Nofujia, Y, Suwa, M, Moriyama, Y, Nakano, H, Ichimiya, A, Nishichid, R, Haruka Sasaki, H, Radak, Z, and Kumagai, S	Decreased serum brain-derived neurotrophic factor in trained men.	Neuroscience Letter	437	29-32	2008

B. 認知機能障害と認知症

1. はじめに

厚生労働省によれば，中高年齢者における肥満，糖尿病患者および高齢者における認知機能低下や認知症の増加は，今後30年間で倍増するものと試算されている．しかしながら，それらの病態の予防や改善の基盤となるエビデンスは極めて不足している．

脳由来神経栄養因子（Brain-Derived Neurotrophic Factor; BDNF）は，脳の可塑性に影響する神経栄養因子であり，神経の成長，分化，生存を保護する特性を有している．近年，うつ病患者およびアルツハイマー病患者では，脳内のBDNFタンパク質濃度およびBDNF mRNA発現が低下していること，ストレス反応にともない減弱すること，BDNFが摂食行動の調節および糖代謝の改善作用を有することなどが報告されており，その生理作用は多岐に及んでいる．さらに，ラットにおける自発運動は，BDNFやその他の神経栄養因子を増加させるとともに神経増殖を刺激し，脳の神経細胞の障害に対する抵抗性を高め，学習や精神的なパフォーマンスの改善をもたらすことなどが近年報告されつつある[12]．これらは，運動がBDNF発現の亢進を促すことにより，近年増加傾向にある認知症や認知機能障害，さらには生活習慣病の基盤である肥満症の予防や改善に貢献しうることを示唆している．

ここでは，認知症および認知機能障害の運動疫学に焦点を絞り，BDNFとの関連性も含め説明を加える．

2. ヒトにおける研究

(1) 観察疫学研究

3つの生活習慣因子
身体活動，精神的活動，および社会的ネットワーク

Fratiglioni ら[13]は，3つの生活習慣因子が認知機能への恩恵や認知症に関して予防的な役割を有すること，およびその予防・改善のメカニズムは，認知症やアルツハイマー病の3つの病因仮説である，1) 認知予備力仮説，2) 血管性仮説，3) ストレス仮説に収斂するのではない可能性，すなわち共通のプロセスが関与している可能性があることを指摘している（表Ⅲ-23，表Ⅲ-24）．身体活動と認知機能との関連性（表Ⅲ-23）については，種々の検査指標で評価された認知機能との間に関連性があるとの報告が多いものの，身体活動単独の影響を検討した研究は半数であった．また，認知症のリスクとの関連性に関する前向き研究（観察期間:1～7年）（表Ⅲ-24）の約半数は，関連がなかったとする報告であったが，日本からの報告を含む5件で，アルツハイマー病のリスクと身体活動との関連が報告されている．スポーツ種目では，ダンスのみに認知症のリスクの低下との関連が観察された．

また，観察疫学研究で明らかとなったアルツハイマー病，認知症および認知機能と身体活動，精神的活動，および社会的ネットワークとの関連性の有無の比較を行なった結果，アルツハイマー病と身体活動および社会的ネットワークとの関連，さらには認知症と社会的ネットワークとの関連を除き，身体活動，精神的活動，および社会的ネットワークの強化は，アルツハイマー病，認知症および認知機能低下に効果があることが示唆された（図Ⅲ-37）．

Barnes ら[14]が行なった6年間の前向き研究では，健康な地域高齢者を対象に調査時点で測定された持久性体力とMMSE（Mini Mental State Examination）で評価された認知機能の低下との間には直線的な量・反応関係があることが観察された（図Ⅲ-38）．すなわち，高齢者において体力依存性に認知機能低下が抑制されることが示唆された．

日本人を対象とした症例対照研究[15]によれば，余暇活動への参加頻度が高い高齢者は，参加の少ない者より認知症のリスクが低いことが報告されている．地域在住の高齢女性（5925名）を対象に実施した6～8年の追跡研究では，歩行量が少ない人に比べて多い人では，認知機能のリスクは0.66倍に下がることが観察されている[16]．また，認知機能が正常であった65歳以上の地域在住の男女6434名を対象に，認知機能低下および認知症をアウトカムとした5年間の前向き研究では，中程度から高いレベルの身体活動に参加している高齢者では，認知機能障害，認知症（アルツハイマー病や他の認知症を含む）への罹患が有意に半減することが示された[17]．

認知機能障害のない65歳以上の高齢者（1740名）を対象とした約6年間の前向き研究によれば[18]，研究開始時に週に3回以上の運動実施者は，週3回未満の者に比べ，アルツハイマー型認知症の罹患率が有意に低いことを報告した．また，これらの結果はアルツハイマー型認知症の遺伝素因（ApoE ε4）の有無によっ

表 III-23 身体活動と認知機能の関連についての長期観察的研究[13]

研究者 / 国	対象者数	ベースライン時の年齢	生活習慣の尺度	フォローアップ期間（年）	認知機能のアセスメント	コントロール因子	報告された関連
Albert *et al*, USA	1011	70-79	身体活動	2-3	神経心理学テスト（言語，記憶，概念，視空間能力）	Eth,inc,CD, dep,PF,SN,ES	活発な身体活動と認知機能の維持との関連あり
Carmelli *et al*, USA	566	65-86	身体活動の自己申告	6	短期記憶の低下，言語の流暢さ，視空間能力	SRH	低身体活動と認知低下との関連あり
Hultsch *et al*, Canada	250	55-86	社会的活動，新しい情報の処理活動，身体活動	6	認知機能の低下（記憶，理解力，速度）	CD,IADL, SH,med,pers	身体活動と認知機能に関連なし
Yaffe *et al*, USA	5925	＞65	軽度，中等度，高強度な身体活動	6-8	国際的な認知尺度の低下（MMSE）	Morb,PF, smok,oestr	中程度および活発な身体活動と認知低下の減少との関連あり
Schuit *et al*, Netherlands	347	平均 74.6	1日の身体活動の時間（中等度または高強度）	3	国際的な認知尺度の低下（MMSE）	PMF,dep,SH, SRH,smok,alc	アポリポ蛋白 E ε4 を持つ人にのみ低度の1日の身体活動と高い認知機能低下の関連がみられた
Ho *et al*, China	2030	＞70	身体活動のセルフレポート（はい/いいえ）	3	国際的な認知機能テスト（CAPE）	PMF,dep	運動なしと認知機能障害との関連あり
Bosma *et al*, Netherlands	830	49-81	身体運動，精神的・社会的活動（時間/週）	3	記憶と言語の流暢さに関する特定のテスト，国際的な認知機能テスト（MMSE）	cog	左記の3つの活動全てと認知機能低下の減少，高度の活動と高い認知機能との関連あり
Richards *et al*, UK	1919	36	余暇時間の活動（社会的，精神的要素の高い），身体運動	7	言語記憶能力	SES,IQ,SH, dep	中年期における余暇時間の活動，身体活動とより良い記憶能力との関連あり

全ての関連は，年齢，性別及び教育歴で調節されている．Eth：民族性，inc：収入，dep：うつ病，ES：感情的支援，CD：慢性疾患，SRH：健康についての自己申告，IADL：手段的日常生活動作，SH：自覚的健康，med：薬物の使用，pers：パーソナリティ，PF：身体機能，morb：罹患率，smok：喫煙，oestr：エストロゲンの使用，cog：認知機能，SN：社会的ネットワーク，PMF：身体・精神的機能，alc：アルコール

