sex, education, duration of illness, MMSE score, and CDR sum of boxes for activity disturbance scores (N = 50).
B = partial regression coefficient; SE = standard error; β = standardized partial regression coefficient.
$R = 0.522$, $R^2 = 0.273$.

Other behavioral and psychological problems including delusion, hallucination and anxiety in the two groups

We also compared other behavioral and psychological problems that might have influenced the aberrant motor behaviors between the AMB group and the NAMB group. The two groups were not significantly different with regard to the delusion score ($F = 0.473$; $df = 1$; $P = 0.495$), the hallucination score ($F = 1.874$; $df = 1$; $P = 0.177$), or the anxiety score ($F = 2.016$; $df = 1$; $P = 0.162$) of the Behave-AD subscales.

Contribution of age, sex, education, duration of illness, FAB total scores, MMSE scores and CDR sum of boxes scores to the severity of aberrant motor behaviors

The FAB score was significantly correlated with the activity disturbance score ($r = -0.490$; $P<0.001$) and the MMSE score ($r = 0.670$; $P<0.001$). The MMSE score was also significantly correlated with the activity disturbance score ($r = -0.317$; $P<0.001$). A stepwise regression analysis showed that the FAB score significantly affected the activity disturbance score ($P<0.001$; $R^2 = 0.273$) (Table 3).

Subtypes of aberrant motor behaviors

Although 22 patients had experienced aberrant motor behaviors, several types overlapped in one patient. Purposeless activity (e.g. opening and closing a pocketbook, packing and unpacking clothing, repeatedly putting on and removing clothing, insistently repeating demands or questions) was the most frequently reported aberrant motor behavior (N = 15). Inappropriate activity (e.g. storing and hiding objects in inappropriate places, throwing clothing in a waste basket or putting empty plates in the oven; inappropriate sexual behaviors such as inappropriate exposure) was reported in 13 patients, while wandering was reported in three patients.

Discussion

The results indicate that the FAB total score in patients with AD was significantly related to the presence of aberrant motor behaviors. While the MMSE total score reflects global cognitive function weighted on orientation and memory function (Folstein *et al.*, 1975), the FAB has been confirmed to reflect executive function and working memory in patients with FTLD (Dubois *et al.*, 2000; Nakaaki *et al.*, 2007). Moreover, the FAB total and subtest scores significantly differ between FTLD and AD, emphasizing the validity of using the FAB to reflect frontal lobe function (Slachevsky *et al.*, 2004; Lipton *et al.*, 2005; Nakaaki *et al.*, 2007). The FAB was also shown to be a valid frontal function test in a SPECT study (Yoshida *et al.*, 2009), with a positive correlation observed between the left callosomarginal and precentral rCBF.

Some previous studies have reported that global cognitive and functional impairments in AD patients are associated with several BPSD, including aberrant motor behaviors (Mega *et al.*, 1996; Devanand *et al.*, 1997; Harwood *et al.*, 2000). Although some studies have indicated that aberrant motor behaviors are associated with cognitive or ADL decrements, only a few studies

have indicated an association between frontal lobe function and aberrant motor behavior (Swanberg *et al.*, 2004; Engelborghs *et al.*, 2006). In the present study, the activity disturbances score was significantly correlated with the MMSE score ($r = -0.317$; $P<0.001$), but a stronger correlation ($r = -0.490$; $P<0.001$) and association with the FAB was revealed using a statistical regression analysis. Among several aspects of neurocognitive dysfunction, we were particularly interested in the association between frontal lobe dysfunction and aberrant motor behavior from a neuropsychological aspect.

