も長い間FTLD-Uの構成蛋白についての検討が進められていた。2004年にvalosin-containing protein (VCP)が[31]，2005年にcharged multi-vesicular body protein (CHMP2B)が[32]が，FTLD-Uの形成に関与する遺伝子として同定されたが，これらの遺伝子変異により発症するFTLDはごく少数であり，その後もFTLDの発症に関与する遺伝子の検索が続けられてきた。

Ⅸ. プログラニュリン（PGRN）とTDP-43

タウ蛋白はマイクロチュブル付随蛋白の1つであり，マイクロチュブルの重合と機能維持に重要な重要な役割を果たしている。過剰にリン酸化されたタウは，ADのNFTの構成蛋白であり，かつ前述したようにFTLDの封入体の構成蛋白でもある。FTDP-17家系におけるタウ遺伝子（*MAPT*）変異の同定は大きな知見であったが，タウ変異により説明できるFTLDは一部分であり，引き続きFTLDの発症に関与する遺伝子の検索が続けられ，ようやく2006年にMAPTから1.7 Mbのすぐ近くに位置するプログラニュリン（*progranulin*：*PGRN*）遺伝子変異が同定された[33,34]。

PGRNは，acrogranin, epithelin precursor, proepithelinなどとも呼ばれるエピセリンファミリーの成長因子である。シグナルペプチドに続く7.5回の繰り返し構造を有する分泌蛋白であり，PGRNはプロテアーゼにより切断され，約6 KDaのペプチドに切断され，それぞれのペプチド（グラニュリンA－Gとパラグラニュリン）はS－S結合により4本ずつが畳み合わされた構造となり，分化，創傷治癒，炎症，腫瘍などにおける作用を担う[35,36]。PGRNの神経成長因子としての作用が推定されるが，脳内でのPGRN，グラニュリンの生物学的作用についてはほとんど知られていない[37]。

FTLDの199家系において66種類の*PGRN*遺伝子変異が同定されている。変異はエクソン13以外のすべてのエクソンにわたっており，ナンセンス変異(14種)，スプライスサイト変異(11種)，フレームシフトをきたす挿入／欠失変異（34種）が知られている。このようなさまざまな種類の変異により発症するという事実はPGRN機能が低下したロス・オブ・ファンクション（loss of function：LOF）によりFTLDが発症することを示唆している。さらに重要なことは，*PGRN*変異はFTLDだけでなく，AD，筋萎縮性側索硬化症(amyotrophic lateral sclerosis：ALS)，パーキンソン病(Parkinson disease：PD)などの神経変性疾患においても見出されるという事実であり，PRGNのLOFはいろいろな病態において神経変性を惹起する可能性が示唆されている。

*PGRN*遺伝子の同定からほどなくして，核内蛋白であるTDP-43 (TAR-DNA binding protein 43)がFLTD-Uの主要な構成蛋白であることが見出され[38]，*PGRN*変異により発症しているFTLD脳には，過剰リン酸化を受け，ユビキチン化を受けたTDP-43由来のペプチドが核内および細胞質内の封入体として沈着していることが明らかにされた。

TDP-43はすべての組織に一般的に発現している核内蛋白であり，転写，スプライシング，mRNA安定性などへの関与（Buratti, 2008），マイクロRNA（miRNA）の生合成に関与する（Gregory, 2004）。もともとTDP-43の沈着はALSにおいて見出されたものであり，その後の検討によりADやDLBの一部にもTDP-43陽性の沈着物が観察された[39-41]。このことから，FTLDやALSに限らず，ADやDLBにおいてもTDP-43あるいはその遺伝子(TARDBP)の関与が推定される。現在までの所，TARDBPの変異はFTLDやADには見出されていないが，家族性および孤発性ALS患者においていくつかの変異が報告されており，このような疾患における神経変性過程にTARDBPの関与が推定されている[42,43]。

FTLDの発症に関わる遺伝子として，MAPT，GRN，TARDBPが同定された。さらに，運動ニューロン疾患を伴うFTLD家系には9p21-13との関連が示されており，この位置にある未同定の遺伝子の関与が推定されている[44,45]。

以上に述べたADおよびFTLDの発症に関わる遺伝子変異の同定の知見は，神経変性機序の解明に大きな示唆を与えることとなった。もちろん現時点でのこのような遺伝子の関与から示されるADおよびFTLDの神経変性過程の理解は，大多数を占める孤発性ADおよび孤発性FTLDの発症機構を直接示すものではないが，FADおよび家族性FTLDの発症機序の理解は孤発性認知症の理解にも大きなヒントとなることが期待されている。

Ⅹ. コピー数変異（CNV），miRNAと神経変性

コピー数変異（copy number variation：CNV）は，ゲノムにみられる1 kb以上の繰り返しであり複数の遺伝子のコピー数の変異であるが，以前に考えられていたよりも多数のCNVが知られるようになり，今では7,000個以上の遺伝子について2万個以上のCNVがあることが知られている。

2006年に，CNVのスクリーニングによりFADの5

家系においてAPP遺伝子を含む領域のCNVが報告された[46]。このCNVは，0.58～6.37 Mbの5～12遺伝子を含む領域のCNVであったが，いずれも表現型はCAAを伴うADであった。この事実は，APPのコピー数の増加によりADが発症し得ることを示している[47]。考えてみると，もともとダウン症は染色体異常により21q21領域の重複により発症する疾患であるが，この領域にはAPPが含まれており，一定年齢以上生存したダウン症にはADの病理が起こる。この事実もAPP遺伝子の重複によりADの病理が起こることの一例である[48]。また遺伝性PDにおけるαシヌクレイン遺伝子のCNV多型も報告されている[49,50]。

これらの知見は，異常蛋白の沈着により起こる神経変性疾患の発症機序として，特定の遺伝子のコピー数の増加が原因として考えられることを示唆している。APP遺伝子のコピー数の増加によりFADが起こり得ることを示唆するだけでなく，アミロイドカスケード仮説を支持する知見でもある。さらに50%程度のAPP発現量の上昇は，CNVによらずとも，さまざまな5'-あるいは3'-領域の変異によっても起こり得るので，このような機序によるAPP発現量の増加はADのリスクを増大させ得るとも考えられる。実際にAPPのプロモーター領域の変異により，APP発現レベルが1.2～1.8倍増加しているAD家系が，オランダとベルギーで見出されている[51,52]

遺伝子の重複だけでなく，FADやFTLDの家系において原因遺伝子の部分的な欠失が見出されている。例えば，PSEN1のエクソン9の欠失は，脳実質内の大量のコットンウールプラークを特徴とするADの亜型を引き起こす[53]。FTLD家系におけるPGRNとMAPTの欠失も報告されている[54]。MAPTの部分欠失がエクソン6～9の領域に報告されているが[55]，この部分欠質により産生されるタウは，マイクロチュブルとの結合が低下しており，MAP1Bとより強く結合することが示されている。このような部分欠失遺伝子によりコードされるタウも神経変性の原因となり得る。

近年miRNAについての知見が蓄積されてきた。miRNAは内因性の小さなRNAであり，mRNAの分解を促進し，あるいは標的RNAに結合して転写後の遺伝子発現を抑制していると考えられている。ヒトゲノムには1,000種類以上のmiRNAがあり30%以上の遺伝子発現に関与していると推定されているが，脳ではほかの組織以上に多種類のmiRNAが存在している。実際に，miRNAアレイによる検索により，ADにおけるmiR-107の特異的な低下が報告されており[56]，このmiR-107の低下はADの病理と相関していること，miR-107はBACE1のmRNAと結合し，miR-107の低下により，BACE1mRNAレベルが上昇することが示されている。このことから，miRNAの減少によりBACE1 mRNAの発現レベルの上昇が起こり，ADの病理過程を惹起すると考えられる。最近，ADと健常者のプールされたmiRNAアレイの検討結果が報告され，特定のmiRNA（miR-146a）の上昇が報告されている[57]。

以上に述べた知見は，特定の蛋白の産生増加や発現レベルの変化は，それだけで神経変性のリスクを高め，ADやFTLDなどの神経変性疾患を惹起させる可能性を示唆している。このようなADについての病理過程をFig. 5に示す。

XI. AD-FTLDスペクトラム

ADの異常沈着蛋白には，Aβ蛋白とタウ蛋白がある。AβはADの老人斑のコアおよびアミロイドアンギオパチー（CAA）の血管壁に沈着している。タウはNFTとして，変性した神経細胞体，あるいはゴーストタングルあるいは変性突起（dystrophic neurite）として沈着している。一方，FTLDにおいては，ピック小体の中にタウの沈着が認められ（FTLD-tau），ユビキチン陽性の沈着物として，細胞質内あるいは核内にTDP-43が沈着している（FTLD-U）。

APPミスセンス変異は，これまで32種類が報告されている。その多くはAD病理を惹起する。代表的なところでは，KM670/671 NLのスウェーデン変異，V717I，P，Gのロンドン変異，V715Mのフランス変異，V715Aのドイツ変異，I716Vのフロリダ変異などが知られている。APP変異はADだけでなく，遺伝性出血性アミロイドアンギオパチー（HCHWA-D）（E693Q），CAA病理（Italian E693K），CAAとADの病理（Flemish A692G）などのCAA病理をも惹起する。

PSEN変異は現時点で177種類が報告されている。PSEN1変異の大部分は若齢発症ADの臨床症状を呈する。PSEN1変異はかなり強い病理性を有しているらしく，最年少では24歳発症のADも報告されている。一方，PSEN1変異の中には，L113P，G183V，insArg352のようにFTLDの臨床症状を呈するものがある

MAPT変異は，44種類の変異が，主としてエクソン9～13にミスセンス変異，エクソン10と11の間のイントロンに見出されている。MAPT変異の主たる臨床症状はFTLDであり，定型的なピック球，神経細胞あるいはグリア細胞内の封入体（FTLD-tau）を呈する。MAPT

