妄想が中心で，異常行動は手を膝の上でさする仕草を繰り返すという繰り返し行動であった．

【その後の経過】タップテスト後には無為や注意の散漫さが特に顕著に改善を認め，活気が生じるようになった．歩行のスピード，安定性も増し，1週間後の検査では以下のような成績の改善を認めた．MMSE 25/30点，FAB 13/18点，10m往復歩行試験40歩19.9秒．

X年6月腰椎腹腔シャント術を受け，症状の改善を得た．X+3年の検査成績は以下の通りであり，週1回のデイケアを継続し独居での日常生活動作はほぼ維持している．MMSE 24/30点，FAB 13/18点，10m往復歩行試験42歩21.1秒，NPI無為：頻度3，重症度1．

Ⅲ 診療のポイント

1．水頭症の症状と診断基準

二次性正常圧水頭症は，先行する疾患の存在と亜急性の症状経過，頭部形態画像検査により，早期に診断・治療に至る場合がほとんどである．

特発性正常圧水頭症の診断基準は，日本正常圧水頭症研究会作成の特発性正常圧水頭症診療ガイドラインにより，表1のように定められている．歩行障害は，歩幅の減少，足の挙上低下，歩隔の拡大が三大特徴で，ゆっくりで不安定となる．また，廃用性の筋力低下からさらに歩行障害が悪化する悪循環に陥ることも多い．排尿障害の特徴は，切迫性の頻尿・尿失禁である．認知機能障害は，注意機能の障害，思考速度・作業速度の低下，語想起能力の障害などの前頭葉機能関連障害，記憶障害を認める．記憶障害は自ら思い出す再生の障害と比較すると，その刺激があったか否かを判断する再認の障害は軽度である．

頭部CTやMRIでは，脳室の拡大を認める．また，高位円蓋部の脳溝とくも膜下腔の狭小化は特発性正常圧水頭症に特徴的である（図1）．一部の例には孤立性で卵形に拡大した脳溝の拡大がみられる．脳室周囲および深部白質変化が高頻度に認められ程度も強いことが多い．脳血流SPECTなどの脳機能画像においては，前頭葉および皮質下白質における機能低下を認めることが多い．

手術治療の適応は，多くの場合，腰椎穿刺による髄液排除後に症状改善の有無をみるタップテストの結果に基づいて決定する．髄液排除後早期に歩行の速度，歩幅

表1　日本正常圧水頭症研究会が作成した特発性正常圧水頭症診療ガイドラインによる特発性正常圧水頭症の診断基準

■ Possible iNPH

・必須項目

1. 60歳代以降に発症する.
2. 歩行障害，認知障害および尿失禁の1つ以上を認める.
3. 脳室の拡大（Evans index ＞ 0.3）を認める.
   Evans index：両側側脳室前角間最大幅/その部位における頭蓋内腔幅.
4. 髄液圧が200mmH_2O以下で，髄液の性状が正常である.
5. 他の神経学的あるいは非神経学的疾患によって上記臨床症状のすべてを説明しえない.
6. 脳室拡大をきたす明らかな先行疾患（くも膜下出血，髄膜炎，頭部外傷，先天性水頭症，中脳水道狭窄症など）がないか不明である.

・参考項目

1. 歩行は歩幅が狭く，すり足，不安定で，特に方向転換時に不安定性が増す.
2. 症状は緩徐進行性が多いが，一時的な進行停止や増悪など波状経過を認めることがある.
3. 他の神経変性疾患（パーキンソン病，アルツハイマー病など）や脳疾患（ラクナ梗塞など）の併存はありうるが，いずれも軽症にとどまる.
4. 高位円蓋部脳溝・くも膜下腔の狭小化およびシルビウス裂・脳底槽の拡大を認めることが多い.
5. PVL（periventricular lucency：脳室周囲低吸収域），PVH（periventricular hyperintensity：脳室周囲高信号域）の有無は問わない.
6. 脳血流検査は他の認知症性疾患との鑑別に役立つ.

■ Probable iNPH

1. Possible iNPHの必須項目を満たす.
2. 以下のいずれかを認める.
   a. CSFタップテスト（髄液排除試験）で症状の改善を認める.
   b. CSFドレナージテスト（髄液持続排除試験）で症状の改善を認める.
   c. 髄液流出抵抗値（Ro）測定やICPモニタリング（頭蓋内圧持続測定）で異常を示す.

■ Definite iNPH

シャント術施行後，症状の改善を認める.

の改善がみられることが多い．認知機能は前頭葉機能を中心に改善がみられる．しかし，タップテストは陰性予測率が低く，症状改善がみられなくてもシャント術が

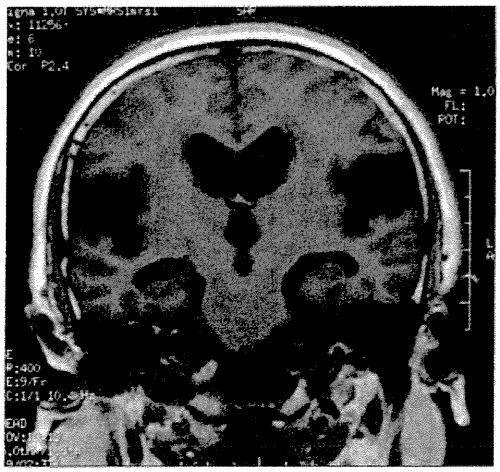

図1　特発性正常圧水頭症患者の頭部 MRI
（T1 強調画像）
高位円蓋部脳溝・くも膜下腔の狭小化，側脳室・シルビウス裂の拡大が認められる．

有効な偽陰性例がありうることには留意する必要がある．治療は脳室腹腔シャント，あるいは腰椎腹腔シャントが現在行われることが多い．三徴について，およそ80％で効果が確認されている[1]．