て影響されないことも観察されている．しかし，遺伝因子の影響に関しては異なる報告もあり，意見の一致をみていない．

しかしながら，全ての前向き疫学研究で身体活動と認知症発症に関する関連性が認められているわけではない．認知症発症に関する前向き研究における成績の不一致をもたらす要因（課題）として，身体活動の自己評価の収集方法，有酸素運動かそうでないかの区分，身体活動の持続時間や強度の問題，さらには対象者のサンプリング時点での認知症の事前徴候性などの排除の有無などが指摘されている．さらに，身体活動による認知症発現の予防効果への遺伝因子の関与に関しても，更なる研究が必要である．

(2) 介入研究

認知症のない高齢者を対象とした認知機能の有酸素運動の介入効果に関するメタ分析[19]においても，運動の認知機能改善に及ぼす恩恵に関して中程度の効果サイズ（スコア：0.48）が確認されている．特に，有酸素運動にともなう体力の

表 III-24　身体活動と認知症の関連についての長期的観察研究[13]

研究者 / 国	対象者数	ベースライン時の年齢	身体活動	フォローアップ期間（年）	コントロール因子	報告された関連
Yoshitake *et al*, Japan	828	＞65	余暇，労働での身体活動	7	BP,CVD,alc,dia,cog,haem,	日常的な身体活動とアルツハイマー病のリスク低下との関連あり
Fabrigoule *et al*, France	2040	＞65	スポーツ	3	Alc,cog,PF,soc	関連なし
Scarmeas *et al*, USA	1172	＞65	13 種目の活動（身体的，文化的，レクリエーション的，社会的）：余暇活動のスコア，3 要因のスコア	1-7 平均 2.9	Occ,PF,dep,VD,hyp,dia	1 つの活動と要因スコアとアルツハイマー病のリスクの低さとの関連あり
Lindsay *et al*, Canada	4615	＞65	規則的な運動（定義されていない）	5		規則的な身体活動とアルツハイマー型痴呆のリスクの低さとの関連あり
Laurin *et al*, Canada	4615	＞65	軽度，中等度，高強度の身体活動レベル（時間，強度）	5	FA,smo,alc,NSAID,ADL,IADL,SRH,CD	高い身体活動レベルと認知症及びアルツハイマー病のリスクの低さとの関連あり
Wang *et al*, Sweden	732	＞75	身体活動（自己申告）：参加の頻度	6	PF,cog,morb,dep	関連なし
Wilson *et al*, USA	801	＞65	身体活動（時間）	平均 4.5	SRH,dep,cog,PF	関連なし
Wilson *et al*, USA	842	平均 76	身体活動のスコア（7 種目の活動時間）	4	Eth,APOE,dep,occ,PMF	関連なし
Verghese *et al*, USA	469	≧75	11 の身体活動：身体活動スコア（時間）	中央値 5.1	CD,dep,PMF	ダンスのみ認知症のリスクの低さとの関連あり

全ての関連は年齢，性別，教育歴で調節されている．BP：血圧，CVD：脳血管疾患，alc：アルコール，dia：糖尿病，cog：認知機能，haem：ヘマトクリット，PF：身体機能，SOC：社会的地位，occ：職業，dep：うつ病，VD：血管疾患，hyp：高血圧，FA：家族歴，smo：喫煙，NSAID：非ステロイド性抗炎症薬，ADL：日常生活動作，IADL：手段的日常生活動作，CD：慢性疾患，morb：罹患率，SRH：自己申告の健康，PMF：身体及び精神的機能

* 認知症は DSM III分類，アルツハイマー病は NINCDS-ADRDA 分類の診断による

増加は，計画性，スケジュール作成，作業記憶，重複作業などの実行制御過程（Executive Control Process）の改善に大きく貢献しているとしている．また，有酸素運動の効果は，有酸素運動に加え筋力や柔軟性運動を同時に実施したほうが効果サイズは大きく，かつ，その効果は女性で大きいことも明らかとなった．

女性において効果サイズが大きい背景には，女性ホルモンの関与が示唆されている．Berchtold ら[20]は，運動効果はエストロゲンの存在に依存しており，かつコンビネーション効果は単独効果を上回るものであることを報告している．さらに，Erickson ら[21]は閉経後の女性を対象に，脳重量と実行制御に関する体力（$\dot{V}O_2max$）とホルモン補充療法（HRT）の影響を検討し，体力が高い人は HRT に関係なく認知機能が優れ，脳重量が重いことを報告した．また，10 年未満の短期使用の場合，脳重量や認知機能への好ましい効果を認めたが，16 年以上の長期使用では，効果は観察されなかったことを報告した．しかし，長期使用であっても，体力が高い群では，その負の効果はオフセットされることも観察されている．これらは，女性への運動効果が高い背景にはエストロゲンの影響があることを示唆している．

一方で，既に認知症を発症した人への介入研究は少ない．Heyn ら[22]は，認知

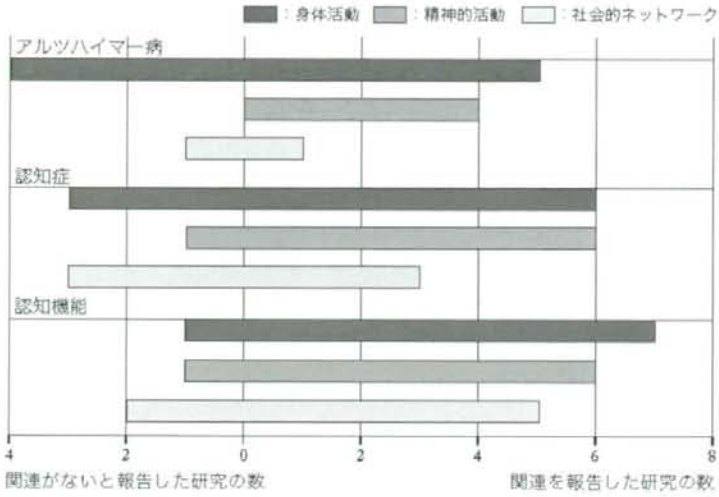

図 III-37 アルツハイマー病，認知症，認知機能低下の予防の根拠[13]

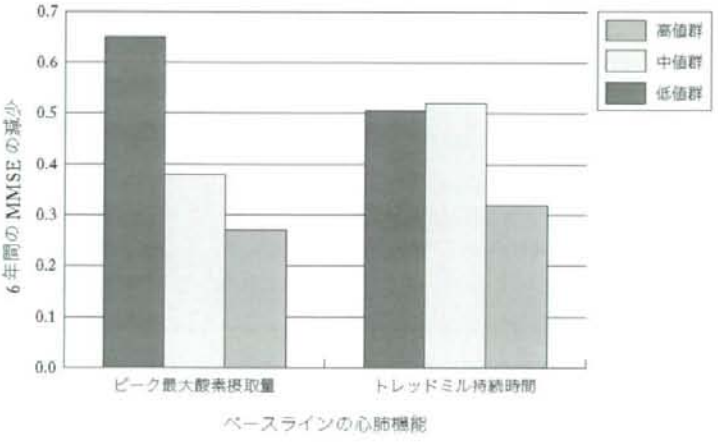

図 III-38 ベースラインのピーク最大酸素摂取量，トレッドミル持続時間の値群別の6年間のMMSEスコア減少[14]
スコアは年齢，性別，教育年数，知能，高血圧，甲状腺障害，自己健康度，喫煙およびベースラインでのMMSE得点によって調整されている．

