普及を促進してゆこうとする姿勢は注目に値する．

2．脳神経疾患への応用

脳血管障害

酸素-15標識ガスを用いたPTEは血流量，酸素消費，酸素摂取率，血液量を定量測定することができるので，脳の各部位における虚血のステージを判定することができる[27]．脳循環動態のゴールデンスタンダードとなる検査法である．これにもとづいて，血行再建術の適応判定を行うことができ，予後の推定にも役立つ[28]．この検査は保険適用が認められている．しかし検査のできる施設が限られ，緊急検査が困難であるため，脳血管障害の急性期治療における役割は，MRIや脳血流SPECTに比べるときわめて限定的である．実際には，長期間にわたって進行するモヤモヤ病や，動脈硬化性内頸動脈閉塞症などにおける慢性脳虚血の評価が適応の中心となる．血行再建術の適応となりにくい高齢者での意義は限られている．

てんかん

現在，難治性てんかんの焦点検索に対してFDG-PET検査の保険適用が認められている．

特に内側型側頭葉てんかんの手術側の決定に有用である[29]．筆者らは中枢性ベンゾジアゼピン受容体リガンドである^{11}C-フルマゼニルによるPETを合わせて施行することで，焦点診断の精度を高めている[30]．外科的治療の適応となりにくい高齢者における役割は，やはり限定的である．

高次脳機能障害

脳血管障害や変性疾患による失語症，失認，失行などの高次脳機能障害は老年者に多く見られる病態であり，その正確な診断は，予後判定や治療計画の上で重要である．MRIやX線CTによる形態画像にもとづく病巣診断だけで高次脳機能障害のメカニズムを理解することはしばしば困難である．その理由は，器質的病変のある部位のみでなく，線維連絡のある形態的には異常のない部位の機能低下も症状に関連している場合があるからである．また，萎縮の目立たない変性疾患の合併が症状を修飾している場合もある．機能画像であるPETによる脳血流，代謝画像を合わせて評価することにより，正確な病態の理解に至ることが多い[31)~34)]．病態診断だけでなく，治療による回復をモニターしたり，機能回復のメカニズムを知る上で，PETによる脳血流代謝測定は，高齢者の高次脳機能障害診療において非常に重要な意義を持っている．

認知症

超高齢化社会を目前に控え，認知症に対するアプローチは緊急の課題である．特に認知症の原因疾患として最も頻度の高いアルツハイマー病の診断，治療法の開発が重要な社会適要請となっている．アセチルコリンエステラーゼ阻害剤の登場がアルツハイマー病の早期治療の可能性を切り開いたのに続いて，ワクチン療法やβ・γセクレターゼ阻害剤など根本的な治療法の開発が精力的に進められている．このような状況の中で，認知症診療と研究におけるPETの役割も大きく変わろうとしている．現在の認知症診断は，病歴聴取，内科・神経学的診察，認知機能検査，尿血液検査，X線CT，MRI，脳血流SPECTなどによって行われている．認知症診断にPETの保険適用は認められておらず，そのため，数多いわが国のPET施設の中でも認知症診断の目的でPET検査を施行しているところはごく限られているのが現状である．しかし，認知症の診断におけるFDG-PETの感度，特異性は他のどの検査法よりも優れていることは既によく知られている[35)36)]．米国ではアルツハイマー病と前頭側頭型認知症の鑑別診断に対して，FDG-PETの保険適用が認められている．更に昨年，Medicareはアルツハイマー病の早期診断についても，prospective studyの対象者に対しては保険適用を認めると発表した．わが国では，アルツハイマー病の早期診断に対するFDG-PETの有用性を検証するための治験（SEAD-Japan）が進行中である[37]．癌診断を目的として全国に多くのPET施設がオープンし，製薬会社によるFDG供給体制も確立した現在，アルツハイマー病診断をPETで行うインフラは既に整っている．わが国における保険適用の見通しはまだないが，米国における状況と治療薬の開発による早期診断へのニーズの高まりが呼び水となるかもしれない．

アルツハイマー病におけるFDG-PETの特徴は，最初期には後部帯状回から楔前部，楔部にいたる内側部分の代謝低下が見られ[38]，進行すると頭頂葉，側頭葉の外側部皮質の代謝低下がみられる（図4）．前頭側頭型認知症，レビー小体型認知症などの疾患ではそれぞれ疾患に特徴的な代謝低下パターンを呈するので，鑑別診断に役立つ[39)~41)]．早期診断を行うためには，正常加齢による変化からのごくわずかな偏位を検出しなければならず，従来の視覚的読影のみでは軽微な変化に対する感度が必ずしも高くない．また，診断医による判断の違いも問題となる．そこで，正常画像のデータベースを元に，画像後と統計処理を行い，有意な低下のある画素を自動的に検出する統計画像法が診断の補助に用いられている．3DSSPやSPMといったソフトウェアを用いる方法が現在普及している[42)~44)]．どの施設でも同じ感度でアルツハ

イマー病診断を行うことができるようにするためには，信頼性のある正常データベースの構築と，画像の施設間差・機種間差がどの程度診断に影響するかの吟味が必要であり，重要な課題となっている．

FDG-PET による診断に加え，近年注目を集めているのが PET によるアミロイドイメージングである[45]．アルツハイマー病の原因は，異常なタンパク質であるアミロイドβ（Aβ）が脳に蓄積し，凝集して老人斑を形成し，シナプス機能の阻害，神経細胞死を引き起こすためと考えられている．アミロイドイメージングはこの Aβ に親和性のある放射性薬剤を用いてアミロイドの蓄積を直接画像化する技術であり，アルツハイマー病の病態を特異的に表現するバイオマーカとして期待されている．ピッツバーグ大学で Klunk と Mathis らによって開発された Pittsburgh Compound-B（PIB）が現在最も広く用いられている[46]．これまでの経験で，アミロイドの蓄積が発症前に既にプラトーに達していることが示唆されている（図 5）．アミロイドイメージングによりアルツハイマー病の超早期診断，特異診断が可能になり，治療対象の選択，治療効果の判定に重要な役割を果たすであろう．

PET などの臨床検査を用いて認知症の早期診断，病態診断や介入治療の研究を行うためには，小規模な単発的な研究では信頼できる結果を得ることが難しく，ある程度の大きさの対照群を長期間観察する前向きフォローアップ研究の手法が必要となる．軽度認知障害やパーキンソン病を対象とし，統一したプロトコールで臨床症状，認知機能検査，MRI や PET による画像，髄液バイオマーカなどを定期的に評価して追跡し，剖検の得られた症例においては病理学的検索結果も加えた症例を多施設で蓄積し，それぞれの疾患の自然経過を明らかにしようとする試みが行われている[47][48]．アルツハイマー病に焦点を絞って画像データの蓄積を行おうとする大規模な多施設研究も北米を中心に始まり[49]，わが国でも間もなく開始される見通しである[50]．

パーキンソン病と関連疾患

パーキンソン病とその関連疾患（多系統萎縮症，進行性核上性麻痺，皮質基底核変性症など）は，運動障害を引き起こし，老年者の転倒や寝たきりの原因となる重要な疾患である．また，認知症とも関連の深い病態である．パーキンソン病は黒質緻密帯に存在し線条体に投射する