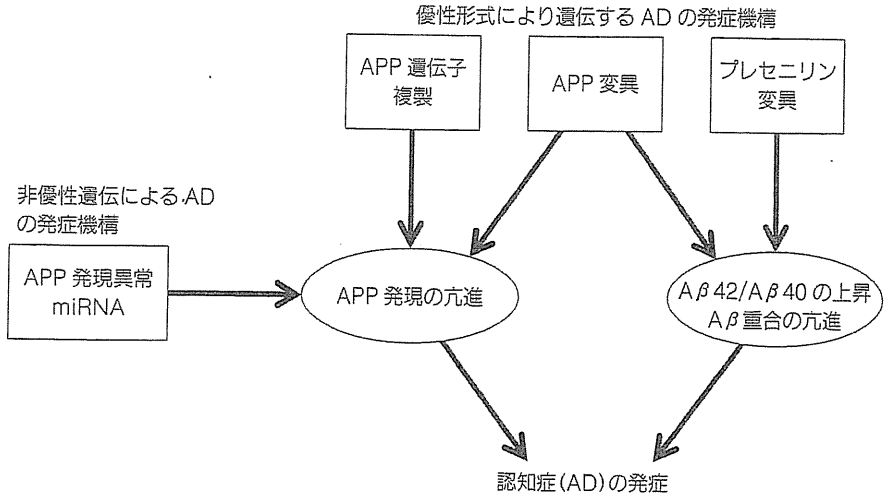

Fig. 5　ADの発症病理
Rademakers et al. Recent insights into the molecular genetics of dementia. Trends in Neurosciences 32, 451-461, 2009より改変

変異は，臨床的には極めて幅広い症状を呈することが特徴である。パーキンソン症状が前景にでるFTLD(FTDP-17)，行動異常が前景にあるFTLD，失語が前景にあるFTLDだけでなく，変異によってはAD類似の臨床症状を呈する。例えばMAPT R406W変異は，記憶障害で発症するが，後期になるとFTLDの症状を呈する。

MAPT変異により惹起されるFTLD-tau封入体を呈するFTLDは，全体の25%ほどであり，大部分のFTLDではタウ陰性，ユビキチン陽性の封入体（FTLD-U）がみられる。FTLD-Uの構成蛋白はTDP-43であることが明らかになり，続いてその発症機序にPGRNのLOFが関与していることが明らかにされた。PGRN変異は家族性FTLDの約25%を説明するし，これはMAPTの頻度とほぼ同じくらいである。MAPT変異とPGRN変異によるFTLDの発症年齢は非常にばらつきが大きい。MAPT変異は20～70歳代までにわたり，PRGN変異も30～80歳代にわたっているが，平均発症年齢を比較すると，PGRN変異は61±9歳であり，MAPT変異の48±10歳と比較して発症年代は遅い。さらに，PGRN変異の中にはADの臨床症状を呈するもの，あるいはALSの臨床症状を呈するものもある。

これまでに述べたように異常蛋白の蓄積を呈する神経変性疾患の発症機構にはかなり共通した機序が考えられる(Fig. 6)。APPはβセクレターゼおよびγセクレターゼによる切り出しを受けてAβとして老人斑あるいはCAA血管壁に沈着している。MAPTは過剰なリン酸化と部分切断を受けてPHFあるいは変異突起として沈着し，TDP-43も過剰リン酸化，ユビキチン化，部分分解を受けてFLTD-Uの構成蛋白として核内あるいは細胞質内に沈着している。そして，PSENの177種あるいはPGRNの68種類の変異はほとんど遺伝子全体にわたるLOF変異である。PSENのLOF変異は主としてAβとNFTの沈着を惹起し，PGRNのLOF変異はFTLD-tauとFTLD-Uの沈着を惹起する。しかしながら，少数例ではあってもFig. 5に示したようなAD-FTLDの間の移行型とも言えるような臨床症状を呈する変異が知られていることは，AD-FTLDの発症機構に共有される過程があることを推察させる。

XII. AD治療薬の開発

1980年代から脳内神経伝達物質の検討が精力的に進められ，AD脳内では大脳基底核を中心にアセチルコリン（acetylcholine：ACh）の低下が著しいことが明らかにされ，ACh低下に対する薬剤開発の研究が推し進められた。ACh前駆体であるコリンの補充，ACh合成酵素(choline acetyltransferase：CAT)の活性化剤，ACh分解酵素（ACh esterase：AChE）の阻害剤，ムスカリン性ACh受容体のアゴニスト，ニコチン性ACh受容体のアゴニスト，ACh受容体下流のセカンドメッセンジャーの増強剤などが開発の目標となった。このようなADのACh仮説に基づく創薬研究から生み出されて臨床的有用性が示されたのは，AChE阻害作用を有するタクリンであった。しかしながらタクリンはその肝臓毒性のために広く使用されるには至らなかった。

世界で広く使用されるようになった最初のAD治療薬は，エーザイが開発したドネペジルであった。ドネペジルは，肝毒性の少ないAChEに高い選択性を有する，長時間作用型のAChE阻害剤であるが，1989年に日本でフェイズ1治験が開始され，1991年に米国でフェイズ1が開始され，1996年11月米国食品医薬品局（food and drug administration：FDA)により認可された。そして，

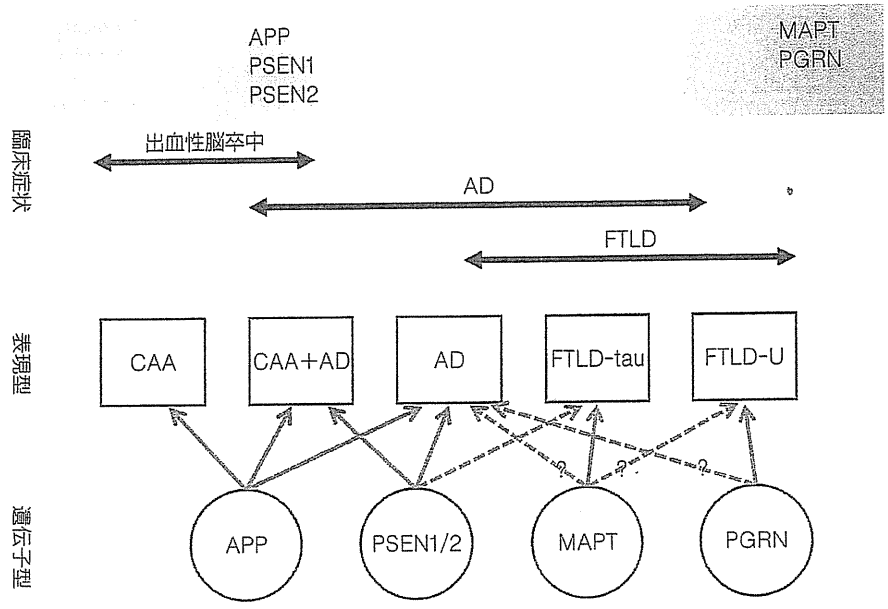

Fig. 6　AD-FTLD スペクトラム
Zee, et al: Neurology 71, 1191-1197, 2008 より改変

わが国では1999年11月に認可された。ドネペジルはファイザー社との共同販売となり，世界で最も使用されるAD治療薬となった。2006年には世界の75カ国で上市されるまでとなり，2007年には重症ADに対する適応が認可された。そして2010年には，米国ではドネペジル23 mg錠が認可された。

ドネペジルには15年間の臨床治験が積み上げられ，その効果とともに限界も明らかにされている。長期効果としては，在宅AD患者（MMSE22.0, ADAS cog.20.7）について3年間のフォローアップにより，自然経過ではMMSE（mini mental state examination）で6～12点の低下が予想されるのに対して，ドネペジル投与患者では平均値3.8というMMSEの低下であった。また，ドネペジル服用により施設入所までの期間を約21.4カ月遅らせることができたとの報告もある。

限界は，すべての患者がドネペジルに反応するのではなく，3人に1人はドネペジルに反応しないことである。MMSE得点でベースラインから2以上を奏効，±1を不変，－2以下を無反応と区分した場合に，ドネペジル投与で奏効あるいは不変の者は6カ月で75%，18カ月では50%であった。

ドネペジルの反応を予測する因子について多くの検討がなされてきたが，目立った成果は上げられていない。ドネペジルの反応を予想できる要因はベースラインのMMSE得点が低いものほど改善度が高いということぐらいであり，年齢，アポE，治療期間，性別などから反応性を予測することはできない。また，早期投与の有用性について，MCIからADへのコンバートに対するドネペジルの効果は6カ月と12カ月の時点ではあり得るものの36カ月では有意差は認められていない。

XIII. 2011年に上市されたAD治療薬

このような時期に，昨年新しい薬剤3剤が臨床に導入されたのであるが，いずれの薬剤も世界ではもう10年以上も前に上市されているものであり，必ずしも目新しいものではない。ただ，ひとえにわが国での開発が遅れに遅れただけともいえる。

ガランタミンはAChE阻害作用に加えてAChニコチン性受容体に対するアロステリック増強効果を有する薬剤であり，神経細胞保護作用が期待されている。世界では2000年にヤンセン社により上市された薬剤であるが，わが国ではようやく2012年3月22日に発売となった。ヤンセンファーマと武田薬品工業の共同販売となり，商品名は世界で用いられてきたレミニール®(Reminyl®)として販売された。

本年6月にはリバスチグミンが上市された。リバスチグミンはAChE阻害作用に加えて，ブチリルコリンエステラーゼ阻害作用を有する薬剤であり，ノバルティスが開発し1997年からエクセロン(Exelon)として世界で使用されてきた薬剤である。わが国では貼付剤（パッチ製剤）として開発され，ノバルティスからイクセロン・パッチ，小野薬品工業からリバスタッチ・パッチとして発売された。一定程度の病期が進行したADの脳内ではAChE活性が低下して，ブチリルコリンエステラーゼ活性が相対的に高まっていることが想定されており，この