The FAB subtests (lexical fluency, conflicting instructions) were significantly lower in AD patients with aberrant motor behavior. Dubois *et al.* (2000) described that in the lexical fluency task, patients needed the ability to recall as many words as possible starting with a given letter within a limited number of seconds. Such literal fluency tasks also require self-organized retrieval from semantic memory and flexible behavioral adaptations to new situations (Dubois *et al.*, 2000). Therefore, the aberrant motor behaviors, including wandering or inappropriate activity, might be caused by an inability to react flexibly with variable stimuli in their environment. The conflicting instruments subtest resembles the Stroop test task and requires the ability to perform a contrary reaction to each of two pattern directions effectively (Dubois *et al.*, 2000). In patients with AD, in addition to memory disorders and visuospatial impairments, the lack of such self-correction in executive functions might particularly cause impairments in their ability to carry out these tasks efficiently, leading to wandering, inappropriate activity or purposeless activity resembling stereotypical behaviors as a result. Moreover, several studies have reported associations between each subtest and specific regions of frontal lobes using various neuroimaging methods. For example, functional magnetic resonance imaging (fMRI) or position emission tomography (PET) studies have reported an association between lexical fluency and the medial frontal cortex, including the anterior cingulate gyrus (Waburton *et al.*, 1996; Crosson *et al.*, 1999) and between the conflicting instruments and the right orbito-frontal and anterior cingulate cortex (Bench *et al.*, 1993). These reports partially support the results of a previous voxel-based morphometry study in patients with neurodegenerative disease and might imply an association between the anterior cingulate cortex and the aberrant motor behaviors (Rosen *et al.*, 2005).

In the present study, among the 22 AD patients (44%) with aberrant motor behaviors, only three exhibited wandering, 15 exhibited purposeless activity, and 13 exhibited inappropriate activity. Previous studies have shown that the prevalence of aberrant motor behaviors in patients with mild- or moderate-stage AD ranges from about 12% to 67% (Mega *et al.*, 1996; Devanand *et al.*, 1997), similar to our reported data. Schonfeld *et al.* (2007) also showed that wandering in nursing homes was frequently (21%) observed in patients with severe cognitive impairments.

The present study has some limitations. First we must consider the relatively small sample size and the lack of objective measures, with only two neuropsychological assessments – the FAB and the MMSE – being performed. In particular, the subjects with wandering might have a high risk of visuospatial memory or perception impairments leading to "getting lost" (Chiu *et al.*, 2004). Secondly, the present study was limited to subjects with mild- to moderate-stage AD whose CDR scores were 1 or 2, because even though the FAB tasks can be performed without tools or instruments, the tasks do contain relatively complex question forms that include several steps. Thirdly, apraxia symptoms as focal signs of AD should be quantitatively assessed, as subjects with severe ideational apraxia cannot carry out sequences of action to achieve an intended purpose in the correct order (Zadikoff *et al.*, 2005). Fourthly, because the FAB score was significantly correlated with the MMSE score ($r = 0.670$; $P<0.001$), we might have used two relevant neuropsychological tests. Therefore, we confirmed that the activity disturbances score was more strongly associated with the FAB score than with the MMSE score or the CDR SB using a stepwise regression analysis. Finally, this study had a cross-sectional design, and significant associations with other BPSD symptoms (delusional ideation, hallucination and anxiety) were not observed. If the clinical courses of the patients were to be pursued longitudinally, another BPSD symptom might be added, resulting in a worsening of the aberrant motor behaviors.

In spite of these limitations, the present study supported the hypothesis that frontal lobe dysfunction might be related to aberrant motor behaviors in patients with AD, supporting the results of neuroimaging studies. Moreover, these results suggest that a simple neuropsychological screening test reflecting frontal lobe function and including mainly executive function – such as the FAB – might be useful for predicting the manifestation of aberrant motor behaviors in patients with AD, providing important information regarding the selection of treatment stages that might reduce the early burden placed on caregivers.

Conflict of interest

None.

Description of authors' roles

Tomoyuki Nagata designed this study, examined the subjects, and wrote the paper. Shunichiro Shinagawa gave advice, including the analysis methods, and reviewed the manuscript. Hirohide Kada, Yusuke Ochiai and Hiroo Kasahara examined the patients with AD at the Jikei University School of Medicine, Kashiwa Hospital. Kazutaka Nukariya and Kazuhiko Nakayama reviewed and commented on the final manuscript.

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Association between executive dysfunction and hippocampal volume in Alzheimer's disease

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ABSTRACT

Background: Some previous research has hypothesized that executive dysfunction in patients with early Alzheimer's disease (AD) occurs as a result of a disconnection between different cerebral areas. The aim of the present study was to evaluate how the hippocampal volume influences executive function as a non-memory cognitive function.