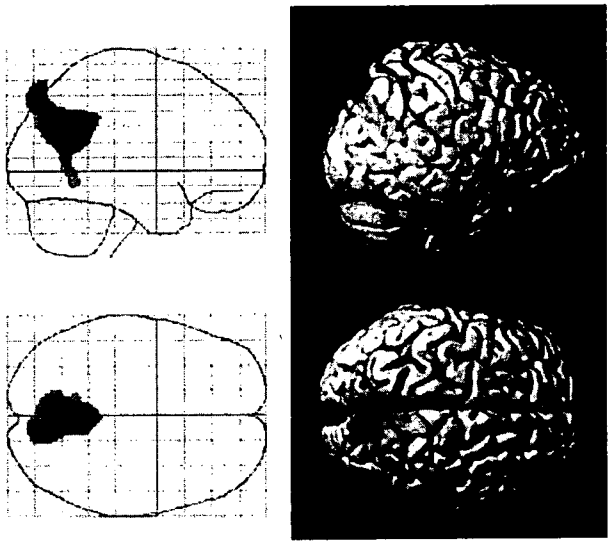

図 4　軽度認知障害の FDG-PET 統計画像診断
78 歳男性，物忘れを自覚して来院，日常生活に支障はない．脳 FDG-PET 画像は視覚的には異常がなかったが，SPM による統計画像法で正常データベースと比較すると，後部帯状回から楔前部，楔部にかけて有意な代謝低下（$p < 0.01$）が検出され，アルツハイマー病の初期と診断された．

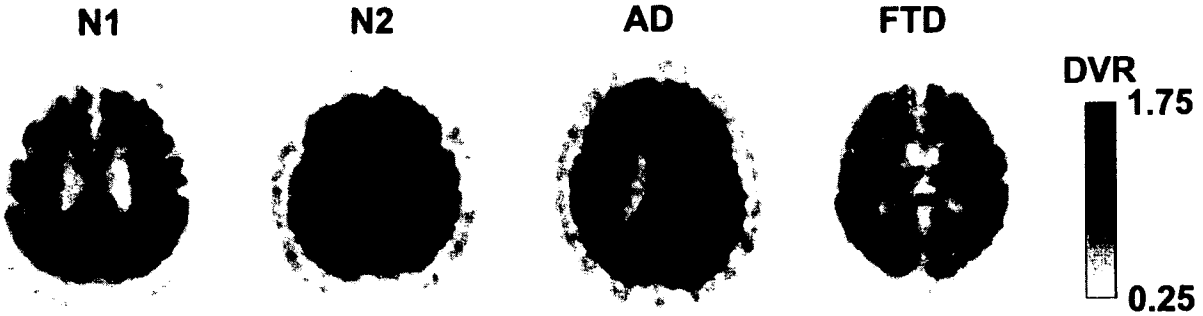

図 5　Pittsburgh Compound-B（PIB）によるアミロイドイメージング
N1：健常者，N2：物忘れを訴えたが認知機能正常者，AD：アルツハイマー病，FTD：前頭側頭型認知症．N1，FTD では PIB の集積は認めないが，AD と N2 では高度な集積が見られた．N2 はごく初期のアルツハイマー病と考えられる．

ドパミンニューロンの変性により生じるドパミン作用不足が病態の中核であると考えられている．線条体におけるドパミン節前・節後機能はPETにより評価することができ，パーキンソン病の早期診断，鑑別診断に有用である．また，PETで測定したドパミン節前機能をマーカとして，どのような治療が神経保護作用を有するかを明らかにするための治験が行われている[51]．また，パーキンソン病関連疾患の鑑別には，ドパミン系のPETだけでなく，FDG-PETによる脳代謝画像を組み合わせることが有用である[52)53)]．

精神疾患

高齢者に特有の問題ではないが，うつや依存症，摂食障害などの行動学的問題を，脳における様々な神経伝達系の機能バランス障害として理解し，治療しようとするアプローチが盛んに行われている．様々な神経伝達機能を測定することのできるPETは，神経精神薬理学的仮説にもとづく病態研究，治療薬開発，治療効果判定に，欠くことのできないツールとして重要な役割を果たして行くであろう．

リハビリテーション

PETは機能画像であるので，機能状況を良く反映する．高次脳機能障害の項でも述べたように，ベッドサイドでは正確な病態診断に基づく機能回復の予後予測，治療計画が求められている．また，回復の背景にある脳の可塑性のメカニズムの研究[54)]や，可塑性を促進する治療法の有効性の検証[55)]などがPETを用いて行われている．

3. 心疾患への応用

虚血性心疾患で，心筋のバイアビリティ診断が必要な場合にFDG-PETの保険適用が認められる．ただし，通常の心筋シンチグラフィで判定困難な例に限られており，現実的な運用は限られている．米国では，医療経済効果の高い検査法として心臓核医学が普及したいきさつがあり，包括医療化の中で，心臓PET検査が見直されてくる可能性もある．

老化・老年病研究への応用

1. 新しい標識薬剤の開発

生体における分子レベルのメカニズムとその変化を画像化することを目指す分子イメージング技術開発への大がかりなてこ入れが行われている．その中で腫瘍診断，認知症診断，精神神経薬理学領域をターゲットとしたトレーサ開発が精力的に行われているが，動脈硬化やメタボリックシンドロームなどの生活習慣病，骨粗鬆症など高齢者医療にとって重要な領域で，PETを用いることができるような，新しいトレーサ開発も期待される．

2. 老化研究におけるPET

高齢者における病態診断は，正常老化を理解することが前提となる．PETなどの非侵襲的検査法は，繰り返し，経時的観察が可能であり，生体機能の老化プロセスを横断的，縦断的に検討するのにふさわしい方法である．脳の形態や循環代謝動態，神経伝達が加齢とともにどのように変化するか，多くの研究がある[56)~58)]．このアプローチは脳に限らず様々な臓器を対象にすることができる．

3. 治療薬開発への応用

中枢神経作動薬の効果判定は，従来行動学的指標によって評価されてきたが，PETを用いて脳血流や代謝，神経伝達の変化を直接測定すれば，対象の数を10分の1に減らすことができるといわれている．動物レベルでの薬効判定，ヒトの治験における投与量設定や薬効判定にPETを用いることで，新薬開発のコストと時間を大幅に減らすことができると期待されている．GLP対応で実験や治験を受託するPET施設も国内外で増えている．

4. 遺伝子発現とPET

アルツハイマー病やパーキンソン病などは，遺伝子の異常が特定されている家族性症例の研究を糸口に，分子レベルでのメカニズムが解明されてきた．アルツハイマー病やパーキンソン病はPETを用いることで発症前診断が可能と考えられており，その病態発現のプロセスをPETにより観察する試みが行われている[59)60)]．小動物を高解像度で撮影する動物PETカメラも開発されて

図6　FDG-PETによる歩行筋の画像化
FDG投与前後で被験者に歩行運動を行わせると，筋肉の使用強度に応じてFDGが取り込まれるので，歩行時の筋肉の使い方がわかる．リハビリや歩行訓練の効果判定に用いることができる．

おり，様々なトレーサを駆使することで，モデル動物における遺伝子発現の経時的モニターを可能にする強力なツールとして期待される．

5. 疾患予防介入・健康増進と PET

高齢者の疾病対策は，生活習慣病や認知症を含め，発症した疾病に対する治療と介護の環境を整えるのではなく，疾病の発症そのものを積極な介入により予防して行こうという方向に大きくパラダイムシフトしている．医学的見地からは見切り発車と考えられるところもあり，このような介入法の有効性を科学的に裏付けるエビデンスの蓄積が現在求められている．PET を用いて，介入が脳機能[61]や歩行機能[62]の維持改善に役立つかを客観的に検証する試みが行われている（図 6）．

6. テーラーメード医療と PET

個々の患者の体質や環境に合わせて治療法を考えるテーラーメード医療にとっても PET は有力なツールとなりうる．正確な病態診断を行うことができるだけでなく，薬物の臓器への移行をモニターすれば，治療法の適応判定や最適な投与量設定が可能になる[63]．この領域も応用範囲がきわめて広範であり，今後の発展が期待される．

おわりに

高齢者における PET の意義について概説した．今後，腫瘍診断と認知症診断の領域で，PET が高齢者の日常診療に普及してゆくと思われる．また，PET は老化，老年病研究のツールとしても多くの可能性を持っていることを強調した．

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＜シンポジウム 7—5＞認知症「治療を展望した Alzheimer 病の早期診断—MCI から初期 Alzheimer 病へ」