2．精神行動障害

正常圧水頭症の精神行動障害は，二次性と特発性で異なる可能性があるが，その違いについて多数例で検討された報告はない．二次性正常圧水頭症では，比較的急速な発症経過のためにその精神行動障害も捉えられやすい．せん妄や意識障害，幻覚妄想状態を呈することがある[2]．

特発性正常圧水頭症については多数例での検討で[3]，無為が70％と最も頻繁に認められ，次いで不安が25％，興奮が17％で認められている．アルツハイマー病患者における精神行動障害と比較するといずれの症状も頻度・重症度ともに同程度かより軽症であり，より重度となる症状は認めない．この脳内基盤について，正常圧水頭症患者において検討された報告はまだない．他の認知症における脳機能画像研究において，無為，不安，興奮などの精神行動障害が前頭葉および視床基底核など

の部位と関連していること，特発性正常圧水頭症の機能画像研究において同部位で機能低下が認められることから，前頭葉皮質あるいは基底核や視床といった中心部分から前頭葉-皮質下回路を通じた前頭葉皮質の機能低下が考えられるだろう．

特発性正常圧水頭症患者における精神行動障害のうち，特に問題となるのが無為である．患者はかなりの頻度で活動性，意欲，自発性が低下した，あるいは無気力になったと周囲から評される．また，歩行障害により一層活動性が低下する，という悪循環に陥りがちである．趣味や外出だけでなく，入浴，更衣，整容などの日常生活動作も自発的に行わなくなり周囲の促しが必要になることも少なくない．介護サービスを利用して規則的に出かけるように生活を組み立て，引きこもりを避けることが重要である．シャント術後には，意欲低下が改善することもあるが，手術の効果を十分に得るためには患者の体力に応じた範囲で活動的な毎日を送るための周囲の促しが必要である．

その他の精神行動障害は，他の認知症疾患と同様，不安感が根底にあることが少なくない．正常圧水頭症患者では認知機能障害が軽い段階で歩行や排尿などの身体障害を伴うことが多く，患者が病識を抱き不安になりやすい．介護者を探し回る，様々なことを何度も確認する，怒りっぽく頑固になる，周囲からの介入に拒否的となるといった行動の背景には多くの場合理由があるが，患者はその理由をうまく説明することができない．薬物治療が有効な場合もあるが，重要なことは，不安感を和らげるような安心感を与える声かけ，雰囲気で対応することである．

■文献

1) Hashimoto M, Ishikawa M, et al. Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study. Cerebrospinal Fluid Res. 2010; 7: 18.
2) Adams RD, Fisher CM, et al. Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure. a treatable syndrome. N Engl J Med. 1965; 273: 117-26.
3) Kito Y, Kazui H, et al. Neuropsychiatric symptoms in patients with idiopathic normal pressure hydrocephalus. Behav Neurol. 2009; 21: 165-74.

〈木藤友実子，數井裕光，武田雅俊〉

1762–6.
6. Iseki E, Marui W, Nihashi N, et al. Psychiatric symptoms typical of patients with dementia with Lewy bodies–similarity to those of levodopa-induced psychosis. Acta Neuropsychiatr 2002; 14: 237–41.
7. 井関栄三．Capgras 症候群．別冊日本臨牀 領域別症候群シリーズ No. 38，精神医学症候群 I，日本臨牀社，2006; p.117–9.
8. 大東祥孝．高齢者の妄想性同定錯誤症候群と視覚—カプグラ症候群を中心として．老年精医誌 2006; 17: 858–65.
9. Devinsky O. Delusional misidentifications and duplications: right brain lesions, left brain delusions. Neurology 2009; 72: 80–7.

Frégoli 症候群

概念

Frégoli 症候群は，普段会っている人物が，他の人物に変装していると確信する病態であり，1927 年に Courbon らの論文にて初めて紹介された[1]．当初は，この病態は錯覚と表現されていたが，現在は，Capgras 症候群や相互変身症候群，自己分身症候群とともに妄想性人物誤認症候群（delusional misidentification syndrome）のサブタイプとされている．Capgras 症候群については前項を参照のこと．

相互変身症候群とは，身近な人物が，他の人物に変身していると感じる症状を呈するが，Frégoli 症候群と違い，本来の人物の同一性が変質している．自己分身症候群とは，患者自身の分身が他人に変装しているという替え玉妄想のことで，ほかの症候群が他者を対象としている点と対照的である．Silva らは，この妄想性人物誤認症候群（原著では，“人物誤認症候群”とされている）のサブタイプに，自己に対する誤認である，リバースタイプを含めている[2]．**表 1** は，Silva らの提唱する分類である．括弧内に現在の疾患名の記載がある．このように同一性が変容する内容に注目すると各症候群の特徴をとらえやすい．

Vié は，Capgras 症候群と Frégoli 症候群に対し，前者が陰性ソジー（sosies negatives），後者が陽性ソジー（sosies positifs）と分類した[3]．ソジーとは，フランス語で瓜二つという意味であり，陰性ソジーとは，同一性の否定，陽性ソジーとは同一性の肯定，ということである．ちなみに，Frégoli とは，早変わりと変装を得意としたイタリア人役者，Leopoldo Frégoli（1867–1936）の名がその由来である．なお，「Frégoli 症候群」という表現であるが，「Frégoli 現象」や，「Frégoli の錯覚」，「Frégoli 症状」など，表現があり，独立した疾患単位として「症候群」とするか，さまざまな基礎疾患