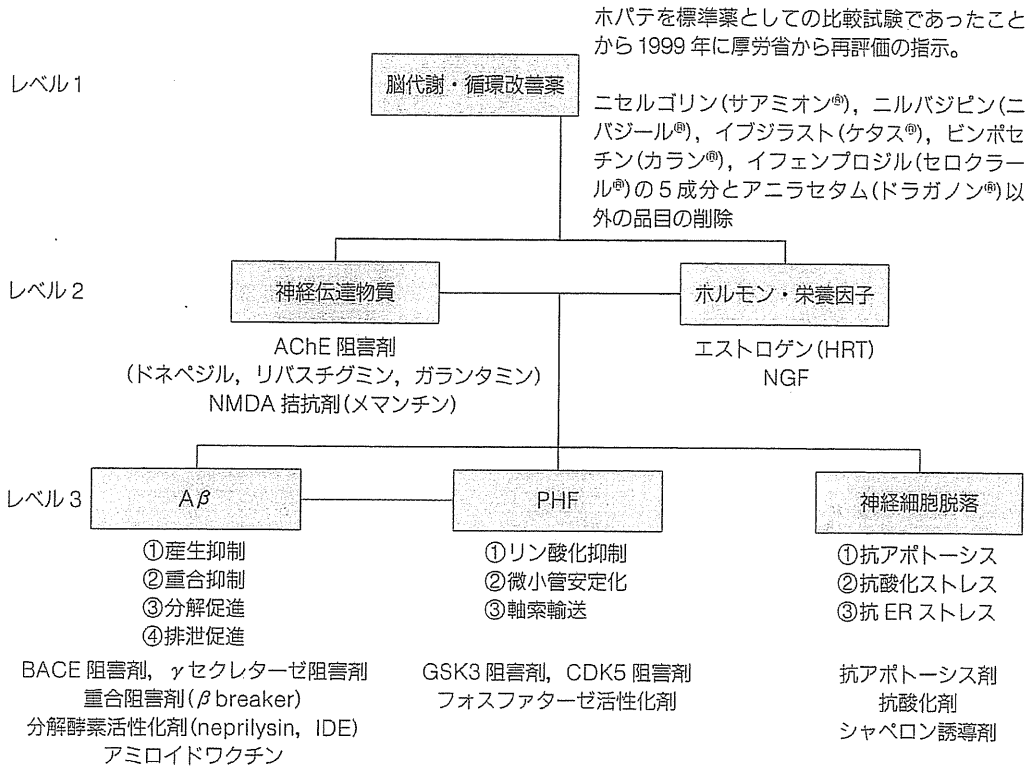

Fig. 7　AD薬のレベル

ような病態においてリバスチグミンのブチリルコリンエステラーゼ阻害作用が臨床的な有用性を示していることが期待されている。

昨年3月に発売が予定されていたメマンチンは，東日本大震災のためにその発売時期が遅れたものの，昨年6月に第一三共からメマリー錠として発売された。メマンチンはNMDA（N-methyl-D-aspartic acid）受容体拮抗作用を有する薬剤であり，もともとドイツの製薬会社であるメルツ社が開発し，世界では2002年以来，中等度から高度のAD患者に使用されてきた。わが国での開発には当初，サントリーが関わり，その後の会社の再編などでアスビオファーマを経て，最終的に第一三共から上市されることになった。メマンチンは，NMDAグルタメイト受容体への拮抗作用を有しており，NMDA受容体の異常発火を制御してCaの流入を防ぐことにより神経細胞に保護的に働くとされている。

わが国のAD治療薬は，2011年になってようやく世界の標準に追いついたことになるが，今後はドネペジル（アリセプト®）に加えて，複数のAD治療薬を臨床の場でどのように活用していくかを工夫することが求められることになる。

XIV. AD治療薬の全体像

わが国で使用されているあるいは今後の開発が期待されているAD治療薬を3つのレベルに区分して示した（Fig. 7）。ドネペジル上市以前をレベル1として，現在はレベル2の段階である。昨年わが国で上市された薬剤は，AChE阻害剤（ガランタミン，リバスチグミン）にしろ，NMDA拮抗剤（メマンチン）にしろ，欧米では既に10年以上前から使用されてきた薬剤である。いずれの薬剤も一定期間の認知機能を改善する症状改善剤（symptomatic drug）であり，ADの病理過程を改善する薬剤ではない。したがって，使用当初には一時的な認知機能改善効果があったとしても，48週以上経過すると認知機能はベースラインを越えて低下してしまう（Fig. 8）。

このような意味からは，レベル3の薬剤の開発が急務であり，ADの病理過程そのものを抑制して病理過程の進行を抑える病理修飾剤（disease-modifying drug）の開発が急がれている。Fig. 7のレベル3に示したアミロイド仮説に基づいた薬剤，タウの病理に基づいた薬剤，あるいは神経細胞死を対象とした薬剤などである。

特に，アミロイドカスケード仮説に基づいた薬剤開発は精力的になされており，世界中の製薬メーカーが取り

組んでいる。しかしながら，ADの病理修飾剤の開発は，動物実験のレベルまではスムーズに進むものの，引き続く臨床治験においては大きな壁に突き当たっているように思われる。これまでのところγセクレターゼ修飾剤として期待されたタレンフルルビル（r-flurbiprofen；Myriad社）もsemagacestat（LY450139）も開発中断を余儀なくされており，アミロイドワクチンについても必ずしも明るい話題ばかりではない。1992年以来に行われたAD薬のP-3臨床治験（バルプロ酸，トラミプロセイト，フェンセリン，ロシグリタゾン，タレンフルルビル，セキガセスタット）はいずれも中断されている。このような状況からアミロイドカスケード仮説の妥当性，Aβ除去がはたしてヒトの認知症に役立つのか，動物とヒトとの間のギャップ，さらにはヒト臨床治験の評価方法の妥当性などについても議論されている。

おわりに

ADはヒトの平均寿命の延長とともに増加した疾患である。19世紀までのヒトの平均寿命は，ゴンペルツの法則に従い，年齢に比例して生存率が低下し，加齢とともに生存する個体数は減少していた。近代医学は，年齢とともに死亡する個体数をできるだけ減らすことを目標にしており，その結果多くの個体が生存し続け，多くの人が最大寿命まで生存するようになった。この高齢者の増加部分はもちろん近代医学の輝かしい成果であることは間違いないが，同時に認知症高齢者の増加という負担を背負い込むことになった。

わが国は平均寿命，高齢者の比率，後期高齢者の比率，社会高齢化のスピードのいずれのパラメーターで見ても世界のトップランナーである。この超高齢社会の解決にあたっては欧米にもその前例はない。わが国が率先して，新しい社会システムを作り上げ，認知症高齢者が生きがいを持って安心して暮らせるような社会を構築することが求められている。単に医薬品を開発する課題というよりは，さらに大きな枠組みで考えるべき人類に課せられた社会的課題である。わが国の，そして世界のヒトが英知を結集して，高齢者が生きがいを持ってその寿命の終わるときまで支えあうような社会を構築しなければならない。

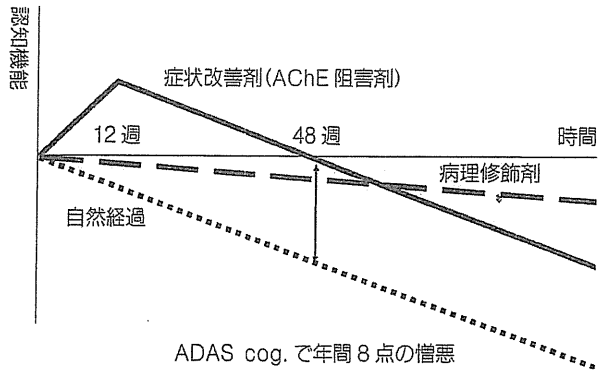

Fig. 8　症状改善剤と病理修飾剤の比較

文　献

1）Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, et al: Global prevalence of dementia: a Delphi consensus study. Lancet **366**: 2112-2117, 2005

2）Breteler MM Claus JJ, van Duijn CM, Launer LJ, Hofman A: Epidemiology of Alzheimer's disease. Epidemiol Rev **14**: 59-82, 1992

3）Graff-Radford NR, Woodruff BK: Frontotemporal dementia. Semin Neurol **27**: 48-57, 2007

4）Nishimura T, Hariguchi S, Tada K, Takeda M. Changes in water-soluble brain protein in normal and abnormal ageing. in (Asao Hirano and Koho Miyoshi eds.) "NEUROPSYCHIATRIC DISORDERS IN THE ELDERLY", Igakushoin, Tokyo, pp.79-84, 1983

5）Nukina N, Ihara Y: One of the antigenic determinants of paired helical filaments is related to tau protein. J Biochem **99**: 1541-1514, 1986

6）Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, et al: Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. J Biol Chem **261**: 6084-6089, 1986

7）Ihara Y, Nukina N, Miura R, Ogawara M: Phosphorylated tau protein is integrated into paired helical filaments in Alzheimer's disease. J Biochem **99**: 1807-1810, 1986

8）Kang J, Lemaire HG, Unterbeck A, Salbaum JM, Masters CL, et al: The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature **325**: 733-736, 1987

9）Chartier-Harlin MC, Crawford F, Houlden H, Warren A, Hughes D, et al: Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. Nature **353**: 844-846, 1991

10）Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, et al: Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A **90**: 1977-1981, 1993

11）Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, et al: Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease.