アミロイドイメージング

石井　賢二

臨床神経学　第47巻　第 11 号　別刷

(2007年 11 月 1 日発行)

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アミロイドイメージング

石井　賢二

（臨床神経，47：915—917，2007）
Key words：アルツハイマー病，アミロイド，PET，早期診断，サロゲートマーカ

アミロイドイメージングの概要

アミロイド仮説を軸としてアルツハイマー病（AD）の病態理解と診断・治療法研究が進められている中，PET によるアミロイドイメージングは病態の進展を特異的に感度良くとらえることのできるサロゲートマーカの切り札として期待されている．この数年で非侵襲的にβアミロイドの沈着を定量的に画像化できる放射性プローブが UCLA[1]やピッツバーグ大学[2]，トロント大学・ペンシルバニア大学[3][4]により相次いで実用化された．これらは，アミロイド親和性のある物質として従来から組織染色に利用されていたコンゴーレッドやチオフラビンを出発点とする類似化合物から，βアミロイドに対する特異的結合性を有し，かつ血液-脳関門を容易に通過する物質をクリーニングすることで開発された（Fig. 1）．集積の特異性や画質の点ではピッツバーグ大学の開発した Pittsburgh Compound-B（PIB）が現在の所もっとも有望視され，2007 年 5 月現在では国内の 3 施設（放医研，大阪市大，都老人研）をふくむ世界の十数施設で臨床評価が進行中である．またわが国では BF 研究所で開発されたプローブ（BF コンパウンド）の臨床が東北大学を中心に始まった[5]．MRI や optical imaging による老人斑の画像化も試みられているが，実用化にはまだしばらく時間がかかりそうである．

本講演では，現在もっとも普及しエビデンスが豊富な PIB について自験例を提示しつつ，アミロイドイメージングの診断，病態理解におよぼすインパクトについて論じる．

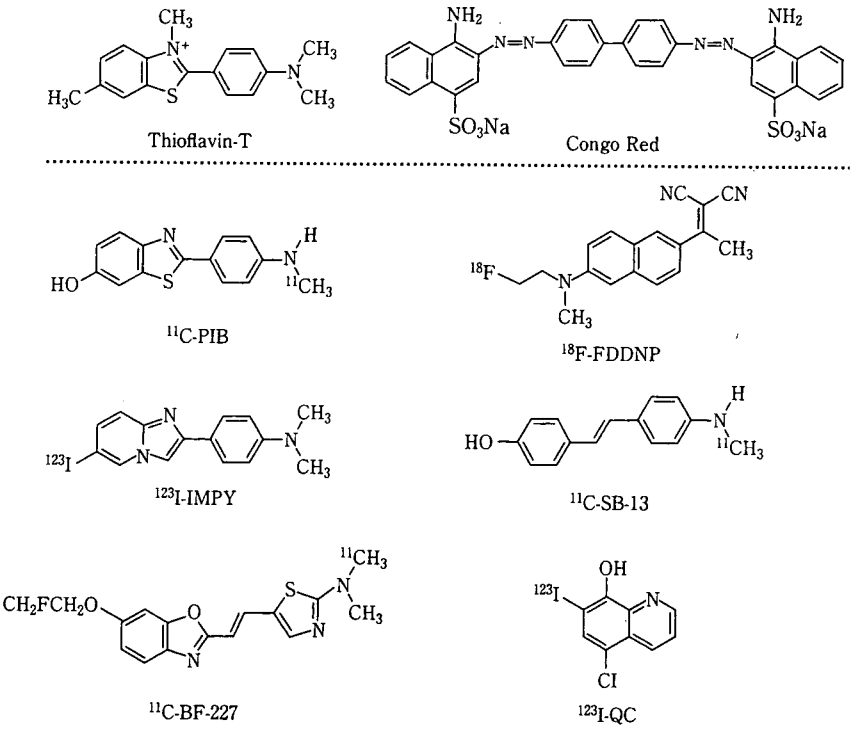

Fig. 1　臨床使用が報告された PET または SPECT 用アミロイドプローブ
大別して Congo-red 類似化合物と tioflavin-T 類似化合物の系統がある．

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（受付日：2007 年 5 月 16 日）

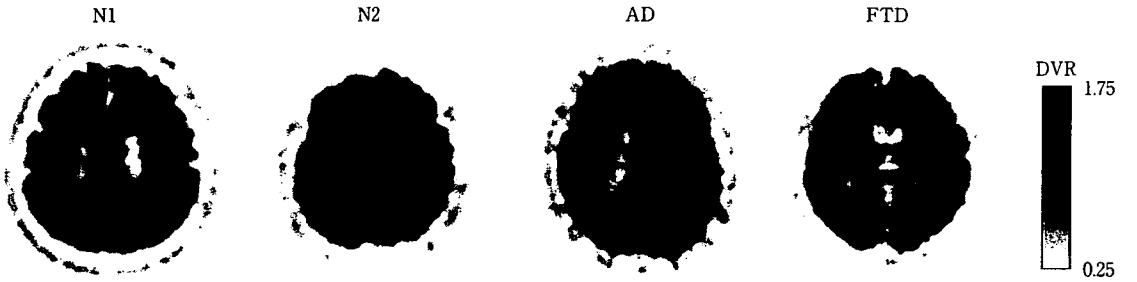

Fig. 2　PIB-PETの自験例
N1（78歳男性），N2（85歳女性）は認知機能正常者．AD（77歳男性）はアルツハイマー病，FTD（62歳男性）は前頭側頭型認知症と臨床診断されている症例．ADでは前頭葉，楔前部，頭頂葉に高度なPIB集積があり，N2も同様のパターンの集積がある．FTDではPIB集積はみとめられなかった．N2は発症前診断されたADなのかどうか，今後の検討が必要である．

AD進展のサロゲートマーカとして

PIB-PETにより生きた脳におけるアミロイド蓄積がいつおこり，どのように進展するかについてのダイナミックなイメージがしだいに明らかになりつつある．軽度認知障害（MCI）におけるPIB集積パターンはADと同等か正常かのほぼ2極に分かれることを，ピッツバーグ大グループが最初に報告して注目を集めた[6]．ADに移行するMCIにおいては，アミロイド集積はすでにほぼプラトーに達しており，その後認知機能低下，血流代謝低下，脳萎縮が進行していくことを支持するデータがつぎつぎと出されている．MCIにおけるPIB-PET陽性率はどの報告でも60%程度で，これはMCIからADにconvertすると予想されている比率とほぼ一致する．

それでは，アミロイドの蓄積はいつから始まるのか．ワシントン大学（セントルイス）グループは，健常者41例に対しPIB-PETを施行し，うち4例でアルツハイマー病患者と同等のPIB集積をみとめた．これらのPIB陽性健常者では髄液$A\beta_{42}$が低下していた[7]．ピッツバーグ大学のグループも，健常群の中にPIB集積をみとめ，2年の経過で集積が増加し，なお認知機能は正常である被験者が存在すると報告している．メルボルン大学のグループも，健常者の中でPIB集積があり，フォロー中にMCIに移行した症例を報告している[8]．われわれもpre-MCI（CDR：0，MMSE：30）というべき状態で，高度なPIB集積をみとめFDGは正常所見の症例を経験し，追跡している（Fig. 2）．これらは今後の経過観察がなお必要であるが，PIBによるADの発症前診断の可能性を示す有力なデータであり，現在開発が進められているセクレターゼ阻害剤，アミロイド凝集阻害剤，アミロイドワクチンなどによる根本的治療との兼ね合いで，治療対象者の選択や，治療開始時期をどのように設定するのが望ましいか，今後その根拠となる前方視的データ蓄積が必要となる．北米でスタートしたAlzheimer's Disease Neuroimaging Initiative（ADNI）は診断法や治療法を開発する上で基礎となるデータであるADの自然経過を明らかにしようとする試みであり，わが国でも今年度から多施設による症例の蓄積が始められようとしている．