表1　現在およびSilvaらが提唱中の人物誤認症候群の名称とその特徴

提唱中（現在）の名称	他者に対する		自己の	
	心理的変容妄想	身体的変容妄想	心理的変容妄想	身体的変容妄想
1. 他者の心理的同一性の変容症候群（Capgras症候群，替え玉症候群，詐称者症候群）	あり	なし	なし	なし
2. 他者の身体的同一性の変容症候群－type I（Frégoli症候群）	なし	あり	なし	なし
3. 他者の心理的および身体的同一性の変容症候群（相互変身症候群）	あり	あり	なし	なし
4. 他者の身体的同一性の変容症候群－type II（自己分身症候群）	なし	あり	なし	なし
5. 自己の心理的同一性の変容症候群（リバース自己分身症候群またはリバースCapgras 症候群）	なし	なし	あり	なし
6. 自己の身体的および心理的同一性の変容症候群（リバース相互変身症候群）	なし	なし	あり	あり
7. 自己の身体的同一性の変容症候群（リバースFrégoli症候群）	なし	なし	なし	あり
8. 無生物に対する同一性の変容症候群（Capgras症候群）	なし	なし	なし	なし

（Silva JA, 1990[2] より）

をもとに生じる「症状」と取るかという問題がある．上記のように，妄想性人物誤認症候群のサブタイプととらえるという概念にのっとり，本項では，「Frégoli 症候群」とする．

症状

1927 年に Courbon らが最初に記載したのは，若い統合失調症の女性患者の症例である．Sarah Bernhardt と Robine という 2 人の女優がさまざまの人物に変装し，患者自身を追跡するという訴えが認められた[1]．この患者は，迫害，誇大妄想を呈しており，この症状は迫害妄想，もしくは追跡妄想ととらえることができるのかもしれない．原著では錯覚としてとらえられており，Frégoli 症候群とされている．

このように，複数の人間が，特定の人物の変装であると確信する症状，つまり知覚すべき差異を知覚しないという症状が Frégoli 症候群の特徴である．この特定の人物は，患者にとって，妄想的な迫害者であることが多いが，必ずしも迫害者である必要はない．知っている人と知らない人を混同するという，1927 年の Courbon らの発表以前から報告のある症状との違いとして，Frégoli 症候群の患者は，知っている特定の人物が，繰り返し外見を変えると信じ，変装前と後で身体的類似点を指摘しないという点があげられる．また，精神的な同一性は保たれているが，身体的な同一性は変化しているという妄想を抱いていることも Frégoli 症候群の特徴である．

近年，自分の心のコピーが見知らぬ人の体に置かれていると信じる，主観的 Frégoli 症候群[4]や，自分が変装しているので，他人が見ても自

分だとはわからないと信じるという，リバース Frégoli 症候群（**表 1** 参照）[2,5]が定義されている．後者については，日本においても症例報告がなされている[6]．

診断

Frégoli 症候群の診断基準に明確なものはなく，人物誤認を主症状とし，前述のように，普段会っている人物が，他の人物に変装し，時に迫害を加えていると確信する症状を呈する疾患である．変装する他者と変装して現れた他者とは身体的類似性はなく，患者にとっては，この両者が身体的には異なると認識している．

鑑別すべき疾患として，上述の妄想性人物誤認症候群に含まれる Capgras 症候群，相互変身症候群，自己分身症候群があげられる．Capgras 症候群では知っている人物が他人の変装であると感じ，逆に Frégoli 症候群では複数の他人が，特定の知っている人物であると感じるという相違点がある．ただ，Capgras 症候群と Frégoli 症候群が合併するという報告もみられる．相互変身症候群との相違点は，上述のように，この疾患において，変身する側とされる側の身体類似性が知覚されるが，Frégoli 症候群においてはこの身体的類似性が知覚されないという点にある．自己分身症候群では，他人が患者の分身の変装であるとするという点に対し，Frégoli 症候群では，複数の他人が特定の他人の変装であるとするという点で異なっている．

脳梗塞をきたし，Frégoli 症候群を呈するという報告があるも，画像や神経生理検査上異常所見が認められないにもかかわらず，Frégoli 症候群を呈する報告もある．**図 1** に脳梗塞により Frégoli 症候群をきたした症例の頭部 MRI（magnetic resonance imaging: 磁気共鳴画像）を示す[7]．

症例 70 歳女性，間欠的完全心ブロックにより頻繁に失神発作をきたす患者（**図 1**）．

心臓ペースメーカーにより，失神発作は消失したが，発作が認められたころより，夫を，3 年前に亡くなった姉と誤認するようになり，夫を姉の名前で呼び，侵入者であるかのように言い争いをし，敵意を示した．電話で話をするときには，誤認はみられないため，誤認をきたすためには，視覚的な接触が必要であったという．また，自宅が賃貸の複製の物であると言ったり，自身の亡くなった家族が，家では見当たらないにもかかわらず，家にいると言ったりしていたという．意識障害はなく，てんかんも否定されていた．また，典型的な相貌失認（顔が顔であることはわかるが，その顔が誰であるかを同定することができない状態）は認められなかった．

この**図 1** と同様の部位の梗塞により Frégoli 症候群を呈した報告がほかにもみられるが，同様の部位の梗塞巣に加え，統合失調症が合併していたという報告もある．

Frégoli 症候群をきたした患者に認められる脳器質性障害が症状に影響はあるかもしれないが，この器質性障害のみでは不十分と考えられている．このために，画像検査が診断の助けとなるケースがあるが，むしろ画像上明らかな異常が認められないケースのほうが多いと考えられている．

Frégoli 症候群の患者には，人物誤認以外に妄想症状が認められる場合が多い．また，一方で，**図 1** のように，紡錘状顔領域（fusiform face area）が部分的に障害されている症例もみられる．紡錘状顔領域は顔の同定に重要な役