Nature **375**: 754-760, 1995
12) Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, et al: Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature **376**: 775-778, 1995
13) Wolfe MS, Xia W, Ostaszewski BL, Diehl TS, Kimberly WT, et al: Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity. Nature **398**: 513-517, 1999
14) Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, et al: Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature **393**: 702-705, 1998
15) Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, et al: Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature **400**: 173-177, 1999
16) Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, et al: Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature **442**: 916-919, 2006
17) Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, et al: Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature **349**: 704-706, 1991
18) Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesgue G, et al: Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature **375**: 754-760, 1995
19) Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, et al: Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science **269**: 973-977, 1995
20) De Strooper B: Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-Secretase complex. Neuron **38**: 9-12, 2003
21) Hardy J: Amyloid, the presenilins and Alzheimer's disease. Trends Neurosci **20**: 154-159, 1997
22) Bird TD: Genetic aspects of Alzheimer disease. Genet Med **10**: 231-239, 2008
23) Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, et al: Apolipoprotein E: high-avidity binding to b-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A **90**: 1977-1981, 1993
24) Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, et al: Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA **278**: 1349-1356, 1997
25) Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, et al: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science **261**: 921-923, 1993
26) Mahley RW, Weisgraber KH, Huang Y: Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci U S A **103**: 5644-5651, 2006
27) Drzezga A, Grimmer T, Henriksen G, Mühlan M, Pemeczky R, et al: Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. Neurology **72**: 1487-1494, 2009
28) Reiman EM, Chen K, Liu X, Bandy D, Yu M, et al: Fibrillar amyloid-β burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proc Natl Acad Sci U S A **106**: 6820-6825, 2009
29) Rademakers R, Hutton M: The genetics of frontotemporal lobar degeneration. Curr Neurol Neurosci Rep **7**: 434-442, 2007
30) Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, et al: Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature **393**: 702-705, 1998
31) Watts GD, Wymer J, Kovach MJ, Mehta SG, Mumm S, et al: Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nat Genet **36**: 377-381, 2004
32) Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, et al: Mutations in the endosomal ESCRTIIIcomplex subunit CHMP2B in frontotemporal dementia. Nat Genet **37**: 806-808, 2005
33) Cruts M, Gijselinck I, van der Zee J, Eugelborgts S, Wils H, et al: Null mutations in progranulin cause ubiquitinpositive frontotemporal dementia linked to chromosome 17q21. Nature **442**: 920-924, 2006
34) Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, et al: Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature **442**: 916-919, 2006
35) He Z, Bateman A: Progranulin (granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin) mediates tissue repair and tumorigenesis. J Mol Med **81**: 600-612, 2003
36) He Z, Ong CH, Halper J, Bateman A: Progranulin is a mediator of the wound response. Nat Med **9**: 225-229, 2003
37) Van Damme P, van Hoecke A, Lambrechts D, Vanacker P, Bogaert E, et al: Progranulin functions as a neurotrophic factor to regulate neurite outgrowth and enhance neuronal survival. J Cell Biol **181**: 37-41,

2008
38) Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, et al: Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science **314**: 130-133, 2006
39) Amador-Ortiz C, Lin WL, Ahmed Z, Personett D, Davies P, et al: TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. Ann Neurol **61**: 435-445, 2007
40) Higashi S, Iseki E, Yamamoto R, Minegishi M, Hino H, et al: Concurrence of TDP-43, tau and a-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies. Brain Res **1184**: 284-294, 2007
41) Nakashima-Yasuda H, Uryu K, Robinson J, Xie SX, Hurtig H, et al: Co-morbidity of TDP-43 proteinopathy in Lewy body related diseases. Acta Neuropathol **114**: 221-229, 2007
42) Kabashi E, Valdmanis PN, Dion P, Spiegelman D, McConkey BJ, et al: TARDBP mutations in individuals with sporadic and familial amyotrophic lateral sclerosis. Nat Genet **40**: 572-574, 2008
43) Sreedharan J, Blair IP, Tripathi VB, Hu X, Vance C, et al: TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. Science **319**: 1668-1672, 2008
44) Morita M, Al-Chalabi A, Andersen PM, Hosler B, Sapp P, et al: A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. Neurology **66**: 839-844, 2006
45) Vance C, Al-Chalabi A, Ruddy D, Smith BN, Hu X, et al: Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3. Brain **129**: 868-876, 2006
46) Rovelet-Lecrux A, Hanneguin D, Raux G, Le Meur N, Laguerrière A, et al: APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. Nat Genet **38**: 24-26, 2006
47) Sleegers K, Brouwers N, Gijselinck I, Theuns J, Goossens D, et al: APP duplication is sufficient to cause early onset Alzheimer's dementia with cerebral amyloid angiopathy. Brain **129**: 2977-2983, 2006
48) Wisniewski KE, Dalton AJ, McLachlan C, Wen GY, Wisniewski HM: Alzheimer's disease in Down's syndrome: clinicopathologic studies. Neurology **35**: 957-961, 1985
49) Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, et al: a-Synuclein locus triplication causes Parkinson's disease. Science **302**: 841, 2003
50) Chartier-Harlin MC, Farrer M, Johnson J, Singleton A, Hague S, et al: a-Synuclein locus duplication as a cause of familial Parkinson's disease. Lancet **364**: 1167-1169, 2004
51) Theuns J, Brouwers N, Engellborghs S, Sleegers K, Bogaerts V, et al: Promoter mutations that increase amyloid precursor-protein expression are associated with Alzheimer disease. Am J Hum Genet **78**: 936-946, 2006
52) Brouwers N, Sleegers K, Engelborghs S, Bogaerts V, Serneels S: Genetic risk and transcriptional variability of amyloid precursor protein in Alzheimer's disease. Brain **129**: 2984-2991, 2006
53) Crook R, Verkkoniemi A, Perez-Tur J, Mehta N, Baker M, et al: A variant of Alzheimer's disease with spastic paraparesis and unusual plaques due to deletion of exon 9 of presenilin 1. Nat Med **4**: 452-455, 1998
54) Rovelet-Lecrux A, Deramecourt V, Legallic S, Manrage CA, Le Ber I, et al: Deletion of the progranulin gene in patients with frontotemporal lobar degeneration or Parkinson disease. Neurobiol Dis **31**: 41-45, 2008
55) Rovelet-Lecrux A, Lecourtois M, Thomas-Anterion C, Le Ber I, Brice A, et al: Partial deletion of the MAPT gene: a novel mechanism of FTDP-17. Hum Mutat **30**: E591-E602, 2009
56) Wang WX, Rajeev BW, Stromberg AJ, Ren N, Tang G, et al: The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of b-site amyloid precursor protein cleaving enzyme 1. J Neurosci **28**: 1213-1223, 2008
57) Lukiw WJ, Zhao Y, Cui JG: An NF-kB-sensitive micro RNA-146amediated inflammatory circuit in Alzheimer disease and in stressed human brain cells. J Biol Chem **283**: 31315-31322, 2008

お知らせ

本誌は Index Medicus に収載されております。Pub Med で検索が可能であり，英文 abstract をご覧いただくことができます。

「BRAIN and NERVE」編集室

Psychiatry and Clinical Neurosciences 2012; 66: 1–7 doi:10.1111/j.1440-1819.2011.02304.x

Editorial

Non-pharmacological intervention for dementia patients

OWING TO THE prolonged average life span of human beings since the 19th century, the ratio of the elderly population in the world has rapidly increased, and it will continue to increase, especially in developing regions, including Asia. One consequence of increased longevity is the growing prevalence of dementia in these regions, especially in Asia.[1] In the year 2005, there were 13.7 million dementia patients in the Asian region (5.5 million in China, 3.2 million in India, and 1.9 million in Japan) and this number is expected to increase to 64.6 million (27.0 million in China, 16.3 million in India, and 4.9 million in Japan) by the year 2050.[1] Reflecting the faster increase of the elderly population in developing countries, more dementia patients will be observed in Asia, and in other developing countries, than in developed countries in the near future.[2]

Donepezil, a choline esterase inhibitor, was developed and approved in Japan in November 1999, and it has been the only drug for Alzheimer's disease available in Japan for 12 years. This year (2011), three new compounds (galantamine, rivastigmine, and memantine) have been approved for Alzheimer's disease by the Japanese Government, which has provided alternatives for patients.[3] Even though all of these drugs, including donepezil, are only symptomatic,[4] the possibility of a choice of drugs is certainly favorably accepted by patients and doctors. These drugs will not cure Alzheimer's disease, leaving a similar or even higher number of patients to be treated.

Recognizing the limited benefits of the symptomatic drugs, the development of the disease-modifying drug for Alzheimer's disease is the urgent target for research laboratories and pharmaceutical companies.[5] There are more than 100 compounds searched for and considered for the disease-modifying drug, and some compounds have successfully undergone pre-clinical studies and have been put forward to clinical trials; however, all compounds tested in clinical trials for Alzheimer's disease have failed to demonstrate clinical usefulness in the past 2 decades.

The list of unsuccessful compounds evaluated in clinical trials for Alzheimer's disease includes AN1792 amyloid vaccine (Elan, 1992), atorvastatin (HMG CoA reductase inhibitor, Pfizer), simvastatin (drug for hyperlipidemia, Banyu), Dimebon (antihistaminergic drug, Pfizer, 2010), Ginko biloba (mitochondrial membrane stabilization, and antioxidant effect), tarenflurbil (non-steroidal anti-inflammatory drug, gamma-secretase modulator, Myriad, 2009), phenserine (choline esterase inhibitor, amyloid-beta production inhibitor), rosiglitazone (anti-diabetes drug, insulin resistance, Glaxo-Smith-Kline), tramiprosate (amyloid-beta aggregation inhibitor, Neurochem, 2007), and xaliproden (5-HT1A agonist for amyotrophic lateral sclerosis).

After paying a huge loss of labor, time, and money, researchers are still struggling to determine the reasons for the consecutive failures in developing the disease-modifying drugs for Alzheimer's disease, discussing the discrepancy between animal studies and human clinical trials, the measure of efficacy evaluation in clinical trials, and the validity of the amyloid cascade hypothesis. Considering the difficulty of developing new drugs for Alzheimer's disease, it might be time to think over the possibility of treatment from broader perspectives.[6–8] In this article, complementary and alternative medicine (CAM) for Alzheimer's disease will be briefly reviewed[9] and the present state of non-pharmacological treatment will be discussed.