AD患者脳において明らかになったPIB集積のパターンは，前頭葉や後部帯状回がもっとも高く，線条体にも高い集積があるなど，従来の病理学的知見から推定され，常識として受け容れられていたADにおける老人斑の分布・進展モデルとはややことなる．この差異に注目することは病態の理解に非常に重要な示唆を与えてくれるであろう．PIB撮影例で病理との対比をおこなった報告はまだきわめて少数であり，症例の蓄積が必要である．

非AD疾患の診断と病態理解への適用

PET用アミロイドイメージング製剤としてPIBに先行したFDDNPが神経原線維変化（NFT）やプリオンアミロイドにも集積して特異性がないのに対し，FTDやCJD症例ではPIB集積はみられないことが報告されている．一方，レビー小体型認知症（DLB）では6～8割の症例でPIBの集積がみとめられている．ADとDLBともに，脳へのPIB集積は髄液中の$A\beta_{42}$濃度と逆相関の関係がみられること，in vitroの検討ではPIBはアルファシヌクレインやレビー小体に集積しないことから，DLBにおけるPIB集積はβアミロイドの蓄積を反映していると考えられている．更に，やはりβアミロイドの集積であるアミロイドアンギオパチーにも，程度や分布はADとややことなるもののPIBが集積することが報告されている．したがって，PIB集積はアルツハイマー病に特異的な画像診断法というよりは，脳組織におけるβアミロイド蓄積を評価するツールであると理解すべきであろう[9]．

このような理解に基づくと，アミロイドイメージングはアルツハイマー病の進展評価だけでなく，非アルツハイマー型認知症疾患の診断や病態理解にも大きなインパクトを与えることを述べておきたい．嗜銀顆粒性認知症や神経原線維変化優位性認知症などの老年者タウオパチーと呼ばれる一群の疾患は，臨床診断基準が確立されていないが，高齢者認知症の背景疾患としてアルツハイマー病に匹敵する頻度があることが連続剖検から確かめられている．われわれの検討でも，MCI

やアルツハイマー病うたがいとして臨床的に評価されている症例の中に，比較的進行が緩徐な健忘症状を呈し，深部側頭葉の高度な萎縮と代謝低下はあるがPIBの集積がない症例が存在し，老年者タウオパチーに相当する症例と考えている．臨床的な特徴の抽出と病理との対応症例の蓄積が重要な課題である．

おわりに

アミロイドイメージングの登場により，ADの早期診断から治療にいたる戦略が具体性を持って想定できるようになった．アミロイド蓄積の時期やその速度，発症との関連，診断の感度特異性など，その裏付けとなるデータが，今後ADNIなどのプロジェクトを通してえられてゆくと期待される．アミロイドβだけでなく，タウやアルファシヌクレインの蓄積を画像化するプローブの実用化も待たれる．認知症のない社会の実現にむけ，今後の研究の発展が期待される．

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Abstract

Amyloid imaging

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Amyloid imaging has recently emerged as a non-invasive neuroimaging technique to visualize the accumulation of amyloid-beta in living brain. Several modalities such as PET, SPECT, MRI, and optical imaging has been adopted for this purpose, the nuclear medicine technique of PET firstly put it to practical use because of its high sensitivity. Among many radioligand tracers proposed, Pittsburgh Compound-B (PIB) has successfully spread over the world as a standard amyloid imaging probe. Several lines of evidence from PIB-PET study have suggest that the accumulation of amyloid beta start during the preclinical stage of Alzheimer's disease (AD) and reaches plateau phase before or during the MCI stage. Therefore, the amyloid imaging may be useful as a biomarker of AD, not only for the very early specific diagnosis, but also for the monitoring the therapeutic effect with agents that reduce the accumulation of amyloid-beta in the brains of AD. The amyloid imaging technique is also useful to differentiate non-AD type degenerative disorders such as argiophilic grain dementia and neurofibrillary tangle dominant dementia, which are cumulatively called as tauopathies. In order to evaluate its diagnostic power, and pathophysiological significance of accumulation, further prospective study and pathology-PET comparison are essential.

(Clin Neurol, 47: 915—917, 2007)

Key words: Alzheimer's disease, amyloid, PET, early diagnosis, surrogate marker

Clinical/Scientific Notes

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ISOLATED FACIAL AND BULBAR PARESIS: A PERSISTENT MANIFESTATION OF NEONATAL MYASTHENIA GRAVIS

The differential diagnosis of congenital facial and bulbar paresis in toddlers includes myotonic dystrophy, congenital myopathies, congenital myasthenic syndromes, Moebius syndrome, and 22q11 deletion syndrome. We report on a 6-year-old boy with a history of neonatal hypotonia and severe feeding difficulties followed by persistent isolated facial and bulbar paresis of unknown etiology. When he was 3 years old, his mother was diagnosed with myasthenia gravis (MG) and we concluded that his condition was a rare and persistent manifestation of neonatal MG.

Case reports. The boy presented with neonatal hypotonia and poor spontaneous movements without respiratory distress or arthrogryposis. Sucking was absent; he was tube fed for 2 weeks. His tone progressively improved; he walked at 13 months but prominent facial weakness and feeding difficulties persisted. He was referred to us at 30 months with severe dysarthria. There was no complaint of fatigue or weakness. At age 5 his weight was 10 kg (<p3), his height was 86 cm (p3), and he had no ptosis or ophthalmoplegia. He had facial weakness, a constantly open mouth, and a high arched palate (figure). The soft palate was immobile and speech was extremely nasal and dysarthric. The tongue was normal. He could not whistle or blow his cheeks. Limb muscle strength and DTRs were normal. Serum CK, quadriceps muscle biopsy, and brain MRI were all normal. Genetic studies for myotonic dystrophy and 22q11 deletion syndrome were negative.

The mother was diagnosed with MG when the child was 3 years old: she reported mild bulbar symptoms and fatigue on exertion for the last 4 years with an exacerbation during pregnancy and just before the diagnosis. Acetylcholine receptor (AChR) antibodies (AB) were positive at 99.9 nmol/L (normal <0.2). Anti muscle-specific kinase (MuSK) were negative.

We concluded that the boy had had neonatal MG with transient hypotonia and weakness but persistent facial involvement. AChR AB were negative when he was 3 years old. Oral pyridostigmine 10 mg TID for 6 months brought no improvement in his speech or swallowing ability. At age 6, pharyngoplasty was done to improve his speech: during anesthesia, right facial and spinal accessory nerves repetitive nerve stimulation with trains of 10 shocks at 3 Hz showed no decrement. The amplitudes of the compound muscle action potentials (CMAPs) were abnormally low when the facial nerve was stimulated (0.2 mV, normal >2 mV).

The boy had two older asymptomatic twin sisters; the mother had no further pregnancies.

Discussion. Neonatal MG occurs in 10 to 20% of babies of mothers with MG; the majority will have transient neonatal weakness while a minority will have arthrogryposis multiplex congenita (AMC).[1] We found reports on only three children with persistent facial involvement in the literature.[2,3] Two had neonatal MG with transient generalized weakness and respiratory distress

Figure Facial weakness in the proband at age 4 years: Showing his teeth (A), puffing his cheeks (B), and closing his eyes (C)

followed by persistent facial diplegia.[2] Feeding difficulties lasting 15 months were present in one and MG was unrecognized at birth in one of the two mothers. The third child had no neonatal symptoms but he had a "hypotonic face with a high arched palate . . ." and later required speech therapy and pharyngoplasty for "unclear speech."[3] His mother was asymptomatic but subsequently had five pregnancies with fatal AMC. She had high levels of anti-AChR AB which selectively inhibited fetal AChR function with no effect on adult AChR.[3,4] It was thought that the mother developed anti-AChR AB in the latter part of her first pregnancy. The same hypothesis can be made for the child presented here, as an earlier in utero exposure to the AB might have led to more severe disease. The mother of our patient had no further pregnancies but would be at high risk of fetal complications.[3,5] What makes the facial and bulbar musculature susceptible to lasting injury when the motor end-plate is exposed to anti-AChR AB in utero is unknown. The time at which the antibodies first cross the placenta might play an important role. The recorded low CMAPs evoked from the facial muscles and the absence of decrement are compatible with a myogenic process.