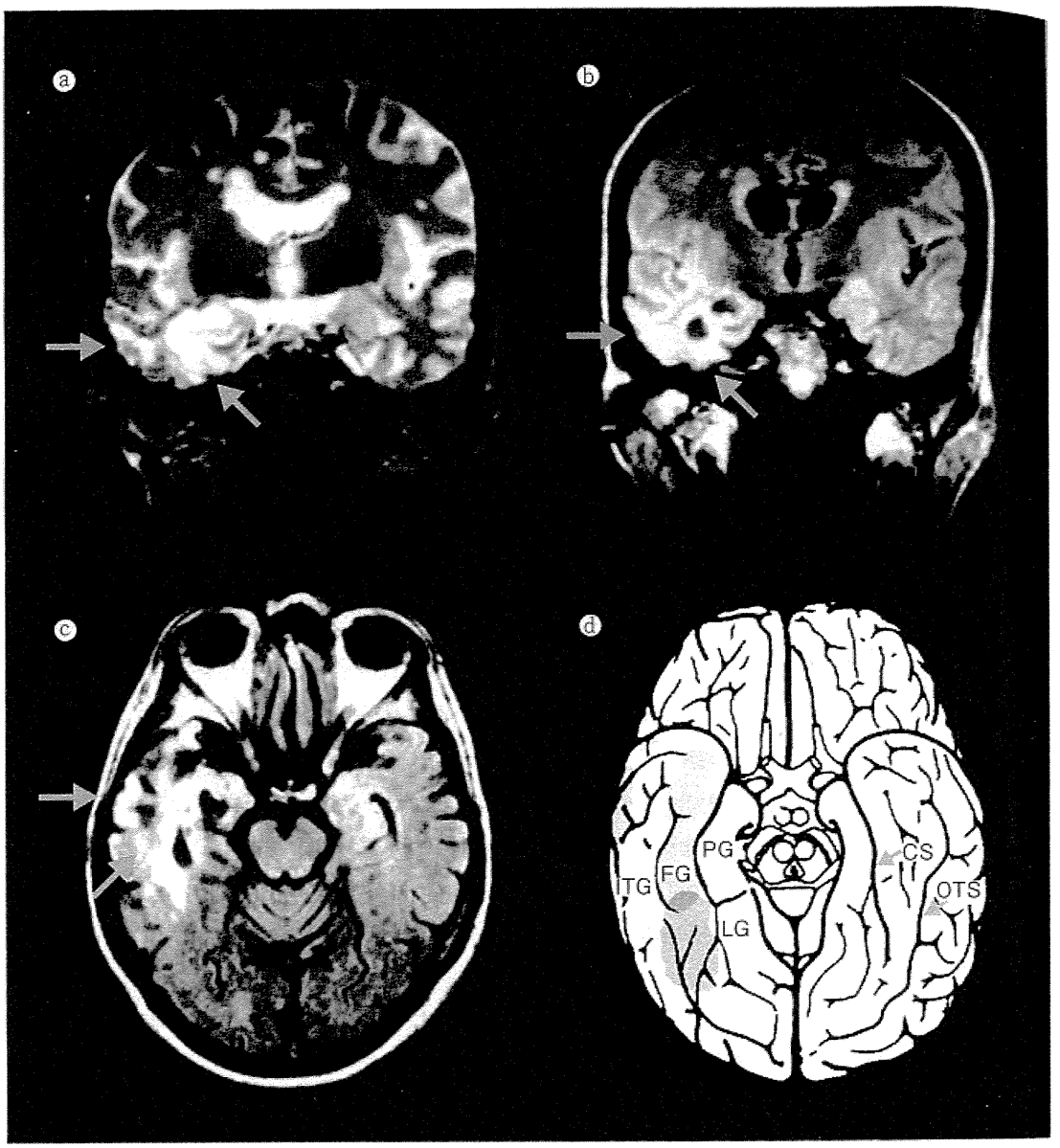

図1　Frégoli症候群を呈した患者のMRI画像

a：T2強調画像冠状断，b：プロトン密度強調画像冠状断，c：フレア画像水平断，d：障害部位の模式図．
障害部位はa～cでは矢印，dでは水色で示している．灰色の部位は紡錘状顔領域を示している．各図の右が右半球を示している．
CS (collateral sulcus: 側副溝)，FG (fusiform gyrus，紡錘状回)，
ITG (inferior temporal gyrus，下側頭回)，LG (lingual gyrus，舌状回)，
OTS (occipitotemporal sulcus，後頭側頭溝)，PG (parahippocampal gyrus，海馬傍回)．
(Hudson AH, et al, 2000[7] より)

割を果たす部位で[8]，紡錘状顔領域近傍に器質的病変を持つ症例に関しては，顔を見て誰であるか，という認知過程の脳内処理になんらかの障害があることが考えられる．Frégoli症候群の患者は，誤認した人物と，もともとの人物に類似点を見いださない（類似点がないから，変装していると訴える）という点から，感覚的知覚の障害が原因ではないという考え方もある．

これらの点から，Frégoli 症候群は，紡錘状回の病変を主とした，明らかな器質的病変を持つ Frégoli 症候群と，器質的病変が明らかではない Frégoli 症候群というように，病態が異なるサブタイプに分けることができるかもしれない．もっとも，画像検査上，明らかな異常が指摘されていなくても，脳内の情報処理になんらかの異常がある可能性を否定することはできない．Frégoli 症候群患者の，適切なタスク施行中の機能画像を検討することで，なんらかの障害が明らかになるかもしれない．

治療法

本疾患に対する，特異的治療法は報告されておらず，基本的には，対症療法が主体であり，抗精神病薬，抗うつ薬などが使用される．抗てんかん薬やリチウムも時に使用されている．また，電気痙攣療法に反応するという報告もある．当然ながら，原疾患の治療が優先される．

原疾患として，統合失調症あるいは妄想性障害が大半を占めるため，これらの疾患の治療が重要となる．また，てんかん性精神病，産褥期精神障害，大うつ病，躁うつ病，非定型精神病，Alzheimer 型認知症や Pick 病といった認知症，Down 症候群といった発育障害，上記のような脳梗塞や，頭部外傷などが原疾患となるという報告もある．また，上述のように，統合失調症患者が脳梗塞をきたし，Frégoli 症候群を呈したという報告もある．