症患者や認知機能障害者を対象とした身体トレーニングの効果に関する論文のメタ分析で効果サイズの検討を行ない，身体トレーニングは認知症および認知機能障害を有する高齢者の体力，身体機能，認知機能，積極的な行動を高めると結論している．運動の内容は，歩行や筋力トレーニングおよびレジスタンス運動を含む低強度の運動が中心で，期間は2週間から28週間であった．

また，アルツハイマー病患者に有酸素運動を7週間実施した結果，コントロール群に比べて介入群では栄養状態，転倒のリスク，問題行動，および認知機能が有意に改善したとの報告があるが，サンプル数が少ないのが課題である．Teri ら[23]は，アルツハイマー病を患っている地域在住高齢者へのホームベース型の運動プログラムを実施し，機能依存を減少させ施設入所を遅らせるかどうかをア

ウトカムとした無作為化比較対照研究（RCT）を行なった．3ヶ月間の持久性運動と筋力，バランス，柔軟性のトレーニングを行なった結果，介入群では身体機能スコアが改善し，抑うつもコントロールに比べて改善したのに加え，2年後の追跡調査でも介入グループでは身体機能，抑うつスコアともに良好で，問題行動による入所者も少ないままであることが報告された．このように，認知症の発症予防に運動はポジティブな貢献が期待されるが，効果的な運動内容についてのエビデンスは不足している．

身体活動や体力の向上にともなう疾病減少および認知機能に及ぼすこれらのメカニズムの概要を図 III-39 に示す．また，ライフステージ別の認知症の発症に関わる危険因子および予防に関わる抑制因子を図 III-40 に示す．それによれば，人生後期の 65 歳以降において，認知症の予防には豊かな社会的ネットワーク，精神・身体活動が重要であることが理解できる．

3. 海馬と認知機能

海馬は古皮質である大脳辺縁皮質に位置し，記憶の形成に不可欠な部位である．海馬を除去された患者では，新しく物事を記憶することができず，加齢にともない海馬は萎縮し，海馬の体積と記憶力や認知機能との間には有意な相関関係が存在する．また，多くの高齢者は認知機能および内分泌機能の低下を示す．これらの変化に関連した主要な脳の領域は，海馬と視床下部である．この2つの脳部位はそれぞれ高い可塑性を有し，さらに認知および内分泌機能に影響を与えている．神経栄養因子のうち，BDNF は成人ラットの海馬と視床下部に高濃度で存在することが確認されている．

4. 血清 BDNF

血清 BDNF のバイオマーカーとしての臨床的意義に関する研究は，精神医学および心身医学領域において，うつ病，不安障害および摂食行動異常（神経性食欲不振症など）などの患者を対象に活発に報告されている．これらの症状を呈する患者では，健常者に比べ血清 BDNF 濃度が有意に減少しているとの報告がある．しかし，アルツハイマー病患者では，疾患の軽症な初期ステージで血清 BDNF 濃度が増加し，一方，重症期では健常者の水準まで低下することが報告された．これには，アルツハイマー病初期での神経新生初期の補償的な修復メカニズムが反映されており，重症期において血清 BDNF は神経細胞死に関与している β アミロイドの減生を高めるのに貢献している可能性がある．

さらに，興味ある知見として，摂食行動異常患者やうつ病患者におけるうつスコア，およびアルツハイマー病患者の MMSE で評価された認知機能スコアと血清 BDNF との間には有意な関連性も観察されている．その背景としては，BDNF は血液脳関門を通過して，脳から循環血液へ，あるいは循環血液から脳へ移動できること，および大脳皮質の BDNF 濃度と血清 BDNF との間に有意な正の相関関係を呈することが明らかにされている．

今後は，代謝調節にとって重要な構成要素である身体活動や体力のバイオマー

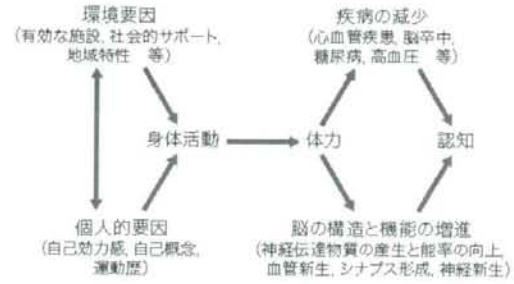

図 III-39 身体活動／体力の向上に伴う疾病減少および認知機能に及ぼすメカニズム[24]
ここに記載されている要因は，動物実験，ヒトの疫学研究，ヒトの無作為化比較対照研究から得られている．各要因，機構，およびその関連性は，推測であるが，最近の高水準の知識の要約から供給されている．

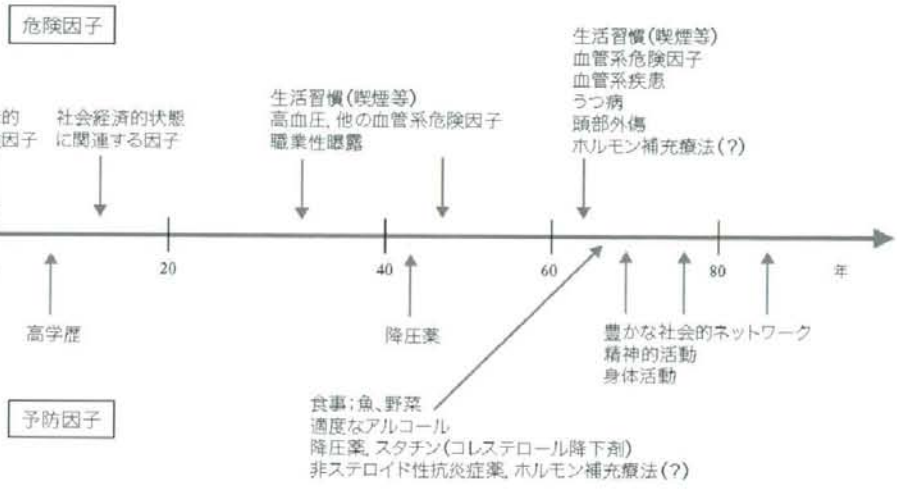

図 III-40 認知症の危険因子と予防因子の年表[13]
どの時期も有用な研究によって確認されたものである．

カー，あるいは関数としての血清 BDNF の意義に関する運動生理学的研究も活発に行なわれることが期待される．

5. BDNF と認知機能

運動は，海馬に依存した学習や神経防御を含む神経機能に明らかな恩恵をもたらす．これらの効果の背景には，部分的な神経栄養因子の発現の増加によって仲介されるメカニズムがあり，BDNF に焦点が絞られて研究されるようになってきた．随意運動は，特に齧歯動物の海馬と皮質の BDNF を有意に増加させることが実証されている．海馬における BDNF の調節は，抗うつ剤投与によって効果が認められている同じ海馬領域で観察されている．運動は，抗うつ剤によってアップレギュレーションされ，抗うつ効果を有している要因であるインスリン様増殖因子 1（IGF-1）や線維芽細胞成長因子 2（FGF2）を含むその他の神経栄養因子や成長因子の発現や，その水準を高めることも報告されている．すなわち，

インスリン様増殖因子 1（IGF-1）
インスリンと配列が高度に類似したポリペプチド．主に肝臓で，成長ホルモンによる刺激によって分泌される．インスリン様効果に加えて，神経細胞の成長・分化，神経伝達物質の合成・放出を調節する．