Prominent facial and bulbar involvement is also encountered in patients with MG with anti-MuSK AB, but the disease mechanism is also unclear.[6,7]

Neonatal MG should be included in the differential diagnosis of a child with neonatal hypotonia with or without persistent congenital facial and bulbar paresis. The mother should have a thorough neurologic examination as well as an anti-AChR AB titer even if she is thought to be asymptomatic and even if several years have passed since the child's birth. An accurate diagnosis is important given the risk of AMC in further pregnancies.[2]

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Disclosure: The authors report no conflicts of interest.

Received February 5, 2007. Accepted in final form May 22, 2007.

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ACKNOWLEDGMENT

The authors thank Dr. Bruno Eymard from the Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France, for input on this case and critical reading of the manuscript.

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CLINICOPATHOLOGIC STUDY OF A *SNCA* GENE DUPLICATION PATIENT WITH PARKINSON DISEASE AND DEMENTIA

There is evidence that α-synuclein gene (*SNCA*) point mutations and gene multiplications play a pivotal role in the development of Lewy bodies (LBs) and Lewy neuritic (LN) pathology. Dysregulation of the production/degradation of the α-synuclein protein, a major component of LBs and LNs, is speculated to result in its accumulation and produce the neuropathological features of *SNCA*-related neurodegeneration.[1]

The identification of *SNCA* multiplications in families with parkinsonism suggests that *SNCA* gene dosage may play a role in the onset of Parkinson disease (PD).[2] Most patients with *SNCA* triplication develop cognitive and autonomic dysfunction in early stage of the disease.[3,4] However, three families with *SNCA* duplication have been reported with symptoms more reminiscent of typical PD.[5,6] Interestingly, a recent study reported that one triplication (a Swedish-American pedigree) and one duplication pedigree have a common ancestor.[7] As a common mechanism of multiplications, the area including the *SNCA-MMRN1* locus could play a role in multiple copy numbers. Another multiplication family has been reported also to have the rearrangement change in

the same region indicating the *SNCA-MMRN1* locus may be fragile.[2,5-7]

With regard to clinical aspects, patients with *SNCA* duplication tend to have milder symptoms compared to those with triplication.[5-7] The onset of disease in *SNCA* duplication patients occurs approximately 15 years later (50 years of age) than that of *SNCA* triplication families (35 years of age). These features suggest that differences in genetic copy numbers could influence the clinical features of PD.

Recently, we identified two families of Japanese origin with *SNCA* duplications.[8] One patient from Family B (named as B-1) developed severe parkinsonism and dementia. These findings indicate that *SNCA* duplication also causes PD with dementia (PDD). Three copies of the locus *SNCA-MMRN1* were identified in the two duplication families. The length of this region was less than 400 kb and smaller than that reported for the previous, *SNCA* multiplication families. The patient (B-1) died of pneumonia in 2006. Herein we assessed the clinical aspects and autopsy findings and propose a relationship between *SNCA* duplication and dementia.

Clinical findings. The patient was a Japanese man. At age 47 years, the first symptom presented was a gradual-onset clumsiness of the hands. Neurologic examination showed mild masked face, hypophonic dysarthria, resting tremor of the left hand, reduced arms swing and slowing of alternating movements of the left hand, and moderate rigidity of the neck and left-side extremities. Administration of levodopa improved the parkinsonism, including tremor, bradykinesia, and rigidity. Some loss of memory and visual hallucinations appeared at age 60, and at age 61, the Mini-Mental State Examination score was 17/30. At 62 years of age, he developed fluctuation of consciousness and showed resting tremor of the left hand, moderate masked facial expression, severe hypophonic dysarthria and dysphagia, and symmetric rigidity of the neck and extremities. Brain MRI at that stage showed medial temporal lobe atrophy on both sides and widening of Sylvian fissures. A 99m-TcECD SPECT study showed hypoperfusion predominantly on both frontotemporal lobes and occipital lobes. The H/M ratio of MIBG myocardial scintigraphy was reduced (early: 1.20, late: 1.09). Polysomnography revealed abnormal behaviors in REM sleep. The apolipoprotein E phenotype was ε3/3. He became bedridden at 64 years of age and died of aspiration pneumonia at age 67 years. Consent was obtained from the relatives for autopsy examination.

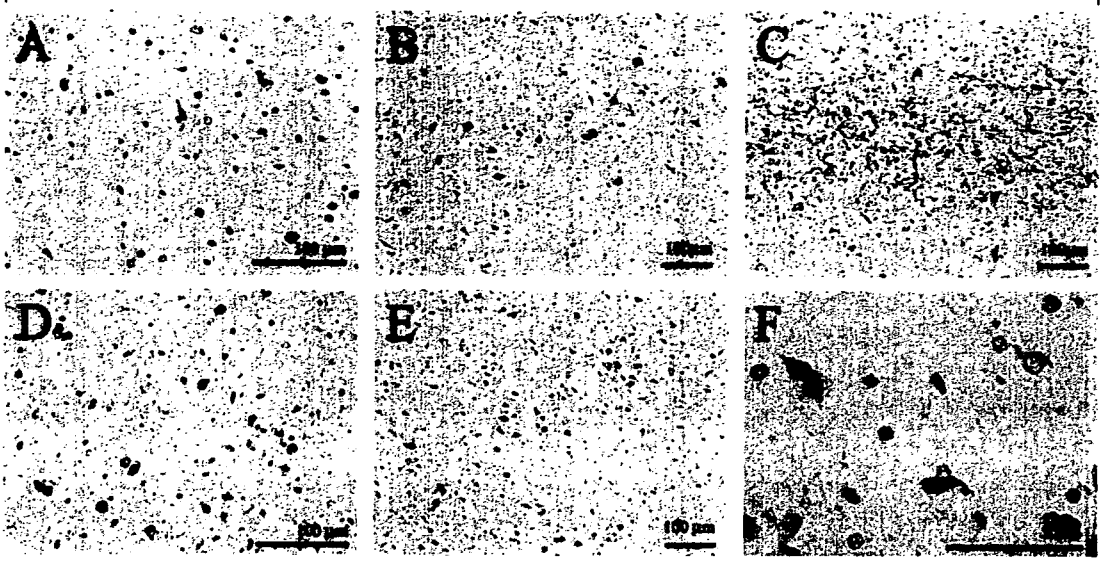
Pathologic methods. Autopsy was performed within 3 hours after death. The left side of the brain was dissected out and stored at −70 °C. The right side of the brain was fixed in neutral buffered formalin. Sections of representative areas were stained with hematoxylin-eosin (H-E), Kluever-Barrera (KB), and immunohistochemical methods. For immunohistochemical staining, we used the following primary antibodies: rabbit anti-α-synuclein polyclonal antibody (Chemicon, Temecula, CA), monoclonal antibody to α-synuclein (human, 15G7, Alexis Biochemicals, Switzerland), anti-phosphorylated α-synuclein (monoclonal, Wako , Osaka, Japan), anti-phosphorylated tau (AT8, monoclonal, Fitzgerald, Concord, MA), and anti-amyloid β 1-42 (polyclonal, IBL, Takasaki, Japan). Lewy-related pathology was assessed according to the third Consensus Guidelines for Dementia with Lewy bodies (DLB).[9]

Neuropathologic findings. The brain weight was 1350 g. Macroscopic examination showed mild frontal lobe atrophy, and severe depigmentation of the substantia nigra and locus ceruleus. Microscopically, severe loss of melanin-containing neurons and gliosis were seen in the substantia nigra pars compacta. Severe neuronal loss was also noted in the locus ceruleus, dorsal motor nucleus of the vagus nerve and the amygdala, and the nucleus basalis of Meynert (nbM). Other findings included moderate neuronal loss with gliosis in the CA2/3 in the hippocampus (figure, A), and LBs in the substantia nigra, locus ceruleus, nbM, small neurons of the oculomotor nuclei, and dorsal motor neurons of the dorsal motor nucleus of vagus nerve. Some pale bodies were present in the remaining neurons of the substantia nigra.