精神療法についても，基本的に原因疾患の治療に準ずるが，治療には抵抗性を示し，精神療法の効果は一定していないといわれている．また，治療者が妄想の中に取り込まれ，治療困難となる可能性もあるが，その状況を逆に精神療法的に活用していくことも可能である，という考え方もある．

（吉山顕次，數井裕光，武田雅俊）

[引用文献]

1. Courbon P, Fail G. Syndrome d'illusion de Frégoli et schizophrénie. Bull Soc Clin Med Ment 1927; 15: 121–4.
2. Silva JA, Leong GB, Shaner AL. A classification system for misidentification syndrome. Psychopathology 1990; 23: 27–32.
3. Vié J. Un trouble de l'identification des personnes: l'illusion des sosies. Annales Médico-Psychologiques 1930; 88: 214–37.
4. Silva JA, Leong GB. A case of "subjective" Frégoli syndrome. J Psychiatry Neurosci 1991; 16: 103–5.
5. Singer SF. Capgras syndrome: the delusion of substitution. J Clin Psychiatry 1987; 48: 147–50.
6. 岩瀬利郎，豊嶋良一，加藤　温，ほか．自己の妄想性誤認．精神医 2000; 42(4): 363–71.
7. Hudson AH, Grace GM. Misidentification syndromes related to face specific area in the fusiform gyrus. J Neurol Neurosurg Psychiatry 2000; 69: 645–8.
8. Kanwisher N, Yovel G. The fusiform face area: a cortical region specialized for the perception of faces. Philos Trans R Soc Lond B Biol Sci 2006; 361: 2109–28.

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

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-

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

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

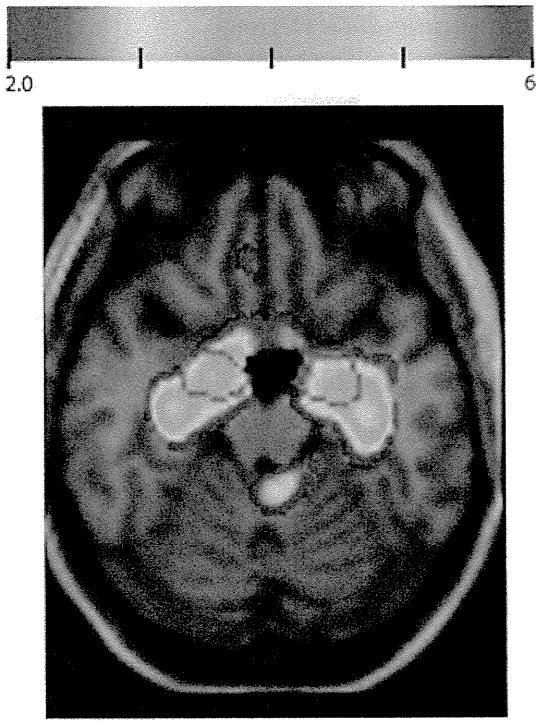

Fig. 1. Z-score map overlaid on an MRI template of a representative patient with AD-aMCI made with VSRAD. This patient was included in the study because of the presence of significant atrophy in the entorhinal cortices on MRI. Parts of the colored areas are in the areas circumscribed by purple lines, 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.

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

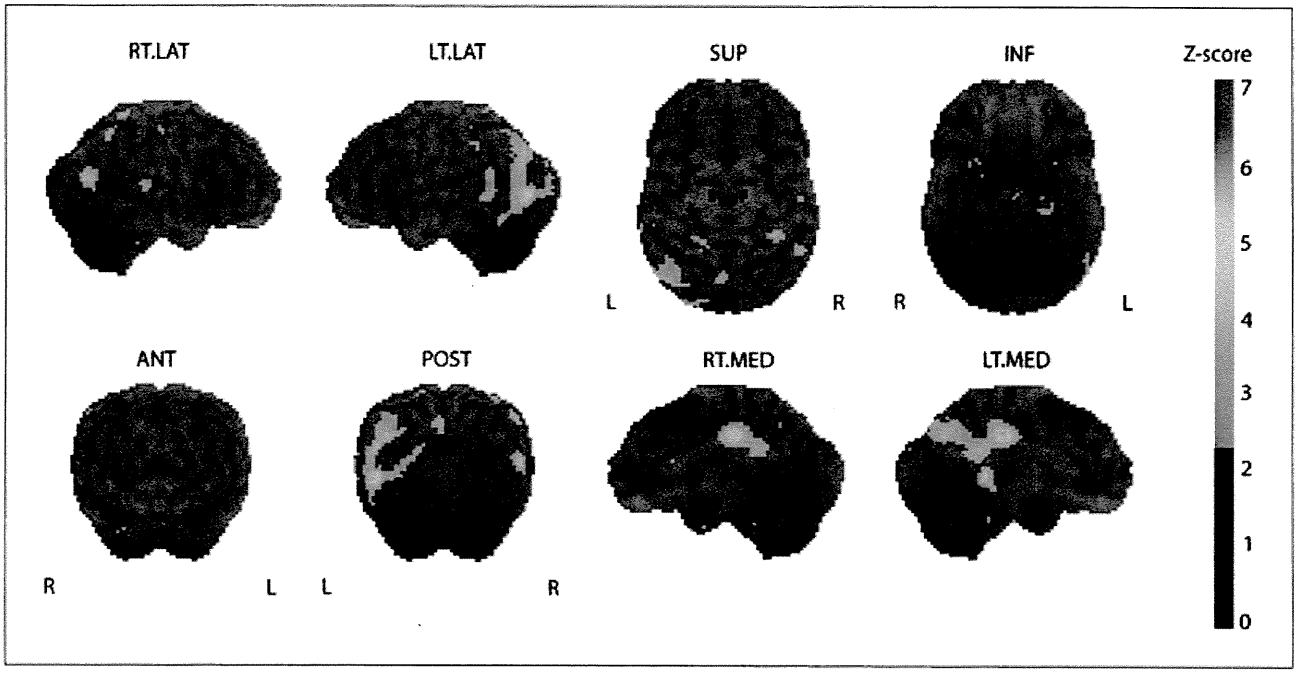

Fig. 2. Z-score map of a representative patient with AD-aMCI made with 3D-SSP. This patient was included in the study because of the presence of hypoperfusion in the PCC and precuneus on SPECT. Colored areas contain PCC and precuneus. Colored areas with significant rCBF reduction with a Z-score of >2.32 were overlaid on original surface images from eight views. Color bar indicates Z-score. RT.LAT = Right lateral; LT.LAT = left lateral; SUP = superior; INF = inferior; ANT = anterior; POST = posterior; RT.MED = right medial; LT.MED = left medial.