線維芽細胞成長因子 2（FGF2）
FGF ファミリーに属している人体に広く分布する強力な血管新生因子で，血管新生，動脈形成を促進し，神経や骨の形成にも関与している．

これらの成績から，運動は神経栄養因子 / 成長因子の発現と神経細胞新生を高めることが示唆されている．

(1) BDNF への運動の影響

1995 年に Neeper[25] が運動によって BDNF mRNA の発現が増加するということを初めて報告して以来，運動の BDNF に及ぼす影響についての研究が数多くなされてきた．また，脳のさまざまな部位における BDNF mRNA 発現の変化を調べ，特に海馬や大脳皮質で顕著に発現が増加したと報告している．

(2) 食事制限の影響

運動と同様に，食事制限は神経栄養因子を増加させることにより，神経細胞新生および神経防御効果を有するようである．また，寿命の延長，年齢に関連した疾患の減少，およびストレスへの反応の改善を含む多くの恩恵をもたらす．さらに，食事制限は BDNF の発現の増加を含む脳に関する強い影響を有し，また，野生型マウスと BDNF ヘテロ欠損マウス双方において新生した神経の生存を高めることで海馬での神経新生を高める．他にも，パーキンソン病およびハンチントン病のモデルにおいて神経防御効果を誘発することも報告されている．

6. まとめと課題

これまで述べてきたように，運動は動物実験同様，ヒトにおいてもさまざまな認知機能（記憶や学習能力など）に加え，うつ病および認知症あるいはアルツハイマー病の発症の抑制および予防・改善に有効に作用する可能性が示唆される．

今後の研究課題は，

1) 運動による認知・脳機能改善とトレーニングの種類，時間，また強度との量・反応関係は未だに明らかではない．年齢の修飾因子的な影響や大きな無作為介入トライアルに加え，上記の因子間の相互関係など，これらの関連性を調査する必要性がある．
2) 高齢者は，身体トレーニングや食事制限介入によって認知機能維持に関する恩恵を得ていることは明らかであるが，それらの背景にあるメカニズムの類似性，または，それらがどのように生涯にわたっての認知機能，脳機能，脳構造に結びついて影響しているのかについては全くわかっていない．
3) 血清 BDNF の認知機能および代謝調節におけるバイオマーカーとしての役割を運動の影響をも含め検討すること．
4) 最近の研究は，うつ病の発症モデルにおけるメカニズムに関して，神経栄養因子の発現と神経新生の増加に関する報告を基盤に，運動の影響の類似性を調査している．さらに，気分に関する運動の恩恵は，うつ病患者でも実証されている．これらの研究では，運動は病態が軽度から中程度なうつ病患者の治療反応を誘発することを実証している．運動の抗うつ効果において，特に IGF-1 や BDNF といった神経栄養因子の役割が最近注目されており，今後の研究の課題である．

5) 日本人の認知機能障害者および認知症患者を対象とした運動プログラムの開発および効果評価を目的としたRCTを行なうこと．ただし，認知症患者を対象とする場合は，その原因疾患別に評価すること．
6) 認知症患者を対象とする場合，その周辺症状の改善を目指した運動プログラムの開発および効果評価を目的としたRCTを行なうこと．

である．

（熊谷　秋三・森山　善彦）

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Brain Pathology ISSN 1015-6305

RESEARCH ARTICLE

Clinicopathological Outline of Dementia with Lewy Bodies Applying the Revised Criteria: The Hisayama Study

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Keywords
dementia, diagnosis, DLB, Lewy body, pathology.

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Received 5 October 2007; revised 13 March 2008; accepted 19 March 2008.

doi:10.1111/j.1750-3639.2008.00169.x

Abstract

To explore the validity of the criteria for dementia with Lewy bodies (DLB) revised in 2005, we examined community based consecutive autopsy cases. 10.3% of the non-demented subjects and 31.2% of the demented subjects showed the Lewy body pathology. Applying the revised pathological criteria to the 205 demented subjects, the types of LB pathology of 11 cases (5.4%) were brainstem-predominant, 24 cases (11.7%) were limbic type and 24 cases (11.7%) were diffuse neocortical type, although there were many subjects not to fit the criteria exactly. The prevalence of Lewy bodies (LBs) was almost same regardless of gender; however, the extent of the LB pathology among females was more severe than that in males. The likelihood of DLB being modified by concomitant Alzheimer's pathology was as follows: 27 cases (13.2%) showed low likelihood, 16 cases (7.8%) showed intermediate likelihood and 16 cases (7.8%) showed high likelihood. Since the numbers of clinical features of DLB were significantly higher in the pathological intermediate and high likelihood DLB groups than in the low likelihood DLB group or no LB group, both the intermediate and high likelihood groups of DLB should be considered as pathological DLB.

INTRODUCTION

Dementia with Lewy bodies (DLB) has been suggested to be the third major dementia in older people, accounting for 15% to 25% of dementia cases (12, 16, 22, 24, 38); however, the history of the study of this type of dementia is still young. Recognition of DLB has become more widespread since the establishment of the first diagnostic criteria in 1996 (24) and the discovery of α-synuclein as the major constituent of Lewy bodies (LBs) in 1997 (30, 32). In particular, immunostaining of α-synuclein makes it easy to identify neocortical type LBs. Consequently, with the liberal definition of the pathological criteria of DLB in 1996, no less than 60% of Alzheimer's disease (AD) cases may be considered to meet pathologic criteria for DLB (23). Virtually none of these patients show the clinical features of DLB, especially those cases with extensive neurofibrillary tangles (NFTs; 7, 26) and those with one or more LBs in the amygdala, but without significant Lewy related pathology in other brain regions (15). The inclusion of such cases as pathologically confirmed DLB may have contributed to the view that the clinical criteria have suboptimal sensitivity (20).

Taking these issues into consideration, new diagnostic criteria for DLB were proposed in 2005 (23). The new criteria took into account both the extent of Lewy related pathology and AD-type pathology in assessing the degree of certainty that the neuropathologic findings explain the DLB clinical syndrome. Immunostaining of α-synuclein was recommended to detect LBs and Lewy related pathology, and a semiquantitative grading of lesion density was recommended. As indicated by the authors, the revised criteria obviously require further research to test their validity; however, to date, almost no study concerning this subject has been performed.

This is the first report of a community-based clinicopathological study of DLB, which verified the revised criteria.

MATERIALS AND METHODS

Subjects

The clinicopathological study of dementia, part of the Hisayama study, was previously described (13, 28, 36, 39). The Hisayama study investigated the epidemiology of cerebrovascular disease in the general Japanese population (17, 18, 34, 39). We carried out autopsies on most deceased subjects to confirm the causes of death and to examine brain pathology. We collected information about new neurological events, including stroke and cognitive

impairment, through a daily monitoring system established by the study team, local practitioners and the town government. Members of our study group visited the town at least once a week to maintain contact with physicians and staff of the local Health and Welfare Office. At least once a week, we also surveyed the three major hospitals with geriatric or psychiatric wards near the town, to which Hisayama residents are usually admitted when necessary. Regular health checks and extensive neuropsychiatric evaluation, including medical history and physical examination, neurological history and examination, semi-structured psychiatric interview and neuropsychological assessment, were given biennially to obtain information on any new neurological events missed by the monitoring network. When we suspected new neurological symptoms, including cognitive impairment, the study physicians carefully evaluated the subject, and an effort was made to obtain further diagnostic information, including brain CT and MRI. The diagnosis of dementia was made clinically based on the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) (3).