Methods: From 157 consecutive patients with AD or amnestic mild cognitive impairment (A-MCI), we recruited 107 subjects who had a global Clinical Dementia Rating (CDR) of 0.5 or 1.0 and whose degree of hippocampal atrophy had been measured using magnetic resonance imaging (MRI); the severity of atrophy was assessed using the voxel-based specific regional analysis for Alzheimer's disease (VSRAD) system. We divided the subjects into three groups: mild atrophy, $0 <$ Z-score < 1.0 ($N = 21$); moderate atrophy, $1.0 \leq$ Z-score < 2.0 ($N = 46$); or severe atrophy, $2.0 \leq$ Z-score < 4.0 ($N = 40$) according to the Z-score and compared the Frontal Assessment Battery (FAB) and its subtest scores between each atrophy group.

Results: The results demonstrated that age, sex ratio, duration of illness, education years, MMSE score, Behave-AD score, and proportion of atrophy area in total brain (%) were not significantly different among the three groups. Only the go/no-go score among the six subtests was significantly lower for increasing atrophy severity ($P < 0.05$). Furthermore, hippocampal atrophy significantly influenced the go/no-go score independently of interactions from whether the diagnosis was early AD or A-MCI ($P < 0.05$).

Conclusion: These results support a significant association between hippocampal atrophy and executive dysfunction as a non-memory cognitive impairment in patients with early AD and A-MCI.

Key words: amnestic mild cognitive impairments (A-MCI), non-memory, disconnection syndrome, Frontal Assessment Battery (FAB), voxel-based specific regional analysis for Alzheimer's disease (VSRAD), Statistical Parametric Mapping (SPM), parahippocampal gyrus, entorhinal cortex

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by memory disorder, visuospatial disorder, attention deficit and executive dysfunction as its core symptoms (Delbeuck *et al.*, 2003; Baudic *et al.*, 2006). In patients with early AD or mild cognitive impairment (MCI), atrophy of the entorhinal cortex and hippocampus is a characteristic finding of brain magnetic resonance imaging (MRI) studies, and these observations serve as valuable biological markers for predicting prognosis (Ferreira *et al.*, 2009; Schroeter *et al.*, 2009). A previous study has reported that hippocampal atrophy of AD patients progresses with the course of aging and the dementia stage (Raji *et al.*, 2009). The association between memory disorder (episodic, recent and delayed recall memory) and atrophy of the hippocampus, entorhinal cortex and medial temporal cortex has often been reported in neuroimaging study (Tulving and Markowitsch, 1998). On the other hand, some controversial concepts concerning the abnormal functional connectivity between the hippocampus and the neocortical associative areas during the initial stage have been reported (Delbeuck *et al.*,

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2003; Bai *et al.*, 2009). In some studies and reviews that elucidated the pathogenesis of episodic memory disorders with functional MRI (fMRI), the authors stated that those disconnections might cause both afferent and efferent corticocortical neurocircuit disruption, or disconnection syndrome (Delbeuck *et al.*, 2003; Bai *et al.*, 2009).

Among the cognitive impairments observed during early AD and amnestic MCI (A-MCI), executive dysfunctions are recognized as a frequently occurring memory disorder (Baudic *et al.*, 2006; Traykov *et al.*, 2007; Hanyu *et al*, 2009). Some previous studies have implicated an association with damage to plural cortical areas, rather than a localized area, as being involved in the pathogenesis of executive dysfunction; moreover, the disconnection of neural networks between the anterior and posterior cerebral areas has been hypothesized to be involved in the initial stages of AD (Collette *et al.*, 2002; Delbeuck *et al.*, 2003). A positron emission tomography (PET) study has shown that the neural networks between the hippocampus and prefrontal cortex areas influenced the executive functions, including the working memory, in healthy controls (Takahashi *et al.*, 2007).