SOCIAL ASPECT OF DEMENTIA

Dementia is a syndrome associated with a progressive loss of memory and cognitive functions that is serious enough to interfere with performing the tasks of daily life. The loss of memory and cognitive function is caused by a variety of disorders, most commonly in the elderly by neurodegenerative disorders, including Alzheimer's disease. Dementia can occur to anyone at any age from an injury or from oxygen deprivation, although it is most commonly associated with aging. It is the leading cause of institutionalization of the elderly. Along with the progression of cognitive impairment due to dementia, the capacity of performing the tasks of daily life is deteriorated. As shown in Figure 1, complex social life capacity is

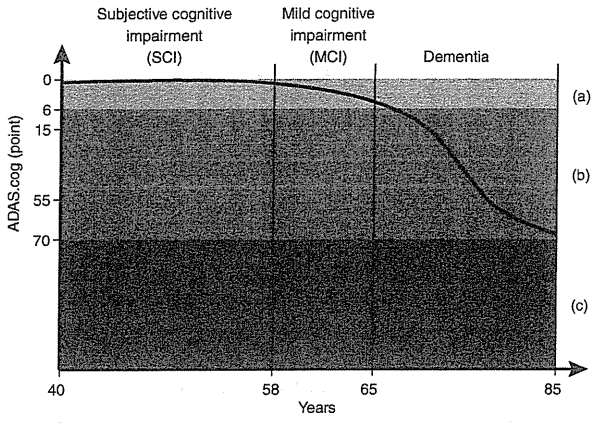

Figure 1. Most people notice memory decline when they become 40 years old on average (subjective cognitive impairment [SCI]), in which the whole capacity including social life, personal life, and biological life are preserved. Some may show mild cognitive impairment (MCI), in which social life capacity is impaired. In dementia stage, social life capacity and personal life capacity are impaired but the biological life capacity is preserved.
(a) Social life capacity. (b) Personal life capacity. (c) Biological life capacity.

gradually deteriorated due to memory impairment during subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) stages, even before the clinical diagnosis of dementia. When the diagnosis of dementia is given, the patient is no more able to function in social life, and their personal capacity will further deteriorate with the progression of the disease; however the biological life capacity will be maintained until the end of life (Fig. 1).

The tasks of daily life are different for each individual, and the timing of diagnosis of dementia may depend on the previous social and occupational complexity of the patient's daily life. If a patient has higher premorbid intellectual function, it is usual that the patient is not diagnosed as having dementia, even though the pathological process in the brain is far advanced, because the patient usually shows a score higher than the cut-off value of a screening test like the Mini Mental State Examination.[9] In this respect, even the diagnosis of dementia is influenced by social factors,[10] including premorbid IQ, level of education, occupation, and complexity of daily life.[6]

The symptoms of Alzheimer's disease differ for each individual patient. At the onset of dementia in some patients, certain personality traits that had been well controlled in the past become accentuated, whereas in others there is a 'loss of personality', where the uniqueness of the patient's personality is lost. Some patients show a more rapid deterioration of cognitive function, whereas others show a slower rate of cognitive decline. Some patients exhibit various types of behavioral and psychological symptoms of dementia (BPSD), whereas others exhibit few abnormal behaviors. Furthermore, the physical, personal, familial, economic, and social environments differ between patients. Thus, each patient should be evaluated as an individual in terms of the needs for intervention, taking into account previous social functioning, family structure, and the patient's living environment in order to deliver the most appropriate care. Interventions for dementia patients need to be individualized further, taking into consideration the different genetic, environmental, and social factors that are specific to each patient.[11–14]

CAM FOR DEMENTIA

Although modern medical science has enabled correct diagnoses to be made and proper treatments to be initiated for acute diseases caused by exogenous pathogenic factors, there are still numerous chronic, incurable diseases caused by endogenous factors, such as dementia, cancer, hypertension, diabetes, chronic pain etc., for which there is no effective treatment, leaving patients with these conditions to suffer. To facilitate the better management of these chronic diseases, recent attention has focused on the use of CAM, together with Oriental and traditional medicines[1,9,14,15] and non-pharmacological intervention.[12] CAM is defined by the American Cancer Society as '... supportive methods used to complement evidence-based treatment. Complementary therapies do not replace mainstream treatment and are not promoted to cure disease. Rather, they control symptoms and improve well-being and quality of life.' In contrast, alternative therapies, or alternative medicine, involve non-mainstream treatments that are sometimes used by patients instead of orthodox treatments.

Reflecting the lack of effective medicine to cure most of dementia, including Alzheimer's disease, a variety of CAM are applied without supporting evidences.[16] Since the symptoms of dementia (even the diagnosis, as mentioned above) are influenced by the social factors of each patient, the effectiveness of CAM is not guaranteed to all of the patients. Some

CAM are effective for some patients, but the same CAM is not effective for other patients. There are scarce data of the effectiveness of CAM and their usefulness with scientifically verified statistical analysis, which could be one of the reasons why so many different kinds of CAM are tried in public.[17]

CAM for dementia include off-label-use of drugs, Chinese herbal medicine, natural supplements, food, exercise, leisure activities, lifestyle, and non-pharmacological interventions. Examples of off-label use of approved drugs (alternative medicine) for dementia are Ginko biloba, acetyl-L-carnitine, lecithin, piracetam, curcumin, vinpocetine, phosphatidylserine, and others.[18]

In Asian countries, Chinese herbs are traditionally used for dementia and other medical conditions, from which active components are extracted for the treatment of dementia. Due space limitations, only the popular examples are briefly described below. Galantamine is originally extracted from *Galanthus woronowii*, a plant of the Amaryllidaceae family, and is now approved as the drug for Alzheimer's disease, marketed worldwide by Janssen Pharmaceuticals.[19] Ginkgo biloba leaf preparations have been marketed in Germany and France for 30 years for the treatment of cardiovascular disease, cerebrovascular disease and dementia, and are sold as natural supplements in the USA and other countries. Huperzin A is an extract from *Huperzia serrata* (*Qian Ceng Ta*) for its potent acetylcholine esterase inhibitor action. Huperzine A is widely used as an effective cognitive enhancer for dementia patients in China and in other countries.[20] Ginsenosides extracted from Panax ginseng are shown to improve learning and memory function through the mechanism of increasing acetylcholine level and also density of muscarinic receptors.[21] Ursolic acid extracted from *Salvia officinalis* is shown to have neuroprotective effects and inhibit acetylcholine esterase *in vitro*, showing memory improvement in clinical study. Epigallocatenin-3-gallate is the active component of green tea, a popular daily drink for Asian people, which has shown to have neuroprotective and antioxidative activity. Curcumin, an extract from the Curcuma root, is shown to be effective for improving learning and memory, which is also shown to decrease amyloid-beta by gamma-secretase inhibitor activity. Clausenamide, a major component of aqueous extract from the leaves of *Clausena lansium*, has been under study as a promising candidate for dementia treatment. The list of the compounds extracted from Chinese herbs is growing, and these are only some examples of the compounds that can be developed for drugs for dementia. A more complete list is available in the literature.[22]

NON-PHARMACOLOGICAL INTERVENTION FOR ALZHEIMER'S DISEASE

Four drugs (donepezil, rivastigmine, galantamine, and memantine) are now available in Japan and many other countries. The benefits for patients treated with one of these drugs (some are treated with a combination of acetylcholine esterase inhibitor and N-Methyl-D-aspartate antagonist) are not satisfactory. Even though the treated patient may show some cognitive improvement for several months, they show a similar level of cognitive function after 1 year or so, showing the same rate of cognitive decline as untreated patients (Fig. 2).

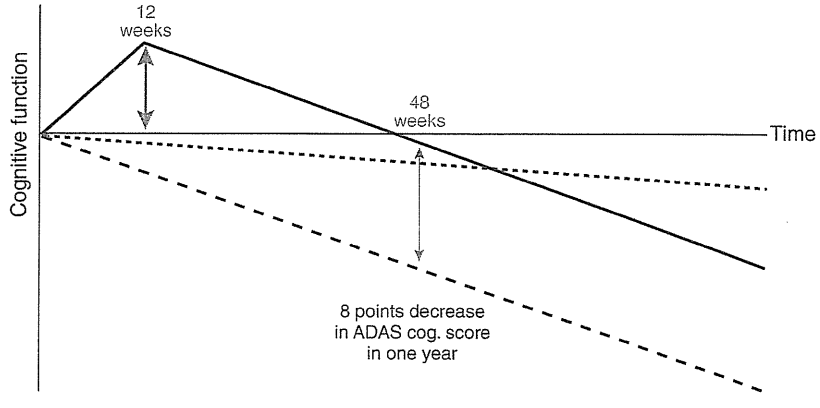

Figure 2. Broken line (– –) shows natural course of cognitive decline with dementia patients. Solid line (——) shows the cognitive function of the patients treated with symptomatic drugs such as AChE inhibitors. Short broken line (- - -) represents the cognitive decline of the patients treated with disease-modifying drugs.

Table 1. Non-pharmacological intervention to Alzheimer patients

Therapy	Cognitive	ADL	BPSD
Cognitive training	+	+	+
Cognitive rehabilitation	+	+	+
Cognitive stimulation therapy	+	+	+
Snoezelen/multisensory stimulation	+	+	+
Reality orientation	+	+	+
Reminiscence therapy	+	−	+
Validation therapy	+	−	+
Physical activity	+	+	+
Light therapy	+	−	+
Music therapy	+	−	+
Aromatherapy	−	−	+
Animal-assisted therapy	−	−	+

ADL, activities of daily living; BPSD, behavioral and psychological symptoms of dementia.

Patients, caregivers, and medical professionals have been searching for an effective intervention for Alzheimer's disease, and there are a variety of non-pharmacological interventions commonly applied to Alzheimer patients. The limited efficacy of drug therapy and the plasticity of the human brain are the two main reasons that explain this growing interest in non-pharmacological intervention for dementia patients. In Table 1, non-pharmacological interventions are listed with the positive results of published randomized controlled trials (RCT) that have targeted at least one of the symptoms of dementia. The symptoms are grouped under three headings: cognitive function, activities of daily living (ADL), and BPSD. Some popular non-pharmacological interventions are discussed in the frame of two main approaches: cognitive approaches, multi-strategy approaches (reality orientation, reminiscence therapy and validation therapy), and miscellaneous approaches (Table 1).