In this study, we analyzed two groups. Group 1 was the 102 consecutive autopsy series of the Hisayama study including both demented and non-demented subjects who died between October 1, 1998 and March 31, 2001 and underwent the autopsy (autopsy rate: 70.5%) and explored the risk factors of synucleinopathy with the revised criteria of LB pathology. Group 2 was the 205 consecutive autopsy series of the Hisayama study including only demented subjects who died between January 1, 1986 and March 31, 2003, including the demented cases of Group 1, and underwent the autopsy and studied the practice of the revised criteria of DLB. Autopsy rate of Group 2 was 64.0% and this rate was very close to that of the whole autopsy rate of this period (62.1%).

Clinical features

The core features and suggestive features of the revised criteria for DLB (23) were retrospectively ascertained from our database including the medical records, the nurse records, the interview records of caregivers and facility staffs for each subject. The results of single photon emission computed tomography (SPECT) or positron emission tomography (PET) imagings were not included in this study because these imaging studies examining the dopamine transporter uptake were not popular in Japan. Also, we picked up such features as repeated vocalizing, flailing limbs and moving around the bed during sleep, and we described these features as "sleep behavior disorder" instead of "REM sleep behavior disorder" because it was very difficult to monitor the sleep brain waves in community based study. Then, we surveyed all clinical core features: fluctuating cognition, recurrent visual hallucinations and spontaneous features of Parkinsonism. However, only sleep behavior disorder and severe neuroleptic sensitivity were investigated as suggestive features. We excluded the visual hallucination and Parkinsonism when these features occurred after more than 5 years since the dementia onset, because these features are also common in the late stage of AD.

Neuropathological assessment

Brains were weighed, evaluated for grossly detectable lesions and abnormalities of the blood vessels, and fixed with 10% buffered formalin for at least 2 weeks. All infarcts (including status lacunaris and Binswanger's disease or leukoaraiosis) and hypertensive hemorrhages were registered with regard to their age, size and topographical location. Brain specimens were taken following the consensus guidelines for DLB, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) guidelines and Braak & Braak stage for NFT (8, 9, 23–25, 27). Thus, the specimens in each case included middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, anterior cingulate gyrus, amygdala, hippocampus with entorhinal cortex and transentorhinal cortex (at the level of the lateral geniculate body, LGB), calcarine cortex, basal ganglia including the nucleus basalis of Meynert, thalamus, substantia nigra, locus coeruleus and dorsal vagal nucleus. Sections were embedded in paraffin and were routinely stained using hematoxylin-eosin, Klüver-Barrera and a modified Bielschowsky's method.

Specimens from every subject were immunostained with a panel of antibodies against α-synuclein (LB509; monoclonal, mouse, 1:100; donated by Dr Iwatubo) (4, 36), tau (polyclonal, rabbit, 1:100; Dako, Demark) and ubiquitin (polyclonal, rabbit; 1:100, Dako). Immunolabeling was detected using a standard indirect immunoperoxidase method and viewed with diaminobenzidine (DAB; Dojindo, Japan). The sections were lightly counterstained with hematoxylin.

Neuritic plaques were estimated by a modified Bielschowsky's method. NFTs were assessed by tau immunostaining. In each case, the frequency of neuritic plaques and NFT were semiquantitatively evaluated, and converted to a plaque score according to CERAD criteria and Braak stage established by Braak and Braak (8, 9, 27). The CERAD score and the Braak stage were combined to estimate the likelihood that dementia was due to AD, according to the NIA-RI criteria (1).

The extent of LB pathology was estimated based on the revised consensus guidelines for DLB (23) and the type of LB pathology (none, brainstem-predominant, limbic, diffuse neocortical) and the likelihood of DLB (no, low, intermediate, high) were assigned for each of the 205 cases. In determining the type of LB pathology, first, we explored the middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, anterior cingulate gyrus, transentorhinal cortex, substantia nigra, locus coeruleus, and dorsal vagal nucleus. In addition, we explored amygdala to distinguish the none, brainstem and limbic type of LB pathology. The nucleus basalis of Meynert was examined when needed (see Table 2). In determining the likelihood of DLB, we used the NIA-RI criteria (1) as the assessment of Alzheimer type pathology. Those cases that did not fit the criteria of the type of LB pathology exactly were assigned according to the pattern of regional involvement rather than total LB count.

Statistical methods

The quantitative data obtained was compared between the groups by Mann-Whitney's U-test or Kruskal-Wallis test, as appropriate. Correlation analysis was done using the Spearman nonparametric method. Statistical significance was defined as $P < 0.05$. In the nonparametric statistical process, the following scale was adopted: CERAD (0 = none; 1 = sparse; 2 = moderate; 3 = frequent), type of LB pathology (0 = none; 1 = brainstem-predominant;

Table 1. Clinical and neuropathological information on the subjects of Group 1. CERAD values are presented according to the following scale; 0—none; 1—sparse; 2—moderate; 3—frequent. Significant difference between LB positive group and LB negative group. Abbreviation: LB = Lewy body.

Group	n (male/female)	Age at death (mean ± SD) (years)	Brain weight (mean ± SD) (g)	CERAD (mean ± SD)	Braak & Braak stage (mean ± SD)
Total	102 (51/51)	80.2 ± 12.2	1221.6 ± 161.6	1.60 ± 1.16	3.31 ± 1.90
LB negative group	79 (43/36)	78.5 ± 12.7*	1235.6 ± 170.9	1.53 ± 1.16	3.13 ± 1.90**
LB positive group	23 (8/15)	86.4 ± 7.7*	1173.5 ± 114.7	1.83 ± 1.15	4.00 ± 1.80**
Brainstem-predominant	8 (5/3)	84.8 ± 8.5	1200.0 ± 100.6	1.50 ± 0.93	3.63 ± 1.85
Limbic (transitional)	5 (2/3)	89.2 ± 11.1	1225.0 ± 72.6	2.40 ± 0.89	4.60 ± 0.55
Diffuse neocortical	10 (1/9)	86.3 ± 5.1	1126.5 ± 131.9	1.80 ± 1.40	3.90 ± 2.18

*$P < 0.01$ and **$P < 0.05$ (Mann-Whitney's U test).

2 = limbic; 3 = diffuse neocortical), the likelihood of DLB (0 = no; 1 = low; 2 = intermediate; 3 = high).

RESULTS

Clinico-neuropathological information of subjects

Group 1

The total number of Group 1 was 102. Among them, 68 subjects were non-demented and 34 subjects were demented. The clinico-neuropathological information on all the subjects of Group 1 is shown in Table 1. The age at death was significantly older in LB positive cases than in LB negative cases (Mann-Whitney U-test, $P < 0.05$) and Braak stage of NFT was more severe in LB positive cases than in LB negative cases (Mann-Whitney U-test, $P < 0.01$). Also, the extent of LB pathology got more severe along with aging and Braak stage of NFT (Spearman's rank correlation test, $r = 0.43$, $P < 0.01$; $r = 0.41$, $P < 0.05$, respectively). The LB pathology tended to spread wider among female than male but this difference did not reach statistical difference (Mann-Whitney U-test, $P = 0.052$).