A significant association between memory disorder and hippocampal atrophy has been previously reported (Tulving and Markowitsch, 1998). However, the effect of hippocampal atrophy on executive dysfunction as a non-memory disorder in patients with early AD and A-MCI has not been previously described. Recently, Hirata *et al.* (2005) developed a statistical imaging analysis system, known as voxel-based specific regional analysis for Alzheimer's disease (VSRAD), using Statistical Parametric Mapping 2002 (SPM2) (Wellcome Department of Imaging Neuroscience, London) to quantify the hippocampal volume using an unbiased automated method. The region of interest (ROI) was fixed within bilateral hippocampal formations, including the entorhinal cortex and parahippocampal gyrus, and the severity of the gray matter atrophy was indicated by the Z-scores; the standardized deviation value was determined by comparing the data with that for age-matched healthy volunteers. Such Z-scores could also discriminate patients with early-stage AD from healthy volunteers with an accuracy of 87.8%. Some previous clinical studies used a Z-score to investigate risk factors, including lifestyle-related disease, of hippocampal atrophy in patients with AD or MCI and to prove the clinical significance of such factors (Hirata *et al.*, 2005; Anan *et al.*, 2010). In the present cross-sectional study, we investigated how the hippocampal volume in patients with early AD and A-MCI influenced executive function among non-memory cognition based on observations made using the VSRAD system.

Methods

Subjects

One-hundred-and-fifty-seven consecutive patients with AD and A-MCI who had been referred to the Jikei University Kashiwa Hospital outpatient clinic were enrolled in this study. All the patients were diagnosed as having probable AD or A-MCI according to the National Institute of Neurology and Communicative Disorder and Stroke/Alzheimer Disease and Related Disorder Association (NINCDS/ADRDA) criteria (McKhann *et al.*, 1984) or the diagnostic criteria for amnestic MCI (Petersen *et al.*, 2001) after an examination of the patients' past medical history, an evaluation of physical or neurological examination results, routine blood tests, and magnetic resonance imaging (MRI) findings by a geriatric psychiatrist. Our A-MCI included both amnestic MCI-single domain and multiple domain type (Petersen *et al.*, 2001). To recruit patients with early-stage AD or A-MCI and homogeneous memory impairments, we selected 120 patients (70 AD subjects: 71.4% female, 77.2 $\pm$ 6.6 years; 50 MCI subjects: 38% female, 74.3 $\pm$ 5.0 years) whose Mini-mental State Examination (MMSE) scores were $\geq$ 15 points (Folstein *et al.*, 1975; Baudic *et al.*, 2006), global Clinical Dementia Rating (CDR) scores were 0.5 or 1.0 (Hughes *et al.*, 1982), and Behave-AD (Reisberg *et al.*, 1987) scores were $\leq$ 20 points, since previous studies have reported that behavioral and psychological symptoms in patients with AD are related to executive function (Nagata *et al.*, 2010).

Neuropsychological tests were administered by a clinical psychologist. The exclusion criteria were a history of another neurological disease, alcohol or other substance abuse, brain injury, major depressive or psychotic disorder, epilepsy, or metabolic disorder. Furthermore, we rechecked the routine brain MRI findings obtained at presentation to support the diagnosis and excluded the following patients: (1) patients with more than four old lacuna infarctions within bilateral subcortical areas including the basal ganglia; and (2) patients with periventricular hyperintensity (PVH) $\geq$ 10 mm or with continuous white matter lesions $\geq$ 25 mm. These patients were excluded to enable the study subjects to be discriminated from patients with subcortical vascular dementia or mixed-type dementia (Erkinjuntti *et al.*, 2000). Finally, the four geriatric psychiatrists discussed the results of all the patients' diagnoses once a month to exclude other forms of dementia, such as frontotemporal

lobar degeneration (FTLD), Lewy body disease, or idiopathic normal pressure hydrocephalus (iNPH). To assess the executive function of patients, we used the Frontal Assessment Battery (FAB) (Dubois *et al.*, 2000; Takagi *et al.*, 2002). The FAB is an easily administered test that can be completed at bedside without tools within 10 minutes.

Written informed consent was obtained after a complete description of the study had been given to all the subjects or their proxies. This study was approved by the Ethics Committee of the Jikei University School of Medicine.

Brain MRI imaging

All the subjects' brain MRI examinations were performed using a 1.5-T MRI system (EXCELART, Toshiba, Japan). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence at 22.4/5.5/1 (TR/TE/excitation) produced a gapless series of continuous, thin sagittal sections with the following parameters: flip angle, 35 degrees; matrix, 256 × 256; field of view, 22 × 22 cm; section thickness, 2.00 mm.