COGNITIVE TRAINING, COGNITIVE REHABILITATION, COGNITIVE STIMULATION THERAPY

Cognitive training has been frequently mislabeled or conflated with other ill-defined therapies, such as cognitive rehabilitation, and cognitive stimulation therapy. Cognitive training is defined as the structured practice of complex mental activity in order to enhance cognitive function. An operational definition of cognitive training, delineating from other interventions, includes repeated practice, on problem activities, using standardized tasks, and target-specified cognitive domains.[23] Cognitive training can be further distinguished to include training in applied memory strategies versus repetitive cognitive exercises. Training in memory strategies involves the instruction and practice of techniques to minimize memory impairment and enhance performance, and involves learning and practicing strategies, such as the method of loci, mnemonics, and visual imagery. In contrast, cognitive exercise requires the repeated practice of targeted cognitive abilities in a repetitions-sessions format: users typically carry out a number of iterations of a cognitive task in one session, then continue to new tasks in the next session, and eventually return to further train the original task at a harder level in future sessions (i.e., staircase design). Recently, several software applications have been developed that implement cognitive exercises on computer.

There is evidence from a modest number of well-conducted RCT that cognitive training, cognitive rehabilitation, and cognitive stimulation therapy confer modest but significant benefits in the treatment of cognitive symptoms of Alzheimer patients. A meta-analysis of longitudinal RCT of cognitive training in cognitively healthy adults demonstrated efficacy on primary cognitive outcomes.[23]

The systematic review found that cognitive training can produce moderate-to-large beneficial effects to MCI subjects on memory-related outcomes. However, the number of high-quality RCT remains low, and so further trials must be a priority.

Cognitive rehabilitation also appears to result in functional benefits in Alzheimer patients. The modest number of RCT focusing on cognitive training in Alzheimer patients is consistent with the results of larger cognitive training trials in healthy older people.

The best evidence base is for cognitive stimulation therapy, although this approach is labor-intensive, and requires further evaluation of cost-effectiveness. There is currently no evidence that brain-training games provide any significant benefit to people with Alzheimer's disease.[24]

SNOEZELEN/MULTI-SENSORY STIMULATION

The concept of Snoezelen was originally developed in the late 1970s by Dutch therapists, Jan Hulsegge

and Ad Verheul as therapy for children with autism and other learning disabilities. Snoezelen or multisensory stimulation (MSS) is visual, auditory, tactile, and olfactory stimulation offered to people in a specially designed room, which relates to the interdependence of both the space (the physical environment) and the 'client-centered' approach of the practitioner (the human environment). This specially designed sensory physical environment, together with the input of the 'enabling practitioner' initiates changes in arousal by affecting the relaxation process, which aims to maximize a person's potential to focus on his own free will and to engage on a motivational stimulus, and thereby to improve communication and functioning. The clinical application of Snoezelen has been extended from the field of learning disability to dementia care over the past decade. The rationale for its use lies in providing a sensory environment that places fewer demands on intellectual abilities but capitalizes on the residual sensorimotor abilities of people with dementia. Practitioners are keen to use Snoezelen in dementia care, and some encouraging results have been documented in the area of promoting adaptive behaviors. Positive results were reported across a range of behaviors, including a reduction in apathy in people in the later stage of dementia from two RCT. In a Cochrane database review published in 2002, only two trials were reviewed and no firm conclusion was reached, even though both studies examined the short-term values of Snoezelen on people with dementia.[25]

REALITY ORIENTATION

Alzheimer's disease patients may withdraw from contact with others and the environment as they become increasingly disoriented, which results in a lack of sensory stimulation. To prevent this understimulation from sensory inputs, 'reality orientation' was developed. It is based on the belief that continually and repeatedly telling or showing certain reminders to people with mild-to-moderate memory loss will result in an increase in interaction with others and improved orientation. This in turn can improve self-esteem and reduce problem behaviors.

Reality orientation can be taught to caregivers and family members; it can be performed in the home and should be structured around the area in which the patient spends most of his or her time. For example, access to a window is recommended to facilitate orientation to the time of day and the weather. Other than the environmental cues, familiar objects to the patients can be used to stimulate their memory in reality orientation, such as a family scrapbooks, flash cards, Scrabble games, a globe, and large-piece jigsaw puzzles.

The effectiveness of reality orientation in dementia was evaluated by conducting a systematic literature review. This yielded 43 studies, of which, six were RCT meeting the inclusion criteria (containing 125 subjects.) Results were subjected to meta-analysis. Effects on cognition and behavior were significant in favor of treatment. The evidence indicates that reality orientation has benefits on both cognition and behavior for dementia patients. However, a continued program may be needed to sustain potential benefits.[26]

REMINISCENCE THERAPY

Reminiscence therapy is frequently used for patients with impaired memory, paying respect to the life and experiences of the individual with the aim to help the patient maintain good mental health. In one approach, participants are guided by a trained person to reflect on a variety of aspects relating to their lives. This may be themed and centered on one period in time or it may be wider and reflect a guided discussion through an issue. The therapist may use music, photographs, replica documents, drama and sensory gardens to stimulate debate and discussion for the participants. Reminiscence therapy is believed to be useful in supporting confused patients to integrate into new living arrangements by acknowledging and respecting their life history. Reminiscence therapy is believed to promote a sense of security by reviewing comforting memories.

The effect of reality orientation was compared with reminiscence therapy for elderly people in a large residential home, using a controlled cross-over design. Both kinds of therapy group were enjoyed by both staff and residents, and enabled staff to get to know moderately and severely confused residents. The group that received reality orientation followed by reminiscence therapy showed improvement in cognitive and behavioral measures, which was not found in the other two groups. It may be important to use reality orientation techniques with dementia residents before involving them in a reminiscence group.[27]

VALIDATION THERAPY

The validation therapy was developed by Naomi Feil in an attempt to address the shortcomings of other approaches, such as reality orientation, used with individuals who have more advanced dementia. Feil developed a model that sought to classify the stage of dementia that an individual has reached according to cognitive and behavioral signs. Its development was the result of an attempt to provide practical solutions for difficulties experienced by patients and caregivers. Important features of validation therapy include: a means of classifying behaviors; provision of simple, practical techniques that help restore dignity; prevention of deterioration into a vegetative state; provision of an empathic listener; respect and empathy for older adults with Alzheimer's disease, who are struggling to resolve unfinished business before they die; and acceptance of the person's reality.[28]

The way in which these values are applied to provide specific interventions depends on the severity of dementia in each individual case classified into four stages: Mal orientation, Time Confusion, Repetitive Motion and Vegetation. Each stage is identified by specific cognitive and behavioral characteristics, and specific validation therapy interventions address the different cognitive and behavioral features manifested by people with dementia at each of these stages, relying upon the central 14 techniques.[28]

Various observational studies have indicated that there are positive effects in using validation therapy in terms of the amount and duration of interactions that participants are able to make during validation groups.[29,30] However, other studies have found no significant effects of validation therapy.[31]

OTHER NON-PHARMACOLOGICAL INTERVENTIONS

There are many other non-pharmacological interventions applied to Alzheimer patients. Physical activity, especially aerobic exercise, is believed beneficial to cognitive function, improving ADL and ameliorating some forms of BPSD. Light therapy is sometimes used to keep the circadian rhythm of dementia patients in daily life, and there are RCT reporting beneficial effects to cognitive function and BPSD. Music therapy is one of the most popular day care programs in residential care as well as day care institutions. Listening to music, singing and playing music is a popular leisure activity for dementia patients, through which some small benefit to cognitive function is also reported. Aroma oils often gives pleasant feelings and calming effect to patients showing BPSD, especially agitation and aggression. Animal-assisted therapy is reportedly effective to reduce the BPSD of dementia patients.

REFERENCES

1. Awata S. New national health program against dementia in Japan: the medical center for dementia. *Psychogeriatrics* 2010; **10**: 102–106.
2. Takeda A, Tanaka N, Chiba T. Prospects of future measures for persons with dementia in Japan. *Psychogeriatrics* 2010; **10**: 95–101.
3. Takeda M, Tanaka T, Okochi M. New drugs for Alzheimer's disease in Japan. *Psychiatry Clin. Neurosci.* 2011; **65**: 399–404.
4. Tanaka T, Kazui H, Morihara T, Sadik G, Kudo T, Takeda M. Post-marketing survey of donepezil hydrochloride in Japanese patients with Alzheimer's disease with BPSD. *Psychogeriatrics* 2008; **8**: 114–123.
5. Tanimukai H, Kudo T, Tanaka T, Grundke-Iqbal I, Iqbal K, Takeda M. Novel therapeutic strategies for neurodegenerative disease. *Psychogeriatrics* 2009; **9**: 103–109.
6. Takeda M, Morihara T, Okochi M, Sadik G, Tanaka T. Mild cognitive impairment and subjective cognitive impairment. *Psychogeriatrics* 2008; **8**: 155–160.
7. Takeda M, Martinez R, Kudo T *et al.* Apolipoprotein E and central nervous system disorders: reviews of clinical findings. *Psychiatry Clin. Neurosci.* 2010; **64**: 592–607.
8. Takeda M, Okochi M, Tagami S, Tanaka T, Kudo T. Biological markers as outcome measures for Alzheimer's disease interventions–real problems and future possibilities. *Int. Psychogeriatr.* 2007; **19**: 391–400.
9. Takeda M, Hashimoto R, Kudo T *et al.* Laughter and humor as complementary and alternative medicines for dementia patients. *BMC Complement. Altern. Med.* 2010; **10**: 28–35.
10. Urakami K. Diagnostic biomarker for early stage of Alzheimer's disease: current state and view in the future. *Psychogeriatrics* 2010; **10**: 49–52.
11. Takai M, Takahashi M, Iwamitsu Y, Oishi S, Miyaoka H. Subjective experiences of family caregivers of patients with dementia as predictive factors of quality of life. *Psychogeriatrics* 2011; **11**: 98–104.
12. Yamaguchi H, Maki Y, Yamagami T. Overview of non-pharmacological intervention for dementia and principles of brain-activating rehabilitation. *Psychogeriatrics* 2010; **10**: 206–213.
13. Nishihara R, Inui F, Kato K, Tomizawa R, Hayakawa K. Genetic contribution to the relationship between social role function and depressive symptoms in Japanese elderly twins: a twin study. *Psychogeriatrics* 2011; **11**: 19–27.