Immunocytochemical staining for α-synuclein showed many LBs in the cerebral cortex, and especially in the entorhinal, insular, and cingulate cortices, and in nbM, amygdala, hippocampus, and brainstem (figure, B and D). In addition, we observed an abundance of LNs in the CA2 of the hippocampus (figure, C) and many Lewy dots in the transentorhinal cortex, which were particularly evident in sections immunostained with anti-phosphorylated α-synuclein antibody (figure, E). There was a moderate deposit of LBs in the sympathetic ganglia. In contrast, only a few LBs were noted in the substantia nigra and locus ceruleus. No striking features were detected in putamen, globus pallidus, and thalamus.

Oligodendrocytes with inclusions, which were shown by α-synuclein immunohistochemistry,

Figure Hematoxylin-eosin (H-E) and anti-phosphorylated α-synuclein results



(A) Severe neuronal loss in the CA3 region of the hippocampus. H-E staining. (B) An abundance of Lewy bodies (LBs) in the CA3 region of the hippocampus. Anti-phosphorylated α-synuclein staining. (C) An abundance of Lewy neurites in the CA2 region of the hippocampus. Anti-phosphorylated α-synuclein staining. (D) Many anti-α-synuclein-positive LBs in the amygdala. Anti-phosphorylated α-synuclein staining. (E) Many LBs in transentorhinal. Anti-phosphorylated α-synuclein staining. (F) Many appearances of oligodendrocytes with inclusions in the substantia nigra. Anti-phosphorylated α-synuclein staining.

were noted in the substantia nigra and other regions including the cingulate gyrus, amygdala, nbM, transentorhinal cortex, substantia nigra, pontine base, cerebellar white matter, and spinal cord (figure, F).

The extent of Lewy-related pathology was graded as diffuse neocortical type based on the pathologic classification of DLB[9] (table). Immunohistochemical staining for tau identified few neurofibrillary tangles in the transentorhinal cortex and amygdala as well as a few diffuse-type senile plaques in the parietal cortex.

Molecular analysis. *SNCA* duplication in Family B was confirmed and refined with copy number variation analysis using the Affymetrix 250K SNP array (Affymetrix, Santa Clara, CA), quantitative real time PCR (ABI prism 7700 sequence detector; Applied Biosystems, Foster City, CA), and FISH analysis as reported previously.[7,8]

Discussion. Recent studies have reported the presence of abundant LBs in the cerebral cortex of PDD, indicating that these neuropathologic features are similar to those of DLB.[10,11] The pathologic features of *SNCA* triplication families (Iowa and Swedish-American pedigree) have been described previously.[3,4,12] These findings indicated that severe neuronal loss and gliosis in the hippocampus (CA2/3) is a striking feature. Severe degeneration of the substantia nigra and locus ceruleus was also common and numerous LBs appeared throughout the brain including the cerebral cortex. The pathology was described as diffuse LB disease, which corresponds to the designation of diffuse neocortical type in DLB. In our patient with *SNCA* duplication, the distribution of LBs also corresponds to diffuse neocortical type based on the pathologic classification of DLB.[9] Oligodendrocytes with inclusions were also seen in our patient, similar to those patients with *SNCA* triplication.[12,13]

These findings suggest that the pathomechanism of *SNCA-MMRN1* multiplication could have a common pathway in families, based on the

Table Pattern of Lewy-related pathology in brainstem, limbic, and neocortical regions

Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cingulate	Temporal	Frontal	Parietal
3	3	2	3	3	3	3	2	2	0

IX = 9th cranial nerve nucleus; X = 10th cranial nerve nucleus; LC = locus ceruleus; SN = substantia nigra; nbM = nucleus basalis of Meynert; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe.

overexpression of the α-synuclein protein in the blood and brain of patients with triplication.[3,14] This gain of function mechanism causing abundant α-synuclein expression could explain the presence of LBs in many areas of the brain. In advanced stages, patients with *SNCA* multiplication perhaps tend to display abundant LBs, in association with severe parkinsonism and dementia, with the pathologic features relating directly to the clinical symptoms.

Apart from the copy number of *SNCA*, other factors such as aging are inextricably involved in the age at onset of dementia. However, the important message is that not only *SNCA* triplication but also *SNCA* duplication could induce severe dementia. Thus, multiple copies of the *SNCA-MMRN1* region are an important cause of parkinsonism with dementia.

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Disclosure: The authors report no conflicts of interest.

Received December 31, 2006. Accepted in final form May 25, 2007.

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ACKNOWLEDGMENT

The authors thank Masako Itaya for preparing and staining the brain tissue samples.

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Journal of the Neurological Sciences 266 (2008) 9–12

Journal of the Neurological Sciences

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Localization of CKII β subunits in Lewy bodies of Parkinson's disease

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Received 2 March 2007; received in revised form 24 July 2007; accepted 14 August 2007
Available online 19 September 2007

Abstract

We reported previously that phosphorylation by casein kinase II (CKII) regulates the interaction between alpha-synuclein and its binding partner synphilin-1, and that both CKII alpha and beta subunits co-localize with alpha-synuclein in cytoplasmic inclusions in transfected cells. In this study, we extended these observations to the brains of patients with Parkinson's disease (PD) and examined whether CKII subunits are present in Lewy bodies. Immunohistochemical studies on PD brains harboring Lewy bodies revealed a positive stain for CKII beta but not for CKII alpha. In addition, CKII beta subunits co-localized with alpha-synuclein in most Lewy bodies. These findings suggest that CKII beta subunits may play a role in the formation of intracytoplasmic inclusions in human alpha-synucleinopathies either through phosphorylation events or through a separate mechanism linked to the beta subunit itself.

Keywords: Lewy bodies; Casein kinase II; α-Synuclein; Phosphorylation; Parkinson's disease

1. Introduction

The accumulation of pathogenic proteins in inclusions is characteristic of several neurodegenerative disorders [1–4]. Although the molecular mechanisms that lead to the formation of these inclusions are not completely understood, elucidating their constituents can provide clues about the pathogenesis of the diseases and about the genesis of the inclusions. For example, α-synuclein, which is an abundant constituent of Lewy bodies [5,6], appears to have an important role in the pathogenesis of Parkinson's disease (PD) and other α-synucleinopathies. In addition, synphilin-1, which interacts with α-synuclein and induces the formation of cytoplasmic inclusion in cultured cells, is another component of Lewy bodies in the brains of patients with PD [7,8].