Group 2

The total number of Group 2 was 205. The mean age at death was 86.2 ± 6.7 years; 78 subjects were male and 127 were female. The mean age at death of females was significantly higher than that of males, and the extent of Alzheimer type pathology (neuritic plaque and NFT) was significantly more severe in females than in males (Mann-Whitney U-test, $P < 0.01$). On the other hand, the prevalence of LBs was almost the same between males and females (male: 30.8%, female: 31.5%, total: 31.2%).

Applying the revised pathologic criteria to the LB positive cases

The distribution of LB pathology among LB-positive cases is shown in Table 2. Of the 68 non-demented subjects, seven subjects exhibited the LB pathology, and the types of LB pathology of five subjects (7.4%) were brainstem-predominant and two subjects (2.9%) were limbic type (but these seven subjects did not exhibit any clinical features related to LB pathology). Of the 205 demented subjects, 64 subjects had the LB pathology, and the types of LB pathology of 11 cases (5.4%) were brainstem-predominant, 24 cases (11.7%) were limbic type and 24 cases (11.7%) were diffuse neocortical type. The types of LB pathology of five subjects (2.4%) were none because the LB pathology was slight.

Group 2 was allocated to likelihood of being DLB. Twenty-seven cases (13.2%) were deemed to have a low likelihood of being DLB, 16 cases (7.8%) had intermediate likelihood of being DLB, and 16 cases (7.8%) had a high likelihood of being DLB. A comparison of LB pathology between the genders or ages is shown in Table 3. The LB pathology among males tended to occur younger than female and to be confined within the brainstem (37.5% of male LB-positive cases) and limbic system (45.8%), although the LB pathology among female tended to occur in their ninth decade and to be spread throughout the neocortex (50.0% of female LB-positive cases). Because the likelihood of DLB was greatly influenced by the associated AD pathology, the composition of each "likelihood of DLB" group was different between the genders. For example, among males, five (71%) of the seven high likelihood DLB cases showed limbic type LB pathology, but none of the high likelihood DLB cases among females showed limbic type LB pathology; all of these showed diffuse neocortical type LB pathology. In addition, the majority of LB-positive cases among the oldest cases were classified as low likelihood DLB, because of the severe AD pathology associated with aging.

Correlation between neuropathological and clinical assessments of DLB

To compare the neuropathological and clinical assessments of DLB, we excluded 52 cases from the 205 cases, because these 52 cases had been diagnosed as other types of dementia during life, based on the exclusive features of the revised criteria (23). The individual diagnoses were as follows: vascular dementia (38 cases), Parkinson's disease dementia (PDD, eight cases), tumor-related dementia (two cases), head injury (two cases), carbon monoxide poisoning (one case) and alcoholic psychosis with dementia (one case). In diagnosing vascular dementia clinically, we used the National Institute of Neurological Disorders and Stroke – Association International pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (31). Those cases that were undiagnosed the type of dementia during life and revealed to be vascular dementia after autopsies were included (many were small-vessel disease with dementia cases without apparent focal

Table 2. Distribution of LB. **A.** non-demented individuals. **B.** demented subjects. Numbers refer to a semiquantitative scoring system: 1 – mild, with sparse LBs; 2 – moderate, with more than one LB in a low-power field; 3 – severe, four or more LBs in a low power field; 4 – very severe, numerous LBs. The specimens that could not be sampled because of infarction or poor preservation are presented by NS. Abbreviation: LB – Lewy body; LC – locus coeruleus; SN – substantia nigra; TE – transentorhinal cortex.

A. Non-demented subjects with LB.

Case no.	Sex	Age at death	Type of LB pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
				DX-X	LC	SN	nbM	Amygdala	TE	Cingulate	Temporal	Frontal	Parietal
1	M	70	Brainstem	2	3	0	0	0	0	0	0	0	0
2	M	85	Brainstem	3	3	3	3	0	0	0	0	0	0
3	M	90	Brainstem	NS	3	2	0	0	0	0	0	0	0
4	M	96	Limbic	1	1	1	2	2	0	1	0	1	0
5	F	84	Brainstem	3	0	0	0	0	0	0	0	0	0
6	F	84	Brainstem	2	3	3	3	0	0	1	0	0	0
7	F	87	Limbic	0	2	3	0	2	0	2	1	0	0

B. Demented subjects with LB.

case no.	Sex	Age at death	Type of LB pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
				DX-X	LC	SN	nbM	Amygdala	T. E.	Cingulate	Temporal	Frontal	Parietal
1	M	83	None	2	0	0	0	0	0	0	0	0	0
2	M	91	None	2	0	0	0	0	0	0	0	0	1
3	M	78	Brainstem	3	3	2		0	0	1	0	0	0
4	M	83	Brainstem	1	3	3		0	0	0	0	0	0
5	M	83	Brainstem	3	3	3		NS	0	0	0	0	0
6	M	87	Brainstem	3	3	0	0	0	0	0	0	0	0
7	M	88	Brainstem	0	1	2		NS	0	1	0	0	0
8	M	90	Brainstem	0	0	3		0	1	0	0	0	0
9	M	93	Brainstem	0	3	0	0	0	0	0	0	0	0
10	M	68	Limbic	3	2	0	0	3	0	0	0	0	0
11	M	71	Limbic	2	1	3			3	3	0	0	0
12*	M	79	Limbic	0	3	3		4	2	3	1	0	0
13	M	81	Limbic	0	0	1	0	3	0	0	0	0	0
14*	M	83	Limbic	3	3	3	4	3	3	2	2	0	0
15	M	85	Limbic	2	2	1		0	3	2	0	0	0
16	M	86	Limbic	NS	NS	NS	NS	NS	3	NS	NS	0	NS
17	M	86	Limbic	2	2	2		4	1	0	0	0	0
18	M	86	Limbic	0	0	1	1	3	2	0	0	0	0
19	M	89	Limbic	3	3	3		4	2	3	0	1	0
20	M	89	Limbic	3	3	2		3	0	0	0	0	0
21	M	76	Neocortical	3	3	3			4	4	3	1	1
22	M	80	Neocortical	3	3	3		3	2	3	1	1	1
23	M	83	Neocortical	2	3	3		0	2	2	1	1	1
24	M	94	Neocortical	3	3	3		4	3	4	3	3	3
25	F	91	None	0	0	0	0	0	1	0	0	0	0
26	F	95	None	1	0	0	0	0	0	0	0	0	0
27	F	95	None	0	1	1	0	0	0	0	0	0	0
28	F	83	Brainstem	3	3	0	0	0	0	0	0	0	0
29	F	84	Brainstem	0	2	1		0	0	0	0	0	0
30	F	91	Brainstem	2	0	1	0	0	0	0	0	0	0
31	F	99	Brainstem	3	3	2		0	1	0	0	0	0
32	F	80	Limbic	3	2	2	4	3	0	0	0	0	0
33	F	82	Limbic	2	NS	3		4	2	3	1	0	0
34	F	84	Limbic	0	1	0	0	3	2	0	0	0	0
35*	F	84	Limbic	2	0	2		0	2	2	2	0	0
36	F	87	Limbic	3	3	3			3	4	0	0	0
37	F	90	Limbic	2	3	2	3	3	2	2	0	0	0
38	F	90	Limbic	3	3	3		NS	3	0	0	0	0
39	F	91	Limbic	0	1	1		3	1	1	0	0	0
40	F	93	Limbic	0	0	3		4	2	3	2	0	0
41	F	93	Limbic	3	3	2			2	2	1	0	0