14. Masutani T, Yamamoto Y, Konishi J, Maeda K. Effects of music and art education in early life and oral functions on the QOL of the Takarazuka Revue Company OG compared with general elderly females. *Psychogeriatrics* 2010; **10**: 4–14.
15. Saito S, Kobayashi T, Osawa T, Kato S. Effectiveness of Japanese herbal medicine yokukansan for alleviating psychiatric symptoms after traumatic brain injury. *Psychogeriatrics* 2010; **10**: 45–48.
16. Angell M, Kassirer JP. Alternative Medicine – The Risks of Untested and Unregulated Remedies. *N. Engl. J. Med.* 1998; **339**: 839–841.
17. Nahin RL, Straus SE. Research into complementary and alternative medicine: problems and potential. *BMJ* 2001; **322**: 161.
18. Kelley BJ, Knopman DS. Alternative medicine and Alzheimer's disease. *Neurologist* 2008; **14**: 299–306.
19. Marco-Contelles J, do Carmo Carreiras M, Rodriguez C, Villarroya M, Garcia AG. Synthesis and pharmacology of galantamine. *Chem. Rev.* 2006; **106**: 116–133.
20. Desilets AR, Gickas JJ, Dunican KC. Role of huperzine A in the treatment of Alzheimer's disease. *Ann. Pharmacother.* 2009; **43**: 514–518.
21. Liu X, Xia J, Wang L *et al.* Efficacy and safety of ginsenoside-Rd for acute ischaemic stroke: a randomized, double-blind, placebo-controlled, phase 2 multicenter trial. *Eur. J. Nueorl.* 2009; **16**: 569–575.
22. Wang Y, Huang LQ, Tang XC, Zang HY. Retrospect and prospect of active principles from Chinese herbs in the treatment of dementia. *Acta Pharmacol. Sin.* 2010; **31**: 649–664.
23. Gates NJ, Sachdev PS, Fiatarone Singh MA, Valenzuela M. Cognitive and memory training in adults at risk of dementia: a systematic review. *BMC Geriatr.* 2011; **11**: 55–69.
24. Ballard C, Khan Z, Clack H, Corbett A. Nonpharmacological treatment of Alzheimer disease. *Can. J. Psychiatry* 2011; **56**: 589–595.
25. Chung JC, Lai CK, Chung PM, French HP. Snoezelen for dementia. *Cochrane Database Syst. Rev.* 2002; (4): CD003152.
26. Spector A, Davies S, Woods B, Orrell M. Reality orientation for dementia: a systematic review of the evidence of effectiveness from randomized controlled trials. *Gelontologist* 1999; **40**: 206–212.
27. Baines S, Saxby P, Ehlert K. Reality orientation and reminiscence therapy. A controlled cross-over study of elderly confused people. *Br. J. Psychiatry* 1987; **151**: 222–231.
28. Feil N. Validation therapy. *Geriatr. Nurs.* 1992; **13**: 129–133.
29. Babins LH. Conceptual analysis of validation therapy. *Int. J. Aging Hum. Dev.* 1998; **26**: 161–168.
30. Deponte A, Missan R. Effectiveness of validation therapy (VT) in group: preliminary results. *Arch. Gerontol. Geriatr.* 2007; **44**: 113–117.
31. Scanland SG, Emershaw EL. Reality orientation and validation therapy: dementia, depression, and functional status. *J. Gerontol. Nurs.* 1993; **19**: 7–11.

Masatoshi Takeda, MD, PhD,
Toshihisa Tanaka, MD, PhD,
Masayasu Okochi, MD, PhD and
Hiromitsu Kazui, MD, PhD
Department of Psychiatry, Osaka University Graduate School of Medicine
Suita, Japan

EXTRA
Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2011;1:20–30
DOI: 10.1159/000323561
Published online: January 6, 2011

Original Research Article

Different Characteristics of Cognitive Impairment in Elderly Schizophrenia and Alzheimer's Disease in the Mild Cognitive Impairment Stage

Hiroaki Kazui[a] Tetsuhiko Yoshida[a, b] Masahiko Takaya[a] Hiromichi Sugiyama[a] Daisuke Yamamoto[a] Yumiko Kito[a, c] Tamiki Wada[a] Keiko Nomura[a] Yuka Yasuda[a] Hidenaga Yamamori[a] Kazutaka Ohi[a] Motoyuki Fukumoto[a] Naomi Iike[a] Masao Iwase[a] Takashi Morihara[a] Shinji Tagami[a] Eku Shimosegawa[d] Jun Hatazawa[d] Yoshiyuki Ikeda[e] Eiichi Uchida[e] Toshihisa Tanaka[a] Takashi Kudo[a] Ryota Hashimoto[a, f] Masatoshi Takeda[a]

[a]Psychiatry, Department of Integrated Medicine, Division of Internal Medicine, Osaka University Graduate School of Medicine, [b]Department of Psychiatry, National Hospital Organization Osaka National Hospital, [c]Department of Psychiatry, Nissay Hospital, [d]Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine, [e]Department of Radiology, Uchida Clinic, and [f]Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Kanazawa University and Hamamatsu University School of Medicine, Osaka, Japan

Key Words
Alzheimer's disease · Attention deficit · Delayed recall · Executive function · Recent memory · Three-dimensional stereotactic surface projections · Voxel-based specific region analysis · Working memory

Abstract
We compared indices of the revised version of the Wechsler Memory Scale (WMS-R) and scaled scores of the five subtests of the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) in 30 elderly schizophrenia (ES) patients and 25 Alzheimer's disease (AD) patients in the amnestic mild cognitive impairment (aMCI) stage (AD-aMCI). In the WMS-R, attention/concentration was rated lower and delayed recall was rated higher in ES than in AD-aMCI, although general memory was comparable in the two groups. In WAIS-R, digit symbol substitution, similarity, picture completion, and block design scores were significantly lower in ES than in AD-aMCI, but the information scores were comparable between the two groups. Delayed recall and

Hiroaki Kazui, MD, PhD

Psychiatry, Department of Integrated Medicine, Division of Internal Medicine
Osaka University Graduate School of Medicine, D3 2-2 Yamadaoka, Suita-City
Osaka 565-0871 (Japan)
Tel. +81 66 879 3051, Fax +81 66 879 3059, E-Mail kazui@psy.med.osaka-u.ac.jp

EXTRA
Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2011;1:20–30
DOI: 10.1159/000323561
Published online: January 6, 2011

forgetfulness were less impaired, and attention, working memory and executive function were more impaired in ES than in AD-aMCI. These results should help clinicians to distinguish ES combined with AD-aMCI from ES alone.

Introduction

Schizophrenia is a common psychiatric disease with onset usually occurring during adolescence or early adulthood. Recently, new atypical antipsychotic drugs for schizophrenia have been developed, and social systems to support schizophrenia patients have been established. As a result, schizophrenia patients are now living longer than they used to [1], and the number of elderly schizophrenia (ES) patients is increasing. The number of Alzheimer's disease (AD) patients has also increased due to the rapid aging of society. Although the incidence of AD rises with age, AD also occurs in younger patients; the prevalence rate of AD in people aged ≤64 years is 0.12 cases per 1,000 people (http://www.mhlw.go.jp/houdou/2009/03/h0319–2.html; Japanese Ministry of Health, Labor and Welfare). Therefore, there are many ES patients who also have AD, and their number is supposed to be increasing. In clinical settings, there is a growing need to differentiate between age-related and AD-related cognitive impairment in patients who have developed schizophrenia in adolescence or middle age.

Because some clinical characteristics of schizophrenia and AD are similar, differentiation between ES and AD can be difficult. Neuropsychiatric symptoms, such as apathy, poverty of speech, and delusional thinking, are common in both types of patients. Neuroimaging studies have shown volume loss in the hippocampus [2] and in the frontal lobe [3] in schizophrenia, and similar losses have been observed in AD [4]. Furthermore, patients with schizophrenia are impaired in various domains of cognition, such as memory, working memory, and executive function [5]. These symptoms are also observed in patients with AD.

Acetylcholine esterase inhibitors have been developed for the treatment of AD. Although administration of these agents does not result in a radical improvement of symptoms, their early administration can improve the prognosis of AD patients [6]. In addition, disease-modifying drugs for AD are now being developed. Thus, early diagnosis and early initiation of treatment are important in AD patients. One method to identify early AD with a high probability is the measurement of amnestic mild cognitive impairment (aMCI), which is a syndrome characterized by memory performance below the age norm, while intellectual functioning and activities of daily living are otherwise unimpaired [7]. A substantial proportion of patients with aMCI later develop clinically diagnosable AD [7]. In order to treat early-stage ES patients who have AD in the aMCI stage (AD-aMCI) for AD, it is necessary to differentiate between ES combined with AD, and ES alone. As a first step toward this goal, in this study, we clarified the degree of cognitive impairment in patients with ES compared to patients with AD-aMCI.

Methods

Subjects

All patients in this study were recruited from the Department of Neuropsychiatry of the Osaka University Medical Hospital, which includes Schizophrenia and Neuropsychological Clinics. At both clinics, patients underwent standard neuropsychological examinations as well as routine laboratory tests and cranial magnetic resonance imaging (MRI). Single pho-

EXTRA
Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2011;1:20–30
DOI: 10.1159/000323561
Published online: January 6, 2011

Table 1. Comparison of characteristics of the ES and AD-aMCI groups with and without WAIS-R

Characteristics	ES group			AD-aMCI group		
	with WAIS-R	without WAIS-R	p value	with WAIS-R	without WAIS-R	p value
Sex, male/female	5/9	10/6	0.14	7/6	7/5	0.57
Age, years	56.6 ± 5.5	57.1 ± 5.7	0.79	72.6 ± 6.0	70.2 ± 9.5	0.44
Education, years	13.1 ± 2.6	13.3 ± 2.2	0.79	13.7 ± 3.3	13.4 ± 1.8	0.8
MMSE total score	–	–	–	26.1 ± 1.9	27.0 ± 2.1	0.27
WMS-R GM index	81.3 ± 15.5	79.1 ± 17.0	0.75	80.5 ± 13.1	74.9 ± 6.1	0.19
WMS-R AC index	84.8 ± 10.3	94.8 ± 16.0	0.09	99.8 ± 11.1	97.3 ± 12.7	0.59
WMS-R DR index	75.9 ± 15.9	76.6 ± 18.4	0.92	61.5 ± 9.7	55.8 ± 6.5	0.1

ton emission computed tomography (SPECT) was performed on patients with aMCI at the Neuropsychological Clinic. The clinical and investigative data were collected in a standardized manner and were entered into each registry. In this study, we selected patients with ES and patients with AD-aMCI who met the inclusion criteria mentioned below for each group from the registry. In the Schizophrenia Clinic, we began using the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) in March 2004 and then switched to the third version of the WAIS (WAIS-III) in October 2006. In the Neuropsychological Clinic, we began using five subtests of the WAIS-R in September 2002 and switched to five subtests of the WAIS-III in February 2009. In this study, we selected patients who were evaluated with the WAIS-R, because few patients with AD-aMCI were evaluated with the WAIS-III and then followed up until they reached the dementia stage. The revised version of the Wechsler Memory Scale (WMS-R) has been used in both clinics as a memory test because the third version of the WMS (WMS-III) is not standardized and cannot be used in Japan. In both clinics, the WMS-R was usually used before the WAIS-R. However, in some cases, there was no opportunity to use the WAIS-R.