^{123}I-IMP-SPECT was performed with a SPECT scanner (SPECT-2000H; Hitachi Medical Co., Tokyo, Japan) and a four-head rotating gamma camera. SPECT data were analyzed using three-dimensional stereotactic surface projection (3D-SSP) software [11] (fig. 2). 3D-SSP contained ^{123}I-IMP-SPECT data of normal control subjects with a wide age range and could automatically compare the regional cerebral blood flow (rCBF) between an aMCI patient and age-comparable normal control subjects. The peak cortical values of the SPECT data were projected back and assigned to the original surface images from eight views on a pixel-by-pixel basis. Z-score was calculated on a pixel-by-pixel basis as (Is – Ic)/SD where Is and Ic are the rCBFs of an aMCI patient and the mean of normal control subjects, respectively, and SD is the standard deviation of the rCBF of the normal control subjects. Areas with a Z-score >2.32 (the significance level of the Z-score) were overlaid on original surface images from eight views. With the computer program Stereotactic Extraction Estimation (SEE) we determined which gyri included the regions with a Z-score >2.32 [12]. In SEE, the percentage of areas with a Z-score >2.32 in each gyrus was calculated and the percentage was called the 'extent'. The presence of areas of hypoperfusion, in which both the Z-score was >2.32 and the extent was >10% [13] in either the PCC or precuneus, was used as the inclusion criteria for AD in the aMCI stage.

Assessment of Cognitive Functions

The attention/concentration (AC) index in the WMS-R was used for measuring attention and working memory, the general memory (GM) index was used for recent memory, and the delayed recall (DR) index for delayed memory. For each index, the normal range is

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

Table 3. Cognitive impairment in ES and AD-aMC patients

Test/subtest	ES group	AD-aMCI group	p value
WMS-R			
GM index	80.0 ± 16.2	77.8 ± 10.5	0.58
AC index	91.0 ± 14.7	98.6 ± 11.7	0.046
DR index	76.3 ± 17.2	58.8 ± 8.6	<0.001
GM-DR	3.6 ± 10.7	19.9 ± 8.6	<0.001
WAIS-R			
Information	10.1 ± 3.7	11.2 ± 2.8	0.37
Digit symbol substitution	8.0 ± 2.7	11.6 ± 2.3	<0.001
Similarity	9.9 ± 3.2	12.5 ± 2.2	0.024
Picture completion	8.5 ± 4.0	11.2 ± 1.8	0.037
Block design	8.4 ± 2.7	11.5 ± 1.9	0.0018

between 80 and 120 and the mean index of normal subjects is 100. We also defined a new index equal to the GM index minus the DR index (GM-DR), which is a measure of the degree of forgetfulness.

For the WAIS-R, five test data were used in this study. Four of the five subtests were information, digit symbol substitution, similarities, and picture completion, which were selected according to the manual of the short form of the Japanese version of the WAIS-R [14]. Another was a block design to evaluate visuoconstructive function directly, as this dysfunction is a common symptom in AD patients. In each age-corrected score of the subtest, the normal range is between 7 and 13 and the mean score of normal subjects is 10.

Statistical Analyses

Age-corrected scores of both the WMS-R and the five subtests of the WAIS-R were compared between the two groups using a t test. The significance level was set at $p < 0.05$.

Results

Results of the WMS-R

In this study, the mean GM indices in the two groups were around the lower limit of the normal range, and the mean AC indices in ES and AD-aMCI were normal (table 3). The mean DR index of ES was slightly below the normal range, but the mean DR index of AD-aMCI appeared to be significantly lower. The GM indices of the two groups were comparable. The AC index was significantly lower and the DR index was significantly higher in ES than in AD-aMCI. The difference in the GM and DR scores (GM-DR), which is a measure of the degree of forgetfulness, was significantly lower in ES than in AD-aMCI.

Results of the Five Subtests of the WAIS-R

The mean scores of all the subtests of the WAIS-R in this study in both groups were within the normal range (table 3). The information scores of the two groups were comparable, but scores of the digit symbol substitution, similarity, picture completion, and block design subtests were significantly lower in ES than in AD-aMCI.

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

www.karger.com/dee

Discussion

We could not confirm that all AD-aMCI patients in this study developed AD to the dementia stage. However, we were able to select aMCI patients that had AD-specific findings on MRI or SPECT in this study. Pathological abnormalities related to AD, neurofibrillary tangles and neuronal loss, were found to be present in the entorhinal cortex of AD in aMCI stage [15], leading to atrophy in the region on MRI [16]. Because the entorhinal cortex is functionally connected to the PCC [17], the reduction of rCBF in the PCC was probably caused by the abnormal pathology in the entorhinal cortex. In addition, atrophy in the entorhinal cortex on MRI [18] and reduction of rCBF in the PCC and precuneus on SPECT [19] predict progression from MCI to AD. We used two reliable and user-independent statistical image-analyzing methods, VSRAD and 3D-SSP, to detect AD-specific abnormalities in the MR and SPECT images.