Voxel-based MRI analysis

Voxel-based morphometry (VBM) was used to map the loss of gray matter objectively on a voxel-by-voxel basis after an automatic normalization procedure for functional neuroimaging (Ashburner and Friston, 2000). The VBM method was developed for the automated diagnosis of very early Alzheimer's disease (AD), designed as a voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) (Hirata *et al.*, 2005). This automatic system demonstrated a significant decline in gray matter in the bilateral entorhinal cortex and parahippocampal gyrus. The region of interest (ROI) was fixed within the bilateral entorhinal cortex and the parahippocampal gyrus, and the severity of the gray matter atrophy was indicated by the following described Z-scores. Imaging data for individual subjects was transformed and matched to the template brain and corrected for differences in brain size and shape. The normalized MRI results were then segmented into gray matter, white matter, cerebrospinal fluid and other compartments using a modified version of a clustering algorithm. The segmented gray matter images were subjected to an affine and non-linear anatomical standardization using a prior gray matter template. The anatomically standardized gray matter images were smoothed using an isotropic Gaussian kernel of 12 mm in full-width at half-maximum to utilize the partial volume effect to create a spectrum of gray matter intensities. The gray matter intensities were equivalent to the weighted average of the gray matter voxel located in the volume fixed using the smoothing kernel. Thus, regional intensities were regarded as being equivalent to the gray matter concentrations. The Z-score for each patient was obtained by a comparison with the mean and standard deviation (SD) for gray matter images from 41 healthy controls (see Hirata *et al.*, 2005 for details regarding the healthy controls' data). After voxel normalization to a global mean, Hirata *et al.* (2005) developed the following equation:

$$\text{Z-score} = (\text{control mean} - \text{individual value})/(\text{control SD})$$

Windows XP was used for the computed procedures. The Z-score is a relative coefficient used to evaluate atrophy in the hippocampus using age-matched methods. In addition, we divided the subjects into the following three groups according to the Z-score: (1) mild atrophy group (Z-score: 0–0.99), (2) moderate atrophy group (Z-score: 1.0–1.99), or (3) severe atrophy group (Z-score: 2.00–3.99). At the same time, VSRAD automatically measured the degree of atrophy in the total brain including the hippocampus: if the Z-score was more than 2.0 within a voxel, it was defined as atrophy (Hirata *et al.*, 2005). Thus, the proportion of atrophic area in the total brain (%) was measured: 100 × ([the number of voxel with Z-score ≥ 2.0]/[the number of total brain voxel]). To predict other areas with a cortical atrophic effect on cognitive impairments, we excluded subjects whose proportion of atrophic area in the total brain was ≥ 15%.

FAB (Frontal Assessment Battery) and its subtests

To examine the executive function of patients, we used the Japanese FAB version consisting of six subtests: (1) similarities (conceptualization); (2) lexical fluency (mental flexibility); (3) motor series (programming); (4) conflicting instructions (sensitivity to interference); (5) go /no-go (inhibition control); and (6) prehension behavior (environmental autonomy) (Takagi *et al.*, 2002). Each subtest was rated from 3 to 0, with a total score ranging from 18 to 0.

Statistical analysis

SPSS 16.0J for Windows (SPSS Japan Inc.) was used for all the statistical analyses. To compare differences between the three groups (mild, moderate and severe atrophy), we used a one-way ANOVA with Tukey post-hoc testing for age, education (years), duration of illness (months),

Table 1. Subject characteristics (Mean ± SD)

	MILD ATROPHY (N = 21) (MCI/AD: 14/7) (MEAN ± SD)	MODERATE ATROPHY (N = 46) (MCI/AD: 19/27) (MEAN ± SD)	SEVERE ATROPHY (N = 40) (MCI/AD: 16/24) (MEAN ± SD)	χ^2 OR F SCORE	P VALUE
Sex (male/female)	8/13	20/26	18/22	0.276[a]	0.871
Age	73.2 ± 5.8	75.3 ± 6.3	76.8 ± 5.9	2.513	0.086
Education (years)	12.6 ± 2.8	12.0 ± 2.4	12.4 ± 2.9	0.419	0.659
Duration of illness (months)	16.9 ± 17.5	31.2 ± 37.0	29.9 ± 22.5	1.896	0.155
MMSE score	24.9 ± 3.3	23.5 ± 3.9	23.6 ± 3.9	1.129	0.327
FAB score	13.9 ± 3.2	12.8 ± 3.1	12.6 ± 2.6	1.458	0.237
Behave-AD score	3.2 ± 2.7	5.3 ± 4.9	5.4 ± 4.0	2.072	0.131
Proportion of atrophic area in total brain (%)	51.38[b)]	48.1[b)]	62.16[b)]	4.581[a)]	0.119