Table 2. *Continued*

B. Demented subjects with LB.

case no.	Sex	Age at death	Type of LB pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
				DX	LC	SN	nbM	Amygdala	T. E.	Cingulate	Temporal	Frontal	Parietal
42	F	95	Limbic	2	2	3		4	3	3	1	0	0
43	F	96	Limbic	0	0	2		4	2	0	0	0	0
44	F	97	Limbic	3	3	2			2	2	0	0	0
45	F	79	Neocortical	3	3	3			3	3	3	1	1
46	F	81	Neocortical	3	NS	3		4	4	4	3	2	2
47	F	82	Neocortical	3	3	3		4	4	4	3	2	3
48	F	82	Neocortical	3	3	3			4	2	2	1	1
49	F	82	Neocortical	3	3	3			4	4	3	3	3
50	F	84	Neocortical	3	3	3		4	4	4	3	3	3
51*	F	84	Neocortical	3	3	3	4	4	4	4	3	3	3
52	F	85	Neocortical	NS	3	3			4	4	3	1	1
53	F	86	Neocortical	3	3	3		4	3	3	3	2	1
54	F	86	Neocortical	3	3	3			3	4	2	2	0
55	F	86	Neocortical	3	3	3	3	4	4	3	2	2	0
56	F	89	Neocortical	3	3	3		4	3	3	2	1	1
57	F	89	Neocortical	3	3	2			2	3	2	1	1
58	F	89	Neocortical	3	3	3			1	2	2	1	0
59	F	90	Neocortical	3	3	3		4	2	2	1	1	1
60	F	93	Neocortical	3	3	3			3	4	3	2	1
61	F	93	Neocortical	3	3	3	4	4	4	4	4	3	3
62	F	94	Neocortical	2	2	3		4	3	3	2	0	2
63	F	94	Neocortical	3	3	3	4	4	3	3	2	2	2
64	F	95	Neocortical	4	3	3			3	4	3	1	0

*Demented patients with pre-existing Parkinsonism.

neurologic signs). To distinguish PDD from DLB, we used the 1-year rule (23). Thus, 153 cases were included in the study analyzing the correlation between neuropathological assessment and clinical assessment of DLB.

The presence rate of core and suggestive features in each type of LB pathology and the likelihood of DLB are shown in Figure 1. Statistically significant differences among the types of LB pathology or the likelihood of DLB were observed, especially in the core features. The average numbers of core features presented in 153 cases are shown in Table 4. The diffuse neocortical LB group showed the greatest number of core features compared with other groups, and reached statistical significance when compared with the limbic LB group (Mann-Whitney U-test, $P < 0.05$) and the no LB group (Mann-Whitney U-test, $P < 0.01$). However, among the groups classified on the basis of likelihood of DLB, the intermediate likelihood of DLB group presented with the highest number of core features, rather than high likelihood group. This is because the cases that showed diffuse neocortical LB pathology associated with severe AD pathology (NIA-RI: high likelihood of AD), which was classified as having an intermediate likelihood of being DLB, presented with core features most often (Table 4). Among cases of high likelihood of DLB, two cases of subcategory in which type of LB pathology is limbic and NIA-RI is low likelihood (cases no. 19 and no. 20 in Table 2) presented no core features, whereas two PDD cases excluded in this study corresponded to this subcategory. Suggestive features were not so common in every group.

DISCUSSION

Here, we applied the new DLB criteria to the Hisayama pathological cohort study, and examined their validity from various pathological angles. We explored the proportions of the types of LB pathology and the likelihood of DLB in demented cases, as well as the correlations of the pathological diagnosis and clinical features of DLB with the minimum selection bias due to recruiting the 102 consecutive autopsy series and the 205 consecutive autopsy series with dementia from the general population.

The major problem in applying the revised pathological criteria of DLB was that there were many subjects not to fit the criteria of the type of LB pathology exactly. Among LB-positive subjects except for five subjects with so slight LB pathology that was allocated to none type, 28 of 59 subjects (47.5%) revealed not to fit the criteria; specifically, 7 of 11 brainstem-predominant cases (63.6%), 17 of 24 limbic type cases (70.8%) and 4 of 24 diffuse neocortical type cases (16.7%) showed conflicting distribution of LBs (see Table 2). Firstly, all of the three brainstem regions scarcely presented the LB pathology together in some brainstem-predominant and limbic type cases, and secondly, the extent of LB pathology in the amygdala got very severe in some cases even though the LB pathology did not involve the neocortex. It is noteworthy that the latter pattern of LB distribution was reported as Alzheimer disease with amygdala Lewy bodies (35). The extension pattern of LB pathology in DLB may show great variability

Table 3. Classification of male subjects (**A, C, E**) and female subjects (**B, D, F**) of Group 2 according to the revised criteria of DLB. **A–B** age at death <80, **C–D** 80≤ age at death ≤89, **E–F** 89< age at death. Abbreviation: LB = Lewy body; NIA-RI = National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease.

A. Male (Age <80)

		NIA-RI (Alzheimer)			Total
		Low	Intermediate	High	
Type of LB pathology	None	13	3	1	17
	Brainstem	1	0	0	1
	Limbic	2	0	1	3
	Neocortical	0	0	1	1
	Total	16	3	3	22

B. Female (Age <80)

		NIA-RI (Alzheimer)			Total
		Low	Intermediate	High	
Type of LB pathology	None	2	1	8	11
	Brainstem	0	0	0	0
	Limbic	0	0	0	0
	Neocortical	0	0	1	1
	Total	2	1	9	12

C. Male (80≤ Age ≤89)

		NIA-RI (Alzheimer)			Total
		Low	Intermediate	High	
Type of LB pathology	None	15	5	9	29
	Brainstem	2	1	1	4
	Limbic	3	1	4	8
	Neocortical	1	1	0	2
	Total	21	8	14	43

D. Female (80≤ Age ≤89)

		NIA-RI (Alzheimer)			Total
		Low	Intermediate	High	
Type of LB pathology	None	18	3	19	40
	Brainstem	1	1	0	2
	Limbic	0	1	4	5
	Neocortical	5	1	7	13
		24	6	30	60

E. Male (89< Age)

		NIA-RI (Alzheimer)			Total
		Low	Intermediate	High	
Type of LB pathology	None	4	2	4	10
	Brainstem	0	1	1	2
	Limbic	0	0	0	0
	Neocortical	0	0	1	1
	Total	4	3	6	13

F. Female (89< Age)

		NIA-RI (Alzheimer)			Total
		Low	Intermediate	High	
Type of LB pathology	None	7	3	29	39
	Brainstem	1	1	0	2
	Limbic	0	1	7	8
	Neocortical	2	1	3	6
	Total	10	6	39	55

of distribution and it is not easy to determine a stage like NFT. Recently, the similar results were reported that almost half (49%) of Lewy related pathology positive cases were not classifiable according to the revised pathological criteria of DLB (19), and the authors suggested that modifying the published criteria by reducing the number of regions requiring examination and adding an amygdala predominant category permitted classification of 97% of Lewy related pathology positive cases from the referral-based sample.

Although a large revision of the pathological criteria of the type of LB pathology was performed, the type of LB pathology was changed in a few cases only. The major changes observed were caused by the adoption of LBs in the amygdala as a hallmark of limbic pathology, resulting in eight brainstem-predominant type cases based on 1996 criteria being reclassified as limbic type. However, these cases often did not present with the clinical core features and suggestive features of DLB. Recently, AD patients with LBs in the amygdala were reported to be susceptible to major depression (21), and this may also be true of DLB patients. The possible clinical correlation of LBs in the amygdala in DLB remains unclear and further studies are required to clarify this.