Casein kinase II (CKII) is a ubiquitous seryl/threonyl protein kinase which has a vital role in eukaryotic cells [9,10]. The holoenzyme is generally composed of two catalytic (α and/or α′) and two regulatory (β) subunits. α-Synuclein has several consensus sites for this kinase and is strongly phosphorylated by CKII, particularly at serine 129 [11]. CamKII, on the other hand, has only a weak phosphorylating activity on α-synuclein *in vitro* [11]. We reported previously that CKII mediated phosphorylation of

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doi:10.1016/j.jns.2007.08.027

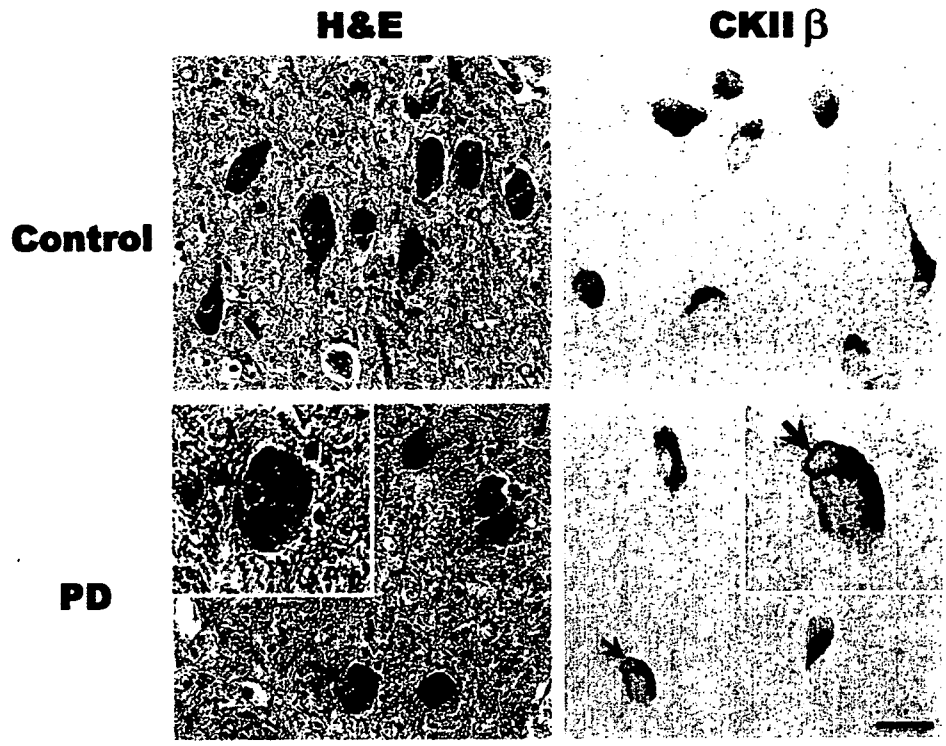

Fig. 1. CKII β subunits are present in Lewy bodies of PD patients. Sections through the substantia nigra pars compacta (SN) were stained with hematoxylin and eosin (H&E) showing an eosinophilic Lewy body (arrow). The SN tissues of PD cases were stained immunohistochemically with anti-CKII β antibody. Three dopaminergic neurons with neuromelanin are seen in the field. The peripheral rim of an LB was predominantly stained with anti-CKII β antibody (*arrow*) in one neuron. The two other neurons in the field are Lewy body negative. The boxed neuron is shown at higher power magnification (*inset*). Omission of primary antibody gave no signal. Scale bar = 50 μm.

synphilin-1 regulates α-synuclein/synphilin-1 interaction and thereby inclusion body formation [12]. We found that both CKII α and β subunits are present in cytoplasmic inclusions of cells transfected with these two protein partners. Therefore, CKII-induced phosphorylation may have an important role in the formation of inclusions in the context of α-synuclein and synphilin-1 interaction. However, the pathological relevance of this kinase to human α-synucleinopathies is unknown.

2. Subjects and methods

Postmortem human brain specimens were obtained from three clinically and pathologically confirmed cases of PD (2 females, 1 male; ages 76–83 years), and two control cases (both 73 year old males). These samples were obtained from the Research Resource Network through the National Center of Neurology and Psychiatry Musashi Hospital (Japan). This study was approved by the Scientific-Ethical Review Board of Ajou University Medical Center (AJIRB-CRO-06-056) and by the National Center of Neurology and Psychiatry (18-2-1).

Postmortem brain tissues from the midbrains of patients with PD and controls were fixed in formaldehyde and embedded in paraffin. Six-micrometer sections from substantia nigra (SN) were sectioned for immunohistochemistry. Tissue sections were deparaffinized in xylene followed by a descending concentration of ethanol solutions. Brain sections were permeabilized with 0.2% Triton X-100 in PBS for 30 min, and washed with PBS. Endogenous peroxidase was blocked by incubating sections in 3% hydrogen peroxide solution for 5 min, and then rinsed in PBS. The sections were then immunostained with mouse monoclonal antibodies to casein kinase II α and β-subunits (1:500, Calbiochem), which were characterized in our previous report [12]. Immunoreactivity was visualized with the avidin–biotin complex detection system (Vector Laboratories) according to the manufacturer's instructions, using 3,3-diaminobenzidine (DAB) as the chromogen. The sections were counterstained with Harris hematoxylin solution (ThermoShandon). To assess the co-localization of CKII subunits and α-synuclein, a double-labeling immunofluorescence study was performed on selected sections with a combination of monoclonal anti-CKII β subunit (1:500, Calbiochem) and polyclonal anti-α-synuclein (1:200, Sigma) antibodies. CKII β was visualized by anti-mouse IgG coupled with FITC (Chemicon), and α-synuclein was visualized with anti-rabbit IgG coupled with rhodamine (Chemicon).

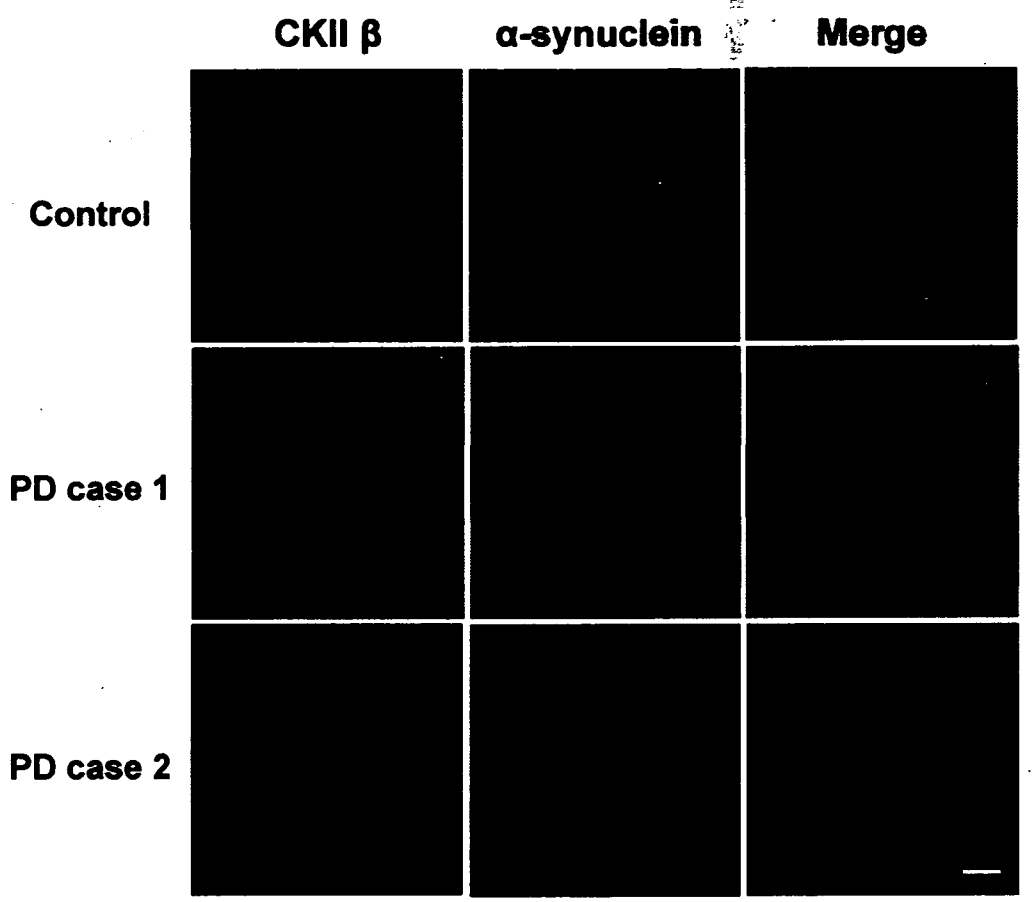

Fig. 2. CKII β subunit co-localizes with α-synuclein in patients with PD. Sections through the SN of PD cases were incubated with a mouse monoclonal anti-CKII β subunit antibody and labeled with FITC conjugated anti-mouse and with a rabbit anti-α-synuclein antibody and rhodamine-conjugated anti-rabbit. Merged images of the double-stained LB with CKII β and α-synuclein immunoreactivities are shown in yellow. Scale bar=10 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sections were observed under a Carl Zeiss LSM-510 laser scanning confocal microscope.