FAB = Frontal Assessment Battery; MMSE = Mini-mental State Examination.
The sex ratio was analyzed using a χ^2 test. The proportion of the atrophic area in the total brain (%) was analyzed using the Kruskall-Wallis test.
[a] χ^2 score. [b] Average rank score.

Behave-AD score, MMSE score, and FAB score. At the same time, we also compared FAB subtest score and the other cognitive functions (memory registration, memory delayed recall, attention and calculation, and 3-stage commands) among the MMSE subtests. The sex ratio (female to male) was assessed using a χ^2 test. The proportion of the atrophic area in the total brain (%) was compared between the three groups using the Kruskal-Wallis test, a non-parametric test. Furthermore, to clarify whether executive function was significantly associated with hippocampal atrophy independent of diagnosis (AD or A-MCI), a generalized linear model analysis was performed to examine the contribution or interactions between hippocampal atrophy and diagnosis (AD or A-MCI) as independent variables of the executive function. In one-way ANOVA with Tukey post-hoc testing, a p value < 0.05 was considered statistically significant. If any variables with a p value < 0.05 were identified using the Kruskal-Wallis test, a Mann-Whitney U-test was then performed among the three groups. A p value $< 0.05/3$ ($= 0.017$) was regarded as being statistically significant.

Results

Neuropsychological and clinical measurements

One-hundred-and-seven subjects were divided into the following three groups according to their Z-scores: (1) mild atrophy group (n = 21; MCI/AD: 14/7), (2) moderate atrophy group (n = 46; MCI/AD: 19/27), and (3) severe atrophy group (n = 40; MCI/AD: 16/24). Table 1 shows the demographics of these groups. When the demographics of the three atrophy groups were compared, no significant differences in the age ($F = 2.513$; $df = 2$; $P = 0.086$), sex ratios ($\chi^2 = 0.276$; $df = 2$; $P = 0.871$), duration of illness (months) ($F = 1.896$; $df = 2$; $P = 0.155$), education (years) ($F = 0.419$; $df = 2$; $P = 0.659$), Behave-AD scores ($F = 2.072$; $df = 2$; $P = 0.131$), MMSE total scores ($F = 1.129$; $df = 2$; $P = 0.327$), FAB total scores ($F = 1.458$; $df = 2$; $P = 0.237$), or proportion of atrophy area in total brain ($\chi^2 = 4.581$; $df = 2$; $P = 0.101$) were observed among the three groups. Among the six subtest scores of the FAB, only the go/no-go score differed significantly among the three groups ($F = 3.795$; $df = 2$; $P = 0.026$), and a Tukey post-hoc test showed a significant difference between the mild and severe atrophy groups ($P = 0.021$) (Table 2). To confirm the almost negative correlation between the Z-score and the go/no-go score ($r = -0.259$, $p = 0.008$) using Spearman's correlation coefficient, we determined the average Z-score for each individual go/no-go score in the chart (Figure 1). On the other hand, memory registration ($F = 0.785$; $df = 2$; $P = 0.459$), memory delayed recall ($F = 1.385$; $df = 2$; $P = 0.255$), attention and calculation ($F = 0.11$; $df = 2$; $P = 0.989$), and 3-stage commands ($F = 0.249$; $df = 2$; $P = 0.780$) did not differ significantly among the three groups. Moreover, we investigated the association between the go/no-go score and such MMSE subtests using Spearman's correlation coefficient but did not find any significant correlations (memory registration: $r = -0.011$, $p = 0.909$; memory delayed recall: $r = 0.143$, $p = 0.148$; attention and calculation: $r = 0.127$, $p = 0.198$; and 3-stage commands: $r = 0.019$, $p = 0.846$).