This is the first report to compare cognitive impairment between ES and AD-aMCI. The WMS-R GM indices of the two groups were comparable, indicating a similarity in the impairment of recent memory between the two groups. Some previous studies compared recent memory in ES and AD at the dementia stage. There is some disagreement on whether recent memory is better [20] or worse [21] in ES than in AD in the dementia stage. aMCI is a relatively homogeneous group with respect to memory impairment, because the definition of aMCI includes the degree of memory impairment. However, the severity of recent memory impairment could vary in patients with ES. The ES patients in this study were mild cases, because they could complete the WMS-R or WAIS-R, which are comprehensive tests, and the mean duration of their hospitalization was short. Thus, the recent memory tests in this study indicated that the recent memory scores of ES patients with mild cognitive impairment were comparable with those of AD-aMCI patients, and, therefore, that recent memory was not useful for distinguishing between ES and AD-aMCI.

The fact that the WMS-R GM indices were comparable in the ES and AD-aMCI groups indicates that the two groups in this study had similar degrees of impairment of recent memory. This narrows down the difference between the two groups to differences in other cognitive impairments, such as forgetfulness, and impairments of DR, attention, working memory and executive function. The WMS-R GM-DR scores were lower and the DR scores were higher in ES than in AD-aMCI, indicating that the degree of forgetfulness was less and DR was better in ES. On the other hand, the AC was lower in ES than in AD-aMCI, indicating that ES patients had more impaired attention and working memory than AD-aMCI patients. DR was found to be better in ES patients than in AD patients in the dementia stage [21], and forgetfulness did not increase in ES patients but increased in AD patients in the dementia stage [20]. The present study confirmed that memory after a short while was retained in ES but not in AD. In addition, we found that the retention in ES patients was better than in AD even at the aMCI stage, which should help to distinguish ES from AD in the very early stage.

The hippocampus, parahippocampus, and entorhinal cortex have traditionally been thought of as the principal structures responsible for the consolidation of short-term stores into long-term memory. Significant associations between hippocampal size and memory have not been observed in schizophrenia [22], although size reductions in the hippocampus have been reported in schizophrenia [2]. In addition, memory capabilities were similar to general intellectual abilities in ES [23]. Therefore, damage in the medial temporal lobe may not play an important role in memory impairment in schizophrenia. On the other hand, memory impairment in AD is inversely associated with hippocampal volume [24].

The ES group was more impaired on the digit symbol substitution, similarities, picture completion, and block design subtests of WAIS-R than the AD-aMCI group, and each subtest score in the ES group was below the mean of each score of the general population in this study. Although the block design subtest was used to evaluate visuoconstructive function in

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

this study, attention and executive function are required to perform the block design subtest [25]. Thus, these findings confirmed that attention, working memory, and executive function are impaired in ES. Previous studies reported that ES patients were impaired in the WAIS-R digit symbol substitution, similarities, picture completion, and block design subtests [21], and in attention, working memory, and executive function [20]. These studies also reported that impairment in these functions were comparable in ES and AD patients in the dementia stage. The differences in cognitive impairment that we found in ES and AD-aMCI deviate from those found in previous studies. This discrepancy may be due to differences in the severity of cognitive impairments in the AD-aMCI patients in this study compared to the AD patients in the dementia stage in previous studies.

Which region of the brain is responsible for the difference in attention, working memory, and executive function in the two groups? Impairments in cognitive function in patients with schizophrenia were found to be related to dysfunction of the prefrontal cortex (PFC) [26]. On the other hand, gray matter loss on MRI [27] and pathological abnormality [28] in the PFC were not observed in AD-aMCI, and gray matter loss on MRI was observed at the time of progression from aMCI to AD [27]. These results suggest that differences in impairment in attention, working memory, and executive function in the two groups probably reflect the difference in impairment in the PFC.

The WAIS-R information scores of the ES and AD-aMCI groups were comparable and within the normal range, being consistent with those of a previous study [29]. Semantic memory may be preserved in ES and AD-aMCI patients because they have less impairment in the inferior and anterior temporal lobe regions, which crucially contribute to semantic cognition [30].

There were some limitations in this study. First, approximately half of the patients in each group were not given the WAIS-R. Second, the ES patients in this study were younger than the AD-aMCI patients, and cognitive function in schizophrenia patients undergoes a marked decline after 65 years of age [8]. Third, we did not control the effects of medication on the cognitive test scores in ES patients. Most ES subjects in this study had received atypical antipsychotic drugs, which might improve cognitive function [31]. These issues should be taken into consideration before the findings are generalized.

In this study, DR and forgetfulness were less impaired in ES than in AD-aMCI, while attention, working memory, and executive function were more impaired in ES than in AD-aMCI. The results of this study should help clinicians to distinguish patients with ES from patients with AD-aMCI and might also give us some clues for distinguishing ES combined with AD-aMCI from ES alone. The next step is to clarify the difference in the characteristics of cognitive impairment in ES combined with AD-aMCI compared to ES alone.

Acknowledgments

Funding for this study was provided by Research Grants for Research on Dementia (H21-Dementia-General-003 and H22-Dementia-General-003) and Grants-in-Aid (H19-kokoro-002) from the Japanese Ministry of Health, Labor and Welfare, and by the Japanese Ministry of Education, Culture, Sports, Science and Technology (17191211, 18689030, 18023045, 20591402, and 21591514).

Disclosure Statement

The authors declare that they have no conflict of interest.