There were 8 subjects in the Group 2 who exhibited the PDD. Of eight subjects, one subject was diffuse neocortical type of LB pathology, three subjects were limbic type and four subjects had no LB pathology; two may be Parkinsonism due to infarction, one may be Parkinsonism induced by drug and one is unknown origin. The relationship between the duration of Parkinson disease prior to the onset of dementia and key neuropathologic and neurochemical characteristics were previously reported (6), but in our study, this relationship was not apparent probably because of the limitation of subjects.

The prevalence of LB was almost the same between sexes, but the severity of LB pathology differed. LBs among males were usually confined within the brainstem and limbic system, although

Table 4. Mean number of 3 core features (fluctuating cognition, recurrent visual hallucinations and spontaneous features of parkinsonism) presented in the subjects within each subdivision. Abbreviation: LB = Lewy body; NIA-RI = National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease.

		NIA-RI (Alzheimer)		
		Low	Intermediate	High
Type of LB pathology	None	0.14	0.40	0.11
	Brainstem	0.33	0.50	0.00
	Limbic	0.00	0.67	0.07
	Neocortical	0.71	0.50	0.75

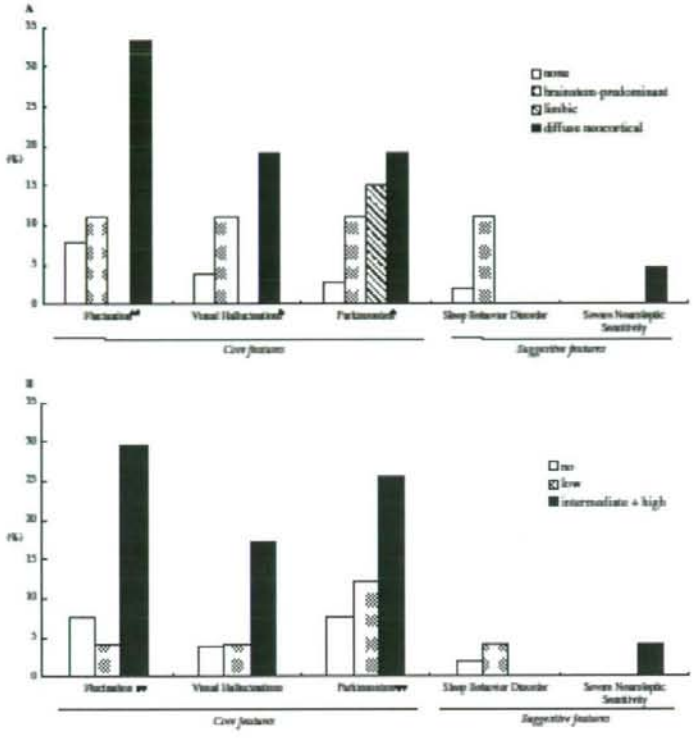

Figure 1. The presence rates of core and suggestive features with respect to each type of LB pathology (**A**) and each likelihood of having DLB (**B**). The intermediate and high likelihood cases of DLB are combined (see Discussion). There was a significant difference among the groups $^{*}P < 0.05$ and $^{**}P < 0.01$ (Kruskal-Wallis test).

those among females tended to spread throughout the regions of neocortex associated with AD pathology (see Table 3). We previously reported this similar sex-related tendency (36), but the number of available studies was too small to determine the potential effect of sex on the result (40). The age difference of males and females makes comparisons difficult to interpret and statistical comparisons should be controlled for the age difference; however, the size of our samples was small for the statistical correction. Nevertheless, we must consider that there may be a difference in the population of cases classified as high likelihood of DLB between the sexes. This considerable difference may be of some inconvenience of further studies, for example, of risk factors.

The effect of age on LB pathology remains unclear. Some studies have concluded that the frequency of LBs becomes higher with age (14, 29, 36); others have reported that aging has no effect on the frequency of LBs (2). This is the first community based pathological study for the LB pathology with the most recently published criteria and the result is very similar to our previous report based on the first pathological criteria (36), that is, the extent of LB pathology got more severe along with aging.

It is important in this study to define the pathological likelihood of DLB. Of the types of LB pathology, the diffuse neocortical type of LB group showed the clinical features of DLB most often, but of the likelihood of DLB groups, the high likelihood DLB group showed fewer clinical features of DLB than the intermediate likelihood of DLB group. This is because the cases that showed diffuse neocortical LB pathology associated with severe AD pathology (NIA-RI: high likelihood of AD) presented the core features most often, but these cases were assigned as having intermediate likelihood of being DLB (see Table 4). Certainly, the previous studies reported that those cases with extensive NFTs showed fewer clinical features of DLB, like visual hallucinations (7, 11, 26), but the difference in LB pathology burden between the mild AD pathology group and the severe AD pathology group was not taken into consideration in these studies. In addition, Alzheimer-type pathology becomes more severe with aging, and as many as 66.2% of our subjects of 90 years old or more at death were assigned as having a high likelihood of Alzheimer's disease according to NIA-RI so the likelihood of DLB tends to become lower at older ages (see Table 3). However, the age at death surely depends on medical aspects; in other words, the level of medical treatment that the subject got in life may have serious effects on the pathological diagnosis of DLB. Therefore, we propose the following amendments. First, cases with intermediate and high likelihood of DLB should be considered as pathological DLB. A diagnosis of "mixed dementia of DLB and Alzheimer's disease" may be the most appropriate for the intermediate likelihood of DLB group. The other suggested amendment is the introduction of some dividing system depending on the age at death, such as CERAD (27).

Of core features, Parkinsonism was often observed even among the brainstem and limbic type of LB pathology groups; however, cognitive fluctuation and visual hallucinations were not constant among none to limbic type of LB pathology groups and were more characteristic symptoms of the diffuse neocortical type of LB pathology group. It is highly suggested that neocortical involvement of LB pathology at certain degree is a prerequisite for cognitive fluctuation and visual hallucinations, and probably for severe neuroleptic sensitivity (Figure 1A).

The limitation of our study was that we did not include the results of SPECT/PET imaging examinations and sleep waves, and did not adopt the objective scaling systems of core features recommended in the DLB clinical criteria in 2005, such as the Clinician Assessment of Fluctuation scale (37), the semistructured One Day Fluctuation Assessment scale (37), the Mayo Fluctuations Composite Scale, the Neuropsychiatric Inventory (NPI) (10) and the Unified Parkinson's disease Rating Scale (UPDRS) (5). With the addition of the results of these imaging studies and scaling protocols, better sensitivity and specificity may be expected. Further prospective clinicopathological studies including these data and novel examinations such as MIBG myocardial scintigraphy (33) are required.

ACKNOWLEDGMENTS

This study was supported in part by a Grant-in-Aid for the 21st Century COE program and Grant-in-Aid for Scientists (No 19300125) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We are grateful to Dr Takeshi Iwatsubo, Department of Neuropathology and Neuroscience, University of Tokyo, for generously donating the α-synuclein antibody LB509. We thank Mr. S. Mawatari and Ms. S. Nagae for their technical assistance.

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JNNP Online First, published on October 31, 2008 as 10.1136/jnnp.2008.155481

Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama Study

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Keywords: Dementia, Alzheimer's disease, Vascular dementia, Epidemiology, Cohort study