3. Results

In the substantia nigra pars compacta (SN) of PD cases, Lewy bodies stained with eosin as expected (Fig. 1). Immunohistochemical experiments revealed that Lewy bodies were CKII β positive (Fig. 1), but no signal was detected for CKII-α (data not shown). Nearly all cytoplasmic inclusions were positive for CKII β, which resembled classical Lewy bodies typically found in α-synucleinopathies. To investigate the specification of CKII β antibody, lysates prepared from human neuroblastoma cells (SH-SY5Y cells) were subjected to Western blot. It had a proper characterization because the band of CKII β disappeared in preabsorbed with CKII enzyme (NEB) (Supplementary data). To further confirm the localization of CKII β subunits in Lewy bodies, a double-labeling immunofluorescence was carried out with antibodies to α-synuclein and CKII β. Most Lewy bodies in SN were immunoreactive for both α-synuclein and CKII β subunits in the halo of these inclusions (Fig. 2). The signal for α-synuclein was stronger than that for CKII β. These findings are consistent with the observation that α-synuclein is the major filamentous component of Lewy bodies particularly in the halo region [5,6]. These observations suggest that CKII subunits are components of Lewy bodies co-localizing with α-synuclein.

4. Discussion

The present study shows that Lewy bodies in PD brains are immunoreactive for CKII β subunits, consistent with our previous finding that CKII β subunits localize in cytoplasmic inclusions induced by the co-expression of α-synuclein and synphilin-1 in 293 cells [12]. Our present *in vivo* finding may be an important clue for understanding the molecular mechanisms that induce the formation of Lewy body-like inclusions.

The α subunit of CKII is catalytically active, whereas the β subunit is inactive. Although the function of CKII β is still not entirely understood, this subunit has the specificity of interaction with substrate proteins [10]. Therefore, CKII β has a greater tendency to interact with its substrates than CKII α.

This may explain why CKII β was detected in Lewy bodies, but not CKII α. To exclude the possibility of antibody specificity, we used another CKII α antibody (Santa Cruz) and obtained a similar negative staining (data not shown).

These observations were made in PD brains with SN Lewy bodies, but we expect that all Lewy bodies likely have CKII β subunits since this kinase is present in most brain neurons [13,14].

The subunit of CKII β was present in Lewy bodies, and was concentrated in the surrounding halo of Lewy bodies. Although CKII β was detected in the halo of Lewy bodies of PD brains, this subunit showed weak staining than α-synuclein in their halos, with their core regions unstained. In many cases, CKII β subunit is directly or indirectly responsible for binding and dissociation of its substrates as a major mechanism for the regulation of specific protein kinases [10]. In this respect, only CKII beta subunit coupled with α-synuclein may be a selective formation of inclusion and leads to facilitate Lewy bodies. Therefore, this subunit may be detected in low intensity than α-synuclein. Further in depth analysis of composition ratio of CKII β and α-synuclein is needed. Other CKII β antibodies may be helpful for the elucidation of our observations in Lewy bodies.

Phosphorylation events have been implicated in certain neurodegenerative diseases. For example, the hyperphosphorylation of *tau* is associated with the pathogenesis of Alzheimer's disease [15], and phosphorylated α-synuclein at Ser129 is deposited in Lewy bodies of Dementia with Lewy bodies (DLB) and in α-synuclein transgenic *Drosophila* [16,17]. Our observations suggest that CKII mediated phosphorylation may contribute to the formation of protein aggregates in human α-synucleinopathies.

Finally, the present *in vivo* study extends and substantiates our previous experiments in cellular models demonstrating that CKII subunits are present in and regulate the formation of α-synuclein inclusions in transfected 293 cells. Most Lewy bodies in PD brains are stained for CKII β. Our cellular and *in vivo* observations collectively suggest that casein kinase II and particularly its β subunit contribute to the formation of Lewy bodies likely through phosphorylation of substrate proteins critical to the pathogenesis of these disorders including α-synuclein and synphilin-1. Alternatively, this subunit of CKII may influence aggregation of α-synuclein and its interacting proteins through a separate unidentified mechanism.

Acknowledgements

This study was supported by a grant from KOSEF/Brain Disease Research Center at Ajou University School of Medicine and in part by a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (0412-DB00-0101-0007). MMM is the William Dow Lovett Professor of Neurology.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jns.2007.08.027.

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Corticobasal degeneration as cause of primary progressive nonfluent aphasia

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Neuropathology. 2006;26:569–78.

AUTHORS' SUMMARY

A patient developed gradual loss of spontaneous speech at age 60. Neuropsychological examination at age 62 showed severe nonfluent aphasia. No alien hand was observed. Magnetic resonance imaging showed progressive cortical atrophy with definite atrophy of the left paracentral gyrus. He died at age 67. The brain weighed 810 grams with atrophy of the frontal lobe, globus pallidus, enlargement of the lateral ventricles, and depigmentation of the substantia nigra. Ballooned neurons as well as numerous astrocytic plaques and argentophilic threads were observed in the cerebral cortex. Clinical diagnosis of corticobasal degeneration is sometimes difficult in individuals with atypical clinical presentations.

Introduction

Corticobasal degeneration (CBD), or cortical-basal ganglionic degeneration, was originally described by Rebeiz et al. as corticodentatonigral degeneration with neuronal achromasia *(1–3)*. CBD is a rare neurodegenerative disorder and clinically characterized by asymmetric limb clumsiness, rigidity, tremor, dystonia, and cognitive dysfunction *(4–7)*. In an increased number of pathologically confirmed cases of CBD, clinical heterogeneity has been recognized. Based on the result of a recent large study, 93% of individuals with CBD showed various signs of higher cortical dysfunction, such as dyspraxia, cortical sensory loss, dementia, and aphasia *(8)*. Aphasia has also been proposed as an important—but not universal—clinical symptom of CBD patients *(4)*. Thus, in those individuals, only limited cases have been pathologically confirmed as CBD. Furthermore, cognitive dysfunction as an initial presentation may be still unusual manifestations of CBD.

In this paper, we report an autopsy case of CBD in which the patient developed primary progressive nonfluent aphasia as initial clinical presentation. This report will provide the information of clinical and neuropathologic heterogeneity as well as characteristic changes in magnetic resonance images (MRI) of CBD.

Case history

The case of the individual here reported, that of a Japanese right-handed man, developed at age 60 difficulties in speaking and in simple arithmetic calculation. He had been working as a baker since he was 28 years old and kept a small supermarket for the recent 10 years. Since he felt dull headache at age 60, a brain computed tomography (CT) scan was carried out but showed no abnormal lesions. He continued to exhibit gradual loss of spontaneous speech, although it was recorded that his memory seemed well preserved. A brain MRI showed an ischemic lesion of the right cerebral white matter adjacent to the posterior horn of the lateral ventricle. At age 61, his speech had further deteriorated. According to the medical chart, he showed difficulty in simple calculation, reading, and writing. Memory disturbance was also recorded. He ceased working because he was unable to function well at the cash register. In the following 2 years his speech became restricted to monotonous utterances. Approximately 1 year later, the patient was referred to the neuropsychiatrist. Neuropsychologically, the condition of his speech was recognized as severe nonfluent aphasia. The patient could answer simple questions such as his name, age, and his hometown. While he identified real objects, such as a pencil and a pair of glasses, his spontaneous speech was nonfluent characterized with residual recurring utterances of *"un"* ("yes") or nodding. Perseveration, as well as simplification of speech and echolalia, was also present. Repetition was slightly impaired. Auditory comprehension appeared somewhat better than speech output but was ▸