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

References

1 Van Os J, Kapur S: Schizophrenia. Lancet 2009;374:635–645.
2 Hirayasu Y, Shenton ME, Salisbury DF, Dickey CC, Fischer IA, Mazzoni P, Kisler T, Arakaki H, Kwon JS, Anderson JE, Yurgelun-Todd D, Tohen M, McCarley RW: Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. Am J Psychiatry 1998;155:1384–1391.
3 Goldman AL, Pezawas L, Mattay VS, Fischl B, Verchinski BA, Chen Q, Weinberger DR, Meyer-Lindenberg A: Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. Arch Gen Psychiatry 2009;66:467–477.
4 Laakso MP, Soininen H, Partanen K, Helkala EL, Hartikainen P, Vainio P, Hallikainen M, Hanninen T, Riekkinen PJ Sr: Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. J Neural Transm Park Dis Dement Sect 1995;9:73–86.
5 Dickinson D, Ramsey ME, Gold JM: Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry 2007;64:532–542.
6 Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, Wetterholm AL, Haglund A, Zhang R, Schindler R: 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord 2006;21:353–363.
7 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
8 Friedman JI, Harvey PD, Coleman T, Moriarty PJ, Bowie C, Parrella M, White L, Adler D, Davis KL: Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: a comparison with Alzheimer's disease and normal aging. Am J Psychiatry 2001;158:1441–1448.
9 Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–186.
10 Hirata Y, Matsuda H, Nemoto K, Ohnishi T, Hirao K, Yamashita F, Asada T, Iwabuchi S, Samejima H: Voxel-based morphometry to discriminate early Alzheimer's disease from controls. Neurosci Lett 2005;382:269–274.
11 Minoshima S, Berger KL, Lee KS, Mintun MA: An automated method for rotational correction and centering of three-dimensional functional brain images. J Nucl Med 1992;33:1579–1585.
12 Mizumura S, Kumita S, Cho K, Ishihara M, Nakajo H, Toba M, Kumazaki T: Development of quantitative analysis method for stereotactic brain image: assessment of reduced accumulation in extent and severity using anatomical segmentation. Ann Nucl Med 2003;17:289–295.
13 Kazui H, Ishii R, Yoshida T, Ikezawa K, Takaya M, Tokunaga H, Tanaka T, Takeda M: Neuroimaging studies in patients with Charles Bonnet syndrome. Psychogeriatrics 2009;9:77–84.
14 Misawa Y: Manual of the Short Form of the Japanese Version of the WAIS-R (in Japanese). Tokyo, Nihon Bunka Kagakusha, 1993.
15 Gomez-Isla T, Price JL, McKeel DW Jr, Morris JC, Growdon JH, Hyman BT: Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J Neurosci 1996;16:4491–4500.
16 Killiany RJ, Gomez-Isla T, Moss M, Kikinis R, Sandor T, Jolesz F, Tanzi R, Jones K, Hyman BT, Albert MS: Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol 2000;47:430–439.
17 Mosconi L, Pupi A, De Cristofaro MT, Fayyaz M, Sorbi S, Herholz K: Functional interactions of the entorhinal cortex: an 18F-FDG PET study on normal aging and Alzheimer's disease. J Nucl Med 2004;45:382–392.
18 Killiany RJ, Hyman BT, Gomez-Isla T, Moss MB, Kikinis R, Jolesz F, Tanzi R, Jones K, Albert MS: MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology 2002;58:1188–1196.
19 Kogure D, Matsuda H, Ohnishi T, Asada T, Uno M, Kunihiro T, Nakano S, Takasaki M: Longitudinal evaluation of early Alzheimer's disease using brain perfusion SPECT. J Nucl Med 2000;41:1155–1162.
20 Heaton R, Paulsen JS, McAdams LA, Kuck J, Zisook S, Braff D, Harris J, Jeste DV: Neuropsychological deficits in schizophrenics. Relationship to age, chronicity, and dementia. Arch Gen Psychiatry 1994;51:469–476.

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

21 Zakzanis KK, Andrikopoulos J, Young DA, Campbell Z, Sethian T: Neuropsychological differentiation of late-onset schizophrenia and dementia of the Alzheimer's type. Appl Neuropsychol 2003;10:105–114.
22 Torres IJ, Flashman LA, O'Leary DS, Swayze V 2nd, Andreasen NC: Lack of an association between delayed memory and hippocampal and temporal lobe size in patients with schizophrenia and healthy controls. Biol Psychiatry 1997;42:1087–1096.
23 Hawkins KA: Memory deficits in patients with schizophrenia: preliminary data from the Wechsler Memory Scale-Third Edition support earlier findings. J Psychiatry Neurosci 1999;24:341–347.
24 Mori E, Yoneda Y, Yamashita H, Hirono N, Ikeda M, Yamadori A: Medial temporal structures relate to memory impairment in Alzheimer's disease: an MRI volumetric study. J Neurol Neurosurg Psychiatry 1997;63:214–221.
25 Chase TN, Fedio P, Foster NL, Brooks R, Di Chiro G, Mansi L: Wechsler Adult Intelligence Scale performance. Cortical localization by fluorodeoxyglucose F18-positron emission tomography. Arch Neurol 1984;41:1244–1247.
26 Ikezawa K, Iwase M, Ishii R, Azechi M, Canuet L, Ohi K, Yasuda Y, Iike N, Kurimoto R, Takahashi H, Nakahachi T, Sekiyama R, Yoshida T, Kazui H, Hashimoto R, Takeda M: Impaired regional hemodynamic response in schizophrenia during multiple prefrontal activation tasks: a two-channel near-infrared spectroscopy study. Schizophr Res 2009;108:93–103.
27 Whitwell JL, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, Petersen RC, Jack CR Jr: 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. Brain 2007;130:1777–1786.
28 Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, Jicha GA, Ivnik RJ, Smith GE, Tangalos EG, Braak H, Kokmen E: Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol 2006;63:665–672.
29 Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR: Is schizophrenia a syndrome of accelerated aging? Schizophr Bull 2008;34:1024–1032.
30 Visser M, Embleton KV, Jefferies E, Parker GJ, Ralph MA: The inferior, anterior temporal lobes and semantic memory clarified: novel evidence from distortion-corrected FMRI. Neuropsychologia 2010;48:1689–1696.
31 Houthoofd SA, Morrens M, Sabbe BG: Cognitive and psychomotor effects of risperidone in schizophrenia and schizoaffective disorder. Clin Ther 2008;30:1565–1589.