ES Group

Thirty patients with schizophrenia (15 women and 15 men) were selected from the Schizophrenia Clinic registry. The mean age of the patients was 56.9 ± 5.5 years, and the mean years of education were 13.2 ± 2.3. All subjects in the ES group (1) met the criteria for schizophrenia based on the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR); (2) were aged ≥50 years [8]; (3) showed first symptoms of schizophrenia before 65 years of age; (4) had been evaluated by either the WMS-R or the WAIS-R; (5) had no other neurological disease, and (6) had no evidence of focal brain lesions on MRI. Of the 30 patients, 14 were given the WAIS-R (group with WAIS-R) and the other 16 were not given the WAIS-R (group without WAIS-R). There were no significant differences in gender, age, education, or WMS-R indices between the ES groups with and without WAIS-R (table 1). Other demographic data on the ES group are summarized in table 2. Mean duration of hospitalization was short, although mean duration of disease was long. Many patients received atypical antipsychotic drugs at the time of neuropsychological assessment in this study. There were no significant differences between the groups with and without WAIS-R in any of the items except for the positive/negative symptom scores of the Positive and Negative Syndrome Scale (PANSS). Both PANSS scores were higher in the group without WAIS-R than in the group with WAIS-R. Four of the 30 patients with ES were not given the WMS-R.

Dement Geriatr Cogn Disord Extra 2011;1:20–30
DOI: 10.1159/000323561
Published online: January 6, 2011

www.karger.com/dee

Table 2. Characteristics of the ES group

Characteristics	ES with WAIS-R mean ± SD	ES without WAIS-R mean ± SD	p value	Total mean ± SD (range)
Age of disease onset, years	32.3 ± 12.0	30.1 ± 12.3	0.64	31.1 ± 12.0 (19.0–61.0)
Duration of untreated psychosis, years	3.6 ± 6.5	4.1 ± 8.4	0.87	3.9 ± 7.5 (0–26)
Duration of disease, years	23.8 ± 11.7	27.4 ± 10.7	0.41	25.8 ± 11.1 (1–45)
Total duration of hospitalization, months	14.0 ± 12.2	9.7 ± 19.6	0.56	11.4 ± 16.8 (0–72)
Daily dose of antipsychotic drugs (chlorpromazine equivalent), mg	554.7 ± 283.6	469.1 ± 387.6	0.5	509.0 ± 340.0 (0.0–1,300.0)
Daily dose of atypical antipsychotic drugs (chlorpromazine equivalent), mg	485.7 ± 306.6	318.8 ± 379.9	0.2	396.7 ± 352.0 (0.0–1,300.0)
PANSS score				
Positive symptoms	12.3 ± 4.6	16.3 ± 4.4	0.03	14.5 ± 4.8 (5–28)
Negative symptoms	12.3 ± 3.2	18.3 ± 6.5	0.01	15.5 ± 6.0 (7–30)
Overall severity in the Drug-Induced Extra-Pyramidal Symptoms Scale (n = 21)	0.90 ± 1.9	0.86 ± 0.7	0.94	0.88 ± 1.3 (0–6)

AD-aMCI Group

Twenty-five AD-aMCI patients were selected from the Neuropsychological Clinic registry. The number of males exceeded the number of females (14 males and 11 females). The mean age of the patients was 71.4 ± 7.8 years, the mean years of education were 13.6 ± 2.6, and the mean MMSE score was 26.5 ± 2.0. All subjects in the AD-aMCI group met the criteria for aMCI, which included (1) a memory complaint documented by the patient or another source; (2) a score in the story A recall task in the logical memory II subtest of WMS-R which is less than the age-corrected and education-corrected cutoff score; (3) a score of ≥24 on the MMSE; (4) a total Clinical Dementia Rating (CDR) score of 0.5 and a memory CDR score >0; (5) normal basic and instrumental activities of daily living evaluated with Lawton's Physical Self-Maintenance Scale and Instrumental Activities of Daily Living Scale [9], and (6) no symptoms of dementia based on a clinical examination and an extensive interview with a knowledgeable informant. All subjects in this group also (7) had been evaluated by either the WMS-R or the short form of the Japanese version of the WAIS-R, (8) had no other neurological disease, and (9) had no evidence of focal brain lesions on MRI. To confirm that the aMCI patients had AD in the preclinical stage, at least one of the following three criteria had to be fulfilled: (1) atrophy in the entorhinal cortex on MRI, (2) hypoperfusion in the posterior cingulate cortex (PCC) and precuneus on SPECT, or (3) progression to AD during annual follow-ups. Progression to AD was defined as meeting the criteria of the National Institute of Neurological Disease and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD and a total CDR score of ≥1.0.

Progression to AD from aMCI during the subsequent follow-ups (up to 8 years) was confirmed in 17 of the 25 patients. Nineteen of the 25 AD-aMCI patients received three-dimensional spoiled gradient echo MRI, which identified atrophy in the entorhinal cortex in 13 of the 19 patients. Twenty-three of the 25 AD-aMCI patients received N-isopropyl-p-[^{123}I]-iodoamphetamine (^{123}I-IMP)-SPECT, and hypoperfusion in either the PCC or precuneus was identified in 12 of the 23 AD-aMCI patients. One patient was recruited due to abnormality on the MRI and 7 patients were recruited due to abnormality on SPECT. Of the 25 patients, 13 were given the five subtests of the WAIS-R (group with WAIS-R) but the other 12 were not (group without WAIS-R). There were no significant differences in gender, age, education,

Dement Geriatr Cogn Disord Extra 2011;1:20–30
DOI: 10.1159/000323561
Published online: January 6, 2011

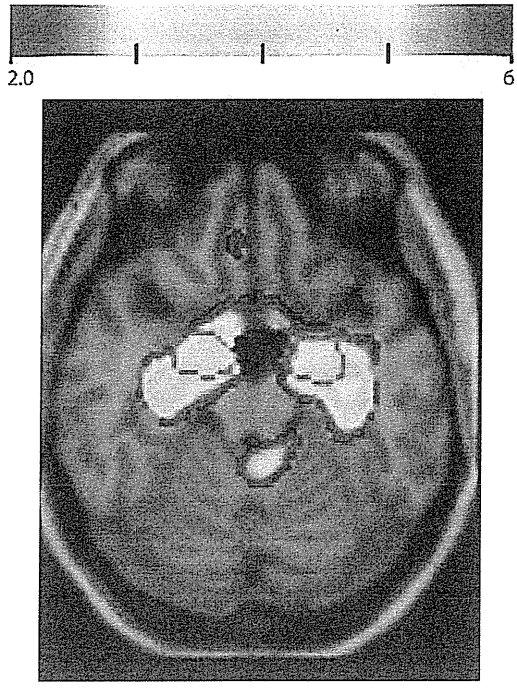

Fig. 1. Z-score map overlaid on an MRI template of a representative patient with AD-aMCI made with VSRAD. This patient was included in the study because of the presence of significant atrophy in the entorhinal cortices on MRI. Parts of the colored areas are in the areas circumscribed by purple lines, indicating significant atrophy in the entorhinal cortices. Purple lines indicate the bilateral entorhinal cortices. Colored areas on MRI are those with a Z-score >2 (significant atrophy). Color bar indicates Z-score.

MMSE score or WMS-R indices between the two groups with and without WAIS-R (table 1). All AD-aMCI patients were administered the WMS-R.

Comparison of Demographic Data in the ES and the AD-aMCI Groups

There was no significant difference between the ES and the AD-aMCI groups in terms of sex ($p = 0.48$, χ^2 test) or education ($p = 0.71$, t test). However, the ES group was significantly younger than the AD-aMCI group ($p < 0.001$, t test).

MRI and SPECT Criteria for the AD-aMCI Group

MRI was performed on a 1.5-tesla system (Signa Excite HD 12x; General Electric Medical Systems, Milwaukee, Wisc., USA). A three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections that covered the whole calvarium. The operating parameters were as follows: field of view = 240 mm, matrix = 256×256, 124×1.40 mm contiguous sections, TR = 12.55 ms, TE = 4.20 ms, and flip angle = 15°. The three-dimensional T1-weighted MRI data of the patients were analyzed with the voxel-based specific region analysis for AD (VSRAD) [10] (fig. 1). VSRAD contained the MRI data of normal control subjects with a wide age range and could automatically compare the gray matter intensities of the MRI data on a voxel-by-voxel basis between an aMCI patient and age-comparable normal control subjects after a series of steps including segmentation, anatomical standardization and smoothing using Statistical Parametric Mapping 2002 (SPM2; Wellcome Department of Imaging Neuroscience, London, UK). The Z-score is calculated on a voxel-by-voxel basis as (Is – Ic)/SD where Is and Ic are the gray matter intensities of an aMCI patient and the mean of normal control subjects, respectively, and SD is the standard deviation of the gray matter intensities of the normal control subjects. The region of interest was set to the entorhinal cortex in the VSRAD software. Atrophy corresponding to a Z-score >2.0 in the entorhinal cortex was used as a criterion for AD in the VSRAD method.